Conference on Computational Neuroscience 2008

February 20-21, 2008

J. Wayne Reitz Union, Lecture Hall 282
University of Florida
Gainesville, FL

Conference Program

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Organizers:
Panos M. Pardalos
W. Art Chaovalitwongse
Onur Seref
Petros Xanthopoulos

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Local Organizing Committee:
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Michael Bewernitz
Dalila B.M.M. Fontes

February 20, 2008 Wednesday

08:00-12:00	**Registration**
	Chair: Panos Pardalos
08:00-08:15	**Panos Pardalos** Conference Opening
08:15-08:30	**Joseph Hartman** Opening Remarks
08:30-09:30	**Evangelia Micheli Tzanakou** Does the Brain Exhibit any Dynamic Approximation Capabilities in Learning and Pattern Recognition?
09:30-10:00	**Coffee Break**
	Chair: Onur Seref
10:00-10:30	**José C. Príncipe** Reproducing Kernel Hilbert Spaces for Spike Train Analysis
10:30-11:00	**Andrew Ottens** Mining the Injured Neuroproteome at the Molecular and Functional Level
11:00-11:30	**Christiana Leonard** Do Individual Differences in Cortical Anatomy Affect Cognition?
11:30-12:00	**Mingzhou Ding** Neural Oscillations: Characterization and Function
12:00-01:30	**Lunch Break**
	Chair: Erhun Kundakcioglu
01:30-02:00	**Kimonobu Sugaya** Use of Stem Cells in Alzheimer's Disease
02:00-02:30	**Paul Carney** Temporal Lobe Epilepsy: Anatomical and Effective Connectivity
02:30-03:00	**Justin Sanchez** Co-Adaptive Brain-Machine Interfaces via Reinforcement Learning
03:00-03:30	**Coffee Break**
	Chair: Petros Xanthopoulos
03:30-04:00	**Monica Oli** Continuous Physiological Monitoring in TBI Patients and their Correlation to Biomarker Values
04:00-04:30	**Sandeep Nair** Age-Related Changes in Dynamics of Spike-Wave Discharges in Rats
04:30-05:00	**Changxu Wu** Optimization in the Brain? -Modeling Brain Activation Patterns and Human Behavior with Queuing Network and Reinforcement Learning Algorithms
05:00-05:30	**Max Garzon** Biomodecule-inspired Methods for Coarse-grain Multi-system Optimization
07:00-10:00	**Conference Dinner**

February 21, 2008 Thursday

08:00-12:00	**Registration**
	Chair: Panos Pardalos
08:00-09:00	**Theoden Netoff** Phase Response Curves, Epilepsy, Networks, Hippocampus, Seizure
09:00-09:30	**Basim Uthman** Unverricht-Lundborg Disease: Challenges in Treatment and Outcome Measures
09:30-10:00	**Coffee Break**
	Chair: Art Chaovalitwongse
10:00-10:30	**Shigeharu Kawai** Parametric Modeling Approach to Optical Imaging Data Finds Close Input Output Relation Between the Central Neuronal Activity and the Respiratory Motor Output in the Neonatal Rat Brainstem
10:30-11:00	**Konstantinos Tsakalis** Failing Feedback as a Mechanism to Generate Epileptic Seizures
11:00-11:30	**Michael Anderson** Investigating Functional Cooperation in the Human Cortex with Graph-Theoretic Methods
11:30-12:00	**Mark Davidson** Iron Imaging and Analysis in Neurodegenerative Diseases
12:00-01:30	**Lunch Break**
	Chair: Michael Bewernitz
01:30-02:00	**Nikita Boyko** Data Mining Application for Processing EEG Obtained from Epileptic Patients Treated with Vagus Nerve Stimulation
02:00-02:30	**Alla Kammerdiner** Seizure Monitoring and Alert System for Brain Monitoring in an Intensive Care Unit
02:30-03:00	**Michael Bewernitz** A Novel Generalized Spike-Wave Detector: Towards Real-Time Applications in Epilepsy
03:00-03:30	**Coffee Break**
	Chair: Chang-Chia Liu
03:30-04:00	**Deng-Shan Shiau** Testing an Seizure Prediction Algorithm: Assessment of Performance
04:00-04:30	**Ya-Ju Fan** Classification of Normal and Abnormal EEG Signals Using K-Nearest Neighbor Rule in Support Feature Machine
04:30-05:00	**Philip Chan** Data Mining for Anomaly Detection
05:00-05:30	**Tsvi Achler** Towards a Dynamic Account of Epigenetic Expression

