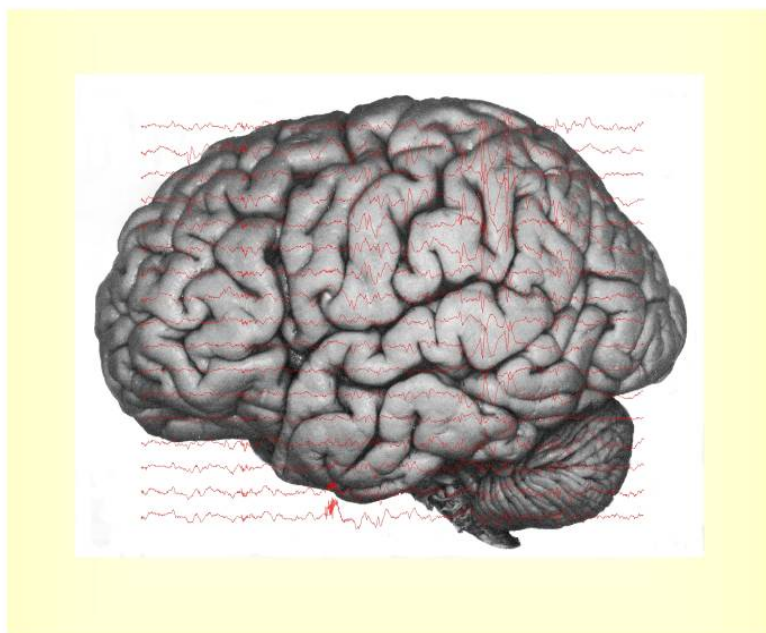


PROGRAM & ABSTRACTS

The 4th International Conference on Epilepsy Research Organized by CINNR and IDDRC



**Thursday May 19th - Saturday May 21th 2011
KCBD, 900 E. 57th Street, Chicago**

For Information: <http://iit.edu/~cinn/events.html>

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*No cost for attendees from UC, Argonne, or IIT;
for all others: \$125 or \$75 (students) for breakfast, lunch and dinner*

PROGRAM

4th International meeting on Epilepsy Research

Thursday May 19- Saturday 21 2011, in Chicago, IL, USA

KCBD, Lecture Hall 1103
900 E. 57th Street
Chicago, IL

Thursday May 19: TUTORIALS

1:00 – 1:25 PM		Registration
1:25 – 1:30 PM	Wim van Drongelen	Welcome
1:30 – 2:30 PM	Marc Benayoun	Modeling in Epilepsy Research
2:30 – 3:30 PM	<u>David Mogul</u>	Application of Engineering in Epilepsy Research
3:30 – 4:00 PM		Coffee/Tea Break
4:00 – 5:00 PM	Jason McLean	Imaging of Neuronal Networks
5:00 – 6:00 PM	Michael Kohrman	Neocortical Epilepsies
6:00 – 8:00 PM		Poster Session and Dinner

Friday May 20: MODELING & ENGINEERING

8:00 – 8:30 AM		Registration and Breakfast
8:30 – 9:30 AM	<u>Jack Cowan</u>	Mathematical Modeling in Epilepsy Research
9:30 – 10:30 AM	John Milton	Seizure Onset in the Noisy and Delayed Nervous System
10:30 – 11:00 AM		Coffee/Tea Break
11:00 – 12:00 AM	Theoden Netoff	Single Cell Properties and Network Behavior
12:00 – 2:00 PM		Poster Sessions and Lunch
2:00 – 3:00 PM	Leon D. Iasemidis	On the Brain Dynamics in Epilepsy: Seizure

Resetting, Prediction, Control and Focus
Localization in Humans and Animals

3:00 – 3:30 PM

Coffee/Tea Break

IMAGING

3:30 – 4:30 PM

Doug Coulter

Imaging of Networks

4:30 – 5:30 PM

Andrew Trevelyan

Using calcium imaging and immunohistochemistry to visualize which neuronal classes participate in epileptiform events

5:30 – 8:00 PM

Poster Session and Dinner

**Saturday May 21: CLINICAL AND FUNDAMENTAL ASPECTS OF
NEOCORTICAL EPILEPSY**

8:00 – 8:30 AM

Registration and Breakfast

8:30 – 9:30 AM

John Ebersole

Neocortical Epilepsy

9:30 – 10:30 AM

Joyce Y. Wu

Significance of High Frequency EEG Oscillations in Neocortical Epilepsy.

10:30 – 11:00 AM

Coffee/Tea Break

11:00 – 12:00 AM

Charles Marcuccilli

Fundamental Aspects of Neocortical Epilepsy

12:00 – 2:00 PM

Poster Sessions and Lunch

2:00 – 3:00 PM

Andrew Trevelyan

Circuit breakers in the brain, in mice and men

ABSTRACTS

Applications of Engineering in Epilepsy Research

David J. Mogul, Ph.D.

Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, IL 60616

Epilepsy is studied at many different scales. At the molecular and cellular levels, differentiation of function during development and diverse genetic coding yields differences in activity and behavior of ion channels and transporters, among other elements cellular traits, that are being examined for their roles in epilepsy. In some cases, mutations in encoding of excitatory ion channels, for example, may underlie some of the derangement in brain electrophysiology characteristic of epilepsy. At a larger scale, the alteration of intercellular communication that occurs even as part of synaptic plasticity during normal brain development may yield clues to altered excitability and the emergence of pathological activity. But epilepsy is ultimately a network phenomenon because more than a few cells or synapses are altered during seizure activity. It may occur as a result of a small group of brain cells that entrain a larger population of cells toward seizure activity or it may be that the very initiation or maintenance of seizures requires an intricate coordination of electrophysiological activity across whole structures within the brain or even across multiple structures. In fact, the very nature of these dynamics may be as unique as each case of epilepsy since brain architecture and cell connectivity is individual to each patient. Although there are many aspects of epilepsy research across many different scales of study that could benefit from the quantitative and biophysical approaches characteristic of engineering principles and technology, we believe that engineering analysis provides the greatest potential benefit to the improved understanding of how network properties evolve during the recurrent seizures characteristic of epilepsy. It is this viewpoint and scientific objective that my laboratory has been exploring for the last decade and half. Since the mid 1990's, we have been applying several different engineering-oriented approaches toward understanding how brain electrophysiology evolves during seizures. The primary motivation behind this research has been our efforts to find alternative treatments for drug-refractory epilepsy. Simple application of electrical perturbation to the brain to treat recurrent drug-resistant seizures has seen only modest successes that have been difficult to reproduce across different patients in part, we believe, to the different dynamics underlying seizures across a diverse patient base. We have been exploring techniques for mapping how electrophysiological dynamics evolves during seizures in both *in vitro* and *in vivo* animal models of epilepsy in order to better grasp how and where to more effectively disrupt the pathological activity that underlies epileptic seizures. We will present how both linear and nonlinear approaches to understanding and modifying brain dynamics yields insights into how network properties evolve during the lifecycle of a seizure.

