Cellular and Sub-cellular Models of Excitable Cells

CNS'04 Workshop
Radisson Plaza Lord Hotel, Baltimore, MD
July 22nd 2004

Pete’s cool picture of some kinda calcium thing!

Organizers: Peter Roper, Brent Doiron, Arthur Sherman
**Schedule of Events**

9:00  Introduction and welcome

Session I: Whole cell models

9:10  John Byrne  
*Computational Models of Neuronal Excitability, Memory Induction and Circadian Rhythms*

10:00 Brent Doiron  
*Differential modulation of burst discharge via somatic and dendritic K⁺ channels*

10:25 20 min coffee break

10:45 Fernanda Saraga  
*Active dendrites and spike propagation in multi-compartment models of hippocampal interneurons*

11:10 Artie Sherman  
*Pulsatile Insulin Secretion - How and Why*

11:35 Lunch

Session II: Models of Calcium Release and Diffusion

1:00 Greg Smith  
*Stochastic Automata Network Models of Instantaneously-Coupled Intracellular Calcium Channels*

1:50 Yulia Timofeeva  
*Sparks and waves in a fire-diffuse-fire framework for calcium release*
2:15 Chris Fall

An intracellular Ca subsystem as a biologically plausible source of intrinsic bistability in a network model of working memory

2:40 Victor Matveev

Synaptic facilitation through saturation of Ca2+ buffers: a computational study

3:05 Coffee break

Session II: Neural Coding

3:25 Andre Longtin

Information transfer with excitable membranes

4:15 Frances Chance

Effects of Background Input on the Temporal Dynamics of Signal Transmission

4:40 Joel Tabak

Relaxation oscillator models for cell/network bursting with two types of negative feedback
Abstracts

Session I: Whole cell models

“Computational Models of Neuronal Excitability, Memory Induction and Circadian Rhythms”
John H. Byrne
Department of Neurobiology and Anatomy
University of Texas-Houston Medical School
Houston, Texas
John.H.Byrne@uth.tmc.edu
http://nba.uth.tmc.edu/resources/faculty/members/byrne.htm

We have developed differential equation-based models to obtain insights into three key neurobiological problems: The feedback interactions between endogenous electrical activity of bursting neurons and intracellular biochemical cascades; the role of temporal dynamics of biochemical cascades in determining the “threshold” for the induction of a long-term memory; and the role of positive and negative feedback loops among gene and protein networks that underly circadian rhythms.

"Differential modulation of burst discharge via somatic and dendritic K\(^+\) channels"
Brent Doiron, Liza Noonan, André Longtin, and Ray Turner
Physics Department
University of Ottawa, Ontario, Canada
bdoiron@science.uottawa.ca

The burst mechanism employed by pyramidal cells of weakly electric fish is well characterized and involves Na\(^+\) dependent dendritic backpropagation of action potentials. As with many burst mechanisms, pyramidal cell bursting is observed for only a range of input depolarizations and tonic firing or resting is observed for all others. We will show experimental and computational results that clearly show how the threshold for burst discharge is raised when somatic K\(^+\) channels are blocked. This is in direct contrast to a lowering of burst threshold when dendritic K\(^+\) channels are removed. This differential result is understood through the opposite effects that somatic and dendritic K\(^+\) channels have on the dendro-somatic return current that accompanies backpropagation. Computational results will show how modulation of burst discharge via dendritic or somatic K\(^+\) channels not only differentially effects dynamic behaviour but also the information processing that electrosensory pyramidal cells perform on broadband inputs.

"Active dendrites and spike propagation in multi-compartment models of hippocampal interneurons"
Fernanda Saraga  
Toronto Western Research Institute  
University Health Network  
University of Toronto  
fernanda.saraga@utoronto.ca

It is well known that interneurons are heterogeneous in their morphologies, biophysical properties, pharmacological sensitivities and electrophysiological responses, but it is unknown how best to understand this diversity. Given their critical roles in shaping brain output, it is important to try to understand the functionality of their computational characteristics. It has been shown that long-term potentiation is induced specifically on oriens-lacunosum/moleculare (O-LM) interneurons in hippocampus CA1 and that these same cells contain the highest density of dendritic sodium and potassium conductances measured to date. We speculate that the highly active dendrites of these interneurons endow them with a specialized function within the hippocampal circuitry by allowing them to regulate direct and indirect signal pathways within the hippocampus. I will discuss several models of O-LM interneurons, with focus on the types and distributions of ion channels along the somato-dendritic tree, spike initiation and propagation, frequency preferences and the role of the cell in the hippocampal network.

