PLENARY SPEAKERS

Larry Abbott

Columbia University College of Physicians and Surgeons

Random Matrices and Neural Networks

The exact connections between neurons in most neural circuits are not know but, instead, must be described statistically. In model networks, the connectivity is thus characterized by a random matrix. I will discuss how calculations of eigenvalue spectra of large random matrices can be extended to apply to neural networks and then used to analyze the dynamics of these systems. I will also present mean-field methods that allow us to distinguish periodic and chaotic phases in these networks, which leads to predictions that can and have been tested experimentally.

Martine Ben Amar

LPS, Paris

Morphogenesis of Living Systems: A Biomechanical Point of View

In this talk I will present two examples of biomechanical modeling to describe morphogenetic processes. The first example concerns epithelial morphogenesis of C.elegans embryo when, from the ovoid shape it elongates to four times its initial size. Taking into account the anatomy of the embryo treated with the mechanics of continuous media, we have established that the cells may behave like hyperelastic systems with an active behaviour and a viscoelastic response. The elastic solution shows that the passive behaviour of the microtubules network in the epithelial cells is necessary to explain the elongation which is induced by the contraction made by the molecular motors as myosin II along actin filaments. The results describe the link between the stress distribution in the embryo and the biophysical properties of subcellular networks. This knowledge is essential to understand the transformation of mechanical signals into biological and chemical responses. The second example concerns the deformations and the stress induced by the growth and the reorganization of living matter examined with the tools of the physics of nonlinearities and the theory of bifurcations. The mechanical properties are coupled to the growth processes using a multiplicative decomposition of the the strain tensor. We have studied the growth of hyper-elastic, initially planar, thin objects. Using the initial thickness as a small parameter we prove that, whatever the hyper-elastic energy, we recover the equilibrium FvK equations where growth appears simultaneously as a source of averaged and Gaussian curvature. Examples with either growth anisotropy or spatial inhomogeneities will be presented. Joint work with P. Ciarletta, J. Dervaux, and M. Mueller.

Stuart Pimm

Duke University

What Makes Food Webs Click?

Food webs are not just another class of complex systems, they are often given top billing in general discussions of networks. Much is known about their dynamics and there is an extensive literature on their various empirical patterns. Important questions remain. Do food webs share important features with other kinds of complex networks? If so, do the similarities reflect common processes to all networks? Or, if they are different, what are the key processes that shape them? In particular, are food web patterns essentially random — meaning there are multiple, external factors that shape them or are there processes internal to the networks themselves?

John Rinzel

Center for Neural Science and Courant Institute of Mathematical Sciences NYU

Dynamics of Perceptual Bistability

When visualizing an ambiguous scene (such as the Necker cube) one may perceive ongoing random alternations between the possible interpretations. Dynamical models implement competition as reciprocal inhibition between neuronal populations; dominance alternates - while slow negative feedback, adaptation, sets the basic time scale (seconds) for switching. When adaptation is strong enough it overcomes dominance and alternations occur intrinsically and periodically; noise perturbs the regularity. In a different framework, attractor-based dynamics, adaptation is weak and switches are induced by noise operating on a bistable system. We find that statistics of the observed alternations provide constraints that favor an operating range near the transition zone between the parameter regimes for the two mechanisms. In some paradigms one can manipulate stimulus cues to bias the competition away from equal dominance. We find with several different psychophysical stimulus types that the alternation rate is maximal when the fraction of time dominant equals 50%. We suggest that alternation evidences a perceptual exploratory strategy with maximal sampling rate when the stimulus is most uncertain.

MINISYMPOSIUM SPEAKERS

Bruce Ayati

University of Iowa

Biofilm as a Physiologically Structured Fluid

We present a physiologically structured multiscale model for biofilm development. The model has components on two spatial scales, which induce different time scales into the problem. The macroscopic behavior of the system is modeled using growth-induced flow in a domain with a moving boundary. Cell-level processes are incorporated into the model using a so-called physiologically structured variable to represent cell senescence, which in turn affects cell division and mortality. We present computational results for our models which shed light on modeling the combined role senescence and the biofilm state play in the defense strategy of bacteria.

Leah Band

University of Nottingham

Multiscale Modelling of Hormone Transport in Plant Roots

Researchers at the Centre for Plant Integrative Biology are constructing multiscale models of hormone-regulated root growth and development in the model species Arabidopsis thaliana. In this talk, I will focus on the role of the hormone auxin in gravitropism (root growth in the direction of gravity). Key to this process is the active transport of auxin through the root elongation zone. We apply asymptotic multiscale methods to a cell-based auxin-transport model to determine the dominant contributions to the effective tissue-scale auxin velocity and to explain the behaviour of wild-type and mutant plants. We are currently investigating the interplay between auxin transport, the auxinperception gene network and cell growth. Joint work with M.J. Bennett and J.R. King.

Andrea Barreiro

University of Washington

Transfer of Correlations in Neural Oscillators

Populations of neurons in a variety of brain regions show temporal correlations between their spike trains. A potential source of such correlations is common external input, which is transformed onto correlated output through the neural dynamics. We are interested in how particular neural dynamics will affect how these inputs are mapped into outputs; in this study we examine correlation transfer in pairs of uncoupled oscillators receiving partially correlated input. Specifically, we consider a one-parameter set of oscillators, which are characterized by a phase-resetting curve (PRC), given by the linear combination of two prototypical examples: the theta model PRC, typical of Type I excitable neurons, and the PRC near a Hopf bifurcation for a Type II excitable neuron. We examine the correlation coefficient between spike counts over a time window T. For very long time (T -> infinity) we use linear response theory for renewal processes to write this quantity as the ratio of integrals related to exit time moments. We find that correlation transfer over long time scales exhibits striking differences from the short-time (synchrony) correlation levels computed by Marella and Ermentrout (PRE 2008); they also differ qualitatively from the results on the linear integrate-and-fire neuron presented in de la Rocha et al. (Nature 2007, PRL 2008). We find that correlation transfer for neural oscillators is nearly independent of both input statistics (mean variance of afferent currents) and output statistics (firing rate and CV). Moreover, Type I neurons maintain a positive limiting correlation coefficient; correlation in the Type II case decays to near zero. Joint work with Eric Shea-Brown and Evan Thilo.

Janet Best

Ohio State University

Sleep-Wake Cycle Dynamics: Insights from Infants

Brief awakenings in humans and other mammals have been observed to follow a power law distribution, while intervening sleep episodes have an exponential distribution of durations. Such observations of the dynamics of sleep-wake regulation provide clues to the nature of the processes underlying sleep-wake cycles and the neuronal circuitry involved. Recent experiments reveal that the characteristic distributions of sleep and wake episode durations typically are not present at birth, instead developing during infancy in parallel with the development of neuronal circuits known to modulate sleep-wake cycles. I will discuss a mathematical model for sleep across postnatal development, combining approaches from stochastic processes and geometric dynamical systems theory to address questions concerning how these circuits generate and maintain sleep states.

Victoria Booth

University of Michigan

Simulating Microinjection of Neurotransmitter Agonists and Antagonists in a Novel Model of the Sleep-Wake Regulatory Network

In sleep-wake regulatory neuronal populations, microdialysis and microinjection experiments suggest that neurotransmitter dynamics play an important role in the initiation and maintenance of different behavioral states. However, the synaptic coupling in traditional population firing-rate models does not explicitly incorporate the dynamics of neurotransmitter concentrations acting at these synapses. We have constructed a novel network modeling framework that describes both neuronal activity and concentrations of the neurotransmitters released by these nuclei. Using this novel framework, we modeled interactions among primary brainstem nuclei involved in rat sleep-wake regulation. Analysis of model behavior provides insights into the state-dependent interactions among these neuronal nuclei and their transmitters. In the model network, we investigate microinjection of GABAergic and cholinergic agonists/antagonists into a key sleep-wake regulatory nucleus. Simulations of different microinjection protocols produce changes in REM sleep bout duration and frequency of REM sleep initiation consistent with experimental observations.

Christoph Börgers

Tufts University

Synchronization of Type II Neurons by Inhibitory Pulses

A neuronal model is of "type I" if the transition from rest to spiking involves a saddle-node bifurcation on an invariant circle, and of "type II" if it involves a Hopf bifurcation. The theta neuron is the simplest type I model, whereas the classical Hodgkin-Huxley neuron is of type II. A single strong, exponentially decaying inhibitory pulse brings a population of type I model neurons into approximate synchrony. This can be explained as the effect of an attracting "river" in a phase space that includes the strength of the (decaying) inhibition as a variable. Synchronization by a pulse of inhibition can fail, however, for type II model neurons. I will demonstrate this using simulations and explain it geometrically. I will also discuss possible implications for the question which neurons in the brain do or don't get entrained in gamma oscillations.

Michael Buice

LBM/NIDDK/NIH

Chaos and Stochastic Dynamics

Chaotic systems are characterized by a sensitive dependence upon initial conditions. While uncertainty in the initial state for a non-chaotic system leads to relatively small uncertainty in the final configuration, any uncertainty in the initial state of a chaotic system is magnified by the dynamics. We explore the evolution of this uncertainty by demonstrating a method for constructing an equivalent stochastic differential equation for any chaotic system given a distribution of initial conditions, facilitating the calculation of moments (mean, variance, etc.) of the final configuration. This method relies on the construction of a functional integration over the flow of the dynamical system from the initial configuration. We show that in certain conditions the equivalent stochastic differential equation can be thought of as an ensemble

average over parameters for some other, potentially non-chaotic, dynamical system. Joint work with Carson Chow.

Daniel Bunker

New Jersey Institute of Technology

Quantifying Ecological Functional Diversity with Convex Hull Volume

Functional diversity is the variation is species characteristics that enable species to perform a variety of roles within ecological communities. Because communities with greater functional diversity are predicted to have more complete resource utilization than less diverse communities, quantification of functional diversity is critical to predict ecosystem functioning and the production of ecosystem services. Here we introduce a novel method to quantify functional diversity by summing species convex hull volume in multidimensional trait space. We argue that convex hull volume is a more apt measure of functional diversity than existing metrics. Joint work with Dan Flynn and Shahid Naeem (Columbia University).

Jianwen Cai

University of North Carolina at Chapel Hill

Joint Modeling of Longitudinal Categorical Data and Survival Data

In many biomedical studies, it is of interest to study the covariate effect on both longitudinal categorical outcomes and survival outcomes. For example, in cancer research, it is of interest to study the treatment effect on both quality of life which is a categorical outcome measured longitudinally and survival time. In this talk, we will discuss such joint models. Random effects are introduced into the simultaneous models to account for dependence between longitudinal categorical outcome and survival time due to unobserved factors. EM algorithms are used to derive the point estimates for the parameters in the proposed model and profile likelihood function is used to estimate their variances. The asymptotic properties are established for our proposed estimators. Finally, simulation studies are conducted to examine the finite-sample properties of the proposed estimators and a liver transplantation data set is analyzed to illustrate our approaches. Joint work with Jaeun Choi and Donglin Zeng.

Chung Chang

New Jersey Institute of Technology

Non-Parametric Estimation of a Lifetime Distribution with Incomplete Censored Data

In the analysis of lifetime data, under some circumstances, censoring times for unfailed units are missing or only known within an interval (e.g., warranty data). Motivated by such examples, we consider a statistical model in which censoring times are incomplete. We propose an iterative method to obtain a nonparametric estimator of the survival function and conduct a simulation study to discuss its property.

