The State of Seizure Prediction:
Seizure Prediction and Detection I

Testing null hypotheses about seizure prediction algorithms

R. G. Andrzejak[1], D. Chicharro[1], F. Mormann[2,3]

[1]Department of Information and Communication Technology, Universitat Pompeu Fabra, Barcelona , Spain
[2]Department of Epileptology, University of Bonn, Bonn, Germany
[3]Division of Biology, California Institute of Technology, Pasadena , USA

Introduction: To test whether a prediction algorithm has any true predictive power, it is necessary to compare its performance with the performance expected under various well-defined null hypotheses. These null hypotheses must include the assumption that the prediction algorithm lacks any true predictive power. In the context of studies investigating the predictability of epileptic seizures, two approaches have been introduced for this purpose: analytical performance estimates and seizure predictor surrogates based on constrained randomizations of the original seizure predictor.

Methods: We recently extended the Monte Carlo framework of seizure predictor surrogates by introducing the concept of alarm times surrogates. We here construct artificial seizure time sequences and artificial seizure predictors to be consistent or inconsistent with various null hypotheses, in order to determine the frequency of null hypothesis rejections obtained from analytical performance estimates and alarm times surrogates under controlled conditions.

Results: Compared to analytical performance estimates, alarm times surrogates are more flexible with regard to the testable null hypotheses and more robust against a biased estimation of the original predictor's performance. Both approaches have similar, high statistical power to indicate true predictive power.

Conclusion: The key question in the field of seizure prediction is whether seizures can in principle be predicted or whether algorithms which have been presumed to perform better than chance are actually unable to predict seizures and simply have not yet been tested against the appropriate null hypotheses. Due to their flexibility with regard to the testable null hypotheses, alarm times surrogates can help to answer this question.

Statistical assessment of event predictors and probabilistic forecasting

Björn Schelter[1,2,5], Hinnerk Feldwisch[1,2,3,4], Michael Jachan[1,2,3], Andreas Schulze-Bonhage[2,3], and Jens Timmer[1,2,5,6]

[1]Center for Data Analysis and Modeling, University of Freiburg, Germany,
[2]Bernstein Center for Computational Neuroscience, University of Freiburg, Germany
[3]Epilepsy Center, University Hospital of Freiburg, Germany
[4]Department of Neurobiology and Biophysics, Faculty of Biology, University of Freiburg
[5]Department of Physics, University of Freiburg, Germany
[6]Freiburg Institute for Advanced Studies, University of Freiburg, Germany

Introduction: The statistical evaluation of prediction performance is of crucial importance in seizure prediction research; especially if yes/no-decisions on upcoming seizures are to be replaced by probabilistic forecasting. Patients, however, will benefit from probabilistic forecasting of seizures.

Methods: We present a comparison of different assessment strategies, both based on analytic and Monte-Carlo based approaches. Moreover, we will discuss to which extent seizure prediction can be based on probabilistic forecasting. A probability of seizure occurrence in the future time interval T, which is computed from the T foregoing seconds, is derived. The statistical evaluation of this probabilistic forecasting will be presented based on seizure time surrogates.

Results: The comparison of seizure assessment strategies shows that the different strategies have advantages under certain circumstances. In general, the Monte-Carlo based approaches are rather flexible bearing however the risk that specific characteristics of the prediction algorithms are tested for but not the performance above chance level. For probabilistic forecasting, performance above chance level can be achieved for some patients with the advantage of avoiding yes/no decisions.

Conclusion: Seizure prediction performance can be evaluated using various strategies with particular advantages/disadvantages under certain circumstances. Probabilistic forecasting enables patients to decide whether or not they want to take action against the upcoming seizure.

Seizure Prediction by Spectral Power in Nine Bands Using Cost Sensitive SVM

Yun S. Park[1], Theoden I Netoff[2], Keshab K. Parhi[1]

[1]Departments of ECE and [2]BME, University of Minnesota, Minneapolis, MN 55455

Purpose: A patient specific algorithm is proposed that can predict seizures based on EEG or ECoG with high sensitivity and specificity. This algorithm classifies pre-ictal (five minutes immediately before seizures) and inter-ictal (ordinary between seizures) signals of EEG or ECoG using spectral power in nine bands.

Methods: The proposed seizure prediction algorithm consists of the four steps: preprocessing, features extraction, classification, and postprocessing. First, preprocessing removed artifacts that raw EEG or ECoG recordings may contain such as line noise. Second, from a sliding 20-second long and half overlapped timewindow, spectral powers in the following nine bands were extracted as features: delta (0.5-4Hz), theta (4-8Hz), alpha (8-13Hz), beta (13-30Hz), four gamma (30-50Hz, 50-70Hz, 70-90Hz, 90Hz-), and across all bands. Third, Cost-Sensitive Support Vector Machine was employed as a classifier, for CSVM can handle unbalanced dataset by putting more weight on fewer but more important data classes, such as preictal. Last, 3 of 5 analysis was performed as postprocessing. If there are more than or equal to 3 positives out of 5 consecutive windows, a series of windows of 5-minute prediction time following the event are considered preictal; otherwise, they are predicted as interictal. For 9 of 21 patients' EEG recordings, each of which contains five seizures in Freiburg EEG data set, the proposed algorithm was applied with double-cross validation. Leave one out validation was performed for estimating the prediction risk of an optimal model with each of five seizure sets and the optimal model had been established through five-fold cross validation with the rest four seizure sets.

Results: The average sensitivity for the proposed algorithm is 77.8% and the false positive rate per hour is zero. This result is achieved based on 9 patients' EEG recordings, which contain 45 seizures and 219-hour long interictal signals.

Discussions: Spectral power in certain bands in EEG or ECoG, especially in high frequency bands, may play a key role in seizure prediction. Also, CSVM seems to perform very well as a seizure predictor; it seems to handle the large and unbalanced data set very effectively.

Seizure Prediction and Detection Research at Optima Neuroscience

J. Chris Sackellares[1], Deng-Shan Shiau[1], Jonathan J. Halford[2], and Kevin M. Kelly[3]

[1]Optima Neuroscience, Gainesville, FL, USA,
[2]Department of Neuroscience, Division of Adult Neurology, Medical University of South Carolina, Charleston, SC, USA
[3]Department of Neurology, Allegheny General Hospital, Center for Neuroscience Research, Allegheny-Singer Research Institute, Pittsburgh, PA, USA,

Purpose: To test the sensitivity and specificity of seizure prediction and detection algorithms.