"Pulsatile Insulin Secretion - How and Why"
Arthur Sherman  
Laboratory of Biological Modelling  
NIDDK, NIH  
Bethesda, MD  
asherman@nih.gov  
http://mrb.niddk.nih.gov/

Insulin is secreted by the endocrine beta-cells of the pancreas. Unlike other endocrine or neuro-endocrine cells, secretion is regulated primarily by the rate of glucose metabolism rather than hormonal or neuronal input, though such inputs do exert a modulatory effect. We will focus on models for pulsatile secretion, which occurs on multiple time scales from seconds to minutes as organizational level ranges from cellular to organism. We will also discuss a hypothesis that the oscillations are dictated by the properties of the exocytotic machinery and/or the properties of the targets of insulin signaling.
"Stochastic Automata Network Models of Instantaneously-Coupled Intracellular Calcium Channels"
Gregory D. Smith
Department of Applied Science
College of William and Mary
greg@as.wm.edu
http://www.as.wm.edu/Faculty/Smith.html

Although there is consensus that Ca\textsuperscript{2+} puffs and sparks arise from the cooperative action of multiple intracellular Ca\textsuperscript{2+} channels, the precise relationship between single-channel kinetics and the collective phenomena of stochastic Ca\textsuperscript{2+} excitability is not well understood. Here we present a memory-efficient numerical method by which mathematical models for Ca\textsuperscript{2+} release sites can be derived from Markov models of single-channel gating that include Ca\textsuperscript{2+} activation, Ca\textsuperscript{2+} inactivation, or both. Such models are essentially stochastic automata networks (SANs) that involve a large number of so-called ‘functional transitions,’ that is, the transition probabilities of the infinitesimal generator matrix (or Q-matrix) of one automata (i.e, an individual channel) may depend on the local [Ca\textsuperscript{2+}] and thus the state of the other channels. Simulation and analysis of the SAN descriptors representing homogeneous clusters of intracellular Ca\textsuperscript{2+} channels show that: 1) release site density can modify both the steady-state open probability and stochastic excitability of Ca\textsuperscript{2+} release sites, 2) Ca\textsuperscript{2+}-inactivation is not a requirement for Ca\textsuperscript{2+} puffs, and 3) a single channel model with bell-shaped open probability curve does not lead to release site activity that is a biphasic function of release site density. These findings are obtained using iterative, memory-efficient methods (novel in this biophysical context and distinct from Monte Carlo simulation) that leverage the highly structured SAN descriptor to unambiguously calculate the steady-state probability of each release site configuration and puff statistics such as puff duration and inter-puff-interval. The validity of a mean-field approximation that neglects the spatial organization of Ca\textsuperscript{2+} release sites is also discussed.

"Sparks and waves in a fire-diffuse-fire framework for calcium release"
Yulia Timofeeva
Department of Mathematics
Heriot-Watt University
Edinburgh, Scotland
yulia@ma.hw.ac.uk
http://www.ma.hw.ac.uk/~yulia/

Calcium waves provide a highly versatile mechanism for intra- and inter-cellular signaling. Cellular calcium signals generally do not occur uniformly throughout a cell but are initiated at specific sites and spread in the form of saltatory waves. The fluorescent imaging of localized calcium release events has now made it clear that calcium release
dynamics is a stochastic process that occurs at spatially discrete sites.

We introduce a model of calcium release based upon a stochastic generalization of the Fire-Diffuse-Fire (FDF) threshold model. One of the main advantages of this model is that it is both biophysically realistic and computationally inexpensive. The stochastic nature of release events is incorporated via the introduction of a simple probabilistic rule for the release of calcium from internal stores.

Numerical simulations of the model (with stores arranged on both regular and disordered lattices) illustrate that stochastic calcium release leads to the spontaneous production of calcium sparks that may merge to form saltatory waves. Illustrations of spreading circular waves, spirals and more irregular waves are presented as well as generation of array enhanced coherence resonance whereby all calcium stores release periodically and simultaneously. Moreover, we establish, from extensive numerical experiments, that the model belongs to the Directed Percolation universality class.

"An intracellular Ca subsystem as a biologically plausible source of intrinsic bistability in a network model of working memory"
Christopher P. Fall
Center for Neural Science
New York University
fall@cns.nyu.edu

We explore a network model of working memory in an integro-differential form similar to those proposed by Amari. The model incorporates an intracellular Ca\(^{2+}\) subsystem whose dynamics depend upon the level of the second messenger [IP\(_3\)]. This Ca\(^{2+}\) subsystem endows individual units with intrinsic bistability for a range of [IP\(_3\)]. This full network sustains [IP\(_3\)]-dependent persistent ("bump") activity in response to a brief transient stimulus. The dynamics of network activation suggest that the time scales of second messenger activity relative to initiation of persistent firing deserves further exploration.

