Workshop on
Cortical Spreading Depression (CSD) and
Related Neurological Phenomena
July 7-11, 2014

ABSTRACTS
(in alphabetic order by speaker surname)

Speaker: **David Andrew** (Queen's University in Kingston, Ontario, Canada)
Title: *Spreading depolarization strength during ischemia determines higher brain susceptibility and lower brain resistance to acute injury.*
Abstract:
Global ischemia caused by cardiac arrest, pulmonary failure, near-drowning or traumatic brain injury often damages the higher brain but not the brainstem, leading to a 'persistent vegetative state' where the patient is awake but not aware. Approximately 35,000 North Americans are held captive in this condition but how the lower brain is preferentially protected in these patients is not known. In the higher brain, ischemia elicits a profound ischemic depolarization (ID) causing neuronal dysfunction and vasoconstriction within minutes. Might brainstem nuclei generate less damaging ID and so be more resilient? Here we compared resistance to acute injury induced from simulated ischemia in 'higher' neurons (from neocortex, hippocampus, striatum ad thalamus) versus 'lower' hypothalamic and brainstem neurons in live slices from rat and mouse. Using whole-cell recordings from 165 neurons from 12 brain regions we show that during 10-15 min of oxygen/glucose deprivation (OGD), higher projection neurons underwent strong and irreversibly damaging ID. In contrast, hypothalamic and brainstem neurons generated a weak and slow-onset ID, easily surviving the same insult. This differential injury to higher neurons was supported by Light Transmittance (LT) imaging and 2-photon microscopy. All of the above responses were mimicked by bath exposure to 100 μM ouabain which inhibits the Na+/K+ pump or to 1–10 nM palytoxin which converts the pump into an open cationic channel. Moreover unlike higher gray, lower gray matter could not generate a CSD-like event in response to elevated bath KCl. Thus spreading depolarizations promote higher, but not lower, brain shut-down during metabolic stress and we propose that this is evolutionarily adaptive, not simply pathological. But what determines shut-down propensity? The Na/K pump 1α3 isoform is expressed in higher proportion in the lower brain and functions more efficiently under ischemic conditions than 1α1. We are currently investigating to what extent regional Na/K pump isoform expression influences susceptibility to spreading depolarization.
Brisson CD, Hsieh Y-T, Kim D, Jin AY, Andrew RD (2014) Brainstem Neurons Survive the Identical Ischemic Stress That Kills Higher Neurons: Insight to the Persistent Vegetative State. PLoS ONE 9(5): e96585. doi:10.1371/journal.pone.0096585.

Speaker: **Cenk Ayata** (Harvard Medical School, USA)
Title: *Spreading depression and the biological heterogeneity of cerebral blood flow response: clues for modeling*
Abstract:
Spreading depression (SD) is an intense wave of pan-depolarization of virtually all cells within the brain tissue, which is the electrophysiological substrate of migraine aura, and an important pathophysiological component in brain injury states such as stroke. Besides the neuronal and glial ionic and metabolic changes, SD has a profound impact on cerebral vasculature. Although the prototypical cerebral blood flow (CBF) response to SD has been a mono phasic hyperemia, accumulating data show a range of vascular responses that are highly reproducible but heterogeneous depending on the species, systemic physiology, drug effects, and the presence of pathological circumstances such as tissue ischemia or subarachnoid hemorrhage. Evidence strongly suggests that SD–induced CBF response is composed of multiple vasomotor components that can be mathematically modeled. In my talk, I will review the range of CBF responses and discuss the vasomotor components that can be incorporated in a predictive model.

Speaker: **Ernest Barreto** (Department of Physics, Geroge Mason University, USA)
Title: *Ion Concentration Dynamics and its Effects on Neuronal Excitability and Bursting*
Abstract:
I will describe a simple conductance-based model neuron that includes intra- and extracellular ion concentration dynamics and show that this model exhibits autonomous periodic bursting with various bursting morphologies. The bursting arises as the fast-spiking behavior of the neuron is modulated by the slow oscillatory behavior in the ion concentration variables, and vice versa. By separating these time scales and studying the bifurcation structure of the neuron, we catalog several qualitatively different bursting profiles that are strikingly similar to those seen in experimental preparations. Control of bursting by periodic stimulation will also be discussed.