Methods: Optima Neuroscience, Inc. is currently testing its proprietary seizure prediction and detection algorithms in scalp EEG recordings from patients admitted to Epilepsy Monitoring Units for diagnostic or presurgical evaluations. These algorithms are based on our findings that there are characteristic spatiotemporal patterns in the EEG that distinguish ictal from interictal and postictal states. Further, the transition from the interictal state to the ictal state is sufficiently slow, making it possible to detect these transitions several minutes to hours prior to a seizure. Evaluation of the algorithms is based on continuous EEG recordings performed at Allegheny General Hospital/Allegheny-Singer Research Institute (Kevin Kelly PI) and the Medical University of South Carolina (Jonathan Halford, PI). The algorithms incorporate well known linear measures of signal characteristics such as amplitude and frequency as well as measures of signal order and stationarity developed for the study of nonlinear systems. The algorithms are based on the previous work of our collaborative research teams at the University of Florida. Algorithm development and performance testing is performed at Optima Neuroscience, Inc. under the supervision of Deng-Shan Shiau. In addition to testing existing automated algorithms for seizure prediction and detection, we are investigating signal characteristics that cause false prediction or false detection of seizures.

Results: Preliminary results of this ongoing research are encouraging. Initial evaluation of the algorithms demonstrate seizure detection of 83%, with a false positive detection approximately every 15 hours, and prediction of seizures over 90%, with a false prediction rate of one every 8 hours.

Conclusions: Seizure prediction and detection algorithms using traditional measures of EEG signal properties along with measures designed to measure order and stationarity are capable of sensitivity and false positive rates that can be useful in clinical applications.

Acknowledgement: Supported by NIH Grant #RO1 NS050582

Stimulation-based state monitoring – new developments

S. Kalitzin[1], D. Velis[2], F. Lopes da Silva[3]

[1]Epilepsy Institute of The Netherlands (SEIN), Medical Physics Department
[2]Epilepsy Institute of The Netherlands (SEIN), Department of Clinical Neurophysiology
[3]Swammerdam Institute of Life Sciences, University of Amsterdam, The Netherlands

Purpose: To refine the technique of stimulation based observation and to test the relative phase clustering index (rPCI) for prediction of epileptic seizure onsets both in time and location.

Methods: In our group we apply active observation paradigms for localization of the site of seizure onset (SOS) in patients undergoing invasive pre-surgical evaluation. We are using several features of the triggered response of the system generating the intracranially sampled EEG, in particularly the relative phase clustering index (rPCI). We have applied the same features to investigate any possible predictive powers of rPCI with respect to the problem of predicting both the seizure onset time and location. We report two essential methodological novelties on account of IWSP4: (1) Different stimulation patterns have been tried, monophasic, biphasic and cyclic alternating patterns (CAP). They all produce similar outcomes but the best results are achieved by biphasic-cyclic alternating patterns (BICAP). This stimulation paradigm compensates for passive responses, for example due to volume conductance and capacitance that “contaminate” the PCI. (2) We have expanded the definition of the rPCI to include collective degrees of freedom in dynamic systems. This allows quantifying the total impact of the stimulation over the observed sites and not just over the neighbouring contacts.

Results: In six patients the rPCI predictions were consistent with the ictal localization performed by certified neurophysiologist (D.V). The CAP and in particular the BICAP stimulation protocol seem to work best for this purpose.

Conclusions: Stimulation based state detection seems to provide reproducible results when measuring the risk of epileptic transition at the site of stimulation. Bi-local properties of rPCI (coded by the stimulation and the measurement sites) may give further insight in the seizure propagation topology.

Recent approaches to seizure prediction at U Bonn

S. Bialonski, A. Chernihovskyi, M.T. Horstmann, D. Krug, K. Lehnertz, A. Rothkegel, M. Staniek, T. Wagner

Neurophysics Group, Department of Epileptology, University of Bonn, Germany

Purpose: There is now accumulating evidence for EEG analysis techniques that quantify interactions within the epileptic brain to allow an improved detectability of pre-seizure states.

Methods: Our research recently focused on the development of new concepts and time series analysis techniques to quantify time-dependent, directed interactions in epileptic networks together with developments that focus on the transferability of analysis techniques to miniaturized analysis systems.

Results: We will present findings obtained with EEG analysis techniques derived from synchronization and network theory. In addition, we will discuss some recent findings obtained from modeling studies.

Conclusions: Our new developments provide new insights into seizure generating mechanisms as well as on the development of alternative directions into seizure prediction and prevention.

The State of Seizure Prediction: Seizure Prediction and Detection II

How probable is seizure occurrence: a time-scale and time-frequency analysis of SEEG

J. Lina[1], F. Laurent[2], J. Jacobs[2], J. Gotman[2]

[1]Ecole de Technologie Supérieure, Montréal, Québec, Canada
[2]Montreal Neurological Institute, McGill University, Montréal, Québec, Canada

Purpose: There is an ongoing debate regarding the existence of a preictal state making seizures more likely. This study uses wavelet-based signal processing to explore the local property of "absence of smoothness" in the signals and its correspondence with the proximity of seizure onset. This study relies on the 'thermodynamical' description of signals that introduces, in the continuous time-frequency plane, the notions of local energy and associated entropy. This approach is applied to the high frequency sub-band of the SEEG signals, looking for a model based on a null hypothesis (specific state) able to separate the preictal from the interictal periods.

Methods: This work uses discrete and continuous wavelet representations of the intracranial EEGs from five temporal lobe epilepsy patients (13 seizures). The discrete framework is used to estimate scaling parameters that are related to local smoothness and that describe local properties of the signals with respect to frequency. The 50-150 Hz energies and entropies estimated in a sliding temporal window and computed on local maxima of the wavelet coefficients give a thermodynamical relationship that defines the notion of equilibrium. This notion is used to characterize the preictal state.

Results: First, the scaling parameters change at seizure onset but do not appear to change prior to seizures. Second, during a 2-minute period immediately preceding seizure onset, we obtain a linear relationship between energy and entropy that is consistent across seizures. This relationship is retained for periods of 5 and 10 minutes and defines the 'equilibrium state' from which seizure occurrence is more probable. However, it is statistically absent from almost 90% of interictal 2-minute periods.

Conclusion: The use of wavelet energy and entropy allow the definition of a preictal equilibrium state during which seizures seem to start. This state appears similar across seizures and is rarely present in interictal periods.

Seizure Prediction and Observability of EEG Sources

Levin Kuhlmann[1], Elma O'Sullivan-Greene[1,4], Dean Freestone[1,2], Alan Lai[2], Andre Peterson[1,2], Andrea Varsavsky[1,4], Karen Fuller[3], David Grayden[1,2], Anthony N. Burkitt[1,2], Mark Cook[2,3] , Iven Mareels[1,4]

[1]Department of Electrical and Electronic Engineering, The University of Melbourne
[2]The Bionic Ear Institute, Melbourne, Australia
[3]St. Vincent's Hospital Melbourne, Melbourne, Australia
[4]National ICT Australia, Victorian Laboratories, The University of Melbourne

Purpose: Investigate the feasibility of phase-synchrony-based seizure prediction through analysis of intracranial electroencephalographic (EEG) data and modeling of the EEG.