Imaging of Neuronal Networks

Jason N MacLean

Department of Neurobiology, University of Chicago, Chicago, IL 60637, USA

Traditionally, the study of the brain has employed electrical and/or anatomical tools. The recent development of functional optical imaging technologies provides complementary methods for the neuroscientist to watch both the inner workings of neurons and brain areas. Functional calcium imaging couples an exogenous fluorescence signal with physiological events: changes of intracellular free calcium concentrations are reported by changes in the fluorescent signal of the dye. This talk focuses on how neuroscientists can use calcium imaging for the study of neuronal networks. Neurons express many classes of voltage gated calcium channels, linking the domain of membrane electrophysiology to the intracellular world of calcium dynamics. In this way it is possible to use calcium indicators to monitor action potential-related activity in populations of neurons, because the depolarization which accompanies an action potential results in a calcium influx. Calcium imaging has been critical to the characterization and quantification of spatio-temporal patterns of action potential activity in networks of neurons with single cell resolution. Unlike other methods calcium imaging allows the researcher to densely sample the population of neurons within the imaged field of view. As a result because neurons are highly interconnected this approach allows the neuroscientist to image the flow of activity from one neuron to another in the network. Using calcium imaging of neuronal populations it is possible to resolve precise patterns of activity within networks are highly stereotyped. It has long been postulated that patterns of activity are the substrate for informational representation in the brain and this data is consistent with this hypothesis.

Frontal lobe epilepsy clinical and surgical considerations as an example of issues related to neocortical epilepsy treatment.

Michael Kohrman

Department of Pediatrics, The University of Chicago

Frontal lobe epilepsy represents approximately 20% of partial complex epilepsy. The anatomic and functional roles of the frontal lobe represent unique challenges for the localization, diagnosis, and treatment of frontal lobe seizures. This talk will review etiology, the functional anatomy, of the frontal lobe and implication for seizure localization and current methods for localization of frontal lobe epileptic foci. Both medical and surgical treatment of frontal lobe epilepsy will be reviewed. An illustrative surgical case will be presented. The issues related to diagnosis and treatment of frontal lobe seizures serve as a basis for discussion of the neocortical epilepsies in general.

Mathematical modeling in epilepsy research

Jack Cowan

**Mathematics Department
University of Chicago**

In recent years many models of large-scale brain activity have started from a mathematical model introduced in the early 1970's by Wilson and myself, now known as the Wilson-Cowan equations. But these are mean-field equations, i.e., they ignore the effects of intrinsic fluctuations and correlations in such activity. However I have recently found a way to describe large-scale neural activity in terms of non-equilibrium statistical mechanics. This allows the calculation of such effects. Here I show how the population dynamics of interacting excitatory and inhibitory neural populations can be described in such terms, and how such a theory can be used to explain the origins and properties of random bursts of synchronous activity (*avalanches*), and of population oscillations (*quasicycles*), and discuss how such phenomena may be related to neocortical seizures.

Synchrony in seizures and seizure prevention

Theoden Netoff, Ph.D.

Dept. of Biomedical Engineering, University of Minnesota.

Grand-mal seizures are characterized by changes in synchrony starting with a rise in synchrony, then drop in seizure during tonic phase and rise again during the clonic phase. To understand how and why networks of neurons synchronize, we study the phase response curves of neurons, a measure of how a neuron changes its firing time when receiving an input. Phase response curves can determine how networks of neurons synchronize. We demonstrate in models that the phase response curves measured from neurons at high firing rates prevent the neurons from synchronizing while promoting synchrony when they slow in firing, as shown in Figure 1. This may explain the phase transition from the tonic to clonic behavior. Neuronal response to deep brain stimulation may induce chaotic activity, preventing synchronization, as shown in Figure 2. This desynchronizing effect of DBS may be the mechanism by which they reduce or even prevent seizures.

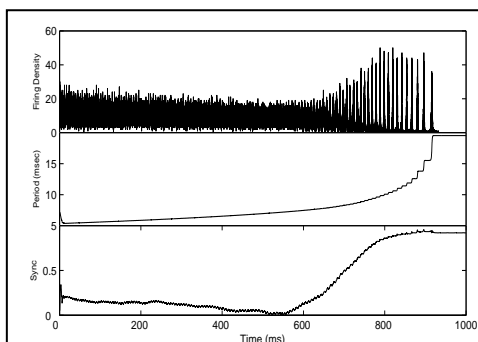


Figure 1 Synchrony in large scale networks. Network simulation of 3000 Morris-Lecar model neurons using second order network topology. Current applied to neurons starts at 8nA and decreases to -4 nA over the duration of the simulation. Top, firing density, the number of neurons firing in 1 msec window. Middle, ISI of average neuron in network. Bottom, the Kuramoto order parameter measuring network synchrony.

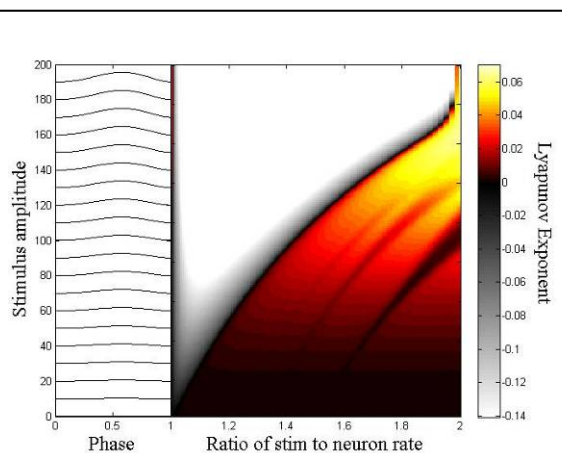


Figure 2. DBS induced phase response curves measured from model neurons. At certain stimulus amplitudes and frequencies the neuron's response are chaotic, as indicated by positive Lyapunov Exponents.

**On Brain Dynamics in Epilepsy: Seizure Resetting, Prediction Control and Focus
Localization in Humans and Animals**

Prof. Leon D. Iasemidis Ph.D.