Speaker: **K.C. Brennan** (University of Utah, USA)
Title: *Minimum conditions for the induction of spreading depression*
Abstract:
Cortical spreading depression (CSD) occurs during various forms of brain injury such as stroke, subarachnoid hemorrhage, and brain trauma, but it is also thought to be the mechanism of the migraine aura. It is therefore expected to occur over a range of conditions including the awake behaving state. Yet it is unclear how such a massive depolarization could occur under relatively benign conditions. We will discuss the historical literature, present recent work using a microfluidic device in a brain slice model, and speculate on ways to continue addressing this important issue, preferably in vivo.

Speaker: **Markus A. Dahlem** (Department of Physics, Humboldt University of Berlin, Germany)
Title: *Ghost behavior: Transient patterns of cortical spreading depression in the gyrified human cortex*
Abstract:
We present a generic model of cortical spreading depression (CSD). The model has a long tradition with its origin in the Grafstein-Hodgkin model and, in hindsight, can be derived from the cellular Hodgkin-Huxley framework with time-dependent ion concentrations—see morning session. Representatively illustrated with this generic model, we propose to explain transient patterns of CSD in the gyrified human cortex by using the universal theoretical concept of '*ghost behavior*'. This concept refers to large fluctuations and critical slowing down, in this case occurring in the ion homeostasis. CSD in migraine attacks and related phenomena in stroke extent in the folded, two-dimensional (2D) cortical sheet over several tens of square centimeters with varying cytoarchitecture and the pattern can last hours, or possibly days and weeks in form of reverberating and standing waves. Therefore, from the neurological perspective there clearly is a need for a macroscopic continuum model of CSD that effectively describe spatio–temporal 2D patterns. Moreover, ghost behavior is an abstract 'space phase' concept that is best understood in generic models. It describes the clash of a critical neural nucleation mass—see tomorrows morning session—with a full-scale

traveling CSD wave. Finally, we ask the question in which respect more detailed models are superior to such a generic formulation, which merely accounts for shape, size, and duration of CSD patterns that, however, can be clinically observed.

Speaker: **Bernice Grafstein** (Weill Cornell Medical College, USA)
Title: *Spreading depression as a holistic process: A historical perspective*
Abstract:
Spreading depression (SD) is a multifactorial phenomenon. Intense depolarization of neurons and/or astrocytes is essential for its initiation. Release of K^+, glutamate, and ATP contribute to its propagation, which is accompanied by neuronal swelling, increase in intracellular Na+ and Ca^{2+}, local anoxia and vascular changes. Neurons, astrocytes, microglia and vascular elements all participate. It is now acknowledged that SD is an essential factor in migraine aura and possibly in most types of migraine headache; it may be linked to some epileptic disorders; it presents as a series of "peri-infarct depolarizations" in traumatic injury, hemorrhage and ischemic stroke. SD may have an especially deleterious effect in the injured brain, enlarging the area of neuron loss. Addressing the mechanisms underlying SD in a clinical setting may make it possible to ameliorate this damage.

Speaker: **Jed Hartings** (Department of Neurosurgery at the University of Cincinnati College of Medicine, USA)
Title: *Spreading depolarizations in acute brain injury: mathematical dynamic instability of cerebral cortex?*
Abstract:
Decades of electrophysiologic studies in animal and man have established the phenomena of spreading mass neuronal depolarizations as a dynamic mechanism of lesion development in the cerebral cortex. In stroke, for instance, core ischemic tissue undergoes anoxic spreading depolarization that is persistent and terminal, marking the start of irreversible cellular damage. In the ischemic border zone, or penumbra, cortical physiology exhibits a dynamic instability marked by periodic ignition of transient spreading depolarization waves. Depending on time and location along the cortical gradient of impaired metabolism, these depolarizations become prolonged and promote lesion growth as further tissue is recruited into the terminally depolarized core. Thus in patients with stroke and traumatic brain injury, spreading depolarizations are associated with new cerebral infarcts and worse neurologic outcomes. Importantly, several features of brain injury depolarizations are suggestive of non-linear behavior amenable to mathematical modeling and geometric analysis, including the occurrence of single vs. continuous repetitive waves, intervals with varying regular periods, all-or-none amplitudes, and waves of arbitrarily long duration. Here we will review key characteristics of spreading depolarizations recorded in man after severe brain injury and suggest approaches to understanding features of these phenomena based on neural mean-field models. It is suggested that essential dynamics could be understood by modeling wave initiation and characteristics at cortical point sources, ignoring spatial aspects. Capturing behavior on this scale could lead to more realistic biophysical models that provide insight into mechanisms of initiation, propagation, and therapeutic inhibition.