Methods: EEG Analysis: The time series of the phase-synchrony measure, mean phase coherence (MPC), was calculated from all channel pairs using long-term continuous intracranial EEG data from 3 patients. Prediction performance was evaluated for all channel pairs for different combinations of the following: (1) prediction based on pre-ictal increases or decreases in synchrony, (2) channel pairs processed with various analysis windows, (3) four minute median filtering was or was-not applied to the MPC time series and (4) prediction horizons within 0-15 minutes were applied. This enabled selection of the channel pair and processing parameters that gave the best performance. Prediction performance was compared against a random predictor. EEG modeling: Networks of linear oscillators were employed to investigate the observability of EEG signal sources. In this framework, each brain region is modeled by a clock pendulum system (oscillator) that is coupled to other regions. Control theoretic methods were applied to determine the observability of signal sources in simulated EEG.

Results: EEG Analysis: Analysis of synchrony-based seizure prediction in three intracranial EEG patients indicated that increases in synchrony are not useful for prediction, and pre-ictal decreases in synchrony only occasionally give performance better than a random predictor. EEG Modeling: Theoretically all the system states are observable. However, in practical terms very little information is observable, since the EEG has limited resolution (210-224 bits).

Conclusions: These results suggest that large scale measurements of EEG are unlikely to reveal any underlying synchrony of oscillators, because the number of underlying oscillators is far higher than the subset that is actually influencing the measure. This is consistent with our seizure prediction results and is important in the quest to find meaningful synchrony measures for EEG analysis.

Circadian Control of Neural Excitability in Temporal Lobe Epilepsy

Paul R. Carney [1-3], Sachin S. Talathi [1,3], Dong-Uk Hwang [1,3], Mark Spano [5], Pramod P. Khargonekar [1], William L. Ditto [4]

[1]J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, Gainesville, FL 32611, USA
[2]Departments of Pediatrics, Neurology, and Neuroscience, University of Florida, Gainesville, FL 32611 USA
[3]McKnight Brain Institute, University of Florida, Gainesville, FL 32611, USA
[4]Harrington Department of Bioengineering, Arizona State University, Tempe, AZ 85287, USA
[5]NSWC, Carderock Laboratory, W. Bethesda, MD 20817, USA

Purpose: "Balanced" neuronal networks account for many cortical activities including sensory information representation, decision-making, and sleep and motor control. A loss of balance in the neuronal network activity has been associated with the emergence of a number of neurological diseases including Parkinson's, Autism, Schizophrenia, Tourette's syndrome, and Epilepsy. Here we investigate the temporal dynamics of firing rates of high amplitude short time duration (100–200ms) spatially localized patterns of spontaneous electrical activity referred to as population spikes (PS), recorded from the hippocampal CA1 area in an animal model of temporal lobe epilepsy.

Methods: Depending on the shape profile two distinct classes of PS were identified in neural recordings from the hippocampal CA1 area labeled as type 1 PS (PS1) with a large negative excursion in the measured electrical activity and type 2 PS (PS2) with a large positive excursion in the measure electrical activity. We test our hypothesis in the framework of a simple two-dimensional Wilson–Cowan model that describes the interaction between firing activities of populations of excitatory (PS1) and inhibitory neurons (PS2).

Results: A sustained increase in the firing rate of PS1 with a concurrent decrease in the firing rate of PS2 occurs prior to seizure onset. PS1 and PS2 firing rates follow a ~24-hour circadian rhythm. Both PS subtypes are in-phase in age-matched control rats. Following status epilepticus, an abrupt phase shift in the circadian activity of the PS firing rates occurs. In vivo experimental results and modeling suggest the emergence of an imbalance in the firing activity of the two distinct classes of PS. The imbalance precedes the onset of spontaneous limbic seizures.

Discussion: We present experimental evidence for an evolving imbalance in brain excitability following injury, as characterized by the firing activity of the two distinct classes of PS. We propose a Circadian Control Hypothesis, which suggests that the evolving imbalance in the PS1 and PS2 firing rates is the result of an abrupt phase-shift in their circadian activity. The imbalanced in PS firing rates in turn leads to spontaneous seizure onset.

Support: National Institutes of Biomedical Imaging and Bioengineering (NIBIB) through Collaborative Research in Computational Neuroscience (CRCNS) Grant Numbers R01 EB004752 and EB007082, the Wilder Center of Excellence for Epilepsy Research, the Children's Miracle Network, and Epilepsy Foundation of America

Machine Learning Based Classification of Patterns of EEG synchronization for Seizure Prediction

Piotr Mirowski[1], Deepak Madhavan[2], Yann LeCun[1] and Ruben Kuzniecky[3]

[1]Courant Institute of Mathematical Sciences, New York University, New York, NY 10003, USA
[2]Department of Neurological Sciences, University of Nebraska Medical Center, Omaha, NE 68198, USA
[3]Comprehensive Epilepsy Center, NYU Langone Medical Center, New York, NY 10016, USA

Purpose: Research in seizure prediction from intracranial EEG has highlighted the usefulness of bivariate measures of brainwave synchronization. Spatio-temporal bivariate features are very high-dimensional and cannot be analyzed with conventional statistical methods. Hence, we propose state-of-the-art machine learning methods that handle high-dimensional inputs.

Methods: We computed bivariate features of EEG synchronization (cross-correlation, nonlinear interdependence, dynamical entrainment and wavelet synchrony) on the 21-patient Freiburg dataset. Features from all channel pairs and frequencies were aggregated over consecutive time points, to form patterns. Patient-specific machine learning-based classifiers (support vector machines, logistic regression and convolutional neural networks) were trained to discriminate interictal from preictal patterns of features. In-sample data consisted of 2/3 of interictal patterns and the earlier 2/3 preictal epochs, whereas out-of-sample data consisted of 1/3 interictal patterns and the latter 1/3 preictal epochs. The preictal period was defined as the 2 hours preceding a seizure. We evaluated out-of-sample seizure prediction performance, and compared each combination of feature type and classifier.

Results: For each patient, at least one method predicted 100% of the seizures on the test dataset, on average 60 minutes before the onset, without false alarm. Convolutional networks combined with nonlinear interdependence or wavelet coherence yielded the best results. Convolutional networks predicted all seizures without false alarm on 20 patients out of 21. Cross-correlation features enabled good seizure predictions with less than 0.3 false positives per hour on 13 patients out of 21; nonlinear interdependence on 19, wavelet phase-locking synchrony and phase difference entropy on 14 patients, wavelet coherence on 15.

Discussion and conclusions: Our machine learning techniques applied to spatio-temporal patterns of EEG synchronization outperformed all previous seizure prediction methods on the Freiburg dataset. This proves the utility of pattern recognition, which can capture patient-specific seizure precursors. Current research focuses on EEG datasets with a large number of electrodes.