Ying Keun Cheung

Columbia University

Randomized Selection Trials with an Active Control

This talk presents SPRT-type selection procedures for phase 2 randomized clinical trials, whose objective is to identify an experimental treatment that is more effective than a prospective control, or to declare futility if no such treatment exists. The SPRT-type procedures has a practical advantage in that the selection boundaries can be easily chosen with respect to a given set of error constraints. This talk will illustrate the methods using normal and binomial outcomes, and compare them to the conventional fixed design and two-stage designs.

Tom Chou

UCLA

Mechanisms of Viral Entry

We present three stochastic models describing how enveloped viruses enter host cell nuclei. The first model predicts the entry pathway of viruses as they initially enter a cell. The second model shows how virus material that is transported through the cytoplasm must be transformed with optimal timing in order to

enter the nucleus. Finally, we revisit a classic ratchet model describing the translocation process through nuclear pores and find exact analytic solutions exhibiting surprising features.

Carson Chow

NIH

Effective Theories for Neural Networks

Population rate or activity equations are a common approach to modeling for neural networks. These equations provide mean field dynamics for the firing rate or activity of neurons within a network given some connectivity. The shortcoming of these equations is that they take into account only the average firing rate while leaving out higher order statistics like correlations between firing. Here, I will describe some recent work with Michael Buice to derive effective activity equations that include correlations starting from a large network of deterministic spiking neurons.

Robert Clewley

Georgia State University

Action Potential Redux: A Case Study in Qualitative Reasoning for Design and Optimization of Neural Dynamic Models

The biophysics of a single action potential (AP) is well understood in terms of phase-plane caricatures, singular perturbation analysis, and heuristic descriptions of ion channel interactions. This study revisits the dynamics of the AP as a case study. We develop a formalization of the transitions between low-dimensional sub-regimes that constitute a single AP in the Hodgkin-Huxley equations, which are encoded as a constrained hybrid dynamical systems model. PyDSTool is used to numerically simulate this model and test the validity of the formalized assumptions. If assumptions fail, we demonstrate how diagnostic error information is used to direct standard optimization algorithms towards restoring the desired behavior. This is a new computational approach to design, inference, and optimization based on qualitative criteria, applicable to more complex neural mechanisms such as bursting.

Matteo Convertino

University of Padova, Italy

River Networks: from Geomorphic Auto-Organization to Biodiversity Pattern Dynamics

Neutral metacommunity models for spatial biodiversity patterns are implemented on river basins at different resolution. Coarse-graining elevation fields under the constraint of preserving the basin's mean elevation produces a set of reconfigured drainage networks. Despite the universal scaling of geomorphic properties shown by river basins regardless of size, climate, vegetation or exposed lithology, we find that species richness at local and regional scales exhibits resolution-dependent behavior. In addition to species richness, we investigate species-area relationships expressed as rank-abundance patterns. Strong interactions occur between network structure and the dispersal of species, and that, under the assumption of neutral dynamics, these interactions produce resolution-dependent biodiversity patters that diverge from expectations following from universal geomorphic scaling laws. The macroecological patterns analyzed are the local species richness vs the diameter of the links of the network, the regional species richness vs and the pairwise species richness vs the lag between the local communities. A general theory emerges on the effects of dendritic geometries on the dynamics operating on river basins. Insights provided by such a theory will lend themselves to issues of great practical importance such as integration of riparian systems into large-scale resource management, spatial strategies to minimize loss of freshwater biodiversity, climate change effects on vegetation distribution, and effective prevention campaigns

Rodica Curtu

University of Iowa

Mixed-Mode Oscillations in a Firing Rate Model for Neural Competition

Mixed-mode oscillations (MMOs) are complex patterns consisting of small amplitude oscillations combined with large amplitude excursions of relaxation type. They occur in multiple timescale dynamical systems and are usually associated with generalized canard phenomena. We show existence of MMOs in a

reduced rate model for binocular rivalry that is symmetric and has two fast and two slow equations. Singular Hopf bifurcations and folded saddle-node singularities of type II are discussed.

Gennady Cymbalyuk

Georgia State University

Neurons with Multiple Personalities: Co-existence of Silent and Oscillatory Regimes

Bursting, tonic spiking, sub-threshold oscillations and silence are basic robust regimes of activity of a single neuron. A neuronal model demonstrates three different types of co-existence: (1) silence and bursting, (2) silence and tonic spiking, and (3) silence and sub-threshold oscillations. We show that these types of co-existence can be explicated by the Rinzel scenario with the unstable sub-threshold oscillations (USTO) separating silence and an oscillatory regime and setting the threshold between them. The range of parameters, where the co-existence is observed, is determined by the critical values at which the USTO appear and disappear. More precisely, the USTO occur through the sub-critical Andronov-Hopf bifurcation, where the rest state loses stability. Then, the USTO disappear on the homoclinic bifurcation near which the oscillatory regime disappears as a regime. The bifurcation values are calculated and shown to match the empirical transition values found in Cymbalyuk et al., 2002. Also, we investigate how modulations of different ionic currents affect the range of co-existence.

Fabio Demarqui

University of Connecticut

A New Bayesian Model for Survival Data Using a Piecewise Exponential Model with a Random Time Grid

We present a fully Bayesian approach to model survival data using the piecewise exponential model (PEM) with a random time grid. A novel approach to generate random time grids for the PEM based on the clustering structure of the product partition model (PPM) is proposed. Conditionally on the generated time grids, a correlated process introduced via gamma prior distributions for the failure rates of the PEM is assumed. Prior elicitation and posterior simulations are discussed in detail. The issue of model diagnostic tools is considered, and Bayes factor (BF) and conditional predictive ordinate (CPO) are used to evaluate the performance of the proposed model for some simulated data sets following Weibull and lognormal distributions. Finally, the analysis of a real data set is performed. Joint work with Dipak K. Dey.

Key words: survival analysis; Bayesian inference; piecewise exponential model; correlated process, MCMC methods.

Berton Earnshaw

University of Utah

A Diffusion-Activation Model of CaMKII Translocation Waves in Dendrites

Calcium-calmodulin-dependent protein kinase II (CaMKII) is a key regulator of glutamatergic synapses and plays an essential role in many forms of synaptic plasticity. It has recently been observed that stimulating dendrites locally with a single glutamate/glycine puff induces a local translocation of CaMKII into spines that subsequently spreads in a wave-like manner towards the distal dendritic arbor. Here we present a mathematical model of the diffusion, activation and translocation of dendritic CaMKII. We show how the nonlinear dynamics of CaMKII diffusion-activation generates a propagating translocation wave, provided that the rate of activation is sufficiently fast. We also derive an explicit formula for the wave speed as a function of physiological parameters such as the diffusivity of CaMKII and the density of spines. Our model provides a quantitative framework for understanding the spread of CaMKII translocation and its possible role in heterosynaptic plasticity. Joint work with Paul Bressloff.

Sarosh N. Fatakia

LBM/NIDDK/NIH

Comparative Genomic Analysis Involving Information Theory to Investigate Evolutionary Traits within G Protein-coupled Receptor Superfamilies

G protein-coupled receptors (GPCRs) constitute one of the most diverse superfamily of proteins in the human genome. They are vital for cellular functions and their signaling governs various physiological and

pathological processes. Hence, they are the most common targets of pharmaceuticals. Nearly a thousand different GPCRs exist in the human genome, while only a handful of whose 3D crystal structure have been resolved. The GPCRs constitute of a single polypeptide chain with seven alpha helical transmembrane domains (7TMs). The 7TMs being embedded in the cell membrane are topologically constrained and are investigated, while the extra-cellular and intra-cellular loops have varying lengths and are not conserved across the superfamily. A comparative study of the informational entropy and mutational information from nucleotide positions represented in a multiple sequence alignment (MSA) of class A, class B and class C GPCRs is shown. For the three classes, the ratio of the non-synonymous to the synonymous substitution rates (=Ka/Ks) for the codons is analyzed for contrasting traits. Preliminary results from class A 7TMs indicate that the are constrained by strongly purifying selection demonstrating that it must have a highly conserved function, while results from specific codons in the class C analysis indicate a positive Darwanian selection, and those from class B are unique too - distinct from class A, but share some Ka/Ks traits with class C as well. This ongoing information theoretic study aims to understand the unique as well as common function of the GPCR superfamily. Joint work with Stefano Costanzi and Carson C. Chow.

Nina Fefferman

Rutgers University

Network Representations and the Evolution of Social Complexity

While the mathematics of iterative game theory has provided insight into the possible evolution of individual cooperation, very little work has been done on the evolution of increasing social complexity in already social groups. We'll discuss a network-based model for exploring the impact of increasingly complex social behavior on the evolutionary fitness of individuals and the populations they form.

Dan Fiscus

Frostburg State University

Theory and Applications of an Ecological Network Model of Life Toward a Sustainable Human-Environment Relation

The current multi-faceted global ecological crisis suggests a deep misunderstanding (or perhaps a novel transformation) of the fundamental nature of life. Actions of industrial societies result in 1) excess carbon dioxide emissions, 2) excess nitrogen loading to surface waters, 3) depletion of non-renewable energy sources and 4) water quality and quantity problems among numerous negative environmental effects that threaten life support capacities on which these societies depend. What if these observed problems are all symptoms of a single, unified underlying "humans in the environment" disorder? In search of a systemic solution, I report on work done at two ends of a wide spectrum – re-conceptualization of the original and fundamental nature of life and development of a new approach to a truly sustainable human-environment relationship. I present the "ecosystemic life hypothesis" that proposes the community-ecosystem co-arose with the cell-organism-individual. This framework depicts life via two coupled complementary models 1) discrete life (organisms-individuals) and 2) continuous life (community-ecosystem, biosphere) analogous to dual models of light. Results from ecological network analysis provide examples of pragmatic application of these ideas. Network design principles can guide changes to human ecological networks (for example in the U.S. food system and for native plant conservation) so that human-environment relations enhance rather than degrade environmental quality.

Edward Green

Mathematical Biosciences Institute

Non-local Models for the Formation of Hepatocyte-stellate Cell Aggregates

Liver cell aggregates may be grown in vitro by co-culturing hepatocytes with hepatic stellate cells. This method results in more rapid aggregation than hepatocyte-only culture, and appears to enhance cell viability and the expression of markers of liver-specific functions. We consider the early stages of aggregate formation, and develop a new mathematical model to investigate two alternative hypotheses (based on evidence in the experimental literature) concerning how stellate cells promote aggregate formation. The first hypothesis is that each population produces a chemical signal which affects the other, and enhanced aggregation is due to chemotaxis. The second hypothesis asserts that direct physical contact between the

different cell types is the dominant mechanism: the stellates extend long cellular processes which pull the hepatocytes into the aggregates). We formulate nonlocal (integro-partial differential) equations to describe the densities of cells, which are coupled to reaction-diffusion equations for the chemical concentrations. The behaviour of the model under each hypothesis is studied using a combination of linear stability analysis and numerical simulations. Comparison with experimental results suggests that the hepatocyte-stellate attraction is strongest in practice; based on this, we predict that a 1:1 seeding ratio of hepatocyte to stellates should be used for promoting rapid aggregate formation.