Speaker: **Niklas Hübel** (Department of Theoretical Physics, Technical University Berlin, Germany)
Title: *Dynamics from seconds to hours in Hodgkin–Huxley model with time–dependent ion concentrations and buffer reservoirs*
Abstract:
The classical Hodgkin–Huxley (HH) model neglects the time-dependence of ion concentrations in spiking dynamics. The dynamics is therefore limited to a time scale of milliseconds, which is determined by the membrane capacitance multiplied by the resistance of the ion channels, and by the gating time constants. We study slow dynamics in an extended HH framework that includes time-dependent ion concentrations, pumps, and buffers. Fluxes across the neuronal membrane change intra- and extracellular ion concentrations, whereby the latter can also change through contact to reservoirs in the surroundings. Ion gain and loss of the system is identified as a bifurcation parameter whose essential importance was not realized in

earlier studies. Our systematic study of the bifurcation structure is a valuable diagnostic method to understand activation and inhibition of a new excitability in ion homeostasis which emerges in such extended models. Also modulatory mechanisms that regulate the spiking rate can be explained by bifurcations. The dynamics on three distinct slow times scales is determined by the cell volume-to-surface-area ratio and the membrane permeability (seconds), the buffer time constants (tens of seconds), and the slower backward buffering (minutes to hours). The modulatory dynamics and the newly emerging excitable dynamics corresponds to pathological conditions observed in epileptiform burst activity, and spreading depression in migraine aura and stroke, respectively.

Speaker: **Béla Joós** (Department of Physics, Université d'Ottawa, Canada)
Title: *The Nav coupled left shift model of axon damage: how minor damage can cause major grief**
Abstract:
The opening of voltage gated Na+ channels, Nav, triggers an action potential (AP). Neural tissue injuries render Navs leaky, thereby altering excitability, disrupting propagation and causing neuropathic pain related ectopic activity. Recombinant Nav channels studied by macroscopic current in cell attached patches robustly respond to patch pipette aspiration, with a correlated hyperpolarizing (leftward) shift of their activation and inactivation kinetics. The shifts are irreversible and increase with aspiration intensity and duration. Like the mechanical forces experienced during brain trauma, pipette aspiration causes bleb damage of the channel bearing membrane. The Nav rich nodes of Ranvier in damaged CNS tissue exhibit blebs. Based on the patch clamp findings we implemented a "coupled left shift" (CLS) model for Nav channel activation and inactivation kinetics. By mathematical modeling we studied nodal excitability and AP propagation in axons with nodal CLS damage. Even mild damage is sufficient to produce rich changes in axonal excitability including hyperexcitability, subthreshold oscillations, ectopic firing, various types of bursting, and for larger damage depolarizing block. Our modeling shows that given the small intra- and extra-cellular volumes at the node of Ranvier, the Nav CLS related leaks stress the Na/K pumps. The result, continually changing ion gradients, continually change the firing threshold. Thus, quiescent nodes with extremely mild damage can become ectopic signal generators simply because incoming APs stress the ion gradients. Unexpectedly, we also found that damaged nodes firing ectopically at high frequency can still propagate input spike trains with good fidelity provided the spike train frequency exceeds the ectopic frequency.
*work done in collaboration with Catherine E. Morris, Pierre-Alexandre Boucher, Mathieu Lachance, André Longtin, and Na Yu.

