

# **Dynamical systems in physiological modeling**

**Purdue University, October 11-13, 2008**

Titles and abstracts are given in order of appearance on the program.

## **Modeling the stochastic dynamics of localized calcium elevations and whole cell calcium responses**

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Abstract: Localized Ca elevations known as Ca puffs and sparks are cellular signals that arise from the cooperative activity of clusters of inositol 1,4,5-trisphosphate receptors and ryanodine receptors clustered at Ca release sites on the surface of the endoplasmic reticulum or sarcoplasmic reticulum. When Markov chain models of intracellular Ca regulated Ca channels are coupled via a mathematical representation of a Ca microdomain, simulated Ca release sites may exhibit the phenomenon of stochastic Ca excitability where the IP3Rs or RyRs open and close in a concerted fashion. Such mathematical models provide insight into the relationship between single-channel kinetics and the statistics of puff/spark duration, and clarify the role of stochastic attrition, Ca inactivation, luminal depletion, and allosteric interactions in the dynamics of puff/spark termination. The stochastic dynamics of local Ca is an important aspect of excitation-contraction coupling in cardiac myocytes, where sarcoplasmic reticulum Ca-induced Ca release is locally controlled by trigger Ca influx via L-type channels of the plasma membrane. A recently developed whole cell modeling approach is able to avoid the computationally demanding task of resolving spatial aspects of global Ca signaling, while accurately representing heterogeneous local Ca signals in a population of Ca release units.

## **The dynamics of emotional dysregulation**

Anca Radulescu

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Abstract: Schizophrenia is a currently incurable mental disorder that affects surprisingly many people, with serious individual and social consequences. Its complex symptoms and central, endocrine and autonomic abnormalities helped schizophrenia withstand many attempts to provide a simple explanation, making its etiology intractable, its diagnosis difficult and its treatment elusive. The “stress/vulnerability” hypothesis is a theory with the potential to unify the complex features of the illness. It attributes schizophrenia to a hereditary predisposition that reduces the individual psychological threshold towards stimuli, to the point where even minor daily stresses, in conjunction with this premorbid personality component, will directly trigger psychotic symptoms: a pre-existing hippocampal/prefrontal deficit, reinforced through neurotoxic effects on the

hippocampus, produces further dysregulation of the excitatory and inhibitory feedback loops involved in brain modulation.

Dynamical systems analysis is a promising approach to investigate the unknown physiology of the illness over time and under perturbation. I will present a dynamical systems model of brain interactions, in which the hereditary vulnerability for schizophrenia is associated with weakened feedback inhibition, yielding a latent Hopf bifurcation in dynamics; the predisposition can remain dormant until a triggering event “activates” the bifurcation, moving the system into a regime of increasing instability. Invariants such as entropy and Lyapunov exponent could be used for constructing statistical diagnosis charts. The brain “dynamical profile” of each patient or high risk individual could be created from a system of such parameters, then compared against a multi-dimensional profile chart, constructed based on common statistics.

### **Roles of Gap Junctions in Neuronal Networks**

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Abstract:

There is much evidence showing the presence of gap junctions in neuronal networks. We study the roles of gap junctions in the dynamics of neuronal networks in two distinct problems. First, we study the circumstances under which a network of excitable cells coupled by gap junctions exhibits sustained activity. We investigate how network connectivity and refractory length affect the sustainment of activity in an abstract network. Second, we build a mathematical model for gap junctionally coupled cables to understand the voltage response along the cables as a function of cable diameter. For the coupled cables, as cable diameter increases, the electrotonic distance decreases, which causes the voltage to attenuate less. However, the input of the second cable decreases, which allows the voltage of the second cable to attenuate more. Thus we show that there exists an optimal diameter for which the voltage amplitude in the second cable is maximized. Thus gap junctions plays role of a "current clamp" at the gap junction location. We observe that the propagation time is also minimized.