**Harrington Department of Bioengineering, Electrical Engineering
School of Biological and Health Systems Engineering
Arizona State University, Tempe, AZ 85287-9709
Department of Neurology
Mayo Clinic Arizona, Phoenix, AZ 85054**

In our quest to understand epileptogenesis and ictogenesis, and design effective neuromodulation interventions, we have developed advanced signal processing techniques, like spatio-temporal stability (short-term maximum Lyapunov exponents - STLmax) and directional information flow (Spatial Average Net Transfer Entropy – SANTE) profiles, to quantify the human and animal brain's intermittent transitions into and out of epileptic seizures and localize the epileptogenic focus from interictal periods respectively (Iasemidis 2003; Iasemidis et al. 2009; Sabesan et al. 2009; Good et al. 2010). These investigations have led us to postulate and pursue three novel hypotheses. A process we have called dynamical entrainment characterizes the convergence of profiles of EEG dynamics of critical brain sites with the ones of the epileptogenic zone progressively over time and long before the occurrence of seizures, and has constituted the basis for the development of *seizure prediction* algorithms. We currently are in the third generation of such algorithms, they are time-reference free, model-free and work real-time and prospectively, with prediction time of 70 minutes before a seizure onset, sensitivity above 80%, and on the average 1 false prediction every 10 hours in humans. Resetting of the dynamics (disentrainment) of critical brain sites follows the seizures. This observation has led us to postulate the brain resetting hypothesis by seizures, may explain why seizures occur when they do, and has provided some very important insights into schemes for *seizure control*. Experimentation with mathematical models of coupled nonlinear and chaotic oscillators, as well as biologically plausible neural population models, provided us with clues for the development of a scheme of seizure control we have called feedback decoupling control (Good et al. 2009; Chakravarthy et al. 2009). The supporting evidence for the above hypotheses, derived from experiments with mathematical models, animal models and in patients with epilepsy, will be presented. Implications of these results for epilepsy therapy via neuromodulation and DBS will be discussed.

1. Iasemidis LD, Epileptic seizure prediction and control, *IEEE Transactions on Biomedical Engineering*, 50: 549-558, 2003.
2. Iasemidis LD, Sabesan S, Good LB, Chakravarthy N, Treiman DM, J. Sirven J and Tsakalis K, A new look into epilepsy as a dynamical disorder: seizure prediction, resetting and control, *Encyclopedia of Basic Epilepsy Research*, Ed. Philip Schwartzkroin, Elsevier, 3: 1295-1302, 2009.

3. Sabesan S, Good LB, Tsakalis K, Spanias A, Treiman DM and Iasemidis LD, Information flow and application to epileptogenic focus localization from EEG, *IEEE Trans. Neural Systems Rehab Engineering*, 17: 244-253, 2009.
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5. Good LB, Sabesan S, Marsh ST, Tsakalis K, Treiman DM and Iasemidis LD, Control of synchronization of brain dynamics leads to control of epileptic seizures in rodents, *Int. J. Neural Systems*, 19: 173-196, 2009.
6. Chakravarthy N, Tsakalis K, Sabesan S and Iasemidis LD, Homeostasis of brain dynamics in epilepsy: a feedback control systems perspective of seizures, *Annals of Biomedical Engineering*, vol. 37, pp. 565-585, 2009.

Using calcium imaging and immunohistochemistry to visualize which neuronal classes participate in epileptiform events

Andrew Trevelyan^{1,2}, and Claudia Racca²

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- 2. Institute of Neuroscience, Newcastle University, Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK.**

Calcium imaging can be a remarkably powerful tool for following neuronal activity. Every time a neuron fires action potentials, Ca^{2+} floods into the cell, not just at the presynaptic terminal but also into dendrites, and most usefully for network imaging, at the soma. If one loads up brain tissue with a Ca^{2+} dye one can visualize the individual somata, and when these cells fire, they literally flash. One can thereby follow the activity of hundreds of neurons simultaneously with single cell resolution, and a temporal resolution of just tens of milliseconds. The usefulness of such a technique for epilepsy research is self evident. I will discuss the uses and limitations of this technique and exemplify these with movies of epileptiform activity.

A further benefit of Ca^{2+} imaging has been that it has put glial cells back in the centre stage. It is a much quoted fact that glia outnumber neurons in the brain, and for epileptologists, their importance is well recognized clinically because glial tumours commonly present with seizures. The electrical silence of glial cells, though, meant that their true dynamic activity went largely unrecognized until Ca^{2+} dyes became readily available. But these dyes have shown that far from being inactive, glial cells show continual surges of intracellular Ca^{2+} , frequently either following or even preceding neuronal discharges. I will show examples of such activity, and also discuss data from other laboratories showing how glial activity may be involved at different stages of epileptiform discharges (Tian *et al.*, 2005; Gomez-Gonzalo *et al.*, 2010).

In this talk, I will show how one can visualize the recruitment of broad swathes of neurons to epileptiform discharges in mouse brain slices. These experiments clearly show a remarkable feature of epileptic propagation which is that rather than sweeping across the network, the wavefront only progresses episodically, recruiting spatially clustered groups of neurons at particular moments, which I refer to as times of “network crisis” (Trevelyan *et al.*, 2006; Trevelyan *et al.*, 2007). Some neurons though appear to be recruited to the ictal events disproportionately early, and an important goal of my recent research has been to identify these cells, and understand what their role is in the spread of epileptiform discharge. To identify these cells, we developed a new technique for matching up the live imaging of network activity with a post hoc analysis of immunohistochemical markers in the fixed tissue.

Until recently, the main technique we had available to us for characterizing cells in Ca^{2+} network imaging, was to identify cells which are doing something interesting or unusual in a brain slice, and then target these for patch clamping. Undoubtedly this technique is very powerful, and can yield a great wealth of information about the individual cells, and this has

been used to great effect by a number of authors (Cossart *et al.*, 2003; MacLean *et al.*, 2005; Bonifazi *et al.*, 2009). The difficulties though are that the imaging analyses must be simple enough that they can be done within the lifetime of the brain slice, and even then, one can generally only patch a very small number (often only one or two) of cells. In a slice in which one can visualize several hundred neurons, this represents a small return. I will show though that by creating a set of “landmarks” in the brain slice, that can be identified both in the living and fixed tissue, one can derive a mapping rule which overlays the immunohistochemical stains onto the live Ca²⁺ imaging with great precision. In this way, one can ascribe up to four immunohistochemical markers to cells identified in the live Ca²⁺ imaging in a single brain slice. We are using this technique to characterize several different, commonly used, in vitro models of epileptiform discharge.

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Gomez-Gonzalo, M., Losi, G., Chiavegato, A., Zonta, M., Cammarota, M., Brondi, M., Vetri, F., Uva, L., Pozzan, T., de Curtis, M., Ratto, G.M. & Carmignoto, G. (2010) An excitatory loop with astrocytes contributes to drive neurons to seizure threshold. *PLoS Biol*, **8**, e1000352.