Speaker: **Frederike Kneer** (Department of Software Engineering and Theoretical Computer Science, Technical University Berlin, Germany)
Title: *Nucleation and front and pulse propagation*
Abstract: TBA

Speaker: **David Terman** (Department of Mathematics, The Ohio State University, Columbus, Ohio, USA)
Title: *Blocking spreading depolarizations in a neuron/astrocyte network model*
Abstract:
We present a detailed network model for key processes involved in ischemic stroke. The model incorporates interactions between neurons and astrocytes and integrates the dynamics of cell membrane potential, ion homeostasis, mitochondrial ATP production, mitochondrial and ER Ca^{2+} handling, and IP3 production. Stroke-like conditions are initiated by decreasing parameter corresponding to either glucose or oxygen input. The model is used to help understand conditions, under which low glucose and/or oxygen levels lead to waves of spreading depolarizations, while high glucose and oxygen levels do not.

Speaker: **Steven J. Schiff** (Pennsylvania State University, Penn State Center for Neural Engineering, USA)
Title: *Unification in the Observation and Control of Spikes, Seizures, and Spreading Depression*
Abstract:
The pathological phenomena of seizures and spreading depression have long been considered separate physiological events in the brain. By incorporating conservation of particles and charge, and accounting for the energy required to restore ionic gradients, we show that we can extend the classic Hodgkin-Huxley formalism and uncover a unification of neuronal membrane dynamics both in numerical simulations as well as in the underlying bifurcation structure of such models. We now account for a wide range of neuronal activities, from spikes to seizures, spreading depression (whether high potassium or hypoxia induced), mixed seizure and spreading depression states, and the terminal anoxic "wave of death". Such a unified framework demonstrates that all of these dynamics lie along a continuum of the repertoire of the neuron membrane. These results offer the prospect of model-based control for such phenomena that can account for the trajectory associated with control manipulation, as well as the prospect of accounting for the energy load placed upon neurons during application of control stimulation.

Speaker: **Ghanim Ullah** (Department of Physics, University of South Florida, Tampa, Florida, USA)
Title: *Towards a model-based control of neuronal systems*
Abstract:
Observability of a dynamical system requires an understanding of its statethe collective values of its variables. However, existing techniques are too limited to measure all but a small fraction of the physical variables and parameters of neuronal networks. We constructed models of the biophysical properties of neuronal membrane, synaptic, and microenvironment dynamics, and incorporated them into a model-based predictor-controller framework from modern control theory. We demonstrate the meaningful estimation of the dynamics of small neuronal networks using as few as a single measured variable. Specifically, we assimilate noisy membrane potential measurements from individual hippocampal neurons to reconstruct the dynamics of networks of these cells, their extracellular microenvironment, and the activities of different neuronal types during seizures. We use reconstruction to account for unmeasured parts of the neuronal system, relating micro-domain metabolic processes to cellular excitability, and validate the reconstruction of cellular dynamical interactions against actual measurements. Our results render the incorporation of the dynamic microenvironment in neuronal models a key for successful tracking of pathological states.

Speaker: **Bas-Jan Zandt** (Department of Mathematics, University of Twente, Netherlands)
Title: *Dynamics of single neurons and populations during spreading depolarization*
Abstract:
During spreading depression/depolarization (SD), neuronal transmembrane ion gradients break down and neurons depolarize. This disturbance can propagate through diffusion of extracellular potassium. Due to its excitatory effect, potassium is released from the neuronal intracellular space (ICS) into the extracellular space (ECS) when its extracellular concentration becomes critically high.

In hypoxic conditions, synapses fail, and propagation and initiation of SD is determined by the behavior of functionally isolated single cells and their interaction with the ECS. The traditional Hodgkin-Huxley model, with additional differential equations that describe the evolution of the ion concentrations, is a great tool to investigate e.g. conditions that trigger SD or how ion channel mutations render tissue susceptible to SD. Bifurcation analysis shows that the HH model displays a wide range of dynamics and transitions when sodium and potassium concentrations change. I will discuss measurements that experimentally validate this bifurcation analysis, showing the traditional HH model adequately describes the dynamics of depolarizing cortical pyramidal cells due to anoxia.

Furthermore, I will address the question whether a single cell model suffices for modeling SD in normoxic conditions, i.e. as occurs in migraine with aura. There, synapses are fully functioning at the onset of the SD wave. Neuronal activity and hence SD propagation and initiation are determined by the local network dynamics, i.e. the interaction between excitatory pyramidal cells and inhibitory interneurons, rather than