### **Study of neural population phase synchronization and its connection to psychological behavior: the case of attention and habituation**

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Abstract: The functional behavior of the brain is encoded in spatio-temporal structures that are characterized by a non-linear dynamics and spatio-temporal interconnection. At present, one of the best methods to extract information from such pattern formation is given by the dynamics of macroscopic quantities that result from the synchronized post-synaptic activity of big ensembles of neurons, such is the case of the EEG and MEG. In such respect, the seminal work of Freeman propelled the use of neural-mass modeling approaches as an alternative to study large-scale effects of big numbers of neurons through the dynamics of neural ensembles.

In this work, we make use of a neural large-scale model together with a stochastic approach so as to simulate the phase dynamics of neural population responses reflected in evoked potentials during human states of focal and non-focal attention and habituation. Our in silico results are compared to experimental human brain potentials so that our hypothesis can be validated. It is concluded that neural mass models incorporating physiological connectivity as well as fine neuronal features offer a great possibility to study mesoscopic neural-mass responses reflected in large-scale human brain potentials.

### **Length regulation of flagella**

Jim Keener

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University of Utah

Abstract: The construction of flagellar motors is a carefully regulated genetic process. Among the structures that are built are a U-joint-like structure called the hook, and, of course, the flagellar filament. The length of the hook is tightly regulated, while the filament length is monitored, so that a broken filament is regrown.

The question that will be addressed in this talk is how *Salmonella* detects and regulates the length of these structures. This is related to the more general question of how quantitative physical properties (such as size or length or numbers) can be determined and what those mechanisms are.

In this talk, I will describe the current ideas of how these measurements of hook and filaments are made and then present mathematical models for these processes.

### **Oscillations in basal ganglia circuits in Parkinson's disease: detection and modeling of intermittent synchronization.**

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Abstract: The basal ganglia are a group of interconnected subcortical nuclei, which are, among other things, involved in control of movement. The physiological mechanisms responsible for this control remain poorly understood. Interest in basal ganglia physiology is also motivated by Parkinson's disease, characterized by chronic dopamine deficiency in basal ganglia, and other basal ganglia disorders. This talk will consider our studies of synchronous oscillations in basal ganglia activity, recorded intraoperatively from Parkinsonian patients and models of these oscillations. The synchronized oscillations in the basal ganglia are believed to be relevant to the generation of motor symptoms of Parkinson's disease. Our analysis of these oscillations indicates that this synchronization is intermittent. We further utilize models of basal ganglia circuits (conductance-based models of subthalamo-pallidal circuits) to reproduce realistic patterns of synchronous activity and to study these patterns in the model. Implications for the therapeutic strategies in Parkinson's disease aimed at the destruction of synchronous activity will also be discussed.

**To be announced**

Jason Bazil  
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**Irregular transitions between different types of bursting in inhibitory and inhibitory-excitatory network of bursting cells**

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Abstract: Transitions between different types of bursting activity may be important for function and dysfunction of different neuronal systems. In the present work we consider the switching between anti-phase bursting with different number of spikes in a burst in a two inhibitory coupled bursting neurons, represented by conductance-based models of subthalamic cells. This switching gives rise to intermittent synchronous activity, which may be related to the experimentally observed dynamics of parkinsonian brain. We study how the interplay of intracellular calcium, slow membrane currents and synaptic activity contributes to the generation of physiologically interesting dynamics.

**Complex bifurcations in tissue culture models of cardiac arrhythmias**

Leon Glass  
Centre for Nonlinear Dynamics  
Department of Physiology  
McGill University

Tissue cultures of cardiac myocytes offer many experimental advantages including cheap

cost, controlled environment, and reproducibility. Tissue cultures can be grown in various geometries, subjected to various types of stimulation, and treated with drugs. Thus, a very rich range of experimental parameters can be varied. In this talk, I will discuss several experiments carried out by our group at McGill in which interesting types of dynamical behavior can be elicited as experimental parameters are varied. These experiments in the past have suggested many theoretical questions related to bifurcations of circle maps, time delay differential equations, and nonlinear partial differential equations. More recent work suggests interesting questions that relate to the interactions between geometry and dynamics, bifurcations in spatially heterogeneous partial differential equations, and the role stochastic effects in modifying the dynamics. This talk is based on the work of several collaborators, including most recently: Alvin Shrier, Michael Guevara, Gil Bub, Alex Hodge, Bart Borek, Min-Young Kim.