MacLean, J.N., Watson, B.O., Aaron, G.B. & Yuste, R. (2005) Internal dynamics determine the cortical response to thalamic stimulation. *Neuron*, **48**, 811-823.

Tian, G.F., Azmi, H., Takano, T., Xu, Q., Peng, W., Lin, J., Oberheim, N., Lou, N., Wang, X., Zielke, H.R., Kang, J. & Nedergaard, M. (2005) An astrocytic basis of epilepsy. *Nat Med*, **11**, 973-981.

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Neocortical Epilepsy: pathophysiology and characterization

John S. Ebersole, MD Department of Neurology, The University of Chicago

In the recent past, neocortical epilepsy was thought to be uncommon among causes of focal seizures, as compared to mesial temporal lobe epilepsy, for example. It has become apparent in the last decade that this is indeed not the case. Non-lesional, non-mesial temporal and neocortical epilepsy now predominates in admissions to adult epilepsy centers. Neocortical epilepsies tend to have etiologies, such as encephalitis or occult dysplasias, that result in more diffuse cortical damage and/or dysfunction without obvious brain structural correlates. This factor plays an important role in diagnosis, localization, and prognosis. Functional, rather than structural, localization of epileptogenic foci becomes key. EEG and MEG source modeling have become essential techniques in non-invasive, pre-surgical characterization of these spike/seizure origins. However, even after identifying the seizure onset zone with intracranial electrodes and removing this area surgically, seizures commonly recur after a latent period of 9-18 months. This is probably related to the more widespread nature of the disease and a pathological cortical plasticity that allows previous “follower” regions to become seizure “pacemaker” zones. How to identify and treat impending seizure recurrence in neocortical epilepsy is a major goal of future research.

Neocortical Oscillations – Intrinsically Simple or Synaptically Complex

Charles J. Marcuccilli, PhD, MD

Medical College of Wisconsin

Abstract: Neuronal oscillatory behavior underlies several important physiological functions, including respiration, cognition, olfaction and slow wave sleep. These continuously present oscillations occur at frequencies ranging from 0.5 Hz to 600 Hz, are embedded with temporal information at different time scales, and are necessary to support these critical functions (Buzsáki 2006). Current evidence also suggests that neocortical and/or hippocampal oscillations, underlie the pathological electrical activity during epileptic seizures (Allen et al., 1992; Worrell et al., 2004, 2008; Blanco et al., 2010). In addition, other data suggests that interictal regional slowing in the delta frequency range (2-4 Hz) may serve as an EEG marker of epileptic networks in patients with temporal lobe epilepsy (Tao *et al.*, 2011). Unfortunately, it is not yet known how these oscillatory states are generated, yet they critically underlie physiological (e.g. sleep) and pathological activity (e.g. seizures). Furthermore, it is not clear if the same or different mechanisms underlie the generation of oscillations at the same (or different) frequencies in one brain area versus another; yet, recent evidence suggests that neuronal bursting properties can differ between focal and parafocal regions (Marcuccilli et al., 2010). Intrinsic neural membrane properties and synaptic mechanisms have been proposed to underlie neocortical rhythms, and it is likely that both mechanisms generate oscillatory behavior. While synchronized oscillations of the neocortex have been proposed to be initiated by layer V intrinsic bursting (IB) neurons in several mammalian species, we demonstrate for the first time the existence of rhythmic IB (rIB) neurons in the human neocortex. Human rIB neurons intrinsically generate neuronal oscillations in the low delta frequency range (0.1 – 4 Hz) in *in vitro*. Further, the human IB neurons retain rhythmic bursting following blockade of chemical synaptic transmission; and, their repetitive intrinsic bursting activity depends on the persistent sodium current (I_{NaP}). These data lend further support to the hypothesis that the I_{NaP} plays an important role in neocortical cellular intrinsic bursting activity, the latter of which has been proposed to significantly contribute to network oscillatory behavior and epileptic discharges. We suggest that intrinsic and synaptic mechanisms underlie neocortical oscillations in a frequency dependent fashion.

Circuit breakers in the brains of mice and men

Andrew Trevelyan, Catherine Schevon

- 1. Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, NE2 4HH, UK**
- 2. Dept of Neurology, Columbia University, New York, NY, USA**

My earlier talk concerned some of the imaging techniques which have enlightened our view of cortical epileptic activity. In this talk, I will examine what these studies have told us about how cortical circuits respond to “network crises”, which I define as surges of neuronal activity which may spread to adjacent cortical territories in an escalating pattern of activation. I will argue that the particular arrangement of inhibitory and excitatory synaptic inputs onto pyramidal cells allow a vetoing inhibition of these cells, and this provides a safety valve, rather like a circuit breaker in an electrical appliance protects against surges of electricity.

The critical observation is described in (Trevelyan et al., 2006). This study utilized the 0 Mg^{2+} model of epilepsy to induce repeated network crises. Removing Mg^{2+} ions from the bathing medium dramatically enhances excitation by removing the voltage dependent blockade of NMDA receptors. Importantly though, inhibition is preserved in this model (at least initially), and surges of excitatory barrages are matched by high frequency interneuronal discharges. The excitatory synaptic barrages may be huge at these times, greatly exceeding anything that would normally occur during normal physiological activation, but despite this bombardment, the pyramidal cells can be kept quiescent by the high frequency inhibitory currents. Their excitation is thus “vetoed” by this inhibition.

I will discuss the source of this powerful vetoing inhibition, and in what ways it may influence cortical function. A further line of studies seeks to understand the electrographic “signature” of this restraint. This is important because it allows us to make comparisons between these recordings in mouse brain slices with recordings from human patients. Particularly useful in this regard has been data recorded from micro-electrode arrays implanted within the clinically defined seizure onset zone (Schevon et al., 2009). I will show how these recordings may inform how we interpret the more conventional and widely used, ECoG and EEG recordings. I will contrast our recordings with those presented in another recently published study of the human epileptic brain (Truccolo et al., 2011).

Finally, I shall discuss how the high frequency inhibitory barrage may influence the local field potential. Great significance has been attached to the association of pathological epileptogenic foci with high frequency oscillations in local field recordings (Bragin et al., 2002). It is notable that the restraining inhibitory veto is associated with very high frequency

oscillations. I will discuss various ways in which these high frequency inhibitory postsynaptic currents can give rise to these oscillations, both directly (Trevelyan, 2009) and indirectly.

Bragin A, Mody I, Wilson CL, Engel J, Jr. Local generation of fast ripples in epileptic brain. *J Neurosci* 22: 2012-2021, 2002.