Wenge Guo

NIH, NIEHS

Adaptive Multiple Testing Procedures under Dependence

In the context of multiple hypotheses testing, the proportion of true null hypotheses among all nulls often plays an important role, although it is generally unknown a priori. In adaptive procedures this proportion is estimated and then used to derive more powerful multiple testing procedures. Hochberg and Benjamini (1990) first presented adaptive procedures for controlling familywise error rate (FWER). However, until now, no mathematical proof has been provided to demonstrate that these procedures control the FWER. In this talk, we present new adaptive multiple testing procedures with control of the FWER under various conditions of dependence. First, we introduce a simplified version of Hochberg and Benjamini's adaptive Bonferroni and Holm procedures. In a conditional dependence model we prove that the former procedure controls the FWER in finite samples while the latter controls it approximately. Second, we present a new adaptive Hochberg procedure and prove it can control the FWER under positive regression dependence. Finally, through a small simulation study and a real data analysis, we illustrate that these adaptive procedures are more powerful than the corresponding conventional procedures.

Yixin Guo

Drexel University

Thalamocortical Model with Human Gpi Data and the Map Reduction of the ModelTBA

We examine the thalamocortical (TC) relay cell responses to an excitatory input train, under GPi inhibitory signals from recordings of dystonic and parkinsonian patients. We also reduce the conductance-based TC model to a one-dimension map for the slow T-current (low threshold T current). Then we investigate the bifurcation which account for the different TC relay responses.

Joseph Heyse

Merck Research Laboratories

False Discovery Rates for Discrete Data

Almost all multiple comparison and multiple endpoint procedures applied in clinical trials are designed to control the Family Wise Error Rate (FWER) at a prespecified level of $\alpha = 0.05$. Benjamini and Hochberg (1995) argued that in certain settings, requiring strict control of the FWER is often too conservative. They suggested controlling the False Discovery Rate (FDR), defined as the expected proportion of true (null) hypotheses that are incorrectly rejected. When one or more of the hypotheses being tested uses a discrete data endpoint then it is possible to further increase the power of both FWER and FDR controlling procedures. Methods proposed by Tarone (1990) and Gilbert (2005) have increased power by using the discreteness in the data to reduce the effective number of endpoints considered for the multiplicity adjustment. A modified fully discrete FDR sequential procedure is introduced that uses the exact distribution of potential outcomes. The potential gains in power are estimated using simulation. Application of FDR in the setting of preclinical safety data analysis is reviewed and other potential uses of the proposed method are discussed.

Lin Huang

Children's Hospital Boston

Sequential Test for Right Censored Data with Linear Transformation Model

Many clinical trials are conducted to compare survival time between treatment arms. Sequential hypothesis testing methods are usually used in these trials because of ethical and practical reasons. Most of the time, besides treatments, there are also some other covariates which may affect survival time significantly. Simply ignoring these covariates may lead to invalid testing results. Different sequential testing methods have been developed for comparing right censored survival time between treatment arms and allowing for the adjustment of covariates at the same time. All these methods developed so far are based on either a proportional hazards model or an AFT model. Here we propose two new sequential testing methods for comparing right censored survival time between two treatment arms with covariates adjustment based on linear transformation models. The linear transformation models are a general class of models including proportional hazards model, proportional odds model and many other models. Thus, the proposed testing methods based on the linear transformation model can be used under more general situation compared with other methods based on Cox model or AFT model. The new methods also take into account patients' staggered entry and interim monitorings conducted at fixed calendar times, which makes the new methods more flexible for different situations in clinical trials. Theoretical properties of the proposed methods are studied. Simulation and real example analyses are also carried out to assess their performance.

M. Zahur Islam

Novartis Pharmaceuticals Corporation

Interim Analysis of Clinical Trials in Pharmaceutical Industry

Interim analysis in clinical trials has been a common practice in pharmaceutical companies. The statistical methods for interim analysis evolved from the group sequential testing procedure. Many articles have been published on this topic in the last four decades. Recently, generalizations of interim analysis have been covered under adaptive design methodology. Implementation of interim analyses in laboratories is much different from that in the pharmaceutical industry, which is highly regulated by regulatory authorities such as FDA. In this presentation, a typical approach for the implementation of an interim analysis in a clinical trial sponsored by a pharmaceutical company will be discussed. Joint work with Farid Kianifard.

Junghyo Jo

LBM/NIDDK/NIH

Dynamics of Fat Tissue Growth

Fat tissue grows by two mechanisms: hyperplasia (cell number increase) and hypertrophy (cell size increase). However, the dynamic microscopic details of the growth has not been elucidated. How many new cells are formed and how do cells with different sizes grow? To answer these questions, we examine the changes of size distributions of fat cells under different diets, because the information gives a statistical view of the growth process of each cell. The total cell number and volume-weighted mean cell size have a strong correlation with fat pad mass. Therefore we develop a mathematical model describing the evolution of the cell-size distributions as a function of the increasing fat pad mass, instead of the increasing chronological time. Our model, a kind of diffusion equation, includes recruitment of new cells (nucleation), size-dependent cell growth (drift), cell-size fluctuation (diffusion), and cell death (extinction). This model can describe the growth of fat tissue under high-fat diet even without the cell-death term; the cell recruitment increases exponentially; the size-dependent cell growth has a maximal rate at medium cell size; and size fluctuations of fat cells are larger under high-fat diet compared with regular diet.

Kresimir Josic

University of Houston

Correlation Transfer in Neuronal Populations

Correlated activity in neural tissue can significantly impact the information carried by a population of neurons. However, there are relatively few analytical results that provide a mechanistic understanding of

how correlations are generated and propagated. We start by examining this question using the integrate and fire model which has inspired many developments in theoretical neuroscience. In the second part of the presentation we demonstrate these results using new numerical methods for the simulation of networks of stochastic integrate and fire neurons. These methods are several orders of magnitude faster than typical Monte Carlo simulations. Outputs of a population of neurons are typically pooled to form the input to cells downstream. We provide simple analytical results that describe this situation and show that correlations can be propagated in a counterintuitive manner: Small correlations in the population can translate into large input correlations after such pooling. On the other hand, an increase of correlations within a populations can decrease correlations between populations. It has recently been observed that the transfer of correlations from input currents to output spike trains depends on the firing rate in neuron models and experiments in vitro. Over rapid time scales, correlation transfer increases with both spike time variability and rate; the dependence on variability disappears at large time scales. We show that the behavior of the perfect integrate and fire (PIF) model is quite different: correlations are transferred perfectly over large windows. We give a full description of correlation transfer in PIFs, and provide an intuitive understanding of how cross-correlograms are transformed in networks of such neurons. Although the PIF preserves correlations over long time windows, it tends to "smear out"' the cross-correlogram, due to thresholding. This analysis shows that the decorrelation typically observed in a feedforward configuration of more realistic neurons results both from the existence of a firing threshold and "memory loss" induced by the leak. Therefore, the peculiarity of the PIF model can be used to provide an intuitive understanding of the behavior of more complex models. To examine when these results apply to more complex models requires numerical simulations. We present a fast and accurate finite volume method to approximate the solution of the Fokker-Planck equation that models the multivariate density of the subthreshold voltages of stochastic integrate and fire neurons. The discretization of the boundary conditions offers a particular challenge, as standard operator splitting approaches cannot be applied without modification. In comparison to Monte Carlo methods, the present approach offers improved accuracy, and decreases computation times by several orders of magnitude.

Haesook T. Kim

Harvard School of Public Health

Competing Risks Data: Design and Analysis

Competing risks occur commonly in medical research. For example, both treatment related mortality and disease recurrence are important outcomes of interest and well-known competing risks in cancer research. In the analysis of competing risks data, methods of standard survival analysis such as the Kaplan-Meier method for estimation of cumulative incidence, the log-rank test for comparison of cumulative incidence curves and the standard Cox model for assessment of covariates lead to incorrect and biased results. In this talk, I will discuss designing a clinical trial with competing risks data and competing risks data analysis. The latter includes methods to calculate the cumulative incidence of an event of interest in the presence of competing risks; to compare cumulative incidence curves in the presence of competing risks; and to perform competing risks regression analysis.

Alexey Kuznetsov

IUPUI

Interlocked Artificial Regulatory Oscillators

Regulatory molecular networks have numerous pharmacological and medical applications. The oscillatory mechanisms and the role of oscillations in these regulatory networks are not fully understood. We explore two oscillatory mechanisms: the hysteresis-based relaxation oscillator and the repressilator. We combine these mechanisms into one regulatory network so that only two parameters, the strength of an additional regulatory connection and the timescale separation for one of the variables, control the transition from one mechanism to the other. Our data supports a qualitative difference between the oscillatory mechanisms, but in the parameter space, we found a single oscillatory region, suggesting that the two mechanisms support each other. We examine interactions in a basic population: that is, a pair of the composite oscillators. We found that the relaxation oscillation mechanism is much more resistant to oscillatory death as the cells are diffusively coupled in a population. Additionally, stationary pattern formation has been found to

accompany the relaxation oscillation, but not the repressilator mechanism. These properties may guide the identification of oscillatory mechanisms in complex natural regulatory networks.

Anita Layton

Duke University

Multistable Dynamics Mediated by Tubuloglomerular Feedback in a Model of Coupled Nephrons

To help elucidate the causes of irregular tubular flow oscillations found in the nephrons of spontaneously hypertensive rats (SHR), we have conducted a bifurcation analysis of a mathematical model of two nephrons that are coupled through their tubuloglomerular feedback (TGF) systems. This analysis was motivated by a previous modeling study which predicts that NaCl backleak from a nephron's thick ascending limb permits multiple stable oscillatory states that are mediated by TGF (Am. J. Physiol. Renal Physiol. 291: F79-F97, 2006); that prediction served as the basis for a comprehensive, multifaceted hypothesis for the emergence of irregular flow oscillations in SHR. However, in that study, we used a characteristic equation obtained via linearization from a single-nephron model, in conjunction with numerical solutions of the full, nonlinear model equations for two and three coupled nephrons. In the present study we have derived a characteristic equation for a model of any finite number of mutually coupled nephrons having NaCl backleak. Analysis of that characteristic equation for the case of two coupled nephrons has revealed a number of parameter regions having the potential for differing stable dynamic states. Numerical solutions of the full equations for two model nephrons exhibit a variety of behaviors in these regions. Some behaviors exhibit a degree of complexity that is consistent with our hypothesis for the emergence of irregular oscillations in SHR.

Changwon Lim

Biostatistics Branch, NIEHS, NIH

Robust Statistical Theory and Methodology for Nonlinear Models with Application to Toxicology

Often toxicologists are interested in investigating the dose-response relationship when animals are exposed to varying doses of a chemical. In some instances a nonlinear regression model such as the Hill model is used to describe the relationship. The standard asymptotic confidence intervals and test procedures based on the ordinary least squares methodology may not be robust to heteroscedasticity and consequently may produce inaccurate coverage probabilities and Type I error rates. On the other hand, the standard weighted least squares based methodology may be computationally intensive and may not be efficient when the variances are approximately equal across dose groups (homoscedasticity). In practice one generally does not know if the data are homoscedastic or heteroscedastic. Also neither method is robust against outliers or influential observations. Since the performance of a method depends on whether the data are homoscedastic or heteroscedastic, we introduce a simple preliminary test estimation (PTE) procedure that uses robust M-estimators. The methodology is illustrated using a data set obtained by the National Toxicology Program (NTP). Joint work with Pranab K. Sen, University of North Carolina at Chapel Hill and Shyamal D. Peddada, Biostatistics Branch, NIEHS, NIH.