### **Dynamic heterogeneity, conduction block, and reentry in cardiac tissue**

Jeff Fox

Vice President for Cardiovascular Research

Gene Network Sciences

**Abstract:** Ventricular fibrillation (VF), a heart rhythm disorder that prevents the normal contraction of the ventricles, remains a leading cause of death in the United States. Although there currently is some controversy concerning the exact mechanism for VF, all hypotheses for fibrillation invoke wave break and conduction block, secondary to spatial heterogeneity of cardiac electrical properties. Heterogeneities may arise from intrinsic properties of the tissue, or they may be dynamically induced. It has been shown that dynamic heterogeneity and conduction block can be induced in 1D models of cardiac tissue by launching a series of rapid, irregular excitations, similar to those often observed clinically prior to onset of VF. In these simulations, dynamically-induced heterogeneities led to a wave block that annihilates wave propagation. However, experimental investigations of similar stimulus patterns in the intact canine indicate that stimuli chosen to maximize dynamic heterogeneity induce VF, rather than complete wave block. Recently we have shown that boundary-induced modifications of action potential duration are sufficient to disrupt conduction block and induce unidirectional propagation in 1D when stimulus intervals that maximize dynamically-induced heterogeneity are applied. However, 3D simulations are needed to test if these behaviors occur in realistic anatomies. To that end, we simulated wave propagation in a 3D model of the canine ventricular anatomy. Preliminary results suggest that block is induced by the premature sequence, but the portion of the wave near the boundary survives, leading to reentry and sustained fibrillation.

### **To be announced**

Saleh Elmohamed

Center for Applied Mathematics

Cornell University

## **Spontaneous pattern formation in large scale brain activity: what visual migraines and hallucinations tell us about the brain**

Jack Cowan  
Mathematics Department  
University of Chicago

In 1952 Turing's paper on the chemical basis of morphogenesis initiated an important approach to the mathematical analysis of spontaneous pattern formation. In 1973 Wilson and Cowan introduced a similar formulation in nets of interacting neurons and in 1979 Ermentrout and Cowan developed the mathematical analysis of such nets using local bifurcation theory and symmetry groups. Bressloff, Cowan, Golubitsky, Thomas and Wiener further developed this approach to characterize and analyze some of the circuitry of the primate visual cortex. The symmetry group used was the Euclidean group in the plane,  $E(2)$ , under a novel rotation action. Such an action is related to the fact that the visual cortex is a network of oriented edge detectors. However it is clear that much more than the orientation of a local edge is detected in the visual cortex: movement, texture and surface information, color and depth, for example. In this talk I will describe a new approach that allows the incorporation of these features into a comprehensive account of the origins of visual hallucinations and migraines.

## **Neuronal Dynamics and the Basal Ganglia**

Dave Terman  
Department of Mathematics and MBI  
Ohio State University

The basal ganglia are a group of nuclei that play an important role in the generation of movement. Dysfunction of the basal ganglia is associated with movement disorders such as Parkinson's disease and Huntington's chorea. Structures within the basal ganglia have, in fact, been the target of recent therapeutic surgical procedures including deep brain stimulation. Numerous experiments have demonstrated that neurons within the basal ganglia display a variety of dynamic behaviors; moreover, patterns of neuronal activity differ between normal and pathological states. Neither the origins of these neural firing patterns nor the mechanisms that underlie the beneficial effects of deep brain stimulation are well understood. In this lecture, I will describe a recent model for neuronal activity within the basal ganglia. Geometric dynamical systems methods will be used to analyze the activity patterns. I will then discuss how the model has been used to propose mechanisms underlying the beneficial effects of deep brain stimulation.