Schevon CA, Trevelyan AJ, Schroeder CE, Goodman RR, McKhann G, Jr., Emerson RG. Spatial characterization of interictal high frequency oscillations in epileptic neocortex. *Brain* 132: 3047-3059, 2009.

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Trevelyan AJ, Sussillo D, Watson BO, Yuste R. Modular propagation of epileptiform activity: evidence for an inhibitory veto in neocortex. *J Neurosci* 26: 12447-12455, 2006.

Truccolo W, Donoghue JA, Hochberg LR, Eskandar EN, Madsen JR, Anderson WS, Brown EN, Halgren E, Cash SS. Single-neuron dynamics in human focal epilepsy. *Nat Neurosci*, 2011.

POSTERS

Interictal regional delta slowing is an EEG marker of epileptic network of temporal neocortex

James X. Tao, Maria Baldwin, Iris Yung, Sandra Rose, David Frim, Susan Hawes-Ebersole and John S. Ebersole

Departments of Neurology and Neurosurgery, The University of Chicago, Chicago, IL 60637

Summary

Purpose: Several studies have suggested that interictal regional delta slowing (IRDS) carries a lateralizing and localizing value similar to interictal spikes and is associated with favorable surgical outcomes in patients with temporal lobe epilepsy (TLE). However, whether IRDS reflects structural dysfunction or underlying epileptic activity remains controversial. The objective of this study is to determine the cortical EEG correlates of scalp-recorded IRDS, in so doing, to further understand its clinical and biological significances.

Methods: We examined the cortical EEG substrates of IRDS (ECoG-IRDS) and delineated the spatio-temporal relationship between ECoG-IRDS and both interictal and ictal discharges by recording simultaneously scalp and intracranial EEG in 18 presurgical candidates with temporal lobe epilepsy.

Results: Our results demonstrated that ECoG-IRDS is typically a mixture of delta/theta slowing and spike-wave potentials. ECoG-IRDS was predominantly recorded from basal and antero-lateral temporal cortex, occasionally in mesial, posterior temporal and extratemporal regions. Abundant IRDS was most commonly observed in patients with neocortical temporal lobe epilepsy (NLTE), whereas infrequent to moderate IRDS was usually observed in patients with mesial temporal lobe epilepsy (MTLE). The anatomic distribution of ECoG-IRDS was highly correlated with the irritative and seizure onset zones in 10 patients with (NTLE). However, it was poorly correlated with the irritative and seizure onset zones in the 8 patients with (MTLE).

Conclusions: These findings demonstrate that IRDS is an EEG marker of epileptic network in patients with TLE. While IRDS and interictal/ictal discharges likely arise from the same neocortical generator in patients with NTLE, IRDS in patients with MTLE may reflect a network disease that involves temporal neocortex.

Scalp spike frequency as an EEG marker of epileptogenesis in temporal neocortex in patients with MTLE

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Rationale: Scalp spike frequency is a strong predictor of surgical outcome in patients with mesial temporal lobe epilepsy (MTLE)¹. Since mesial temporal ECoG spikes are typically not recordable on scalp EEG, scalp spike frequency may reflect seizure progression from mesial to lateral temporal cortex. The objective of our study is to determine the value of scalp spike frequency as a potential EEG marker of epileptogenesis in temporal neocortex in patients MTLE.

Methods: We recorded simultaneously scalp and intracranial EEG spikes using 26 channels of scalp EEG with sub-temporal supplementary electrodes and 46 to 98 channels of intracranial EEG in 5 patients with medically-intractable temporal lobe epilepsy. Subdural electrodes were implanted extensively on the anterior through mid-temporal lobe². The scalp and intracranial interictal spikes were analyzed for their location and frequency during the first-hour sleep on the 1st day of intracranial study. The intracranial EEG correlates of scalp EEG spikes were then determined.

Results: Mesial temporal seizure onset was recorded in all the 5 patients. A total of 462 ECoG interictal spikes were identified in mesiobasal temporal cortex, and none of these ECoG spikes were recordable on scalp EEG. A total of 1639 ECoG spikes were identified in the lateral temporal neocortex with or without mesiobasal spiking source and only 117 of these ECoG spikes (8%) were recordable on scalp EEG. The percentage of ECoG spikes recordable on scalp EEG is dependent upon their cortical source area and synchrony³, and is significantly variable among the 5 patients.

Conclusions: Mesial temporal ECoG spikes need recruiting sufficient basolateral temporal cortex in order to be recordable on the scalp EEG. Scalp interictal spike mainly correlates with the spiking source in temporal neocortex. Therefore scalp spike frequency is a useful EEG marker reflecting epileptogenesis in temporal neocortex.

Reference:

- 1 Krendl R, Lurger S, Baumgartner C. (2008) Absolute spike frequency predicts surgical outcome in TLE with unilateral hippocampal atrophy. *Neurology*. 71(6):413-418.
2. Tao JX, Hawes-Ebersole S, Baldwin M, Shah S, Erickson RK, Ebersole JS. (2009) The accuracy and reliability of 3D CT/MRI co-registration in planning epilepsy surgery. *Clin Neurophysiol*. 120(4):748-753.
3. Tao JX, Ray A, Hawes-Ebersole S, Ebersole JS. (2005) Intracranial EEG substrates of scalp EEG interictal spikes. *Epilepsia*. 46(5):669-676

Neocortical Circuits Lead the Transition from Hyperexcitability to Epileptiform Activity in the Thalamo-Cortical System

Florian B. Neubauer and Jason N. MacLean, Department of Neurobiology, University of Chicago

There is a long standing debate about the relative role of neocortex and thalamus during the onset and maintenance of generalized epileptic seizures. While thalamic nuclei have been found to facilitate seizure activity across neocortex (Buzsaki 1991, Castro-Alamancos 1999), there is also evidence that intracortical changes alone can trigger the pathophysiological state switch towards thalamo-cortical hypersynchrony (Meeren et al 2002). This uncertainty partly arises from a methodological sampling problem. Single cell recordings, local field potentials and EEG measures fail to capture the inter-areal interplay of populations of neurons at seizure onset with sufficient detail.

Here we use the zero-magnesium model of epilepsy to evaluate the relative role and timing of thalamus and neocortex in generalized seizure activity. By imaging up to 1000 neurons simultaneously with single cell resolution using a multiphoton approach, in combination with dual, inter-areal patch-clamp recordings in acute mouse brain slices (P13-14), which preserve reciprocal connectivity between thalamus and cortex, we measure the initial localization and subsequent spread of epileptiform synchrony within and between areas. In addition we evaluate whether the interplay between both areas reinforces the aberrant activity.

