

(Session C)

1:00 - 1:30 (C1) Information geometric analysis of neural spikes  
*Masami Tatsuno (University of Lethbridge), and Jean-Marc Fellous*

The brain processes information by exchanging action potentials between a large numbers of neurons. Analyzing these neural interactions is fundamental for understanding and interpreting electrophysiological data. Information geometry (IG), a mathematical method based on differential geometry, has been shown to provide useful insights into the statistical interactions within a population of neurons. We have demonstrated that IG measures can infer the connection weight between neurons from spike train data. This property is useful because it provides a new way to estimate learning-induced changes in synaptic strengths. However, previous studies have been limited to the case where external inputs to neurons are not correlated. Since neurons in the brain often receive common inputs, this hinders the application of IG to real data. To overcome this limitation, we investigated the IG measures under conditions of correlated inputs. First, we mathematically showed that the estimation of synaptic weight can be improved by taking into account higher-order log-linear models. Second, considering the typical number of connections in the brain ( $10^3$ - $10^4$  connections), we numerically showed that IG measures calculated with the fourth- or fifth-order log-linear models can estimate connection strengths within a 10% accuracy. These results suggest that the IG measure, with higher-order log-linear expansions, is a robust estimator of connection strengths, providing a useful analytical tool for real neural spikes.

NSF-CRCNS 1010172

Publications

Yimin Nie, Masami Tatsuno, Information-geometric measures for estimation of connection weight under correlated input (under review).

Yimin Nie, Karim Ali, Jean-Marc Fellous, Masami Tatsuno (2012) Analysis of neural network structure by information geometric measure, Conference Abstract: Society for Neuroscience 2012.

Yimin Nie, Masami Tatsuno (2012) Information geometric analysis for multi-neuronal spike data, Conference Abstract: Canadian Spring Conference on Behaviour and Brain 2012.

1:30 - 2:00 (C2) Correlated excitation and inhibition allows high-fidelity transmission of activity within the theta frequency band  
*John White (University of Utah, and Carmen Canavier)*

In active networks, excitatory and inhibitory synaptic inputs are often precisely balanced and correlated. Through mutual cancellation of excitation and inhibition, correlations in synaptic activity change the size of membrane voltage fluctuations and thereby can potentially modulate excitability. In recordings from entorhinal stellate cells, we explored the effects of input correlations on membrane voltage and spike timing in response to periodic "test" inputs. We found that correlated excitation and inhibition leads to amplification of responses to test inputs, especially in the behaviorally relevant theta (4-12 Hz) range. This effect is very general and depends mainly on the strength of correlation, the ratio of variance of excitation and inhibition, and the kinetics of the inputs. In the physiologically relevant regime, these factors combine to noise cancellation within the 4-12 Hz range, allowing probe inputs within this band to be communicated with high fidelity. The boosting of theta-frequency test inputs is particularly strong in stellate cells because of the effects of HCN channels. Our results show that phase locking to the theta rhythm can be modulated by statistical qualities of inputs that are known to depend on behavioral state, independent of pharmacological modulatory affects.

2:00 - 2:30 (C3) The impact of network structure on criticality in cortical circuits  
*John Beggs (Indiana University), Alan Litke, and Andrew Lumsdaine*

Nir Friedman, Shinya Ito, Braden Brinkman, Masanori Shimono, Lee DeVille, Karin Dahmen, Tom Butler, Andrew Lumsdaine, Alan Litke and John M. Beggs

The tasks of neural computation are remarkably diverse. To function optimally, neuronal networks have been hypothesized to operate near a nonequilibrium critical point. However, experimental evidence for critical dynamics has been based on demonstrations of power laws and therefore inconclusive (Beggs and Timme, 2012). Here, we show that the dynamics of cultured cortical networks are critical. We used a dense 512 electrode array to record spiking activity with millisecond precision from up to 340 neurons for up to 4 hours at a time. Using the framework of nonequilibrium phase transitions, we confirmed that the mean temporal profiles of avalanches of widely varying durations were quantitatively described by a single universal scaling function. We also show that the data had three additional features predicted by critical phenomena: approximate power law distributions of avalanche sizes and durations, samples in subcritical and supercritical phases, and scaling laws between anomalous exponents (Friedman et al., 2012).

To probe factors contributing to criticality in these networks, we extracted effective connectivity maps using transfer entropy (Ito et al., 2011). These maps allowed us to construct simulations with different network topologies. Interestingly, topologies from actual networks led to simulations that produced critical dynamics with exponents that matched those found in the data. In contrast, all-to-all connectivity, even when appropriately tuned, did not produce exponents that matched the data. This work indicates that network structure plays a powerful role in determining critical dynamics.