Seizure prediction and control of epilepsy via resetting of brain dynamics

Leon D. Iasemidis[1,2], Shivkumar Sabesan[1], Kostas Tsakalis[2], David Treiman[3], Joseph Sirven[4]

[1]Department of Bioengineering, [2]Electrical Engineering, [3]Neurology Arizona State University, Tempe, AZ,
[4]Department of Neurology, Mayo Clinic, Phoenix, Arizona

Purpose: To develop a just-in-time (JIT) closed-loop deep brain stimulation (DBS) seizure control system based on real-time, on-line, automated seizure prediction.

Methods: The system was applied to the lithium-pilocarpine (LP) animal model for chronic epilepsy. Long-term EEGs (29 to 50 days per rat) were recorded from 6 male Sprague-Dawley rats via six microwire monopolar electrodes in four cortical and two hippocampal locations. Stimulation was applied to the centromedial thalamic nucleus via two Teflon coated tungsten bipolar twisted electrodes. JIT utilized our first-generation algorithms for prediction of seizures long prior to their occurrence [1]. Warnings of an upcoming seizure were issued on average 60 minutes before a seizure's occurrence. The stimulator delivered 1 minute pulse stimuli (130-200Hz; 200-600μA) at each JIT's seizure warning. A comparison to periodic stimulation with identical stimulation parameters was also performed per rat. The two stimulation schemes were compared in terms of their efficacy in controlling seizure rate and resetting of the observed preictal spatio-temporal entrainment of the dynamics in the epileptic brain.

Results: The JIT seizure control scheme showed reduction of daily seizure frequency and duration in 5 of the 6 rats, with significant reduction of seizure frequency (>50%) in 33% of the rats [2]. This constituted a significant improvement over the efficacy of the periodic control scheme in the same animals. Actually, periodic stimulation showed an increase of seizure frequency in 50% of the rats, reduction in 3 rats and significant reduction in 1 rat. Importantly, successful seizure control was highly correlated with resetting of entrained brain dynamics.

Conclusions: This study provides initial evidence for seizure control via closed-loop feedback control systems based on seizure prediction and deep brain stimulation (JIT-DBS). It shows that, under similar conditions, JIT outperforms periodic open-loop schemes for seizure control. It also offers an interpretation of the successes and failures of seizure control schemes in terms of resetting of brain dynamics.

References:

1. L.D. Iasemidis, D.S. Shiau, W. Chaovalitwongse, J.C. Sackellares, P.M. Pardalos, J.C. Principe, P.R. Carney, A. Prasad, B. Veeramani & K. Tsakalis, "Adaptive epileptic seizure prediction system", IEEE Trans. Biomed. Engineering, vol. 50 (5), pp. 616-627, 2003.
2. L. Good, S. Sabesan, Steven, K. Tsakalis, D. Treiman, L.D. Iasemidis, "Control of synchronization of brain dynamics leads to control of epileptic seizures in rodents", Int. J. Neural Systems, vol. 19 (3) (in press)

Real Time Seizure Prediction using an Adaptive Wiener Algorithm.

Pooja Rajdev, Pedro Irazoqui

Brain Computer Interface Lab, Dept of Biomedical Engineering, Purdue University, West Lafayette, IN, USA

Purpose: A real-time algorithm for automated seizure prediction from local field potentials (LFPs) is presented. It is hypothesized that LFPs not only have better spatial resolution and signal to noise ratio but also possess the capability of indicating epileptic spikes before they are observed on the EEG recordings.

Methods: A Wiener filtering based prediction algorithm was implemented on a Texas Instruments (TI) Digital signal processor and tested on kainite-treated rats, an animal model of human temporal lobe epilepsy. Model parameters were chosen based on the Akaike information criterion, and the modified Gersch criteria. Although the statistics of ictal data show non-stationarities, the baseline data can be considered to be quasi-stationary. Filter coefficients are thus updated in every epoch to model the data. The adaptive nature of the algorithm ensures that the coefficients provide effective prediction of baseline activity. The low computational complexity of the algorithm is an additional advantage, making its implementation in real-time feasible.

Results: Testing of the algorithm via offline Matlab analyses on kainate treated rats results in prediction of seizures 27±17 seconds before clinical onset, with 94% sensitivity and a false positive rate of 0.009 per minute. When implemented on a real-time TI C6713 signal processor, the algorithm results in prediction of seizures 6.7±5.6 seconds before their clinical onset, with 92% sensitivity and a false positive rate of 0.08 per minute.

Conclusions: The parameters of the time varying auto-regressive process were successfully able to detect preictal changes in the underlying model. Future directions involve optimizing thresholds to further reduce the false positive rate, decrease latency, and bring the hardware implementation results in-line with those obtained in Matlab.

Designing Epileptic Seizure Detection Algorithms towards a Miniature Implantable Epilepsy Prosthesis

Shriram Raghunathan[1], Sumeet K. Gupta[2], Kaushik Roy[2] and Pedro P. Irazoqui[1]

[1]Brain Computer Interface Lab, Dept of Biomedical Engineering, Purdue University, West Lafayette, IN, USA
[2]Nano-electronics Research Lab, Dept of Electrical and Computer Engineering, Purdue University, West Lafayette, IN, USA

Aim: One of the primary goals of the research project is to be able to record, detect and electrically stimulate to suppress epileptic seizures, with the goal of treating about 30% of the epileptic population that remains non-responsive to medication or other therapy. Our focus is to enhance the efficacy of responsive neurostimulation by designing new optimal mathematical models with the primary priority of real-time operation and miniaturization on hardware to detect seizures.

Methods: We present preliminary results from an event-based seizure detection algorithm that is designed off the hypothesis that electrographic seizures are usually accompanied by a significant increase in the amplitude and frequency of neural activity. A neural recording amplifier is used to mark out and timestamp ‘events’ in recorded local field potential data from the hippocampal regions of Kainic acid treated rats. Extracting frequency information indirectly by measuring the interval between successive events allows the algorithm to demarcate baseline activity form seizures. A multimodal approach to detection incorporates a variation of the discrete wavelet transform on chip in combination with the event based algorithm.

Results: The trade-offs between algorithmic efficiency are contrasted with hardware implementation metrics such as power and delay. Preliminary in-vivo validation of the event based algorithm indicates a selectivity of 90% and sensitivity of 94% from real-time testing on status epilepticus data from the implanted animals. The algorithm is implemented using sub-threshold CMOS circuits to consume under 350nW of power and within an area of 0.06mm2 per circuit simulations on an 180nm SOI technology node.

Discussion: The ultra-low power hardware implementation allows for the algorithm to be integrated with multi-channel neural recording systems to accurately identify and track the focus of epileptic seizures. An ongoing comparison of multiple approaches to seizure detection aims to incorporate a multi-modal detection engine on chip that share common feature extraction algorithms and combine them to reduce false detections, while still maintaining real-time low power operation.