Our data indicate that cortex always develops hypersynchrony first and subsequently recruits thalamus into joint oscillatory activity, whereas thalamus never drives cortex. The transition from unilateral activity in cortex to cortico-thalamic co-activity coincides with a significant increase in pairwise correlations between cortical cells, suggesting that a functional state transition within neocortex is the key for reliable thalamic recruitment.

This detailed quantification of epileptiform activity is ideal to inform theoretical models of generalized epilepsy by providing measures such as the fraction of activated neurons in cortical and thalamic populations, the time course of their activity onset, and pairwise intercellular cross-correlations. Elucidation of the precise role and contribution of neocortex and thalamic nuclei with these detailed metrics will be of great utility in the understanding and development of therapeutic approaches to generalized epileptic seizures.

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Skuld: Simulation Visualization Software

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Simulations of large neural networks can provide new insights in the workings of our brain and related disorders. But next to the modeling aspect within these projects, in which decisions have to be made regarding the structure of the network and values for the parameters, the computational part has to be considered carefully as well, especially if the network size is too large to fit on a single desktop computer. But once these problems are overcome and desired networks can be evaluated without trouble, all data have to be analyzed in order to be useful for the research. This gives rise to a whole different problem: how should one interpret all the obtained results from these large networks?

As some simulations easily generate hundreds of megabytes of data, eyeballing is no more a feasible option. A very common way is to analyze the 'bulk statistics' of the network, e.g. mean membrane potential or a (simulated) microelectrode. However these quantities might be too bulky to reveal properties of cells and microcircuits within the large network and thereby negating the effects of causality. It could be the case that some behavioral changes of the network are caused by a small number of neurons only; too small to pop up in the bulk statistics of the network. For that reason, a convenient way has to be found that allows analysis of the causality within the network. Hence one should be able to see how the input from certain cells relates to their output and how other neurons are affected by this output.

The Skuld program allows users to analyze simulations of large neural networks both on the level of individual neurons and their communications to other neurons as well as their relation with the higher-level statistics. The user interface shows the physical position of all cells within the network, together with detailed information of the connections from and to other cells. Furthermore, time series of the membrane potentials can be plotted and raster plots can be made to analyze the behavior of a cell with respect to other cells.

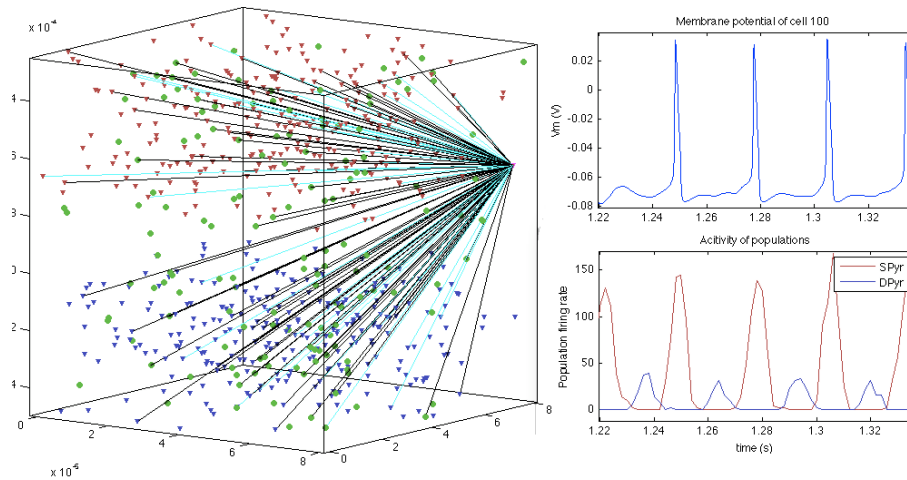


Fig 1. An overview of some of the diagrams produced by Skuld. Clockwise, starting from left: three-dimensional representation of a neocortical neuron showing all connections related to a single cell; the membrane potential of the selected neuron; instantaneous firing rate for neurons of a specific type.

Analysis of steady states, bifurcations and periodic solutions to study epileptiform activity in a lumped model of neocortex.

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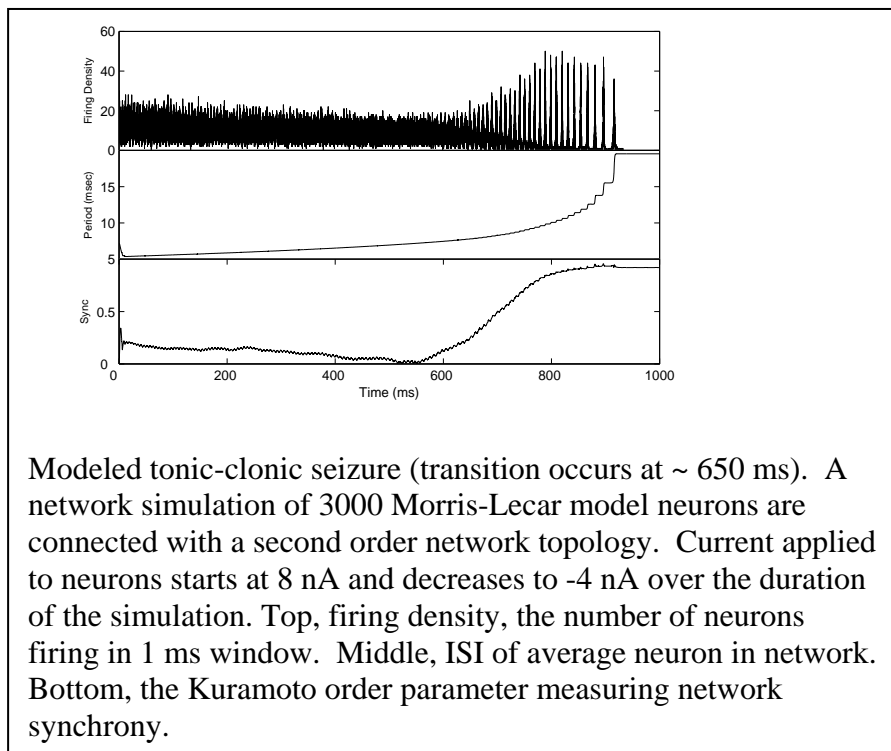
A lumped model of neuronal activity in the neocortex is presented to study the onset of synchronized epileptiform activity. The model consists of two non-linear delay differential equations with two fixed delays. The model's bifurcations of the steady states are studied analytically and the periodic solutions starting at some of these bifurcations are analyzed numerically. Large collections of bifurcations, periodic solutions and multi-stability are identified. The results of the two-parameter bifurcation analysis are shown to correspond with the observed behavior of a detailed model of neocortex under similar conditions.