Xiaodong Luo

Mount Sinai School of Medicine

Pseudo-Partial Likelihood Estimators for the Cox Regression Models with Missing Covariates

By embedding the missing covariate data into a left-truncated and right-censored survival model, we propose pseudo-partial likelihood estimators for the Cox regression models with missing covariates. We show that the estimators are consistent and asymptotically normal. Compared with the popular inverse-probability-weighting approach, this method performs better when the missing data probability is small and improve the estimation of the missing covariate effect in our simulation studies.

Renita Machado

New Jersey Institute of Technology

Clustered Wireless Sensor Networks

Wireless sensor networks (WSNs) enable distributed data gathering and computation with the help of tiny, power-limited devices for use in various monitoring applications. We study coverage in clustered

topologies, and show that clustering increases vacancy. However, by exploiting the redundancy for adaptive density control, we show that coverage in clustered WSN can be optimized while still improving network lifetime. As the range of applications envisioned for WSNs increases, the need for smart networks that utilize algorithms for intelligent data gathering and processing also increases. In this context, the role of a sensor network can be viewed as that of a system that pays attention to a phenomenon of interest. Thus, the current body of literature on WSNs falls into two major categories: developing networks that a) pay attention to the environment to detect the phenomenon under consideration and b) improving the quality of attention paid by WSNs to these phenomena. We take the first step in understanding the association between the nature of attention in WSNs and their real-world applications. Although we structure this framework for cognitive WSNs around clustered WSNs, it can easily be extended to various topologies of WSNs.

Georgi Medvedev

Drexel University

Reliability and Frequency Control in Stochastic Neuronal Networks

We consider networks of interacting excitable cells. The dynamics of each cell in the network is modeled by a set of differential equations. Small noise is included to simulate random synaptic input. The model is used to test how the variations in the strength of interactions and different network topologies affect the output of the network. We show that the activity of the network and its response properties can be effectively controlled by varying the strength of coupling. Furthermore, we present analytical estimates characterizing variability and coherence of the activity across the network. The analysis shows that the variability of the neurons in the network can be significantly smaller than the variability of a single neuron under the same conditions, provided the coupling is dissipative.

Martin Mueller

Laboratoire de Physique Statistique, Ecole Normale Supérieure

Modeling the Growth of Thin Soft Tissues

During their growth soft biological tissues are often subjected to forces that affect the tissue geometry. For simple cases the weakly nonlinear elastic theory of growth is tractable: we have shown that a thin elastic disc forms a shape reminiscent of a saddle when growing anisotropically. In the fully nonlinear regime the theory could be extended to more complicated cases with the help of differential geometry. Strains and stresses were determined, as well as the shapes during growth.

Duane Nykamp

University of Minnesota

Toward a Second Order Description of Neuronal Networks

The complexity of the activity of large numbers of neurons and their interconnectivity creates a challenge for understanding computations within the brain. The high dimensionality of the activity patterns and connectivity patterns, combined with the difficulty of estimating them from limited data sets, is a tremendous obstacle to an analysis of the relationships between the connectivity and the behavior of the network. I present a kinetic theory approach toward distilling complicated network connectivity into a simplified description of network features and estimating resulting network behaviors. In addition, I outline a connectivity analysis to connect the theoretical analysis with experiment by constraining network estimates from experimental data. The kinetic theory approach neglects higher order statistics of network connectivity, revealing key features of network connectivity and their influence on network behavior. The connectivity analysis estimates first and second order statistics of connectivity patterns from experimental data while explicitly controlling for effects of hidden neurons. By linking the simplified network analysis to network structure in the brain, the connectivity analysis combined with the kinetic theory analysis could prove to be a powerful combination for probing relationships between network connectivity patterns and behavior.

R. Todd Ogden

Columbia University

Regression Models with Signals or Images as Predictors

Regression of a scalar response on functional predictors (or signals), such as spectra or images, presents a major challenge when, as is typically the case, the dimension of the signals far exceeds the number of signals in the dataset. Fitting such a model meaningfully requires some form of dimension reduction. Some approaches to this problem include the extension of common multivariate methods to the functional situation by penalizing roughness. Another approach is to express the data and the coefficient functions in terms of a set of basis functions (e.g., wavelets) that will allow for a sparse representation. These approaches will be discussed and illustrated using simulated and real datasets.

Liam Paninski

Columbia University

Statistical Models for Neural Encoding, Decoding, and Optimal Stimulus Design

There are two basic problems in the statistical analysis of neural data. The "encoding"' problem concerns how information is encoded in neural spike trains: can we predict the spike trains of a neuron (or population of neurons), given an arbitrary stimulus or observed motor response? Conversely, the "decoding"' problem concerns how much information is in a spike train: in particular, how well can we estimate the stimulus that gave rise to the spike train?

This talk describes statistical model-based techniques that in some cases provide a unified solution to these two coding problems. These models can capture stimulus dependencies as well as spike history and interneuronal interaction effects in population spike trains, and are intimately related to biophysically-based models of integrate-and-fire type. We describe flexible, powerful likelihood-based methods for fitting these encoding models and then for using the models to perform optimal decoding. Each of these (apparently quite difficult) tasks turn out to be highly computationally tractable, due to a key concavity property of the model likelihood. Finally, we return to the encoding problem to describe how to use these models to adaptively optimize the stimuli presented to the cell on a trial-by-trial basis, in order that we may infer the optimal model parameters as efficiently as possible.

Choongseok Park

IUPUI

Irregular vs. Synchronized Activity in Basal Ganglia

The basal ganglia (BG) are a group of interconnected subcortical nuclei which are involved in neural control of movement, as well as certain aspects of cognition and emotion. Dysfunction of the basal ganglia is associated with movement disorders such as Parkinson's disease (PD), a common and progressive age-related neurodegenerative disorder of movement. Recent studies indicate that patterns of oscillatory synchronous activity in BG are strongly relevant to BG physiology and BG disorders. In particular, neuronal activity in the beta-band significantly contributes to akinetic symptoms. We use extracellular spiking activity and LFPs which are recorded from PD patients during surgery for implantation of DBS electrodes. We also use conductance-based models of subthalamic and pallidal cells in BG. The results of the analysis indicate that the dynamics of beta-band oscillations in BG are marked by intermittency of synchronized episodes. Oscillations tend to be desynchronized for relatively short time while the desynchronizing events are quite frequent. Modeling work shows that the domain of the existence of intermittent dynamics is in between incoherent regime and synchronized regime, in the area which is characterized by the presence of different types of dynamics. These results suggest that in a disease (Parkinsonism), BG circuits are relatively close to the presumably healthy uncorrelated state. This closeness of the irregular healthy state to the pathological regular synchronized state may be justified by the efficiency of producing synchronized oscillations for movement generation.

Ram Ramaswamy

Jawaharlal Nehru University, New Delhi, India

The Effect of miRNA on the Dynamics of Regulatory Networks

We study the dynamics of miRNA regulation in circadian oscillator models. miRNAs are known to regulate gene expression at the post-transcriptional level by reducing the amount of proteins produced by translation, by blocking translation or by degradation of mRNAs. The regulation of gene expression by miRNAs is introduced in the oscillator models, and the dynamics is studied via standard stochastic simulation techniques. We find that in addition to a reduction in the amplitude of the oscillation, inclusion of miRNAs has the effect of altering the frequency of oscillation and thereby regulating the dynamics of protein production. miRNAs thus have a profound effect on the dynamics of regulatory modules by control of amplitude and by control or alteration of frequency, namely by interference with the temporal sequence of gene production or delivery which destroys synchrony and other temporal correlations.

David Rindskopf

CUNY Graduate Center

Using Latent Class Analysis in Medical Diagnosis

Most medical tests and indicators of disease are imperfect. An indicator can be characterized by its sensitivity (probability of being positive when a person has a disease) and specificity (probability of being negative when the person does not have the disease). Estimating sensitivity and specificity requires knowing whether a person truly does or does not have the disease, which is not always possible. Latent class analysis (LCA) allows estimation of sensitivity and specificity when no gold standard diagnosis is available. In addition, one can then determine how accurately one can diagnose a patient, given the results of a series of medical tests/indicators, and also how accurate is the final diagnosis given by clinicians.

Jonathan Rubin

University of Pittsburgh

Rhythmic Activity in Central Pattern Generators

The idea of a central pattern generator (CPG), consisting of a collection of neurons that is able to generate a repetitive, rhythmic pattern of activity in the absence of input, is quite old, and CPGs appear to underlie behaviors such as respiration, locomotion, and mastication. Nonetheless, many open questions remain about the mechanisms through which intrinsic cellular properties interact with properties of coupling within CPGs to select rhythms and to modulate phases within rhythms. In this talk, I will discuss new results on rhythmic mechanisms in single cells, based on evidence from the mammalian respiratory brain stem, and in small networks of cells.

David Rumschitzki

City College of New York

How Aquaporin-1 affects Transmural Water Flow in Large Arteries: Possible Link to Early Aatherosclerosis

Atherosclerosis is the leading cause of death, both above and below age 65, in the United States and all Western countries. Its earliest prelesion events appear to be the transmural (across the wall)-pressure ΔP-driven advection of large molecules such as low-density lipoprotein (LDL) cholesterol from the blood into the inner wall layers through the junctions around rare (~one cell every few thousand) endothelial cells whose junctions are wide enough to allow large molecules to pass. These LDL molecules can bind to extracellular matrix in the wall's thin subendothelial intima layer and accumulate there. On the other hand, the overall transmural water flow can dilute the local intima LDL concentration, thereby slowing its kinetics of binding, and flushes unbound lipid from the wall. An understanding of the nature of this water flow is clearly critical.

We have found that rat aortic endothelial cells express the ubiquitous membrane water-channel protein aquaporin-1, and that blocking its water channel or knocking down its expression significantly reduces the apparent hydraulic conductivity Lp of the endothelium and, consequently of the entire wall. Interestingly, this decrease has a strong ΔP -dependence. We present a theory based on the premise that ΔP compacts the intima, which, as we show, lowers its Lp. Moreover, we show that blocking or knocking down

aquaporin flow changes the critical ΔP at which this compaction occurs and this potentially explains our observed dependence of Lp's dependence on ΔP. This may affect lipid transport and accumulation *in vivo*. The importance of aquaporin-based, rather than simply junctional water transport is that transport via protein channels allows for the possibility of active control of vessel Lp by up- or down-regulation of protein expression. Time permitting, we show that rat aortic endothelial cells indeed appear to significantly change their aquaporin numbers in response to chronic hypertension (high blood pressure), and this may help explain the as yet poorly-understood fact that hypertension correlates with atherosclerosis. Joint work with Shripad Joshi, Teiuvi Nguyen, Jimmy Toussaint, Yu Sun, and Kung-Ming Jan.

Serguei Saavedra

CABDyN Complexity Centre

Common Organizing Mechanisms in Ecological and Socio-economic Networks

Previous work has shown that species interacting in an ecosystem and actors transacting in an economic context may have notable similarities in behavior. However, the specific mechanism that may underlie similarities in nature and human systems has not been analyzed. Building on stochastic food-web models, we propose a parsimonious model that reproduces the key features of mutualisic networks–degree distribution, nestedness and modularity--for both food webs and socio-economic networks. Our analysis uses three diverse networks. Cooperative interactions between plants and their pollinators, mutually beneficial economic exchanges between designers and their contractors, and alliance relations between the producers of Broadway musicals and theatre owners that display the show. The surprising correspondence across mutualistic networks suggests their broadly representativeness and their potential role in the productive organization of exchange systems, both ecological and social.