#### References

*Extending Transfer Entropy Improves Identification of Effective Connectivity in a Spiking Cortical Network Model.* Ito S, Hansen ME, Heiland R, Lumsdaine A, Litke AM, Beggs, JM (2011) PLoS ONE 6(11): e27431. doi:10.1371/journal.pone.0027431  
<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0027431>

*Universal critical dynamics in high resolution neuronal avalanche data.* Friedman, N., Ito, S., Brinkman, B., Shimono, M., DeVille, L., Dahmen, K., Beggs, J.M., and Butler, T. Physical Review Letters, in press, 2012.

*Being Critical of Criticality in the Brain.* Beggs, JM and Timme N. Frontiers in Fractal Physiology, in press, 2012.

2:30 - 3:00 (C4) Synchrony of pairs of neurons explained via PRC-derived maps and a noise-with-memory process  
*Robert Butera (Georgia Institute of Technology), and Carmen Canavier*

Synchrony within and between brain regions has been implicated in many aspects of cognition, movement, and disease. In order to explore general principles of synchronization between synaptically coupled neurons, we constructed hybrid circuits of one model and one biological neuron using the dynamic clamp. We identified several well-defined classes of dynamics of the coupled system, which correspond to the number and type of fixed-points of phase-relationship maps derived from the PRCs. Simulations derived from iterating such maps were only able to reproduce the activity observed in coupled experiments when the appropriate form of noise was introduced. This noise is a slow process with memory that modulates the intrinsic period of each neural oscillator. The resultant drift in intrinsic period of the biological neuron causes bifurcations in which fixed points emerged or disappeared, accounting for non-stationary experiments exhibiting transitions between phase locking and phase walkthrough. Experimental evidence for such noise will be presented.

3:30 - 4:00 (C5) Modeling calcium signaling in spines  
*Mary Kennedy (Caltech), Terrence Sejnowski, and Thomas Bartol*

Synaptic plasticity is mediated by calcium signaling in the postsynaptic spine. Particular firing patterns at a glutamatergic synapse can result in either long-term potentiation or long-term depression. The strength and direction of plasticity are controlled by the amplitude, duration and frequency of calcium inputs [Sjostrom and Nelson, 2002]. We have undertaken computational modeling of some of the elements in the spine that control the calcium influx, and elements that initiate biochemical signaling in the spine in response to calcium influx. Our goal is to gain intuition about how proteins within this complex signaling pathway are regulated and regulate each other in the tiny spine compartment. Several features of the spine signaling system are challenging for computational modelers: First, the small absolute numbers of molecules present in a dendritic spine makes reactions stochastic in nature and can exaggerate the effects of competition for binding among proteins that bind to common partners. Second, unlike the situation in a test tube, many enzymes and their activators are present in similar numbers in the cytosol and rapid changes in their interactions in response to transient stimuli occur under non-equilibrium conditions. Third, the specific geometry and spatial constraints within the dendritic spine affect diffusion and are believed to create distinct, dynamic signaling microdomains. Fourth, the large number of possible modifications of signaling proteins such as CaMKII increases combinatorial complexity and requires modeling strategies that are able to deal with large numbers of possible states. To manage these challenges, we are using the spatial stochastic simulator MCell 3 [Kerr et al., 2008]. MCell is an agent-based Monte-Carlo simulator that allows stochastic modeling in arbitrarily complex geometries. It is therefore ideally suited to model systems with small molecule numbers and spatial constraints. We have completed a realistic reconstruction of a portion of neuropil from hippocampal area CA1 and used MCell to model calcium transients within spines in the reconstruction [Keller et al., *submitted*]. We are presently combining this technology with kinetic models of calmodulin activation by calcium [Pepke et al., 2010] to explore the relationships among calcium influx, calmodulin activation and the regulation of calmodulin targets in the spine. We have adopted an “experimental” strategy in which we successively add individual components to the model to determine their predicted effects on the system as a whole. We will present results of several such experiments.

#### **References**

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- Kerr, R. A., Bartol, T. M., Kaminsky, B., Dittrich, M., Chang, J.-C. J., Baden, S. B., Sejnowski, T. J., and Stiles, J. R. (2008). Fast Monte Carlo simulation methods for biological reaction-diffusion systems in solution and on surfaces. *SIAM J Sci Comput* , 30(6):3126.
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- Pepke, S., Kinzer-Ursem, T., Mihalas, S., and Kennedy, M. B. (2010). A dynamic model of interactions of Ca<sup>2+</sup>, calmodulin, and catalytic subunits of Ca<sup>2+</sup>/calmodulin-dependent protein kinase II. *PLoS Comput Biol* , 6(2):e1000675.