List of presenting authors

Tsvi Achler
University of Illinois Urbana-Champaign (achler@uiuc.edu)
Towards a Dynamic Account of Epigenetic Expression

Michael Anderson
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Investigating Functional Cooperation in the Human Cortex with Graph-Theoretic Methods

Michael Bewernitz
University of Florida (bewerni2@ufl.edu)
A Novel Generalized Spike-Wave Detector: Towards Real-Time Applications in Epilepsy

Nikita Boyko
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Data Mining Application for Processing EEG Obtained from Epileptic Patients Treated with Vagus Nerve Stimulation

Paul Carney
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Temporal Lobe Epilepsy: Anatomical and Effective Connectivity

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Data Mining for Anomaly Detection

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Iron Imaging and Analysis in Neurodegenerative Diseases

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Neural Oscillations: Characterization and Function

Ya-Ju Fan
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Classification of Normal and Abnormal EEG Signals Using K-Nearest Neighbor Rule in Support Feature Machine

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Biomodecule-inspired Methods for Coarse-grain Multi-system Optimization

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Seizure Monitoring and Alert System for Brain Monitoring in an Intensive Care Unit

Shigeharu Kawai
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Parametric Modeling Approach to Optical Imaging Data Finds Close Input Output Relation Between the Central Neuronal Activity and the Respiratory Motor Output in the Neonatal Rat Brainstem

Christiana Leonard
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Do Individual Differences in Cortical Anatomy Affect Cognition?

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Age-Related Changes in Dynamics of Spike-Wave Discharges in Rats

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Use of Stem Cells in Alzheimer's Disease

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Does the Brain Exhibit any Dynamic Approximation Capabilities in Learning and Pattern Recognition?

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Unverricht-Lundborg Disease: Challenges in Treatment and Outcome Measures

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Optimization in the Brain? -Modeling Brain Activation Patterns and Human Behavior with Queuing Network and Reinforcement Learning Algorithms

Towards a Dynamic Account of Epigenetic Expression

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Abstract. Regulation through feedback is a common theme found in biology including gene expression and physiological homeostasis. Yet, the role of feedback is often under-appreciated.

For example, it is common that several copies of a genes and their promoters can are found in the genome. Though these gene copies are now separate they can still interact because they make the same or similar products. Furthermore their promoters may respond to the same or similar products. This can give rise to complex interactions between these genes.

Suppose product x_1 can be found on genes y_1 & y_2, while product x_2 is found only on gene y_2. If gene y_1 is regulated by product x_1 and gene y_2 is regulated by products x_1 & x_2, then the activation of gene y_1 can depend on the level of product x_2. If products x_1 & x_2 are consumed equally, then gene y_2 will be promoted at the expense of gene y_2.

This scenario can be expanded to show how genes can interact in a distributed fashion. If there is now a third gene y_3 which produces products x_2 & x_3 (and regulated by products x_2 & x_3), then genes y_1 and y_3 can together sequester gene y_2. If products x_1, x_2 & x_3 are consumed equally, gene y_2 will be sequestered.

In this model it is assumed that each promoter aims to produce a certain amount of product. If the product is scarce its expression is increased. Conversely, if too much product is present it is decreased. Also promoters regulated by multiple products are regulated by the products equally.

This example demonstrates how genes can be expressed dynamically based on product consumption. Through this product-promoter regulation, genes can interact and produce efficient expression configurations or dynamic epigenetic expression

Keywords: Feedback, Regulation, Epigenetic phenomena, multiple gene copies, Promoters, Protein Expression

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Investigating Functional Cooperation in the Human Cortex with Graph-Theoretic Methods

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Abstract. This paper introduces a very simple analytic method for mining large numbers of brain imaging experiments to discover functional cooperation between regions. I then report some preliminary results of its application, illustrate some of the many future projects in which we expect the technique will be of considerable use, and describe a research resource for investigating functional cooperation in the cortex that will be made publicly available through the lab website.
For instance, the techniques have been used to investigate some predictions made by the massive redeployment hypothesis (MRH). MRH is a theory about the functional topography of the cortex, rooted in the claim that cognitive evolution proceeded in a way analogous to component reuse in software engineering, whereby existing components-originally developed to serve some specific purpose-were used for new purposes and combined to support new capacities, without disrupting their participation in existing programs. So far, we have been able to support four specific predictions made by MRH. First, any given brain area is typically redeployed in support of many cognitive functions, and such redeployment will not respect traditional domain boundaries (that is, brain areas are not domain-restricted entities). Second, differences in domain functions will be accounted for primarily by differences in the way brain areas cooperate with one another, rather than by differences in which brain areas are used in each domain. Third, more recently evolved cognitive functions will utilize more, and more widely scattered brain areas. And fourth, evolutionarily older brain areas will be deployed in more cognitive functions.
Future research using the techniques includes investigating a novel method for relating fMRI data to EEG data. Bringing EEG and fMRI together in the way envisioned would make it possible to mine the vast trove of fMRI data to provide baseline expectations for normal brain function, in terms of the temporal correlation between brain areas. Since this can be observed cheaply, non-invasively, and in real time with EEG, it would be of great use in clinical settings for detecting deviations from normal function, such as might be observed prior to the onset of an epileptic seizure.