The State of Seizure Prediction:
Seizure Generation

Interictal Fast Ripples Recorded from a Dense Microelectrode Array in Human Epileptic Neocortex

C. A. Schevon[1], A. J. Trevelyan[2], C. E. Schroeder[3], R. R. Goodman[4], G. McKhann Jr[4], R. G. Emerson[1,2]

[1]Dept of Neurology, [2]Dept of Pediatrics, [3]Dept of Psychiatry, [4]Dept of Neurological Surgery, Columbia University, New York, NY
[2]School of Neurology, Neurobiology and Psychiatry, University of Newcastle, Newcastle Upon Tyne, UK

Purpose: To investigate the spatial extent, distribution, and feature correlation of high frequency oscillations in neocortical epilepsy.

Methods: Chronic recordings were made from a dense 4 x 4 mm two-dimensional microelectrode array implanted in the neocortex of four patients undergoing epilepsy surgery. High frequency oscillations were auto-detected in interictal samples and visually reviewed for screening, classification, and association with epileptiform discharges, microdischarges, and increased multiunit activity.

Results: Nearly all of the HFOs detected had a fast ripple component, which correlated well with increased multiunit activity. Fast ripples were much more likely to be associated with epileptiform discharges than with microdischarges. The spatial distribution of HFOs was limited to 10-20% of recording channels, however an interesting phenomenon was seen when spatial distribution during simultaneous events ("HFO events") was examined. While most HFO events were limited to single channels, about 10% occurred on a larger spatial scale, with simultaneous but morphologically distinct detections in multiple channels. 80% of these large-scale fast ripples were associated with epileptiform discharges.

Discussion: We propose that large-scale fast ripples, rather than the more frequent highly focal events, are the substrates of the high frequency oscillations detected by typical clinical electrodes. Although our sample size is limited, we found this feature only within epileptogenic brain regions. The observation that fast ripples were commonly associated with epileptiform discharges, many presumably the result of neural propagation, but not with locally generated events e.g. "microdischarges" suggests that, rather than being initiators of epileptiform activity, fast ripples may be markers of a secondary local response.

Large-scale Electrophysiology: Acquisition, Storage and Analysis

Matt Stead, Mark Bower, Ben Brinkmann, Chris Warren, Greg Worrell

Mayo Systems Electrophysiology Laboratory, Department of Neurology, Mayo Clinic, Rochester, MN

Purpose: Large-scale electrophysiology recordings are a powerful tool for systems neurobiology. It is now possible to probe neural activity across a wide range of spatiotemporal scales; from extracellular action potentials of single neurons, local field potentials of small neuronal assemblies, to macroscale clinical EEG. We describe preliminary results and some of the challenges of large-scale data acquisition, storage, analysis.

Methods: To investigate the spatiotemporal scales characterizing human epileptic brain we perform continuous, long-term iEEG recordings. The wide bandwidth iEEG are obtained from hybrid electrodes containing macro (clinical) and microelectrode arrays in epileptic and non-epileptic brain from patients undergoing evaluation for epilepsy surgery, and in control brain from patients with intractable facial pain implanted for motor cortex stimulation.

Results: In 19 patients a total of 2544 hours of continuous intracranial EEG (iEEG) was recorded from hybrid electrodes, during which time 57 clinical an electrographic seizures were recorded. Interictal ripple and fast-ripple high frequency oscillations (HFO) were detected from both microwires and clinical macroelectrodes. In addition, interictal seizure-like discharges (microseizures) were recorded from individual microelectrodes in patients with epilepsy. Microseizures and HFO were increased in epileptic brain compared to control brain.

Discussion: Large-scale iEEG recordings show that human epileptic brain is organized on spatial scales not probed by clinical iEEG. In epileptic brain microseizures isolated to were detected on single microelectrodes and not seen on macroelectrodes. Interictal HFO and microseizures were increased in brain regions generating seizures and rare in brain regions not generating seizures. In some cases microseizures evolved into clinical macroscale seizures.

Conclusions: These findings support that epileptic brain is composed of pathological microcircuits generating microseizures and HFO, which are electrographic signatures of epileptic brain and may be involved in the generation of seizures.

Acknowledgments: This work was supported by funding from the National Institutes of Health grants R01-NS039069 & K23-NS4795, Minnesota Partnership for Biotechnology, and Epilepsy Therapy Development Program.

High-frequency oscillations in the epileptic brain: What is good and what is bad?

M. Le Van Quyen[1], R. Staba[3], A. Bragin[3], C. Dickson[2], M. Valderrama[1], J. Engel[3]

[1]Centre de Recherche de l'ICM, INSERM UMRS 975 - CNRS UMR 7225, Hôpital de la Pitié-Salpêtrière, 47, Bd de l'Hôpital, 75651 Paris Cedex 13, France
[2]University of Alberta Edmonton, Alberta, Canada
[3]Dept Neurol, David Geffen School of Medicine at UCLA, Los Angeles, USA.

Purpose: In patients with neocortical epilepsy, gamma oscillations (40-120 Hz) are often seen in EEG recordings at seizure onset and are highly localized in the seizure onset zone. In light of their strong presence in, and possibly initiation of, seizures, we have undertaken a study of gamma oscillations during the sleep-wake cycle in humans. During seizure-free periods of epilepsy patients undergoing presurgical clinical setting, we examined the existence of gamma patterns using large-scale microelectrode recordings, collected in parallel with macroscopic scalp EEG.

Methods: 9 epileptic patients were recorded with 64 chronically implanted microelectrodes (0.1-5kHz; sampled at 20kHz). Episodes of gamma activity were automatically identified with previous methodology (Staba et al., 2004) and were visually confirmed. Single-unit activities were extracted with spikes sorting using the KlustaKwik 1.5 program.

Results: Gamma band oscillations recurrently emerged over time windows of several hundreds of msec in many cortical sites during slow-wave sleep (SWS) and they are also present, but generally less pronounced, during waking and REM sleep. During SWS, gamma oscillations were correlated with positive peaks of EEG slow oscillations showing that they were associated with UP states. Several discrete spectral peaks were systematically identified in the low gamma range, around 50 Hz and 70 Hz, and also, occasionally, in the high gamma range around 90 Hz and 110 Hz, suggesting that multiple gamma generators are present within the human neocortex. After single unit isolation, we observed that the majority of cells (144 / 206) exhibited a strong increase in spike firing during gamma patterns and that many of these cells (52%) were significantly phase-locked to the oscillations, preferentially around the troughs of the gamma cycle. Furthermore, coincident firings with millisecond precision were significantly enhanced during gamma oscillations between cells over the same cortical area, suggesting that fast oscillations facilitate local neuronal synchronization.

Conclusion: We reported here the presence of neocortical gamma oscillations during seizure-free periods and have shown that these oscillations coincide with nonparoxysmal activities such as the slow sleep-like oscillation. We speculate that the increased high frequency activity seen at the onset of some neocortical seizures is the result of an aberration of the same physiological mechanisms underlying gamma activations in SWS, possibly restoring "micro-wake" activity patterns and reinforcing local epileptogenic circuits.