4:00 - 4:30 (C6) Optical analysis of Calmodulin kinase signaling in single synapses  
*Ryohei Yasuda (Duke University Medical School), Sridhar Raghvachari,  
and John Lisman*

Long-term potentiation (LTP) of synaptic transmission at hippocampal synapses is an important mechanism for learning and memory. LTP is initiated by  $Ca^{2+}$  entry through NMDA receptors into dendritic spines, small (~0.1 femtoliters) post-synaptic compartments protruding from dendritic shafts. This leads to activation of  $Ca^{2+}$ /Calmodulin-dependent protein kinase II (CaMKII), the enzyme required for LTP and many forms of learning and memory. Recently we have developed a technique to image CaMKII activity in single spines during LTP based on a FRET sensor for CaMKII activity in combination with 2-photon fluorescence lifetime imaging microscopy (2pFLIM; Lee et al. 2009, Nature). By imaging CaMKII activity while inducing LTP in single spines using 2-photon glutamate uncaging, we demonstrated that CaMKII is activated in the stimulated spines and decays within ~1 minute. However, the limited temporal resolution of 2pFLIM (~10 seconds) did not permit us to gain detailed information about the kinetics of CaMKII activation. To better understand the mechanisms linking  $Ca^{2+}$  elevation (lasting ~0.1 s) and CaMKII activation, we have improved the temporal resolution of 2pFLIM to ~10 Hz, and found that, after a glutamate uncaging pulse, CaMKII is activated within ~0.1 s and decays with the time constant of ~5 s. When repeated uncaging (0.5 Hz, 1 min) was applied to induce LTP, CaMKII activity was accumulated in a stepwise manner after each uncaging pulse. The activity decays over ~5 s after the cessation of the uncaging train. Next, to determine the duration of CaMKII activation required for LTP, we developed a genetically encoded, light-inducible inhibitor of CaMKII activation. By combining this inhibitor with 2-photon glutamate uncaging, we succeeded in controlling the duration of CaMKII activation with the resolution of ~seconds. Using this technique, we found that activation of CaMKII for 1 min is sufficient for inducing LTP.

(NIDA 5R01DA027807)

4:30 - 5:00 (C7) Fast statistical methods for mapping synaptic connectivity on  
dendritic trees  
*Liam Paninski (Columbia University), and Rafa Yuste*

A detailed understanding of the organization of local neural circuits requires determining not just which neurons are connected, but also the location and strength of synaptic interactions in the dendritic tree. To achieve this goal, we can combine the ability to stimulate individual presynaptic neurons with simultaneous imaging of postsynaptic neurons at subcellular resolution. In this work we develop fast statistical methods to filter voltage measurements and determine the location and strength of synaptic dendritic connections. For this we use two types of data: 1) anatomical measurements of the postsynaptic neuron, 2) voltage measurements. Determining the synaptic weights becomes a convex optimization problem, which may be solved using sparse estimation methods from machine learning. A major computational challenge comes from the large number of compartments of typical dendritic arbors; we adapt fast approximate dendritic filtering methods to help solve this problem efficiently. We illustrate our results on simulated measurements in toy and real neurons, comparing the efficacy of a variety of different voltage sampling techniques. Joint work with A. Pakman and J. Huggins.

5:00 - 5:30 (C8) Nonlinear processing at retinal bipolar-ganglion cell synapses underlying temporal precision and adaptation to contrast  
*Daniel Butts (University of Maryland), Yanbin Wang, and Jonathan Demb*

Nonlinear processing in the retina has been implicated in a variety of response properties important for natural vision, including precise spike timing and contrast adaptation. Such processing arises through mechanisms of the underlying retinal circuitry, but a direct relationship between such mechanisms and more abstract functional descriptions of retinal ganglion cell (RGC) output is difficult to establish with traditional modeling approaches. Here, we present a series of nonlinear models applied to recordings of excitatory currents from several identified RGC classes in the *in vitro* mouse retina during temporal white noise stimulation of different contrasts. Standard linear-nonlinear (LN) characterizations of the currents could describe RGC responses at fixed contrasts, but these models could not generalize across contrast, and they also failed to capture transient responses in the currents. However, these transient responses could be predicted by nonlinear models structured around putative physiological mechanisms such as presynaptic inhibition and synaptic depression. Furthermore, these nonlinear models successfully predicted responses across contrast, outperforming LN models fit separately at each contrast. These results suggest a unified explanation for transient response components and contrast adaptation. Because of the resemblance to known physiological mechanisms, the nonlinear models suggest a series of experimentally testable predictions and may directly link the physiological mechanisms of retinal circuitry with visual processing.