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A Novel Generalized Spike-Wave Detector: Towards Real-Time Applications in Epilepsy

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Abstract. We present an application of one-class support vector machines (SVMs) to the detection of generalized spike-wave discharges from patients with generalized absence epilepsy. This particular detection approach aims to produce a real-time seizure detection apparatus with time resolution on the order of hundreds of milliseconds. The results for various combinations of relevant SVM parameters and detection rules are presented and discussed. Such a device could be utilized for rapid offline EEG annotation, online diagnostic purposes, and potential online seizure control applications.

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Data Mining Application for Processing EEG Obtained from Epileptic Patients Treated with Vagus Nerve Stimulation

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Abstract. This work presents a pilot study of EEG recordings from six epileptic patients undergoing treatment with Vagus Nerve Stimulator(VNS). Raw EEG signal was transformed to a sequence of maximum Lyapunov Exponents ($STLmax$). Then the two data mining techniques Logistics Regression and Support Vector Machines were applied to the STLmax time series. Both techniques allowed us to separate stimulation states versus non-stimulation states with a different degree of separation for different patient. The result of the experiment indicated that the separation quality for Local Lyapunov Exponents provides a possible physiologic marker for optimal VNS parameters based on measures of scalp EEG signals. These results motivate further studies to provide additional characterization of $STLmax$ and its relationship to the stimulation parameters.

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Temporal Lobe Epilepsy: Anatomical and Effective Connectivity

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Abstract. While Temporal Lobe Epilepsy (TLE) has been treatable with anti-seizure medications over the past century, there still remain a large percentage of patients whose seizures remain untreatable pharmacologically. To better understand and treat TLE, our laboratory has used multiple connectivity-based paradigms to understand epileptigenesis, the transition between a normal health brain and an abnormal spontaneously seizing brain. We will demonstrate the various approaches taken to better understand the epileptigenic and seizure dynamics of a spontaneous animal model of TLE. First, gross anatomical changes within the hippocampus have been explored over epileptigenesis using magnetic resonance imaging. Second, fiber track imaging is used to resolve changes in axonal outgrowth during epileptigenesis. Finally, we have used Granger Causality to study dynamic connectivity at the synaptic level in vivo over the time course of seizure. These various approaches will be combined to better understand the process of limbic epileptogenesis and where and how to intervene to possibly prevent impeding seizure with targeted delivery of electronic or pharmacological therapy.

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Data Mining for Anomaly Detection

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Abstract. Anomaly detection has the potential to detect novel events, however, keeping the false alarm rate low is a challenging task. We discuss some data mining methods that can generate models of normalcy and detect anomalies. Particularly, we describe data mining algorithms for feature-vector data, time-series data, and spatio-temporal data. We will present results in applications such as intrusion detection, space shuttle monitoring, and mobile device monitoring.

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Iron Imaging and Analysis in Neurodegenerative Diseases

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Abstract. It has been shown in numerous studies that iron chemistry is disrupted in association with a number of neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's diseases. Dobson, et. Al. as well as others have shown that some of the iron compounds formed in association with some of these diseases are magnetic minerals such as magnetite. However, these early studies were extractive studies which did not reveal the location of the particle in association with the tissue or pathology. In the past, there have been studies performed using conventional histological staining techniques, however, we have shown that these techniques can change the oxidation state of the iron present or be insensitive to some chemical states of iron. We have developed a unique set of protocols that allows for the analysis of the iron compounds present within the tissue using a powerful synchrotron x-ray source in such a way that preserves the iron chemistry and the tissue structure. The high-intensity, focusable x-ray source allows localization of widely dispersed particles within tissue sections. In addition, the tunability of the x-ray source energy allows x-ray energy spectroscopy to be performed on each particle found, providing chemical state and crystal structure information. We are now correlating the information thus learned with MRI image and spectroscopic data to develop techniques that may be useful in early objective diagnosis of Alzheimer's disease. The data generated involves multiple levels of spectroscopic data associated with image pixels (or voxels in the case of the MRI). This leads to many new data processing challenges and some new opportunities for data mining that may lead to new results in the study of neurodegenerative disease.