## **A model of the unfolded protein response in beta-cells**

Santiago Schnell  
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University of Michigan

Pancreatic beta cell failure is increasingly recognized as central to the progression of diabetes mellitus. Different causes are implicated in the onset of beta cell stress, dysfunction or death. Recent genetic and biochemical evidence both in humans and mice shows that failure in modulating the capacity and quality of the endoplasmic reticulum protein-folding machinery leads to beta-cell death. The quality control of protein-folding is regulated by several signaling pathways, which are collectively termed the unfolded protein response. In the beta-cells, proinsulin represents up to 50% of the total protein synthesis, and the rate of glucose-stimulated proinsulin translation is approximately 1 million molecules per minute per cell. The high burden imposed by the insulin biosynthesis on the unfolded protein response is the leading cause of certain diabetes phenotypes. We have developed a model of the unfolded protein response during proinsulin maturation in beta cells to test the two prevailing hypotheses in the field: beta-cell failure can result either from deterioration of the proinsulin folding pathways or from deterioration of the unfolded/misfolded protein degradation pathways responsible of eliminating unfolded proinsulin. Our model suggests that neither hypothesis alone is responsible for the preservation of the proinsulin homeostasis in beta-cells, but rather they both contribute to it.

### **The switching dominance mechanism for apamin-induced high-frequency firing in the coupled oscillator model of the midbrain dopaminergic neuron**

Andrey Dovzhenok

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In vitro, midbrain dopaminergic neurons are characterized by tonic spiking at rates below 10 Hz, while in vivo irregular low-frequency activity is occasionally interrupted by high-frequency bursts in connection to unpredicted rewards. Burst firing can also be evoked in vitro under apamin-induced blockade of calcium-dependent potassium (SK) currents. A switching dominance mechanism (Kuznetsov et al. 2006) has been suggested for high-frequency firing in vivo in the framework of the coupled oscillator model of the neuron. On the other hand, apamin-induced high-frequency firing in vitro has not been captured in the model since repetitive spiking failed in the absence of the SK current.

We have modified the model of the dopaminergic neuron to reproduce high-frequency firing induced by apamin. The repetitive firing has been achieved by changing the dendritic, but not somatic delayed rectifier potassium current in a way that it contributes to the spike afterhyperpolarization (AHP). In the absence of the SK current, the dendrites in isolation spike repetitively at a high frequency, and dominate firing of the model neuron when connected to the soma. While present, the SK current suppresses dendritic firing by hyperpolarization and allows the soma to dominate, causing a low-frequency pattern, similar to that in the previous model.

Application of N-methyl-D-aspartate (NMDA) to dendrites, which switched the pattern to high-frequency firing in the previous model, also elevates the frequency in the absence of the SK current in our new model.

By the switching dominance mechanism, our model has combined all basic ways to evoke a high-frequency firing in the dopaminergic neuron. The model predicts possible inhomogeneity of the AHP currents, which was used to obtain above results.

### **Statistical Mechanics of Large-Scale Neural Activity**

Jack Cowan

Mathematics Department

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We have recently found a way to describe large-scale neural activity in terms of non-equilibrium statistical mechanics [Buice & Cowan, PRE 75, 051919 2007]. This allows us to calculate (perturbatively) the effects of fluctuations and correlations on neural activity. Major results of this formulation include a role for critical branching, and the demonstration that there exist non-equilibrium phase transitions in neocortical activity which are in the same universality class as directed percolation. This result leads to explanations for the origin of many of the scaling laws found in LFP, EEG, fMRI, and in ISI distributions, and provides a possible explanation for the origin of alpha, beta, gamma, delta and theta waves. It also leads to ways of calculating how correlations can affect neocortical activity, and therefore provides a new tool for investigating the connections between neural dynamics, cognition and behavior.