Dynamical changes in neurons during seizures determines tonic to clonic shift**Bryce Beverlin II¹, James Kakalios¹, Duane Nykamp², Theoden Ivan Netoff³**

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Abstract

The tonic-clonic seizure transition mechanism, a specific manifestation of seizure dynamics, remains poorly understood. We propose a cellular dynamical shift mechanism leading to a change in neuronal firing rate and apply phase-resetting curves (PRC) from a Morris-Lecar model neuron to explain the transition phenomenon. PRCs are measured from the conductance based model cell within a range of input currents. A large network of excitatory neurons is simulated with a biologically relevant network topology. During the tonic phase marked by a high firing rate, a high current input PRC is used to describe the post-synaptic response to synaptic input. The PRC is gradually changed to a low current input PRC over the simulation duration. The population synchrony of the cells is measured with the Kuramoto order parameter, which reveals a transition from tonic to clonic phase exhibited by the model network. The cellular dynamical change is a possible mechanism for this particular seizure transition and reproduces the population behavior closely when compared to EEG data.



Evolution of Synchrony across Brain Structures during Limbic Epilepsy.

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Neuronal populations in the brain achieve levels of synchronous electrophysiological activity as a consequence of both normal brain functions as well as during pathological states such as in epileptic seizures. Understanding the nature of this synchrony and the dynamics of neuronal oscillators in the brain is a critical component towards decoding such complex behaviors. We have sought to achieve a more in-depth understanding of the dynamics underlying the evolution of seizures in limbic epilepsy by analyzing recordings of local field potentials from three subcortical nuclei that are part of the circuit of Papez in a kainic acid rat model of temporal lobe epilepsy using the empirical mode decomposition technique. The empirical mode decomposition allows for an adaptive and non-linear decomposition of the local field potentials into a series of finite oscillatory components. We calculated the frequencies, power, and measures of phase synchrony of these oscillatory components as seizures evolve in the brain and discovered patterns of phase synchrony that varies between the different stages of the seizures.

Two Types of ECoG Activity Induced by Verbal Memory Tasks

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Introduction: The use of chronic ECoG recordings from epilepsy patients undergoing neurosurgical work-ups provides an opportunity to examine the rich spectrum of electrophysiologic phenomena distributed across the cortex. We describe here our investigations of the neurophysiologic correlates of verbal tasks, focusing on event-induced cortical gamma oscillations (70-250 Hz) and inter-electrode lateral coherence (4-8 Hz).

Subjects: Twelve normal control subjects and 12 epilepsy patients with surgically implanted subdural electrodes for medically refractory epilepsy participated in this study. The patients ranged from 8 to 17 years old.

Methods: The subjects were given a series of verbal tasks designed to invoke long-term verbal memory storage and retrieval processes. After a short practice trial, the subjects studied a series of 20 words (10 visual, 10 auditory, 7 sec ISI) which they were asked to free-recall after a 1 min arithmetic distraction task. They then performed a recognition task containing the 20 original words mixed with 20 similar words, and were asked to state whether or not each word was on the original list by saying “yes” or “no.” The tasks were performed three times at the bedside, and lasted about 30 min. An additional word repetition task was performed in which the subjects named stimuli that were presented as visual objects, written text, or aurally presented words.

Results: The patients recalled substantially fewer words than the normal control subjects during the free-recall task. Interestingly, they scored almost as well as the normal subjects on the cued recognition task. Localized event-induced increases in gamma activity were noted over different parts of the cortex in response to various aspects of the tasks. In addition to activation of primary auditory, visual and motor cortices, distant areas of frontal, parietal and temporal association cortex were dynamically involved. As we have reported before (Brain, 2008, 131:2013), gamma activations were associated with auditory perception (posterior temporal lobe) and expressive speech (posterior frontal lobe).

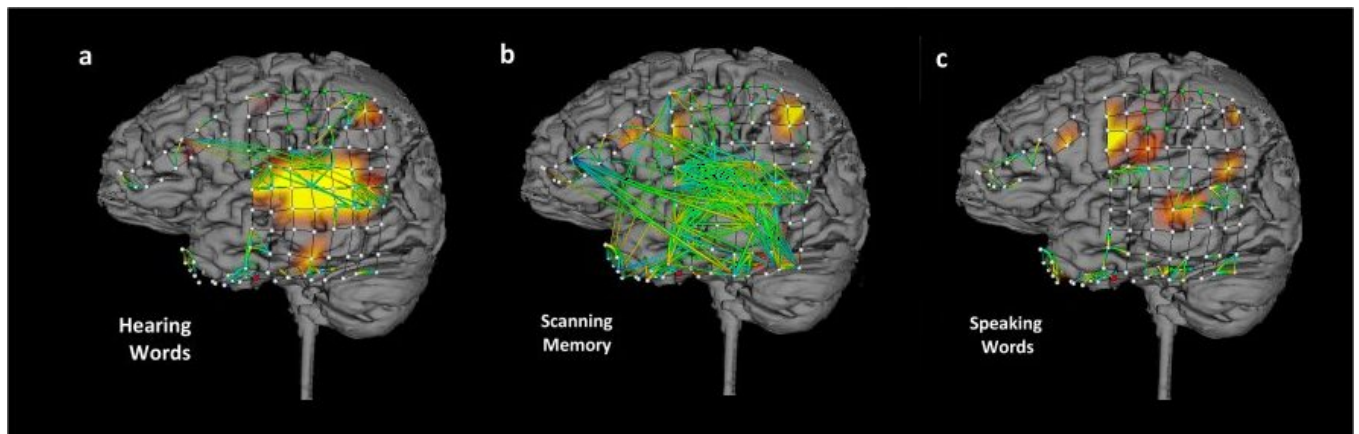


Figure 1. Task-induced gamma activity (gold) and theta band inter-electrode coherence (green).

Although the patients recalled substantially fewer words than the normal control subjects during the free-recall task, they scored about as well as the normal subjects on the cued recognition task. Localized event-induced increases in gamma activity were noted over primary auditory, visual and motor cortices, and frontal, parietal and temporal association cortex. During the period of memory scanning there was a dramatic increase in inter-electrode coherence in the delta, theta and alpha bands lasting about 600 msec, between posterior temporal cortex, frontal cortex, and the anterior temporal lobe (Figure 1)

. Memory scanning appears to be associated with a widely distributed low-frequency frontal/parietal/temporal network.