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Neural Oscillations: Characterization and Function

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Abstract. Oscillatory neural activity is ubiquitous in the nervous system. Despite many years of effort, its precise role in cognitive processing remains not clear. In this talk I will describe some results from recent memory and sensory perception experiments which shed light on the functional role of neural oscillations.

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Classification of Normal and Abnormal EEG Signals Using K-Nearest Neighbor Rule in Support Feature Machine

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Abstract. Electroencephalogram (EEG) signals are the standard data format obtained from electrodes placed at human brain for evaluating neurophysiological functions. This study is to identify normal and epilepsy patients using EEG signals of those patients. Dynamical information of EEG signals at first step is extracted into a form of STLmax profiles (time series). Using the STLmax time series, Support Feature Machine (SFM) optimizes electrode combination that provides best classification results, most separation between two group of EEGs. A k-nearest neighbor (KNN) rule is applied in SFM to gain better classification performance. The results suggest that the proposed framework can be used as a computerized, automated brain diagnosis tool.

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Biomodecule-inspired methods for coarse-grain multi-system optimization

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Abstract. A major goal in multi-objective optimization is to strike a compromise among various objective functions subject to diverse sets of conflicting constraints. It is a reality, however, that we must face optimization of systems in which multiple objectives make it nearly impossible to formulate these objective functions and constraints in the required form. We present an approach to this type of problems using simulations techniques that have been or are being inspired by biomolecules in order to afford a more comprehensive and integrated understanding of complex chains of local interactions that affect an entire system, such as the chemical interaction of biomolecules in vitro, a mammalian brain, or a living cell. We briefly describe a system of this type, Edna (a high-fidelity simulation of chemical reactions in a test tube), that can be used to understand large neural networks, and virtual cell projects (models of the living cell in silico). With these prototype in hand, we explore three basic principles critical to the successful development of robust synthetic models of these complex systems: physical-chemical optimization; computational optimization, and biological optimization. We conclude with evidence for and discussion of the emerging hypothesis that multi-system optimization problems can indeed be solved, but only approximately, by so-called coarsely optimal models of the type discussed above, in the context of a biomolecule-based asynchronous model of the human brain.

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Seizure monitoring and alert system for brain monitoring in an intensive care unit

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Abstract. Although monitoring for most organ systems is commonly used in intensive care units (ICU), brain function monitoring relies almost exclusively upon bedside clinical observations. As a result, a large number of non-convulsive seizures go undiagnosed every day. Recent clinical studies have demonstrated the clinical utility of continuous EEG monitoring in ICU settings. Continuous EEG is a well-established tool for detecting non-convulsive seizures, cerebral ischemia, cerebral hypoxia, and other reversible brain disturbances in the ICU. However, the utility of EEG monitoring currently depends on the availability of expert medical professionals, and interpretation is labor intensive. Such experts are available only in tertiary care centers. We have designed a seizure monitoring and alert system (SMAS) that utilizes a seizure susceptibility index (SSI) and seizure detection algorithms based on measures that characterize the spatiotemporal dynamical properties of the EEG signal. The SMAS allows distinguishing the organized seizure patterns from more irregular and less organized background EEG activity. The algorithms and initial results in human long-term EEG recordings are described.

Keywords: EEG, seizure monitoring and alert system (SMAS), seizure susceptibility index (SSI)

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Parametric modeling approach to optical imaging data finds close input output relation between the central neuronal activity and the respiratory motor output in the neonatal rat brainstem