Sanat K. Sarkar

Temple University

On Storey's q-value Method for Small-Scale Multiple Testing

Storey (2002, J. Roy. Statist. Soc. B 64, 479 -498) introduced a measure of significance in multiple testing, called the *q*-value, based on the positive false discovery rate (pFDR), and developed the *q*-value method utilizing a particular conservatively biased point estimate of the pFDR. In this talk, I will show that there is a slightly different estimate of the pFDR that performs better in small-scale multiple testing than the one Storey originally considered. In particular, the newer estimate, while asymptotically (when the number of hypotheses is quite large) equivalent to Storey's estimate, is proven to be always less conservatively biased and is numerically shown to have smaller mean squared error often in small-scale multiple testing. The *q*-value method is refined using this new estimate before applying it to a real data set to illustrate its improved performance compared to its original version.

Eric Shea-Brown

University of Washington

Neural Coding and Dynamics under Cochlear Implant Stimulation

In joint work with Joshua Goldwyn and Jay Rubinstein, we study cochlear implants -- neural prostheses that provide sound information by stimulating the auditory nerve with electrical pulse trains. We model the response of the auditory nerve via point process and integrate-and-fire type models, and quantify the temporal encoding properties of these models using ideal observer analyses and decoding algorithms that predict some features of observed psychophysical data. We emphasize the characteristics of both the auditory nerve and decoding systems that are required to make this connection.

Gustavo Stolovitzky

IBM Corporation

Ordered Cyclic Motifs Contribute to Dynamic Stability in Biological and Engineered Networks

Representation and analysis of complex biological and engineered systems as directed networks is useful for understanding their global structure/function organization. Enrichment of network motifs, which are over-represented subgraphs in real networks, can be used for topological analysis. Because counting network motifs is computationally expensive, only characterization of 3- to 5-node motifs has been previously

reported. In this study we used a supercomputer to analyze cyclic motifs made of 3-20 nodes for 6 biological and 3 technological networks. Using tools from statistical physics, we developed a theoretical framework for characterizing the ensemble of cyclic motifs in real networks. We have identified a generic property of real complex networks, antiferromagnetic organization, which is characterized by minimal directional coherence of edges along cyclic subgraphs, such that consecutive links tend to have opposing direction. As a consequence, we find that the lack of directional coherence in cyclic motifs leads to depletion in feedback loops, where the number of nodes affected by feedback loops appears to be at a local minimum compared with surrogate shuffled networks. This topology provides more dynamic stability in large networks.

Yanqing Sun

University of North Carolina at Charlotte

A Semiparametric Random Effects Model for Multivariate Competing Risks Data

We propose a semiparametric random effects model for multivariate competing risks data when the failures of a particular type are of interest. Under this model, the marginal cumulative incidence functions follow a generalized semiparametric additive model. The associations between the cause-specific failure times can be studied through the dependence parameters of copula functions which are allowed to depend on the cluster level covariates. A cross-odds ratio type measure is proposed to describe the associations between cause-specific failure times and its relationship to the dependence parameters are explored. We develop a simple two-stage strategy, the marginal models are estimated in the first stage and the dependence parameters are estimated in the second stage. The large sample properties of the proposed estimators are derived. The proposed procedures are applied to the Danish twin data to model the cumulative incidence functions for the ages of natural menopause and to investigate the associations in the occurrence of natural menopause between monozygotic and dizygotic twins. Joint work with Thomas H. Scheike, Mei-Jie Zhang, and Tina Kold Jensen.

Sarah Waters

University of Oxford

Mathematical Models for Tissue Engineering Applications

The broad goal of tissue engineers is to grow functional tissues and organs in the laboratory to replace those which have become defective through age, trauma, and disease and which can be used in drug screening applications. To achieve this goal, tissue engineers aim to control accurately the biomechanical and biochemical environment of the growing tissue construct, in order to engineer tissues with the desired composition, biomechanical and biochemical properties (in the sense that they mimic the in vivo tissue). The growth of biological tissue is a complex process, resulting from the interaction of numerous processes on disparate spatio-temporal scales. Advances in the understanding of tissue growth processes promise to improve the viability and suitability of the resulting tissue constructs. In this talk, I highlight some of our recent mathematical modelling work that aims to provide insights into tissue engineering applications.

Daniel Zelterman

Yale University

A Distribution for P-Values

What is the distribution of the p-value under the alternative hypothesis? We describe the properties of a parametric distribution defined on the interval (0,1). This distribution includes the uniform as a special case. The functional form is derived as the distribution of the p-value in a statistical test of a pair of close hypotheses in a wide variety of settings. The distributional form is retained when it is compounded with a uniform or when the individual p-values are sampled from a variety of different hypotheses. We describe properties of the parameter estimate and the distribution of extreme order statistics. The distribution is fitted to data from a study of breast cancer patients comparing many genetic markers using a microarray chip. Joint work with Chang Yu (Vanderbilt University).

Svitlana Zhuravytska

Graduate student, Drexel University

Transitions to Bursting in the Stochastic Model of Electrically Coupled Beta Cells

Conductance-based models of electrically coupled beta cells feature a variety of modes of activity. In the presence of noise, the strength of coupling becomes an important factorshaping the network output: Even small changes in the strength of coupling may have counterintuitive effects on the firing patterns and even cause transitions between qualitatively distinct regimes such as spiking and bursting. We use asymptotic methods for randomly perturbed slow-fast systems to study how the firing patterns in electrically coupled groups of beta cells depend on the key control parameters: the noise intensity, the strength of coupling, and the network topology. The empahasis is made on characterazing the statistical properties of the emerging firing patterns. The analytical results are compared with the results of numerical simulations. Joint work with Georgi Medvedev (Drexel University).

POSTERS

Soumya Banerjee
University of New Mexico

A Hybrid Agent Based and Differential Equation Model of Body Size Effects on Pathogen Replication and Immune System Response

It has been empirically observed that individual cell metabolic rates scale as M^(-1/4), where M is host mass, suggesting that metabolic rates are slowed down in larger hosts. Since pathogens utilize host cellular machinery for replication, it is reasonable to expect that rates of pathogenesis are fundamentally constrained by host cell metabolic rates and by implication, whole body mass M. It is hence hypothesized that pathogenesis is a function of both host mass (M) and phylogeny. To test this hypothesis we constructed a model of Ordinary Differential Equations (ODE) to represent host-pathogen dynamics. ODE parameters were estimated from an experimental study of West Nile Virus (WNV) infection involving 25 avian species. Our results suggest that rates of pathogen replication are slowed down in larger hosts. In contrast, immune system rates of search and replication are not dependent on host mass. We also propose a mathematical model to predict peak viral load in hosts, from its mass and phylogeny. Such approaches will help progression from within-host models to extra-host epidemiological models and facilitate prediction of disease-spread determinants like R0 (basic reproductive ratio) from conveniently measurable parameters like host mass.

Ernest Barreto
George Mason University

Ion Concentration Dynamics: Implications for Single Neurons and Networks

We develop models of individual neurons and of networks that include intra- and extra-cellular ion concentration dynamics. A reduction of the single neuron model is used to identify the bifurcation structure, leading to the identification of a novel mechanism for bursting and seizure-like events that are similar to that seen in experiments. In addition, we examine the stability of persistent states of activity in the network as well as excitatory-inhibitory interplay.

Justin Blackwell
The University of Texas at Arlington

Spontaneous and Evoked Glutamate Release of NMDA Receptors

Spontaneous synaptic fusion is a feature in all synapses. These random release events have been extremely instrumental in the analysis of unitary properties of neurotransmission. In this talk we present a mathematical model for the kinetic scheme of NMDA receptors in a synapse. We first examine the diffusion of the neurotransmitter Glutamate within the synaptic cleft and use this data to numerical solve a system of ODEs that determines the open probabilities of the receptors at the postsynaptic cleft. From this we are able to better understand the mechanism behind spontaneous synaptic fusion by determining how the location of a release site affects this phenomenon. We also examine other parameters such as the diffusion constant within the cleft as well how other receptors, such as AMPA receptors will affect the kinetics as well.

Jyoti Champanerkar
William Paterson University

Phase Resetting and Entrainment in Cardiac Cells

Phase-resetting occurs when impulses from one cell advance or delay the rhythm of another cell coupled to it. Entrainment of cells, in which one cell has m cycles for every n cycles of another cell, occurs as a consequence of phase-resetting. Phase-resetting and entrainment have been observed in cardiac cells (exhibited in EKGs) and is believed to be the onset of some arrhythmias. We study phase-resetting and

entrainment of cardiac cells, by modeling the conduction components of the heart as sets of differential equations, coupling them with coupling currents and solving the system numerically. Joint work with Robert Miura (New Jersey Institute of Technology).

Stanca Ciupe
Duke University Medical Center
Mathematical Models of T-cell Development
The immune response to infectious agents involves the presence and maintenance of a large number of T cells with highly variable antigen receptors and functional diversity. We define a metric that quatifies T cell receptor diversity and investigate its bias to measurement errors. We then develop a stochastic population-dynamic mathematical model that studies the mechanisms responsible for the establishment of T cell receptor diversity. We fit the model to human data from immunocompromised DiGeorge anomaly patients undergoing thymus transplantation. The dynamics we see in the evolution of T cells gives valuable information about the characteristics of the healthy immune system. Joint work with Louise Markert, Blythe Devlin, Thomas Kepler.

Rafael Farias
University of Connecticut
Efficient Algorithms in Bayesian Binary Regression with Skew-Probit Link
We have proposed here different Gibbs sampling algorithms in the context of the binary response regression models using auxiliary variables and the skew-probit link. Analytical expression for the full conditional posterior distributions are obtained. These algorithms are compared through two measures of efficiency, the average Euclidian update distance between interactions and the effective sample size. We have concluded that the new algorithms are more efficient than the usual Gibbs sampling, where one of them leads to around 160% of improvement in the effective sample size measure.
Key Words: Gibbs algorithm; auxiliary variables; skew-probit link; blocking. Joint work with Márcia D'Elia Branco.

Mitra Feizabadi
Seton Hall University
Two-Compartment Model Interacting with Anti-mitotic Drugs
Fitting the Gompertzian function within the context of two-compartment cell population dynamics predicts an analytical solution for the evolution of two types of subpopulations within the tumor (F. Kozusko, Z. Bajzer, Mathematical Biosciences, 185, 2003, 153). The aim of this work is to extend the two-compartment model interacting with anti-mitotic drugs. This work is considered that the dynamic drug increases the death rate of the proliferating and quiescent cells, as well as regulates the reproduction rate of the proliferating cells. The model and the analytical solutions are presented and analyzed through a model simulation.

Jonathan Forde
Hobart and William Smith Colleges
Dynamics of Hepatitis B Virus Infection: What Causes Viral Clearance?
Hepatitis B is a virus that infects liver cells and leads to either acute or chronic liver disease. The mechanisms responsible for the infection outcome are not well understood, with immune responses being involved in both curing and killing of cells. The formation of cured cells and their role in the infection outcome is studied analytically and validated numerically. Mathematical models for the hepatitis B viral dynamics are developed, and local and global stability analysis of their long term behavior is performed. The models are then fitted to patient data of viral decay following the peak of infection. The results show that viral clearance is only dependent on the strength of the combined killing and curing and independent of the characteristics of the cured cells.