"Synaptic facilitation through saturation of Ca\(^{2+}\) buffers: a computational study."
Victor Matveev
Department of Mathematical Sciences
New Jersey Institute of Technology
Newark, NJ
matveev@oak.njit.edu
http://web.njit.edu/~matveev/

Synapses are known to exhibit complex stimulus response dynamics, changing their transmission efficiency in an activity-dependent manner on a variety of time scales, a feature termed synaptic plasticity. One ubiquitous form of short-term plasticity is
synaptic facilitation, elicited with just a few pulses, and decaying on time scales of 10s to 100s of ms. Although facilitation is known to depend on the presynaptic accumulation of Ca\(^{2+}\), its precise mechanisms are still under debate. It has been suggested that facilitation may result from the growth of stimulus-evoked Ca\(^{2+}\) transients, caused by the gradual depletion of the free concentration of endogenous Ca\(^{2+}\) buffers, which bind most of the Ca\(^{2+}\) charge that enters the cell with each pulse. Proposed theoretically by Klingauf and Neher (1997), such buffer saturation mechanism has been recently shown to play a role at certain calbindin-containing central synapses (Blatow et al., 2003). Using computational modeling, we systematically explored the conditions on endogenous buffering properties necessary to produce significant facilitation of Ca\(^{2+}\) transients (FCT). In particular, we will show that the buffer mobility is the crucial parameter for facilitation: interestingly, achieving significant FCT requires endogenous buffers to be either very mobile, or completely immobilized. Further, we find that the FCT magnitude depends non-monotonically on the total buffer concentration, consistent with the properties of the experimentally observed pseudo-facilitation phenomenon. Finally, we will compare our modeling results with the properties of facilitation recorded at the crayfish neuromuscular junction, which exhibits pronounced facilitation under physiological conditions.

Session III: Neural Coding

"Information transfer with excitable membranes"
André Longtin
Département de Physique
Université d'Ottawa, Ontario, Canada
alongtin@physics.uottawa.ca
http://www.science.uottawa.ca/~alongtin/default3.html

We consider the dependence of information transfer of neurons on the Type I vs Type II classification of their dynamics. Our computational study is based on Type I and II implementations of the Morris-Lecar model. It mainly concerns neurons, such as those in the auditory or electrosensory system, which encode band-limited amplitude modulations of a periodic carrier signal. We compare the encoding of band-limited random amplitude modulations for both dynamical types. The comparison relies on a calibration of both models that closely matches firing rates across a range of parameters. In the absence of synaptic noise, Type I performs slightly better than Type II, and its performance is optimal for perithreshold signals. However, Type II performs well over a slightly larger range of inputs, and this range lies mostly in the subthreshold region. Further, Type II performs marginally better than Type I when synaptic noise is present. These results are discussed in terms of the tuning and phase locking properties of the models with deterministic and stochastic inputs.
I will present results from a study of an integrate-and-fire neuron receiving a high level of balanced background synaptic activity. I characterize the temporal dynamics of this neuron’s response to a signal carried by the balanced background synaptic activity in comparison to the temporal dynamics of the neuron’s response to a signal carried by the mean input (an oscillating current). Previous work has demonstrated that changing the level of background activity produces multiplicative gain modulation (Doiron et al, 2001; Chance et al., 2002; Mitchell & Silver, 2003; Prescott & DeKoninck, 2003) and thus may represent a separate information channel. My results suggest that the temporal dynamics governing this gain modulation signal differ from those of neural responses to the mean input. When the synaptic input to a neuron increases suddenly, the neuronal firing rate first shows a transient response to the change in mean, followed by a reduced response due to the effects of gain modulation. Thus the mean and overall level of synaptic input not only may encode different information, but appear to be encoded at different times in the neuronal response.

Many individual neurons and excitatory neural networks exhibit rhythmic behavior consisting of active phases, AP, separated by silent phases, SP. These episodic patterns may underlie motor, secretory, epileptiform or developmental processes and therefore it is important to understand how AP and SP durations (which can be seconds or minutes) depend on system parameters. APs are initiated and sustained by positive feedback (neuron: inward current; network: recurrent excitatory coupling) and are turned off by one or more slow negative-feedback processes. These slow processes can be manifested in multiple forms, for example, as a more-or-less subtractive component (neuron: outward current; network: any cellular process that effectively increases spike threshold) or as a multiplicative factor that suppresses directly the positive feedback (neuron: inactivation of inward current; network: depression of excitatory synaptic input).

We have shown previously that mean field models using either type of AP-terminating mechanism alone react differently to changes in two control parameters (amount of positive feedback, level of tonic excitation). Here, we use these results as a basis to study the behavior of models incorporating both types of termination mechanisms. We show
that having two termination mechanisms increased the range of control parameters allowing rhythmicity. Moreover, the qualitative dependences of AP and SP duration on the control parameters do not depend on the relative time scales of the slow terminating processes. This implies that the rhythmic behavior is not simply controlled by the faster termination mechanism.

Finally, these results have implications on the experimental determination of exact biophysical mechanism(s) implied in a given rhythmic system.