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Abstract. An advantage of optical imaging is the ability to simultaneously record multiple neuronal activities. However, it requires a sophisticated counterpart to analyze large-scale time series data. In respiratory neuronal activities, two respiratory-related brainstem regions, the parafacial respiratory group (pFRG) and the preBtzinger complex (PreBtC), have been recently identified by physiological experiments. However, the dynamical interaction between the two regions and the dynamical process to form the respiratory motor output remain unanswered. Here we show that the application of a parametric model to optical time series data successfully characterizes spatiotemporal neuronal activities associated with the central respiratory pattern formation. We recorded respiratory-related optical signals from the ventral surface of the rat brainstem in vitro using a voltage-sensitive dye. In our previous analysis using the cross correlation method, we showed that pixels with a greater dead time were distributed rostrally in P0-P1 rats, whereas such distribution was not observed in older rats (Oku et al., 2007). In the present study, we aimed to provide more detailed information as to dynamic characteristics of neuronal activities. We considered a parametric model assuming the respiratory motor output as the output and optical signals of each pixel as the input. The model consisted of a sigmoid function and a [first-order delay + dead time] transfer function to express the non-linear relationship between the respiratory motor output and an optical signal. We classified each pixel into five types based on three parameter values of the gain(K) ,the dead time(L) and the estimation error ratio(R) as follows: Type-1: R is not large, L is large, and K is not large Type-2: R and L are small, and K is not large Type-3: R is medium, L is small, and K is not large Type-4: R is large, L is small, and K is not large Type-5: K is large, or R and L are large. Based on this classification, we characterized neuronal respiratory activities in the ventral brainstem of P0-P1 rats. When the respiratory motor output variation had a single peak, the above classification was applicable as it was. There were many type-2 pixels concentrated in the PreBtC region. Type-1 pixels were in the pFRG region, whose appearance probability was smaller than that of type-2 pixel in the PreBtC

Keywords: Optical imaging data, Respiratory neuronal network, Neonate, Parametric model, Akaike Information Criterion

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region. For these cases, the respiratory motor output could be estimated by optical imaging data of a single type-2 pixel. When the number of peaks was two, there was a specific set of pixels by which the respiratory motor output could be estimated for the whole period of respiration. When the number of peaks was more than three, the respiratory motor output could not be estimated by a specific set of pixels. However, dividing the respiratory period into a number of ranges and computing the model parameters for each range, it could be estimated by a weighted sum of estimated values using selected type-2 pixels. The number of pixels selected and the number of ranges divided were decided by Akaike Information Criterion. In summary, if we estimate the respiratory motor output from the optical imaging time series data, then the result of estimation is a reflection of respiratory neuronal characteristics, or even a reflection of mechanisms of the central respiratory pattern formation. We conclude that our parametric modeling approach is a powerful technique to characterize optical imaging data.

Do individual differences in cortical anatomy affect cognition?

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Abstract. Human brains are functionally asymmetric. The left hemisphere appears to be a digital processor, specialized for processing rapid discreet stimuli, while the right hemisphere operates in a slower analog mode. These functional differences are mirrored in structural differences between the left and right hemisphere. The temporal lobe is relatively expanded in the left hemisphere of most people while the parietal lobe is expanded on the right. Cognitive impairments such as dyslexia can be associated with extreme asymmetries while more severe language disorders are more likely to be associated with a reduction in asymmetry. New automated techniques for examining brain structure now make it possible to examine the extent to which individual variation in brain structure may influence cognitive style and strategy.

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Age-Related Changes in Dynamics of Spike-Wave Discharges in Rats

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Abstract. Several studies with animal models of aging, including studies in our laboratory (Kelly et al, 2001), have shown an age-related increase in the incidence and duration of 7-9 Hz generalized spike-wave discharges (SWDs; absence seizures) as the animal ages. In an effort to elucidate the mechanisms underlying aging-related changes in the expression of SWDs, we studied the dynamical electroencephalographic (EEG) properties associated with spontaneously occurring SWDs in young (4 month) and aged (20 month) Fischer 344 rats. The short term maximum Lyapunov exponent (STLmax), a measure of chaoticity, was utilized to extract a dynamical profile of the EEG signal. A statistical comparison of preictal dynamical values (2 min before a SWD) showed no significant difference between the two age groups in STLmax (p=0.18). However, the same statistical test performed on postictal dynamical values (2 min after a SWD) revealed a significant difference between the two groups in STLmax (p=0.009). A comparison of the difference between average preictal and postictal dynamical values suggested that brain r̈esettingẗo its normal interictal state was more effective in the 4 month cohort compared to the 20 month cohort by STLmax (p=0.007) values. These preliminary results suggest that brain recovery following SWDs was more sustained in young adult animals compared to aged animals. Supported by a Targeted Research Initiative for Seniors grant from the Epilepsy Foundation to S Nair. asks between human operator(s) and a computer.

Keywords:Epilepsy, Lyapunov Exponent, Absence Seizures, Aging

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Phase Response Curves and Epilepsy

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Abstract. Neurons use homeostatic mechanisms to maintain the proper balance of activity in the brain. However, under extreme conditions that induce seizures, and following a seizure, those mechanisms may not result in the desired stabilization of network activity. I will present a case where changes in density of the Ih channel can decrease synaptic excitability but increase network synchrony. This paradoxical result could lead a normal homeostatic response to result in seizures by enhancing the synchrony of the excitatory neurons.