Caroline Geisler, Kenji Mizuseki, Eva Pastaklova, Kamran Diba, Sebastien Royer, and Gyorgy Buzsaki
Rutgers University, Center for Molecular and Behavioral Neuroscience
Delayed Coupling of Oscillating Hippocampal Place Cell Assemblies Generates Slower Oscillating Population Activity at Theta Frequency
The firing of hippocampal pyramidal cells is known to correlate with the rat's position during exploration ("place cells" discharge in their "place field"), building an internal representation of the rat's environment. The coordinated firing of these active cells is organized by the prominent "theta"-oscillations in the local field potential (LFP): place cells discharge preferably at earlier and earlier theta phases on a cycle-by cycle basis as the rat crosses the respective place field ("phase precession"). The discrepancy between the oscillation frequency of all active neurons and their summed population activity (i.e., the theta LFP and mean output spiking) creates a paradox. How do faster oscillating neurons generate a slower oscillating LFP locally and at their targets? To investigate this issue, we recorded both field and unit activity in the hippocampus of the behaving rat. We show that the summed activity of all recorded hippocampal place cells oscillates at theta LFP frequency even though they individually oscillate faster. To gain better insight into the population dynamics of hippocampal place cells we built a mathematical model based on the experimental findings. Individual cells are characterized by their discharge probability and the time offset between neurons is determined by their preferred locations. We show that the oscillation frequency and amplitude of the summed activity of the model neurons depend on their temporal offset and place field size. Further, the LFP theta frequency can be predicted from the oscillation frequency of single place cells and the their temporal offset, in agreement with the experiments. Our results suggest that the faster-than-theta oscillations of pyramidal cells is inherent and thus phase precession is a result of the coordinated activity of temporally shifted cell assemblies, relative to the population activity, reflected by the LFP.

Roy H. Goodman and Jacek Wrobel
New Jersey Institute of Technology
Adaptive Method for Computing Invariant Manifolds of 2-D Maps
We present an efficient and accurate numerical method for computing invariant manifolds of planar maps which arise in the study of dynamical systems. In order to decrease the number of points needed to compute a given curve, we propose using higher-order interpolation techniques from geometric modeling. We use Bezier curves, one of the fundamental objects in curve design, to create an adaptive Catmull-Rom method. The methods are based on tolerance conditions derived from properties of Bezier curves. We have developed and tested the methods for ordinary parametric curves, then adapt the methods to invariant manifolds.

Joon Ha
IUPUI
Frequency Switching in the Two-compartmental Model of the Dopaminergic Neurons
Midbrain dopaminergic (DA) neurons display two functionally distinct modes of electrical activity: low- and high-frequency firing. The high-frequency firing is linked to important behavioral events in vivo. However, it cannot be elicited in vitro by standard manipulations in vitro. A two-compartmental model of the DA cell that unites data on firing frequencies under different experimental conditions has been suggested. We analyzed dynamics of this model. An artificial timescale separation was introduced to conduct the singular perturbation analysis first. By comparison to that, the original case of poor timescale separation was investigated. Conditions under which the frequency of the coupled system was high were shown to require sufficient folding of a nullcline for the fast subsystem. Changes responsible for lowering frequency altered the regime gradually, without complex transitions, by contrast to the case of a poor timescale separation. However, the difference in frequencies obtained under conditions corresponding to different experiments vanished under the additional timescale separation. Taken together, the results explain how the geometry of the phase space and the poor timescale separation in the model contribute to its characteristics replicating those of the DA neuron.

Joseph Hanna
New Jersey Institute of Technology
Does the PY Neuron Exhibit Resonance?
Membrane resonance is the property that describes the neuron's preferred response to inputs of injected current. To produce membrane resonance, a cell must possess a low-pass filter and a high-pass filter. If membrane resonance exists, then the neuron is capable of differentiating between its inputs, thereby being able to recognize an oscillatory input at a preferred frequency where the largest response will be produced. Using a combination of experiments and mathematical modeling, we set out to determine whether the PY neuron of the STNS (Stomatogastric Nervous System) of Cancer borealis exhibits resonance.

William J. Heuett
LBM/NIDDK/NIH
Modeling Metabolism in Pancreatic Beta-Cell Mitochondria
Pancreatic beta-cells sense the ambient blood-glucose concentration and secrete insulin to signal other tissues to take up glucose. Mitochondria play a key role in this response as they metabolize nutrients to produce ATP and reactive oxygen species (ROS), both of which are involved in insulin secretion signaling. We have developed a model of beta-cell mitochondrial respiration, ATP synthesis, and ROS production in response to glucose and fatty acid stimulation, based on available data in the literature and mathematical models derived from first principles. The model is consistent with a number of experimental observations reported in the literature. Most notably, it explains the non-ohmic rise in the passive proton-leak rate at high membrane potential and its dependence on increased ROS production. Results from our model suggest increasing mitochondrial density while decreasing uncoupling protein activity may be an effective way to increase glucose-stimulated insulin secretion while decreasing oxidative stress. It also predicts that glucose-stimulated insulin secretion may be inhibited by long-term fatty acid exposure. Using glucose and fatty acid profiles from individuals in a diet study, we find a negative correlation between the amount of ROS produced per ATP, as predicted by the model, and the individual insulin sensitivities. The model can also be applied in a clinical setting to predict the insulin secretion rate and quantify beta-cell function for a single individual.

Xinxian Huang
New Jersey Institute of Technology
The Activity Phase of Neurons in a Reciprocally Inhibitory Network
In a network of two reciprocally inhibitory neurons, the firing time of one neuron has an effect on the period of the other one, and vice versa. We investigate the phase of activity of neuron A as a function of the relative firing time of neuron B. We examine the conditions for the existence and stability of phase-locked activity. We determine the phase of activity of the mutually inhibitory network from information about two different feed-forward inhibitory networks. One characterizes the dependence of the cycle period of A on the relative firing time of B, and the other determines the relation between the phase of B and the period of A. In the special case that the period of A is linear function of the relative firing time of B, we obtain conditions on the existence and stability of phase-locked solution and describe the circumstances under which the solution is unique. Joint work with Farzan Nadim and Amitabha Bose.

Aridaman Jain
New Jersey Institute of Technology
Modeling of Metal and Organic Concentration Measurements in Water Samples from Secaucus High School Wetland
The New Jersey Meadowlands Commission's Meadowlands Environmental Research Institute (MERI) is conducting a study to analyze the accumulation of contaminants in clean wetland soils in an engineered high marsh in Secaucus High School (SHS) area. The enhancement of the SHS wetland included the construction of two high-marsh locations (elevation 3.0 – 3.5 ft) along the eastern side of the site totaling approximately eight acres. Soil samples were taken in six locations at three contour elevations (3.5 feet, 3.0 feet, and 2.0 feet), two depths (surface, 0-10 inches and deep - >12 inches), and two marshes (Northeast and Southeast) during October 31, 2007 and June 27, 2008. Measurements of 9 metals and 2 organics concentration were made along a transect connecting the highest elevation in each marsh. This paper

describes the results of fitting a generalized linear regression model to estimate the effects of different levels of elevation, marsh, depth, and time period on metal and organic concentration. The main statistically significant results at the 5% level (i.e., $p < 0.05$) are: (i) 3.0/3.5 feet elevation has lower concentration than 2.0 feet, (ii) Southeast marsh has lower concentration than Northeast, (iii) the elevation has a bigger effect at Northeast than at Southeast, and (iv) the elevation has a bigger effect at surface than at 12" depth. Joint work with Francisco Artigas, Christine Hobble, and Ed Konsevick (MERI).

Yogesh Joshi
New Jersey Institute of Technology
Discrete Dynamical Population Models: Higher Dimensional Pioneer-Climax Models
There are many population models in the literature for both continuous and discrete systems. We begin with a general discrete model that subsumes almost all of the discrete population models currently in use. Some results related to the existence of fixed points are proved. We then concentrate mostly on a 3-dimensional Pioneer-Climax model. Most of the previous studies of such models have been for 1-dimensional or 2-dimensional systems only. An extensive investigation of the dynamics of discrete 3-dimension Pioneer-Climax models is conducted in this work, including an analysis of fixed and periodic points, bifurcations, and chaotic regimes.

Melissa LaTona
Arizona State University
Melissa LaTona, Angela McBryan, and Rebecca Raub
Mathematical Model of the Immune Response to Mycobacterium ulcerans with Clay Treatment
Mycobacterium ulcerans is a slow growing bacterium that is known to cause necrotizing ulcers on patients-a disease termed Buruli ulcer. The bacterium produces a destructive toxin, mycolactone, which has an immunosuppressive effect. Generally, large ulcers are surgically treated by removing the diseased portion of the body. However, this is both costly and dangerous, leading to considerable amounts of tissue loss and disability. In 2001, a French philanthropist started to treat patients with Buruli ulcer by putting natural clay from France on the wound. This method of treatment has opened the doors to research to determine the mechanism for the clay healing process. It is possible the application of this natural clay helps neutralize toxins released by the bacteria. Mathematical models can be used to give new insights on the dynamics of interactions between bacterium, immune cells, and clay. A system of three ordinary differential equations is used to quantitatively investigate the treatment and provide a tool for predicting parameter values of biological significance.

Xiaomu Li
New Jersey Institute of Technology
Region Selection in the Study of Major Depression: Using Backward Haplotype Transmission Association Algorithm
Serotonin 1A receptors (5-HT1A) are implicated in the pathophysiology of major depressive disorder (MDD), and difference in binding potential (BP) between controls and MDD subjects, adjusted by gender and aggression scores, was reported. However, the information of higher-order interactions between regions is not easy to capture. In this poster, we use the "Backward Haplotype Transmission Associated Algorithm", originally used in genetics study for detecting genes related to complex diseases, to address this problem. Using [C-11]WAY100635 as the ligand of the 5-HT1A receptors, we apply the algorithm to detect regions associated with the MDD. Joint work with Chung Chang (NJIT) and Shaw-Hwa Lo (Columbia University).

Yi Mao
Michigan State University
Multiscale Simulations of Protein Engineering in Bioluminescence Systems
Recently, a myriad of bioluminescence-based imaging tools have been emerged for in vitro, in vivo and whole animal applications. These tools have provided methods to monitor biological processes in living organisms in real time. The sensitivity and specificity of bioluminescence imaging especially bioluminescence tomography depends on the penetration depth of the emitted light, which in turn depends

on the frequency of the emitted light. Therefore, it is highly desirable to have bioluminescence probes whose emission spectra are within the biological optical window, i.e, 700nm-1100nm. Here we are developing a multiscale modeling method in designing protein probes used in cellular imaging with the desired optical property. The detailed hierarchical procedure is outlined as follows:
(1) Quantum mechanics/classical mechanics simulations of protein crystal structure are to reproduce the observed spectrum. The purpose is to find the link between protein's structure and function.
(2) Normal mode analysis on the elastic network model of the protein identifies the key residues influencing the spectrum. The purpose is to find the potential mutation site for protein engineering.

Victor Matveev
New Jersey Institute of Technology
Calcium Current vs. Calcium Channel Cooperativity of Synaptic Neurotransmitter Release
Recently there has been significant interest and progress in the study of spatio-temporal dynamics of calcium concentration that triggers exocytosis at a fast chemical synapse, which requires understanding the contribution of individual calcium channels to the release of a single vesicle. Experimental protocols provide insight into this question by probing the sensitivity of exocytosis to calcium influx. While varying extracellular or intracellular calcium concentration assesses the intrinsic biochemical calcium cooperativity of neurotransmitter release, varying the number of open calcium channels using pharmacological channel block or the tail current titration probes the cooperativity between individual calcium channels in triggering exocytosis. Despite the wide use of these calcium sensitivity measurements, their interpretation often relies on heuristic arguments. Here we provide a detailed analysis of the calcium sensitivity measures probed by these experimental protocols, present simple expressions for special cases, and demonstrate the distinction between the calcium current cooperativity, defined by the relationship between exocytosis rate and the whole-terminal calcium current magnitude, and the underlying calcium channel cooperativity, defined as the average number of channels involved in the release of a single vesicle. We find simple algebraic expressions that show that the two are different but linearly related. Joint work with Richard Bertram (Florida State University) and Arthur Sherman (NIH).