Complexity of Early Ictal Onset Patterns

Christophe Jouny, Piotr J. Franaszczuk, Greg K. Bergey

Johns Hopkins University School of Medicine, Epilepsy Center, Baltimore, MD USA

Rationale: The prediction of epileptic seizures is a paradigm that may be hindered by the lack of knowledge of what exactly is an epileptic seizure and how it starts. In an effort to better be able to identify changes that are relevant to the accurate detection of the onset of epileptic seizures, we focused on describing the early behavior of the ICEEG at the onset of epileptic seizures.

Methods: Based on the matching pursuit, a time-frequency decomposition algorithm that can be applied with no a priori knowledge of the content of the signal, we used the Gabor atom density, GAD to assess the variations in signal complexity of the onset of epileptic seizures. We compared GAD patterns to other assessments of the ictal onset such as signal power and entropy-based measurements to have a broader view of the changes of properties in the ICEEG during these periods and the interdependence of these measures. We studied fifty consecutive patients with intra-cranial monitoring recorded during presurgical evaluation.

Results: We analyzed 339 seizures including simple and complex partial seizures with or without secondary generalization. 330 out of 339 seizures have significant complexity level changes, with 319 (97%) having an increase in complexity. GAD increases occur within seconds of the onset of the partial seizure but are not observed in channels remote from the focus. Similar analysis of power shows less reliable association with electrographical onset. The complexity increase was similar for seizures from mesial temporal origin, neocortical temporal and extra-temporal origin.

Conclusion: Despite the predominant rhythmic activity that often characterizes onset and early evolution of epileptic seizures, onset of partial seizures is associated with an early increase in complexity.

Synergy of cellular dynamics and network structure in spatio-temporal pattern formation in excitatory networks

Andrew Bogaard[1], Jack Parent[6], Michal Zochowski[1,2,3,7], Victoria Booth[3,4,5]

[1]Department of Physics, University of Michigan;
[2]Biophysics Research Division, University of Michigan;
[3]Neuroscience Graduate Program, University of Michigan;
[4]Department of Mathematics, University of Michigan;
[5]Department of Anesthesiology, University of Michigan;
[6]Department of Neurology, University of Michigan;
[7]Michigan Center for Theoretical Physics, University of Michigan

Purpose: Changes in spatio-temporal patterning of neural networks are known to be associated with modulations of cellular and network properties, but the interaction between both properties is not well studied. Here, we investigated the complex interactions between membrane excitability and network structure in the context of seizure-like synchrony.

Methods: Using NEURON, a simulation environment, we considered excitatory networks consisting of neurons with excitability properties varying between Type I-like and Type II-like. Such cells exhibit significantly different spike frequency responses to external current stimulation, especially at firing threshold. The multi-compartmental cell model consisted of a passive dendritic cable and soma, containing Hodgkin-Huxley Na+ and K+ delayed rectifier currents, as well as the K+ A-type current and the hyperpolarization-activated, non-specific cation current Ih, that are known to occur in CA1 hippocampal pyramidal neurons. The cells were coupled locally with excitatory synapses, and the network was constructed following Small World Network rules. We studied the effects of shifting cellular membrane dynamics from Type I-like to Type II-like and mimicked network reorganization by varying network topology using the rules of Small World Networks.

Results: We showed that cell composition affected network behavior for the same Small World parameters over a wide range of network topologies and connectivity levels. Type I-like neurons resisted global synchrony, while Type II-like neurons favored global bursting. Networks of heterogeneous cell composition exhibited emergent behavior not seen in homogeneous networks.

Discussion: These findings show that modification of membrane currents and network cell composition could have strong effects in the spatiotemporal patterning of network activity, suggesting that a single ictogenic mechanism alone is not responsible for seizure generation.

Acknowledgements: University of Michigan Center for Computational Medicine and Biology (all), NIBIB EB003583 (MZ), NSF DBI-0340687, NIMH 076280 (VB)

Large scale networks in epilepsy: local and long-range connectivity

Hitten P. Zaveri[1], Steven M. Pincus[2], Irina I. Goncharova[1], Robert B. Duckrow[1,3], Susan S. Spencer[1,3]

[1]Departments of Neurology and [3]Neurosurgery, Yale University, New Haven, CT 06520, USA;
[2]Guilford, CT 06437, USA

Purpose: We employed bivariate measurements of the background intracranial EEG (icEEG) of patients with localization related epilepsy to define and contrast network topology in two groups of patients.

Methods: The background icEEG of twelve patients with localization-related epilepsy (n=6 medial temporal (MTLE), and n=6 either frontal or fronto-parietal (F-P) onset of seizures) were studied. All electrode contacts were co-registered to the MRI of a standard brain and subsequently categorized in one of 10 ROIs (ipsi and contra: frontal, parietal, medial temporal, lateral temporal and occipital). We evaluated and ranked linear bivariate measurements between all pairs of contacts in each patient. Bivariate measures within an ROI were considered local measures, and those between ROIs were considered long-range measures. The rank order of the bivariate measurements was averaged for each ROI separately for the MTLE and F-P patient groups. The average rank-order of the bivariate measurements was considered to constitute network definitions for each group.

Results: The highest bivariate measurements in the two groups were observed within the seizure onset ROI, within the contralateral homotopic ROI and between these two ROIs. In addition, in the MTLE group there were high values in the ipsilateral-frontal ROI. The average rank-order measurements of each patient were compared to the MTLE and F-P group averages. Four comparisons were performed: (1) between MTLE patients and the MTLE definition (performed with the leave-one-out method), (2) between F-P patients and the MTLE definition, (3) between MTLE patients and the F-P definition, and (4) between F-P patients and the F-P definition (performed with the leave-one-out method). For both MTLE and F-P patients the within-group measurements were smaller than across group measurements.

Conclusions: The tests performed suggest that a relatively well-defined network topology can be inferred, to first-order, from the background intracranial EEG of patients with localization related epilepsy.

The State of Seizure Prediction: Seizure Control

Seizure Evolution and Control in Animal Models

Bruce J. Gluckman[1,2], Nick Chernyy[1], Sridhar Sunderam[1], Madineh Sedigh-Sarvestani[1,2], Steven L. Weinstein[3], Steven J. Schiff[1,2,4]

[1]Dept. of Engineering Sciences and Mechanics, [2]Dept. of Neurosurgery, [4]Dept. of Physics, Penn State University, Center for Neural Engineering, PA
[3]Dept. of Pediatric Neurology, Weill Cornell Medical College, NY

Purpose: Polarizing low frequency electric fields (PLEFs) have been shown to modulate neuronal membrane excitability as well as population excitability In Vitro and to modulate seizure activity In Vivo. We have developed a prototype device for neural modulation with PLEF and simultaneous recording in a chronically implanted application. We are currently testing the prototype in chronically implanted rats, especially in the context of long term recordings with the tetanus toxin model of temporal lobe epilepsy.