Keywords: Cognitive modeling, P300, ERP, Queueing Network, Optimization, Human Factors

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Continuous Physiological Monitoring in TBI Patients and their Correlation to Biomarker Values

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Abstract. A key component of our TBI study is the continuous and automatic capture of patient physiological monitoring data from the bedside monitors. The purpose of the continuous monitoring is to better define and quantify periods of secondary insults that can then be correlated to changes in biomarker levels. Management of traumatic brain injury is performed by a group of neurointensivists and utilizes a therapeutic algorithm based on the guidelines for the management of severe TBI recently published in the Journal of Neurotrauma (2007). Continuous monitoring of eight physiologic parameters was performed with a custom made multi-channel digital recording system 1. Mean arterial blood pressure (MABP); 2. Intracranial pressure (ICP);3. Brain tissue oxygenation (PbO2 recorded using the Integra Licox); 4. Brain temperature (recorded using the Integra Licox); 5. Jugular venous oxygenation (SjvO2); 6. Core body temperature; 7. End tidal CO2; and 8. Heart rate. Additionally, cerebral perfusion pressure (CPP) was calculated as MABP less ICP. We programmed the MMM to collect data every 10-60 seconds.
Quantification of secondary insult was performed with the following method: after elimination of spurious values, the median of the first 1 minute measurements (6 measurements of 10 sec interval) was calculated. Then the mean of the 1 minute values was calculated for 5 minute increments. These data were then analyzed in 6 h intervals (according to biofluid collection schedule) for time and amount of secondary insults. The remaining physiological parameters, radiological studies and therapeutic interventions were recorded as clinically indicated, with a frequency not higher than ever one hour and are currently evaluated for their influence on the patient and the biomarker levels.
Statistical analysis of this large amount of data is hampered by a number of interferences caused by the patient's treatment and the monitoring device. Data have to be rigorously analyzed for non-physiological values and other erroneous data.

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Mining the Injured Neuroproteome at the Molecular and Functional Level

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Abstract. The pursuit of neurotrauma biomarkers has spurred the use of proteomics to characterize biochemical changes in injured brain. Neurotrauma is a leading cause of death and disability in America, particularly among the young prone to traumatic injuries and the elderly prone to stroke. Rapid, repeatable biomarker assays would thereby improve neurotrauma patient care. We present novel findings employing the mining of the neurotrauma proteome with correlation of dynamics with altered cellular processes. In this experiment, we compare uninjured (control) to injured cortex regions harvested 48 hours post reperfusion using a middle cerebral arterial occlusion rat model of brain ischemia, in a similar fashion to our previously published TBI neuroproteomic study. In all, 78 proteins were identified with a prominent change in abundance 48 hours post-ischemia / reperfusion injury compared with 59 at 48 hours following severe traumatic injury to the same cortical region. The majority (54) decreased in abundance while of those that increased (24) ten appeared as proteolytic fragments. All proteins were confirmed by correlating quantitative protein and peptide data, demonstrating an increased or decreased differential abundance. The data include minimal false-positive identifications as validated by immunochemical assays (on proteins with available antibodies). Importantly, the functional significance of the altered protein population was dependent on ischemic injury severity, and with some differences between modalities. In all, mining of the neuroproteome data revealed a mixed story of cell survival versus cell death processes. The varied nature of the neurotrauma biochemistry strikingly emphasized the importance of developing multiple biomarkers into assay panels.

Keywords: Neurotrauma, Proteomics, Protein Mining, Pathway mining, brain ischemia

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Reproducing Kernel Hilbert Spaces for Spike Train Analysis

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Abstract. This paper introduces a generalized cross-correlation (GCC) measure for spike train analysis derived from reproducing kernel Hilbert spaces (RKHS) theory. An estimator for GCC is derived that does not depend on binning or a specific kernel and it operates directly and efficiently on spike times. For instantaneous analysis as required for real-time use, an instantaneous estimator is proposed and proved to yield the GCC on average. We present experiments illustrating the usefulness of the RKHS approach.