Angela McBryan
Arizona State University
Angela McBryan, Caroline Appleton, Yujin Zheng, Ilyssa Summer, and Victoria Balogh
Using Mathematical Models to Optimize Algal Lipid Production for Alternative Biofuel Applications
Algal lipid processing has been shown to be one of the most promising ways of producing biofuel. It has been further shown that under stress, most species of algae tend to increase their cell content of triacylglycerols (TAG) lipids, which can be used for the production of biofuel. Algal cultures can become stressed under low light and/or nutrient conditions. Mathematical models can aid in the understanding of the dynamics of algal growth and lipid synthesis. The UBM algae team at ASU has performed indoor and outdoor experiments on how cultures of Scenedesmus and Pesudochlorococcum genera of green algae respond to varying light and nutrient conditions. Our research goal is to study the stress and limitation conditions on algal cultures that would optimize their neutral lipid production.

S. E. McBurnie and S. J. Chapman
University of Oxford
Effective Equations for the Acoustic Response of Bubbly Liquids, for Application to Medical Ultrasound
Ultrasound is a commonly used medical imaging modality. The process is similar to that used by dolphins and bats; sound waves are fired at the target area to be ``seen'' and the echoes returned are interpreted to map out the boundaries between different anatomical structures. In certain types of diagnostic imaging, tiny bubbles are injected into the blood to improve the backscatter (or echo) from blood tissue and hence enhance the image. However, sometimes artifacts appear in the image. It is hoped that an improved model for ultrasound propagation through the bubble clouds can be used to understand and remove these artifacts. Inspired by this medical application, we use homogenization techniques to derive averaged equations for the pressure induced in bubbly liquids by a sound wave. In particular, for media with small gas volume fraction we use matched asymptotic expansions to recover and review the famous scattering result of Foldy and the nonlinear phenomenological equations of Van Wijngaarden. We then use multiple

scales techniques to extend the work of Caflisch et al. on the acoustic response of media with finite gas volume fraction.

Catherine Morrison
New Jersey Institute of Technology
Modeling Plant Succession Using Markov Matrices
Plant community succession is the at least somewhat predictable sequence of species compositions that follows a landscape disturbance (for example, clear-cutting). We assisted with the planning process for a proposed experiment to test whether this successional process is amenable to manipulation. First, we tested the magnitude of the influence of two kinds of stochasticity on the prediction of community composition from estimated Markov models of the successional process. The first kind of stochasticity comes from the probabilistic nature of the Markov process, although this is only a factor if individual plant species transitions are modeled (rather than proportions of species in an infinitely large population). The second kind of stochasticity comes from uncertainty about the true underlying Markov model, which can be incorporated if separate estimated transition matrices are available from different experimental plots, for example by the use of an interval, or "set" matrix. We drew conclusions about the appropriate number of plots relative to their size. Second, we examined the relationship between the history length of a successional process available to estimate its transition matrix, and the accuracy of predictions of community composition immediately following the estimation interval. We show how this relationship will differ for homogenous and non-homogenous Markov processes, and present some real-world examples.

Christina Mouser
Medgar Evers College
Hematopoietic Stem Cell Proliferation Modeling under the Influence of Hematopoietic Inducing Agent
The process by which hematopoietic stem cells (HSC) residing in the bone marrow differentiate into blood cells is known as hematopoiesis. In the event of hemorrhagic shock, it is crucial for the HSC to rapidly differentiate into new committed erythroid progenitor cells that will give rise to erythrocytes. Growth factors and cytokines enhance the self-renewing process of HSC and are, therefore, crucial to restoring normal levels of blood cells in the body. Hematopoietic inducing agents (HIAs), such as the cytokine erythropoietin (EPO) and granulocyte-colony stimulating factor (G-CSF) play a vital role in hematopoiesis because they are capable of inducing the proliferation of stem cells. The aim of the current study is to mathematically model the effect of HIA on the proliferation rate of hematopoietic stem cells at varying levels of oxygenation. The role of HIA is analyzed by constructing a set of coupled ordinary differential equations upon which mathematical analysis is performed. The model makes predictions of hematopoietic activity during low pO_2 levels (ranging from 3% to 15%) similar to conditions ranging from acute blood loss to normal conditions.

Mohammad Nawaz
New Jersey Institute of Technology
Do Membrane Proteins Play Any Role in Microspordia Infection?
This research is about a very unique parasite called microsporidia. These parasites can remain dormant for many months, but once it is “awaken” under the right conditions, it will infect nearby host cells in an exceptional way. The way the infection happens is through what is called a “polar tube”; this is a very long tube that is literally launched from the parasite at a very high velocity and pierces the host cell. Once this step has happened successfully, the polar tube acts like a bridge between the parasite and the host cell. This allows genetic material to flow from the microsporidia through the tube and into the host cell for reproduction of the parasite. The objective of this research is to determine whether or not the proteins and other intramembranous molecules found on a host cell play a role in the infection. Using giant unilamellar vesicles, which are cell membranes without any molecules or proteins on it, is the best option to answer this question.

R. O'Dea and J.R. King
University of Nottingham
A Multiscale Continuum Model for Pattern Formation via Intercellular Signalling
The development of biological tissue is a complex process resulting from the interaction of numerous processes, many of which exhibit both cell- and tissue-scale variations. The development of spatial organisation within a cell population is fundamental to the construction of specialised body parts; juxtacrine signalling mechanisms have been shown to be a robust mechanism for the formation of such fine-grained spatial patterns in tissues. We develop a continuum (tissue-scale) description of this pattern-forming mechanism. Most applications of multiscale asymptotic methods are to continuous systems, while here we must account explicitly for discreteness on the short lengthscale. We show that, on the macroscale, the contact-dependent juxtacrine signalling interaction manifests itself as linear diffusion, motivating the use of reaction-diffusion-based models for cell-signalling systems.

Myongkeun Oh
New Jersey Institute of Technology
Negative Phase and Extended Spike-Time Response Curve
The PRC-based analysis of the cell response involves describing the effect of perturbation as a change of the phase variable characterizing the state of the spiking cell, whereby the phase is bounded on the interval [0,1] or [0, 2π]. However, we show that for some biophysical models of spiking cells, a one-dimensional phase reduction of a non-weakly perturbed limit cycle oscillator may require the extension of the phase variable defining the state of the oscillator to a multi-branched phase domain. Such multi-branched domain is easiest to implement by extending the [0,1] phase interval to negative values. This notion of negative phase enables us to extend the phase return map analysis based on the spike-time response curve (STRC) characteristic to describe novel dynamical states of non-weakly coupled oscillators. We show that the extension of STRC to negative value of phase is necessary to accurately predict the response of a model cell to several close non-weak perturbations. Such an extended STRC can then be used to analyze the dynamics of three or more non-weakly coupled cells, whereby more than one synaptic perturbation arrives per oscillation cycle into each cell. Joint work with Victor Matveev.

Farzan Nadim
New Jersey Institute of Technology
Myongkeun Oh[1], Shunbing Zhao[2], Farzan Nadim[1,2], Victor Matveev[1]
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A Mechanism Underlying Short-Term Synaptic Dynamics Regulated by Neuromodulator Based on Kinetics of Ca Currents
The inhibitory synapse from the lateral pyloric (LP) to the pyloric dilator (PD) neuron in the crab pyloric network consists of spike-mediated and graded components. The graded component of this synapse shows short-term depression in control saline, but in the presence of proctolin, low-amplitude (<30mV) presynaptic stimulation causes the facilitation, while high-amplitude (>30mV) stimulation causes depression. We build a model to explore the mechanisms underlying proctolin's effects on the short-term dynamics of the LP to PD synapse based on kinetics of Ca^{2+} current in the presynaptic LP neuron. This model captures the postsynaptic response of the PD neuron in both control saline and the presence of proctolin. The main effect of proctolin in this model is two-fold: First, proctolin slows down the activation kinetics of presynaptic Ca^{2+} current. As a result, there is a slow accumulation of free residual Ca^{2+} current in presynaptic terminal. Second, proctolin activates a non-specific ion channel. We assume that this channel is permeable to Ca^{2+}, suggesting that the baseline of background Ca^{2+} concentration in the presynaptic terminal is increased by proctolin. Together, these two effects are sufficient to explain the modulation of both spike-mediated and graded components of the synapse by proctolin.

Peter Roper
University of Utah
Mean Field Reduction of a Synchronized Bursting Network
We analyze a recently published model of a neuronal network from the rat hypothalamus (Rossoni et al, PLOS 4(7) e1000123 (2008)). Rossoni's network models the synchronised bursting seen in oxytocin neurons during lactation, and comprises 3,000 neurons coupled by diffusive messengers, and that burst repeatedly with an intrinsic period of 8 minutes. We show that, under mean field assumptions and fast/slow averaging, we can reduce the network to a system of 5-ODEs. We analyze the resulting system and investigate mechanisms underlying the slow 8 minute oscillation.

Horacio G. Rotstein and Dongwook Kim
New Jersey Institute of Technology
Mechanistic Aspects Underlying the Effects of in-vivo-like Synaptic Inputs on an Entorhinal Cortex Stellate Cell Model
Stellate cells in layer II of the medial entorhinal cortex display subthreshold rhythmic oscillations at theta frequencies (4 - 12 Hz).
These patterns are generated mainly as the result of the interaction between a persistent sodium and a hyperpolarization-activated (h-) currents. Recent 'in vitro' experimental results (Fernandez & White) show that when stellate cells receive Poisson distributed trains of combined excitatory and inhibitory "synaptic conductance" inputs, subthreshold oscillation are abolished, but they persist if they receive "synaptic current" inputs. We use a biophysical (conductance-based) model of stellate cell to reproduce the experimental results and to investigate the corresponding mechanisms.

Horacio G. Rotstein
New Jersey Institute of Technology
The Transition to Hyperexcitability in Stellate Cells (SCs) from Layer II of the Medial Entorhinal Cortex during Temporal Lobe Epilepsy: A Modeling Study
Previous studies have shown that stellate cells (SCs) are hyperexcitable in animal models of temporal lobe epilepsy. A recent 'in vitro' study using pilocarpine-treated rats (Kumar et al. 2007) found evidence for the existence of recurrent excitatory connections among SCs, reduced recurrent inhibition among SCs in epileptic animals and no change in recurrent excitation. In this work we investigate the biophysical mechanism that governs the transition from normal to hyperexcitable spiking activity in SCs. We use biophysical (conductance based) modeling, simulations, dynamical systems techniques and dynamic clamp experiments. The SC model includes a persistent sodium, an h- and an M- currents. We show that a minimal network model including SCs and interneurons is able to qualitatively reproduce the experimental findings. This model displays an abrupt transition between the two frequency regimes as the result of small changes in the amount of inhibition. This abrupt transition also occurs in the absence of inhibition, as a result of small changes in the amount of recurrent excitation. To further investigate the biophysical mechanism that governs these phenomena we considered a single SC connected to itself via an autapse. This approximation mimics the network activity and is justified since SCs synchronize in phase and slightly out of phase in the theta and hyperexcitable regimes respectively. We show that the abrupt changes in firing frequency can be induced by increasing the amount of autaptic conductance, but not by increasing the level of the applied (tonic) current in an isolated SC; i.e., they are the result of phasic but not tonic excitation. 'In vitro' experimental results using a single, isolated SC and dynamic clamp to generate an autapse confirmed our theoretical predictions. Our results show that a single, isolated SCs have intrinsic dynamic properties that endow them with the potential ability to evolve on both fast and slow time scales, and that the combination of excitatory and inhibitory network properties determines the SC's frequency regime. Joint work with Tilman Kispersky and John A. White.