Methods: Sprague-Dawley rats are implanted with both stimulating and recording electrodes. Stimulation electrodes are coated with an Iridium Oxide thin film to increase charge-passing capacity, and are implanted in the ventral hippocampus aligned with the axis of the CA3. Tetanus toxin is focally injected into the hippocampus to induce spontaneous seizures. We record continuously for weeks to months, and episodically stimulate with a broad range of stimuli to modulate activity.

Results: Animals spontaneously seize with a primary envelope of seizure beginning ~1 week after implant, with a peak seizure rate after ~2 weeks, and trailing off to a few per week after ~6 weeks. Seizure rate varies with a strong diurnal pattern that is time-locked to the light/dark cycle. We demonstrate successful modulation of ictal behavior with periodically applied PLEF.

Discussion: The PSU prototype for PLEF application under chronic implant conditions is successful. We can simultaneously apply PLEF and record neural activity with minimal artifact. We demonstrate successful modulation of spontaneous seizures with PLEF. We are now working to use PLEF both to probe the nature of the interictal and preseizure states, and to control seizure.

Acknowledgment: Work supported under grants: R01EB001507, R01MH50006, K02MH01493, and Pennsylvania Dept. of Community & Economic Development Keystone Innovation Grant

Modulating seizure-permissive states with weak electric fields

Davide Reato, Lucas C. Parra, Marom Bikson

Department of Biomedical Engineering, The City College of New York of CUNY, New York, USA

Purpose: The study of electrical stimulation of normal or seizure permissive neuronal states may be useful for electrical control of neuronal networks away from seizure states. Gamma oscillations are normally present in the brain and changes in gamma-band power have been investigated in the context of seizure initiation. A quantitative description of how electrical stimulation interacts with the state of neuronal networks will ultimately support rational epilepsy electrotherapy.

Methods: Carbachol-induced gamma oscillations in acute brain slices are stable oscillations, coherent across hundreds of microns, suitable to study in detail the effect of electrical stimulation on the neuronal dynamics. The effects of spatially uniform electric fields were studied; waveform (DC, sinusoidal), frequency (0 to 60 Hz) and amplitude (0.5 to 10 mV/mm) were varied. Multi-channels and intracellular recording was used to quantify the coherence of the endogenous activity under stimulation. A neuronal network model (800 excitatory, 200 inhibitory Izhikevich-based neurons) was implemented to study these phenomena.

Results: The effects of electrical stimulation on neuronal activity was highly stimulation waveform and network state dependent. Generally, DC fields resulted in only transient modulation of activity, low-frequency (<10Hz) resulted in amplitude modulation gamma-activity, while high-frequency fields (>20Hz) shifted the dynamics of the network toward sub-harmonics of the stimulation frequency (e.g. half the frequency). Changes in network dynamics reflected changes in firing rate and timing (e.g. neuron spiking precision inside the gamma cycle).

Discussion: The dynamics of gamma activity can be acutely controlled by electric fields. A relatively parsimonious computational model can reproduce experimental findings and drive electrotherapy protocol development. The modulation of gamma oscillation reflects the response on the entire integrated network, rather than simply single neuron polarization, and is thus dependent on the network state.

Conclusions: Epilepsy electrotherapy strategies using weak fields to target sub-convulsive network, including gamma field activity, activity merit consideration.

Vagus Nerve Stimulation Triggered By Patient-Specific Detection of Seizure Onset: Initial Clinical Implementation and Evaluation

Ali Shoeb[1], Trudy Pang[2], John Guttag[1], Steve Schachter[2]

[1]Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, Boston, MA
[2]Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA

Purpose: To demonstrate the feasibility of using a computerized system to detect the onset of a seizure and, in response, initiate Vagus nerve stimulation (VNS) in patients with medically refractory epilepsy.

Methods: We designed and built a non-invasive, computerized system that automatically initiates VNS following the real-time detection of a pre-identified seizure or epileptiform discharge. The system detects these events through patient-specific analysis of the scalp electroencephalogram (EEG) and electrocardiogram (ECG) signals.

Results: During an 81 hour clinical test of the system on a patient, the computerized system detected 5/5 seizures and initiated VNS within 5 seconds of the appearance of ictal discharges in the EEG; VNS did not seem to alter the electrographic or behavioral character of the seizures in this case. During the same testing session the computerized system initiated false stimulations at the rate of 1 false stimulus every 2.5 hours while the subject was at rest and not ambulating.

Discussion: Initiating Vagus nerve stimulation soon after the onset of a seizure may abort or ameliorate seizure symptoms in some patients; unfortunately, a significant number of patients cannot initiate VNS by themselves following the start of a seizure. A system that automatically couples automated detection of seizure onset to initiation of VNS is therefore desirable.

Low Frequency Sine Wave Stimulation as a Therapy for Epilepsy

Jeffrey H. Goodman

Dept. of Developmental Neurobiology, Institute for Basic Research, Staten Island, New York; Dept. of Physiology and Pharmacology; SUNY Downstate Medical Center, Brooklyn, New York.

Purpose: The majority of studies that have examined the efficacy of deep brain stimulation as a therapy for epilepsy have focused on the use of high frequency stimulation. The purpose of this study was to test the efficacy of low frequency sine wave stimulation (LFSWS) and low frequency pulsatile stimulation (LFPS) in amygdala and hippocampal kindled rats.

Methods: Bipolar stainless steel electrodes were bilaterally implanted into the basolateral amygdala or dorsal hippocampus of male Sprague-Dawley rats. A preemptive LFSWS (1Hz, 50µA, sine wave, 30sec) was delivered immediately before each kindling stimulus (60Hz, 400µA, 1msec pulse, 1-2sec) during kindling acquisition and in rats fully kindled in the amygdala or hippocampus. Preemptive LFPS (1Hz, 50µA, 1msec pulse, 15min) was tested in rats fully kindled in the hippocampus. In a separate study the effect of postictal LFSWS (1Hz, 50µA, 1min) and LFPS (1Hz, 50µA, 1msec pulse, 15min) were examined in rats fully kindled in the amygdala.

Results: Preemptive LFSWS significantly decreased the incidence of afterdischarge (AD) during kindling acquisition by 30% ($p<0.0001$). The same stimulus decreased the incidence of stage 5 kindled seizures in the amygdala by 58% ($p<0.0001$) and in the hippocampus by 30% ($p<0.001$) in fully kindled animals. When preemptive LFSWS was effective it completely blocked the incidence of AD and behavioral seizures. Postictal LFSWS delivered 90sec after the end of the AD decreased the incidence of stage 5 seizures by 40% ($p<0.03$) but was graded in that behavioral seizures less than stage 5 were often observed. The effectiveness of postictal LFSWS improved over time. Postictal LFPS had no effect on seizure incidence.

Conclusion: These results provide evidence that LFSWS may be an effective new therapy for epilepsy. The mechanism responsible for this anticonvulsant effect is unknown. Further studies are required to determine if altering the stimulus parameters will increase its effectiveness.