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Co-adaptive brain-machine interfaces via reinforcement learning

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Abstract. Closed-loop neural interfaces are one of the most exciting emerging technologies to impact biomedical research, human health, and rehabilitation. By combining engineering and neurophysiologic knowledge into bio-interactive brain-machine interfaces (BMI), a new generation of medical devices is being developed to functionally link large ensembles of neurons in the central nervous system (CNS) directly with man-made systems. These neuroprostheses open new avenues to restore communication and control in the disabled while at the same time enables the study of sensori-motor function in goal directed behavior. While many studies have shown the feasibility of BMIs, the experimental and decoding frameworks used are ill prepared for the availability and complexity of signals acquired in the clinical setting. The goal of this work is to develop and test in vivo a new neural interface framework where the decoding algorithm is autonomous and includes the assistance of a computational agent (CA). Here, both the user and CA have to agree and discover how to accomplish a reaching task using a robotic arm. Using principles of reinforcement learning (RL) the user and CA must work together to maximize the cumulative return of rewards for a given task. The principles of neural control are learned by both the user and CA through experience and interaction with the environment. We hypothesize that this method of co-adaptive shaping using RL to achieve brain control of a prosthetic enables the development of complex tasks while reducing the "learning curve" for patients using a BMI. In particular, this paradigm also offers a way to continuously study the changes in neural response to co-adaptive motor control of a BMI and how the ultimate accumulation of rewards leading to the goal drives the learning process. The proposed experiments will provide new knowledge of the cortical activation involved in motor BMIs and will validate new decoding models.

Keywords: Reinforcement Learning, Co-Adaptation, Brain-Machine Interface, Neuroprosthetics

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Testing an Seizure Prediction Algorithm: Assessment of Performance

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Abstract. Seizure prediction research to date has focused on discovering and defining measurable changes in the EEG preceding seizure onset and developing and testing automated algorithms based on these measures to detect pre-seizure changes. Translation of this research into useful clinical tools will depend upon establishment of performance standards for specific clinical applications and the design of experimental protocols and statistical methods that will answer clinically-driven hypotheses. These hypotheses should be formulated according to the intended use of the prediction algorithm and, more importantly, a well defined "effectiveness" of an algorithm. Design of the study should also be well justified statistically so that the probability of making a false conclusion, either false "rejection" (i.e., type I error) or false "fail to reject" (i.e., type II error), is small. In addition, assessment of a prediction algorithm can be from different aspects and hypotheses. Fail to reject a specific null hypothesis does not mean that the test algorithm is totally ineffective. Assessment with different design and hypothesis could reveal its usefulness.

Keywords: Seizure Prediction, Statistical Assessment, Sensitivity, False Prediction rate

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Use of stem cells in Alzheimer's disease

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Abstract. We have found much evidence that the brain is capable of regenerating neurons after maturation. In our previous study, human neural stem cells (HNSCs) transplanted into aged rat brains differentiated into neural cells and significantly improved the cognitive functions of the animals, indicating that HNSCs may be a promising candidate for cell-replacement therapies for neurodegenerative diseases including Alzheimer's disease (AD). However, ethical and practical issues associated with HNSCs compel us to explore alternative strategies. Here, we report novel technologies to differentiate adult human mesenchymal stem cells, a subset of stromal cells in the bone marrow, into neural cells by modifying DNA methylation or over expression of nanog, a homeobox gene expressed in embryonic stem cells. We also report peripheral administrations of a pyrimidine derivative that increases endogenous stem cell proliferation improves cognitive function of the aged animal. Although these results may promise a bright future for clinical applications of stem cell strategies in AD therapy, we must acknowledge the complexity of AD. We found glial differentiation of stem cells transplanted into amyloid- precursor protein (APP) transgenic mice. We also found that over expression of APP gene or recombinant APP treatment causes glial differentiation of stem cells. Although RNA interference of APP or glial differentiation signaling cascade genes significantly reduced glial differentiation of stem cells, further detailed mechanistic studies are required because of a risk of shutting down signaling cascade, which may be important to regulate physiological function of stem cells. Importance of adult neurogenesis is not clear, however premature glial differentiation of HNSCs may harm maintenance of normal brain function and may contribute to the pathophysiology of AD. Also, successful neuroplacement therapy for AD may depend on a management of APP level in the optimal range for neuronal differentiation of HNSCs. We found treatment with (+)-phenserine, reduced APP protein and active astrocytes in the brain of APP23 mice. HNSCs transplanted into the (+)-phenserine treated APP23 mice migrated and differentiated into neurons. These results indicate that regulation of APP level may prevent astrocytosis under AD pathology and may be essential for the stem cell therapy for this disease.
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Failing Feedback as a Mechanism to Generate Epileptic Seizures