Joseph Salisbury
Brandeis University
Unsupervised Classification of MALDI-MS Data from Organ Tissue Homogenates
Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) imaging can detect the spatial distribution and relative abundance of a wide range of compounds found in intact tissue. Comparing the molecular profiles within and between tissues has many potential applications including identifying biomarkers which could be useful for diagnosis and treatment of cancers and neurodegenerative disorders. Due to the high dimensionality of data derived from MALDI-MS, statistical classification techniques are required to identify which characteristics define different sample conditions. In supervised classification, a training set of data is used to determine what the defining characteristics of sets are. In contrast, unsupervised classification includes the grouping of data into classes using similarity measures without a *priori* knowledge of the number or defining features of the classes. This is a powerful tool for knowledge discovery, but it may not always yield biologically relevant groupings. To determine which unsupervised classification methods could most robustly classify MALDI-MS data into biologically relevant categories, we analyzed mass spectra taken from tissue homogenates of over twenty organs from six mice. The performance of unsupervised classification methods including K-means, hierarchical clustering, and self-organizing maps was compared while gradually increasing the number of organs involved in the analysis. A virtual MALDI-MS image, which maps of all the samples used in the analysis to a cartoon diagram of the internal anatomy of a mouse, is used to visualize classification results. Joint work with Jeffrey Agar.

Peizhe Shi
University of Washington
Multiple States or Conformational Fluctuation? Monomeric Enzyme with Positive Cooperativity
Positive, sigmoidal cooperativity is known to occur to a monomeric single-site enzyme with slow conformational fluctuations in its unbound (E) states when the enzyme undergoes steady-state catalytic turnover (mnemonic enzymes, hysteretic enzyme). Through a coupled diffusion model, we show that positive cooperativity occurs even when the E state is a single thermodynamic state, provided that the fluctuation amplitude of the state is sufficiently greater than that of the enzyme-substrate complex ES and the fluctuation times being comparable. This can occur even without mean structural change between E and ES. Slow conformational fluctuations are widely observed in enzymes. This theoretical result suggests that enzymes with substrate association that reduces conformational fluctuations while maintaining fluctuation temporality can exhibit sigmoidal binding inside of living cells.

Asya Shpiro
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Asya Shpiro[1], Nava Rubin[2], and John Rinzel[3]
Neuronal Dynamics of Early Alternations During Bistable Perception
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Both theoretical and experimental studies of bistable perception have been focused on its long term dynamics, when alternations between the percepts are well established. The first few intervals of exclusive visibility of each percept ("exclusive visibility epochs") are typically disregarded when the statistical properties of perceptual alternations are calculated. In this work, we use neuronal competition models with both slow negative feedback process (adaptation) and noise [1] to describe the early, transitional stages of bistable perception. We show that due to the slow adaptation in the models, the durations of the first few epochs are different from the durations of the epochs in the long run. This result is not consistent with experimental observations for at least one bistable perception paradigm, namely, binocular rivalry, where no differences in the duration of the early and late epochs have been found [2]. Our result suggests that noise plays a dominant role over! adaptation in producing alternations during bistable perception.
Modeling the early stages of bistable perception allows us to consider also the time between the onset of stimulus and the start of the first exclusive visibility epoch, which can be interpreted as decision-making

time. We investigate how this time depends on the details of the models, in particular, on the strength of the competing percepts.

[1] Shpiro A, Moreno-Bote R, Rubin, N, and Rinzel J, Balance between noise and adaptation in competition models of perceptual bistability. (2009). Journal of Computational Neuroscience, in press.
[2] Rubin, N., & Hupe, J. M. (2004). Dynamics of perceptual bistability: Plaids and binocular rivalry compared. In D. Alais, & R. Blake (Eds.), Binocular rivalry. Cambridge: MIT.

Sundar Subramanian and Peixin Zhang
New Jersey Institute of Technology

A Generalized Inverse Censoring Weighted Survival Function Estimator

We propose an inverse censoring weighted estimator of a survival function when the data are doubly censored but the left censoring is always observed. The estimator reduces to its right censored version when there is no left censoring. The well-known equivalence between the Kaplan-Meier and inverse censoring weighted estimators for the right censored scenario, however, does not extend to the double censoring case that we investigate. We present an illustration of the proposed estimator using data from an AIDS clinical trial, in which both the left and right censoring variables are always observed, and, therefore, comparison with an alternative inverse censoring weighted estimator that uses the additional available information is of interest.

Ramana Susarla and N.W. Loney
New Jersey Institute of Technology

Mathematical Modeling of the Affect of Rate of Absorption on Drug Release from Biodegradable Nanospheres

Mathematical modeling of drug delivery systems can help us understand the underlying mass transport mechanisms involved in the control of drug release. It also plays an important role in providing us with valuable information such as the amount of drug released during a certain period of time and when the next dosage needs to be administered. Thus potentially reducing the number of in-vitro and in-vivo experiments required, which in some cases are infeasible. A large spectrum of mathematical models and approaches describing drug release are available in the literature ranging from the classical models by crank, Higuchi, Hopfenberg and Cooney to some of the recent work by N.A.Peppas and others describing drug release from swellable and erodible systems. However there are very few papers which focus on study of the affect of factors like rate of absorption, rate of elimination of drug etc... on drug release. In this work we propose a mechanistic model for drug release form spherical naospheres taking into account the affects of rate of absorption.

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Clustering and Classification through Density Estimation

A unified variational methodology is developed for classification and clustering problems, and tested in the classification of tumors from gene expression data. It is based on three main ingredients: a) the blurring of the distinction between training and testing populations through the soft assignment of the latter to classes, in an expectation-maximization framework, b) an algorithm for density estimation by a descent flow that transforms an arbitrary distribution into an isotropic Gaussian, and c) a measure of the clustering capability of a set of observables, which leads to an effective procedure for variable selection. The methodology is particularly applicable to situations where there are relatively few observations of a comparatively large set of variables, and no a priori knowledge that strongly links a small subset of the observables to the classification sought.

Shashaank Vattikuti
NIDDK, NIH
Shashaank Vattikuti and Carson C. Chow

Synaptic Excitation and Inhibition Imbalance as a Model of Local Circuit Information Processing in the Autism Neocortex

In this study, we ask whether a computational local cortical circuit model capable of persistent tuned activity can mimic Autism clinical traits by adjusting the synaptic excitation versus inhibition current ratio. Mutiple molecular studies and the fragile-X syndrome (fragile-X syndrome has a significant co-morbidity of Autism traits) mouse model suggest that local circuit synaptic inhibition may be deficient in subjects with Autism. We adapt a working memory model described by Compte et al (2000) to explore whether decreasing synaptic inhibition in such a system results in several Autism traits including: 1) hypersensitivity to an efferent input at rest, 2) prolongation of a tuned response (perseveration without a directed external current), 3) decreased shifting of encoded information (accuracy of shifting between tasks with a directed external current), 4) increased variability in shift task response, and 5) increased probability of a "seizure" transition (transition from tuned response to an all-on state). We use saccade motor-planning to illustrate some of these variables and relate those findings to Autism saccade studies. While the Compte model refers to a local circuit in the dorsolateral prefrontal cortex, our context is a local circuit within the lateral intraparietal region involved in intentional saccade planning and thought to have similar recurrent-network derived persistent tuned activity.

Compte A, Brunel N, Goldman-Rakic PS and Wang X-J (2000) Synaptic mechanisms and network dynamics underlying visuospatial working memory in a cortical network model. Cerebral Cortex 10, 910-923.

Joseph Doggett, Anthony Witten, Erika Camacho, Stephen Wirkus, Pamela Marshall
Arizona State University

In-Vivo Microarray Analysis and Nonlinear Differential Equations: An Interdisciplinary Approach to Gene Network Regulation

We are interested in mathematically modeling and then experimentally validating a transcription factor network in Saccharomyces cerevisiae in response to extracellular hyperosmolarity. In yeast, hyperosmolarity triggers calcium release from the vacuole, which in turn activates calmodulin. Calmodulin activates calcineurin to dephosphorylate proteins such as the Crz1p transcription factor. This transcription factor is then transported into the nucleus to activate target gene transcription. Utilizing nonlinear differential equations, we are modeling the change in the concentrations of mRNA over time for genes in the gene expression network regulated by calcium as a response to environmental stress. We first begin by analyzing cell responses to extracellular calcium, modeling gene expression changes over time. We will then use these equations to simulate the activation/depression of a gene and thereby its corresponding effect in the entire network. The model will be tested and refined after determination of transcriptional changes after extracellular stimuli, in wild type and null mutant cells. This work provides the basis for an interdisciplinary systems biology approach to understand more completely the regulatory transcriptional networks that are affected by hyperosmolarity that trigger calmodulin/calcineurin activity.

Mazen Zarrouk
University of Wisconsin-Milwaukee

Truncated Incomplete Hessian Newton Minimization Method and Application in Biomolecular Potential Energy Minimization

In a recent paper, we proposed and analyzed a new type of a modified Newton linesearch method for minimizing a twice continuously differentiable real-valued function whose Hessian matrix is dense but can be well approximated by a sparse incomplete Hessian matrix. This method is called the truncated incomplete Hessian Newton method (T-IHN) and is proved to be globally convergent even with an indefinite incomplete Hessian matrix or an indefinite preconditioner, which may happen in practice. We also prove that T-IHN can admit a steplength of one that satisfies the Wolfe's conditions and have a Q-linear rate of convergence. As an application, we constructed a particular T-IHN algorithm for minimizing a biomolecular potential energy function, and numerically tested it for a protein model problem based on a widely used molecular simulation package, CHARMM. Numerical results confirm the theoretical results,

and demonstrate that T-IHN can have a better performance than most CHARMM minimizers. In this talk, we will describe the T-IHN method, show its major analytical convergence results, describe the construction of the incomplete Hessian matrix using a simple cutoff strategy and present some of promising numerical results of T-IHN in comparison with the other CHARMM minimizers. This a joint work with my advisor Dexuan Xie.

Ruijun Zhao
Purdue University

Maximum Flux Transition Paths

The dynamics of complex systems is often driven by rare but important events. In this talk, we focus on finding transition pathways of conformational changes in macromolecules, in which these activated processes occur on a time scale is much larger than the microtime scale in the system. Given two metastable states A and B of a biomolecular system, the problem is to calculate the likely paths of the transition from A to B. The minimum energy path (MEP) was shown to be such a path for simple system with smooth energy landscape, but it becomes misleading for complex system. Here, we study a transition path in collective variable space in which the original model is replace by a coarse-grained one. In particular, we introduce the maximum flux transition path (MFTP), defined as a path that crosses each isocommittor at a point which (locally) has the highest crossing rate of distinct reactive trajectories. The algorithm and its performance will be discussed.