A SVM Assembly Classifier for Epileptic Seizure Detection

Yuang Tang and Dominique Durand

Neural Engineering Center, Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH 44106 USA

Purpose: An automated epileptic seizure detection algorithm is presented.

Methods: The proposed algorithm implements a Gabor filter bank to decompose EEG signals into physiological functional sub-bands. Feature vectors including the mean Teager energy, the Lempel-Ziv complexity are constructed within each sub-band for 500 ms EEG segments with 400 ms overlaps. The final classification of the feature vectors is performed via a support vector machine (SVM) chosen from a SVM assembly. The assembly is composed of SVMs that are trained over the same training set but with different weighting factors assigned to the seizure and non-seizure datasets. During operation, the user can tune the proposed algorithm by simply choosing a particular SVM within the assembly to adjust the sensitivity/specificity of the classification.

Results: SVMs trained with a higher weight for seizure data generally exhibits an increase in sensitivity and a decrease in onset detection latency and specificity while SVMs trained with a higher weight for non-seizure data offers improved specificity but at a cost of sensitivity and onset detection latency. With a training ratio of $WEIGHT_{Seizure\ Data}$: $WEIGHT_{Non\text{-}seizure\ Data}$ = 2:1, the proposed algorithm achieves a mean sensitivity of 100% and specificity of 84% by events. For a training ratio of $WEIGHT_{Seizure\ Data}$: $WEIGHT_{Non\text{-}seizure\ Data}$ = 1:2, a mean sensitivity of 99% and specificity of 87% are achieved with a relative increase in mean seizure onset detection latency of 60ms.

Discussion: The results demonstrate the feasibility of the proposed algorithm to offer not only effective seizure onset detection performance but also easy tuning of sensitivity/specificity/onset detection latency by the user. By composing an assembly of SVMs trained on the same dataset but with different class weighting ratios, the user can easily tune the detection algorithm by choosing the best SVM, in the assembly, for any given situation.

Acknowledgement: This work was supported by a grant for the National Institutes of Health #1R01NS060757-01A1

The State of Seizure Prediction

Brian Litt

University of Pennsylvania, Philadelphia, Pennsylvania

The field of seizure prediction continues to mature, engender more interest from a diverse research community, and appears to be leading relentlessly along several parallel paths: (1) Complementing a rich history of analysis of continuous and abstract variables there are growing efforts focused on a more intensive search for physiological markers of seizure generation multi-scale, with particular focus on broad-band clinical and experimental recordings. (2) There is renewed interest in understanding exactly what constitutes a seizure, and in identifying the fundamental neural substrate for seizure initiation, such as distributed, functionally connected microdomains, perhaps with dimensions on the order of cortical columns. (3) There is a relentless move towards conducting research on natural “free range” data acquired from ambulating patients, and away from induced seizures in Epilepsy Monitoring Unit Data, which may introduce confounding variables into prediction research. This development will require close, responsible collaboration with industry. (4) Prediction research in chronic animal models of epilepsy continues to flourish, but with a growing realization that continuous, 24/7 recording is likely necessary to characterize model behaviors, as well as prolonged recording up to months, to understand stability of appropriate models. (5) Now that there is growing consensus on statistical validation of prediction studies, there is a great focus on amassing large, shared archives of well “scrubbed” human and animal data for validating and comparing algorithmic approaches, and for laying the groundwork for human trials. Finally (6) there are converging approaches between electrophysiological evaluation of seizure generation and patient-based observations that will likely converge on joint research studies in the near future.

Novel insights into the dynamics of intractable human epilepsy

Ivan Osorio[1,2], Mark G. Frei[2], Didier Sornette[3], John Milton[4]

[1]The University of Kansas Medical Center, Kansas City, KS 66160
[2]Flint Hills Scientific, LLC, Lawrence, KS 66049
[3]D-MTEC, D-PHYS and D-ERDW, ETH Zurich, Zurich, Switzerland,
[4]W.M. Keck Science Center, The Claremont Colleges, Claremont, CA

Purpose: Knowledge of relevant statistical features such as probability distributions of energies (E) and inter-seizure intervals (ISI) of clinical and subclinical seizures is lacking in epileptology. This work endeavors to gain insight into the dynamics of Sz and their interactions by adopting a “systems” (non-reductionist) approach to their study, using powerful mathematical tools.

Methods: Probability density functions and the probability of Sz occurrence conditional upon the time elapsed from the previous Sz were estimated using the energy and intervals of SZ in prolonged recordings from 58 subjects with localization- related pharmaco-resistant epilepsy, undergoing surgical evaluation.

Findings: Clinical and subclinical seizure E and ISI distributions are governed by power laws in subjects on reduced doses of anti-seizure drugs. There is increased probability of Sz occurrence 30 minutes before and after a seizure and the time to next seizure increases with the duration of the seizure-free interval since the last one. Also, over short time scales, “seizures may beget seizures”.

Conclusions: The cumulative empirical evidence is compatible with and suggests that at least over short time scales, seizures have the inherent capacity of triggering other seizures. This may explain the tendency of seizures to cluster and evolve into status epilepticus. Power law distributions of E and ISI indicate these features lack a typical size/duration and may not be accurate/sufficient criteria or sufficient for classifying paroxysmal activity as ictal or interictal. This dependency and the existence of power law distributions raise the possibility that Sz occurrence and intensity may be predictable, without specifying the likelihood of success.

Seizure abatement with single DC Pulses: Is Phase Resetting at play?

Ivan Osorio[1,2] and Mark G. Frei[2]

[1]The University of Kansas Medical Center, Kansas City, KS 66160
[2]Flint Hills Scientific, LLC, Lawrence, KS 66049

Purpose: Topological approaches for seizure abatement have received scarce attention. The ability to reset the phase of biological oscillations has been widely exploited in cardiology, as evidenced in part by the usefulness of implantable of defibrillators, but not in epileptology. The aim of this work is to investigate the feasibility of seizure blockage using single or brief monophasic (DC) pulse trains.

Methods: Single DC or brief (0.1s) pulse trains were delivered manually or automatically to generalized seizures, induced in rats with the convulsant 3-mercaptoprionic acid, a GABA inhibitor. Treatment outcome (blocked vs. not blocked seizures) was ascertained visually and correlated with the “rhythmicity index”, an indirect estimate of neuronal synchrony level.

Results: Blockage using single or brief (0.1s) DC pulses was consistently achieved for seizures with a rhythmicity index equal to or greater than >0.6, while seizures with rhythmicity indices below 0.6 were not, although transient phase changes in their oscillations were often effected.

Conclusions: This work reveals that level of neuronal synchronization may be an important factor in determining the probability of seizures blockage. Seizure blockage using single or brief DC pulse trains and its effects on neural tissue merit further investigation. The clinical applicability of this therapeutic modality and means to enhance it are discussed.