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Abstract. Simulation models of coupled neural populations with varying parameters have been used as tools to understand the basic mechanisms that can produce epileptic seizures and derive possible algorithms for their prediction. Here, interested in developing feedback control methods to suppress seizures, we study such models by allowing the variation of both model parameters and functional characteristics. We observe that if we consider a high level feedback, then epileptic seizures can be produced by failures in this feedback. Such feedback is motivated as a functional model achieving homeostasis in various quantities like firing rate or neural output correlation. This mechanism is a consequence of the functional behavior of the populations rather than a generic connectivity property. Nevertheless, it is a general mechanism in that the same principle can generate seizures in different types of models of neural populations, cortical neural populations with inhibitory-excitatory inputs, or even networks of coupled chaotic oscillators.
Transitions to epileptic seizures with the pathological feedback mechanism agree with experimental observations of increased synchronization. It is of particular interest here that the simulation models also indicate that a potential seizure suppression strategy is through feedback decoupling. This may be achieved by a variety of stimulation signals, some of which have been used in practice (e.g., biphasic pulses) and others that are new (e.g., diffusive coupling based feedback). However, both the simulation models and preliminary experimental data indicate that it is likely that multiple stimulation points will be required, making the computation of the feedback signals and their implementation a very challenging problem.

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Does the brain exhibit any dynamic approximation capabilities in learning and pattern recognition?

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Abstract. A biofeedback computer-based ALOPEX system was designed to present all visual stimuli and record pattern VEP's in real-time. Such a system would allow VEP response trends to direct the generation of more effective visual stimuli and the so generated could then be analyzed quantitatively, without a-priori knowledge of their information content. VEP parameters which change in relation to changes in image content were identified by modeling an ALOPEX pattern convergence, offline, and utilizing the resulting images as VEP stimuli in ten healthy subjects. Another set of experiments involved real-time ALOPEX stimulus/response biofeedback optimization of these VEP biofeedback response parameters. After identification of appropriate VEP stimulus/response biofeedback parameters, real-time ALOPEX experiments were performed. In some cases, VEP amplitudes were improved by 100 percent. Comparisons were made between images which elicited low VEP response amplitudes and images which produced strong responses. Quantitative image analysis revealed that VEP response trends were strongly correlated with global image contrast ($p < 0.01$), image entropy ($p < 0.01$), and two-dimensional spatial frequency. Spatial frequency tuning curves for the pattern sets used were computed, based on a novel ALOPEX black-box solution technique, developed for data analysis.

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Unverricht-Lundborg Disease: Challenges in treatment and outcome measures

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Abstract. Unverricht Lundborg Disease (ULD) is the most common type of progressive myoclonus epilepsy (PME), a rare seizure disease. ULD is typically diagnosed in children between the ages of six and 15 years who display the following clinical features: 1) involuntary, action-activated myoclonic jerks, 2) generalized tonic-clonic seizures, 3) exacerbation of neurodegenerative symptoms (myoclonus and ataxia) over time, 5) Abnormal EEG, 6) elevated SSEPs, and 7) thalamocortical hyperreactivity in the sensorimotor system. Electroencephalogram (EEG) is always abnormal in ULD patients, even before the symptoms appear; background activity is labile and usually slower than normal. Symmetric, generalized, and high-voltage spike-and-wave and polyspike-and-wave paroxysms are characteristic, and marked photosensitivity is the most prominent feature. Magnetic resonance images of the brain in ULD patients typically appear normal. Myoclonus is most debilitating in ULD patients and is very frequent occurring up to hundreds of jerks hourly. As the disease progresses, ataxia and decline in communication, swallowing and higher cortical functions compound more disability in ULD patients. Antiepileptic drugs (ADEs) are the mainstay treatment for ULD, although there are no clinical trials to support one particular drug over another. The rarity of ULD and the high frequency of myoclonus are major challenges to conduct controlled prospective clinical trials. A comprehensive measure of treatment efficacy supplementing clinical observations and patients' reports is desired. Innovative methods of quantitative EEG analysis as a surrogate measure for treatment efficacy will be discussed.

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Optimization in the Brain? -Modeling Brain Activation Patterns and Human Behavior with Queuing Network and Reinforcement Learning Algorithms

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Abstract. Neuroscience and behavioral research found several interesting brain activation and behavioral patterns in a visual-motor task: during the extensive practice process of a visual-motor task, fewer brain areas got involved but faster motor movement and lower variability were observed; after the visual-motor task is well learned, with an increase of the complexity of stimuli, more brain areas were recruited. This interesting "optimization" phenomenon in the human brain has not been covered by many existing computational models. The current work proposed a queuing network architecture of human brain and used reinforcement learning algorithms to optimize the routes of entities (information) traveling in the network, producing simulation results which are consistent with these findings in neuroscience and behavioral research. Future research of modeling human brain with queueing network and reinforcement learning algorithms is also discussed.

Keywords: Queueing Network, Optimization, Reinforcement Learning, Visual-motor Task

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