Conclusions: Epilepsy patients with verbal recall deficits have generally normal verbal memory storage, but not retrieval. Verbal tasks are associated with widely-distributed local areas of gamma activation, including primary cortical areas. Moments in the tasks related to memory scanning were associated with increased coherence between the parietal, temporal and frontal lobes, suggestive of a widespread network underlying verbal memory processes.

Implications: The ability to identify cortical areas that participate in the various aspects of language task enriches, complements, and partially confirms the findings from direct brain stimulation mapping. The speed and ease with which functional information can be obtained simultaneously from all of the implanted electrodes suggests this technique could be used to quickly identify widely distributed language areas, which could be confirmed with stimulation studies. Memory scanning appears to be associated with a widely distributed network. Further analysis of such recordings may yield a dynamic distributed model of human verbal information processing.

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Activation of Innate and Adaptive immunity by Recurrent Seizures in Mice and Human

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Objectives: To detect and quantify CNS-infiltrating and CNS resident immune cells, we used an unbiased multi-color flow cytometric analysis of inflammatory cells and immunohistochemistry in surgically resected human tissue and temporal lobes of mice.

Rationale: A dysregulated innate immune response, peripheral inflammatory cell infiltration and breakdown of the blood-brain barrier have been implicated in the initiation, progression and perpetuation of seizures. We tested the hypothesis that recurrent seizures prime the brain and allow the infiltration of leukocytes, causing exaggerated microglia activation, increased seizure susceptibility and exacerbation of neuronal injury following subsequent seizures.

Methods: Wild-type C57BL/6 mice were subjected to KA-SE on P14 followed by a “second-hit” KA-SE on P28 (KA/KA). Controls included mice injected with KA only at P28 (PBS/KA) and mice not experiencing any seizures (PBS/PBS) ($n=6$ /group). 24 hour after KA-SE (or PBS) at P28, temporal lobes were harvested from saline perfused animals. Human cortical tissues ($n=4$) were collected from the operating room and immersed immediately in ice-cold PBS. CNS mononuclear cells isolated from fresh brain tissue using enzymatic digestion and Percoll gradients and quantified using multicolor flow cytometry..

Results: Following KA-SE at P28, we detected activation of microglia and infiltration of peripheral leukocytes in the temporal lobes of mice. There were increased numbers of CD4+ and CD8+ T cells in the brains of KA/KA mice compared to PBS/KA or PBS/PBS controls. Similarly, epileptogenic cortices showed significantly increased number of CD4+ and CD8+ T cells compared to less epileptogenic regions.

Conclusions: We detected microglia activation and significant increases in CNS-infiltrating peripheral inflammatory lymphocytes after KA-SE in the temporal lobes of mature animals sensitized by early-life seizures and in epileptogenic cortical tissue resected from children with drug-resistant epilepsy. Our results suggest that recurrent seizures may exacerbate blood brain barrier leakage and infiltration of peripheral leukocytes in the brain and potentiate seizures and seizure-induced changes.

Scaling Behavior of a Computational Model of Neocortex on Parallel Machines

Hyong Lee, Mark Hereld, Sid Visser, Lorenzo Pesco, and Wim van Drongelen

The availability of relatively cheap, medium-sized clusters consisting of nodes that contain one or more multicore CPU's have made it feasible to simulate large, realistic networks of neurons computationally. We report on the parallel scaling behavior of two implementations of a computational model of neocortex [1]. One code, pneo [2], is a C implementation of the model based substantially upon the structure of pGenesis; the other, Verdandi [3], is a hybrid OpenMP/MPI implementation of a similar model. Simulations spanning networks of $3 \cdot 10^3$ -- $4 \cdot 10^5$ cells were created, mapped onto 4-144 MPI processes, and run on two machines: fusion, a 320-node linux cluster at Argonne National Laboratory, and Beagle, a 744-node Cray XE6 belonging to the University of Chicago that is expected to rank between 40th and 60th on the list of fastest supercomputers in the world. We describe run times and memory footprints for these simulations, and also examine the impact of long-range fast connectivity on the resource consumption of the models.

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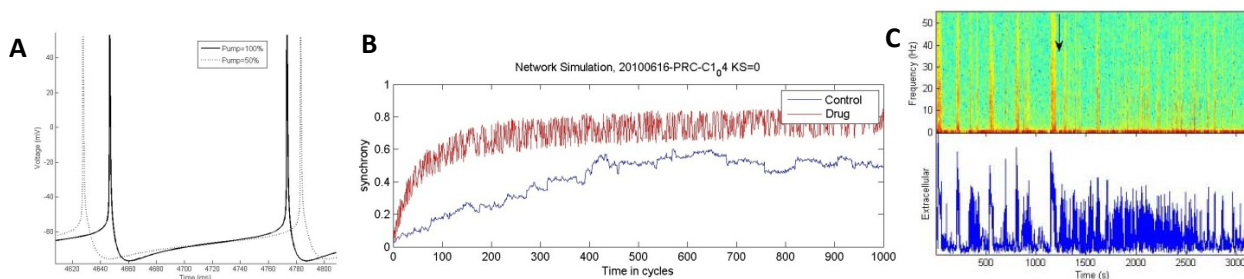
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Targeting Metabolic Pathways to Terminate Seizures with Ouabain

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Status epilepticus (SE) is one of the most deadly conditions that an epileptic patient can experience. Over 200,000 cases are reported annually, resulting in 40,000 deaths annually (Levy, 2002). While AEDs are effective for preventative control of many types of epilepsy, they are less effective in the acute treatment of SE. I hypothesize that seizure prevention and seizure termination are fundamentally different and metabolic pathways, specifically Na/K ATPase (NKA), provide novel targets for seizure termination (Bonting & Carravagio, 1962; Lüpfert et al., 2001). Here I demonstrate the use of ouabain, a NKA blocker, to facilitate seizure shortening and termination (Aperia 2007; Bonting et al, 1963; Fujikawa et al 1988). I have used a combination of computer modeling, network theory, and electrophysiology to test this theory. The multi-dimensional nature of neuronal dynamics can make interpretation of data very difficult. Using a dimensional reduction method called phase response analysis; one can reduce a neurons dynamics and create a 1-D representation called a phase response curve (PRC). This method is also useful because PRCs can be used to quickly simulate network activity.



(A) The results of the neuron model indicate that the primary effect of ouabain simulation is reduction in firing rate. (B) We show that ouabain application increases network synchrony for this network. Network simulations were run using PRCs from CA1 pyramidal neurons before and after ouabain application. (C) Spectrogram of a local field recording in rat slice low Mg^{+2} , 100 μM 4-AP seizure model. Black arrow indicates time of ouabain application. Long duration seizures are suppressed after ouabain application and inter-ictal bursting becomes more prevalent.

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