### **Characterization and merger of oscillatory mechanisms in an artificial regulatory network**

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**Abstract:** Along with traditional examples of the cell cycle and circadian clock, oscillatory regulatory networks have been found in many pathways, including apoptotic, metabolic and morphogenic ones. The oscillatory mechanisms and the role of oscillations in these regulatory networks have not been fully understood. The design and experimental implementation of *artificial* networks provide a natural framework for reducing the complexity of gene regulation. Several synthetic oscillatory regulatory networks are introduced in the literature. However, no systematic comparison of the oscillatory mechanisms has been made. The questions addressed in this presentation are if the oscillatory mechanisms can be differentiated in experiments, and if they compete or support each other being implemented in one network. We considered two regulatory networks, for which oscillatory mechanisms are suggested to be distinct: the repressilator (Elowitz and Leibler, 2000) and the hysteresis-based relaxation oscillator (Kuznetsov et

al. 2004). We have combined these mechanisms in one regulatory network so that only two parameters control the transition from one mechanism to the other. These parameters are the strength of an additional regulatory connection and the timescale separation for one of the variables from the rest of the system. Our data supports a qualitative difference between the oscillatory mechanisms: the relaxation oscillator requires the separation of timescales as well as bistability in a subnetwork achieved via the additional connection, whereas the repressilator doesn't use bistability and requires all timescales to be similar. On the other hand, in the parameter space, we found a single oscillatory region that includes both relaxation oscillations and those by the repressilator mechanism as limiting cases, suggesting that the two oscillatory mechanisms support each other in our composite network. Distinctions found for the oscillators earlier were displayed in interaction with their copies encapsulated in cells across a population. We, therefore, examine interaction in a basic population: a pair of the composite oscillators. We found that oscillations by the repressilator mechanism die out in the population as the interaction (intercell signaling) is introduced, whereas relaxation oscillations persist and synchronize. Only for strong interaction, (synchronous) oscillations of repressilators are reestablished, and if in isolation all timescales were required to be similar, now a difference in timescales is necessary for oscillations. Therefore, in a systematic comparison, we have 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 (artificial cell differentiation) has been found to accompany the relaxation oscillation, but not the repressilator mechanism in the composite network. These properties may guide identification of oscillatory mechanisms in complex natural regulatory networks.

### **Mechanisms of firing frequency limitation in the coupled oscillator model of the midbrain dopaminergic neuron.**

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*In vitro*, midbrain dopaminergic (DA) neurons fire spontaneously at 1 to 4 Hz and will not exceed 10 Hz limit even when driven by somatic current injection. The SK-type calcium-dependent potassium current is known to contribute to this frequency limitation. However, even when the SK current is blocked, the frequency hardly exceeds 20 Hz in steady state and 30 Hz in transients, which is still very low compared to other types of neurons. Therefore, we focus our study on additional mechanisms of frequency limitation in the DA neuron.

We have adopted the model from Canavier and Landry (2006 J Neurophys. 96) with several changes to match experimental data and calibrated it to reproduce the above frequency limitation. This resulted in the spike-initiation Na<sup>+</sup> current and the repolarization complex to be chosen weak in comparison to other models, e.g. for fast spiking neurons. This weakness makes repetitive spiking fragile with respect to an

applied current and allows reproducing qualitatively the long duration of DA neuron spikes. A much longer range of applied currents where spiking persists under control conditions compared to apamin is due to counteraction of the applied current by the SK current, which follows elevation of the intracellular  $\text{Ca}^{2+}$  concentration. With current injection, the SK current lowers the transient and steady frequencies, acting throughout the whole interspike interval. By contrast, a  $\text{Ca}^{2+}$  and voltage-dependent BK potassium current implemented in our model affects the range of applied current where spiking persists rather than the spiking frequency. Thus, we predict that the BK current may counteract the applied current without lowering the frequency due to its primary contribution to spike repolarization. We have found that the transient frequency is highly dependent on the phase of oscillation at which the current is applied. In the model, the frequency limitation observed in experiments is achieved only if this initial  $\text{Ca}^{2+}$  concentration is high enough, and the frequency can be further decreased by the contribution of the A-type potassium current. Slow changes in the average A current as well as somatic and dendritic calcium concentrations are major sources of frequency adaptation in the model. We are testing our predictions in experiments.