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SEIZURE PREDICTION: THE FOURTH INTERNATIONAL WORKSHOP

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Abstract

The recently convened Fourth International Workshop on Seizure Prediction (IWSP4) brought together a diverse international group of investigators, from academia and industry, including epileptologists, neurosurgeons, neuroscientists, computer scientists, engineers, physicists, and mathematicians who are conducting interdisciplinary research on the prediction and control of seizures. IWSP4 allowed the presentation and discussion of results, an exchange of ideas, an assessment of the status of seizure prediction, control and related fields and the fostering of collaborative projects.

Keywords

seizure prediction; seizure anticipation; seizure dynamics; seizure generation; seizure detection; seizure control; device

Introduction

The unpredictability of seizures is one of the most debilitating aspects of epilepsy, seriously impacting patient safety and quality of life. Over the past 25 years, and particularly since the turn of the century, an international interdisciplinary effort involving epileptologists, neurosurgeons, neuroscientists, computer scientists, engineers, physicists, and mathematicians, (the International Seizure Prediction Group, ISPG) has sought to define a pre-seizure period and predict and control the onset of seizures based on the detection of this state. The significance of this effort is twofold: 1) improving quality of life and decreasing morbidity and mortality in a cost-effective manner, through warning of an impending seizure and early delivery of pharmacological or non-pharmacological therapy to abort, or otherwise ameliorate its deleterious effects, and 2) improving our understanding of how seizures are generated.

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The Fourth International Workshop on Seizure Prediction

The ISPG convenes workshops approximately every 18 to 24 months and the Fourth International Workshop on Seizure Prediction (IWSP4), the most recent in this series of workshops, was hosted in Kansas City on June 4–7, 2009 by the Alliance for Epilepsy Research to 1) facilitate and enhance communication among researchers with diverse backgrounds, 2) expose the ISPG to concepts and approaches employed in other fields, 3) allow all participants to share results and ideas and debate controversial issues, 4) involve patients in shaping the future of this important effort by understanding their expectations and reservations, 5) attract and educate graduate students interested in this problem, and 6) introduce investigators to the process of commercialization. IWSP4 consisted of several forums and initiatives to facilitate these multiple goals including didactic sessions on neuroanatomy, epileptology, neuroscience, engineering, dynamical systems, prediction and control; keynote presentations by invited experts; platform and poster presentations on the state of seizure prediction, seizure generation and seizure control; and a seizure prediction and detection competition. Furthermore, there were debates on controversial topics; presentations on technology for brain implantable devices and commercialization; a presentation on and discussion of patient perspectives; a presentation on collaborative efforts to collect and share icEEG data; a consensus session where workshop participants discussed IWSP4, the workshop series, and progress towards goals; support for women, minority and junior investigators; and prizes for best posters. Previous meetings in this series were held in Bonn, Germany in 2002 [1], Bethesda, MD, USA in 2006, and Freiburg, Germany in 2007 [2].

Invited experts addressed topics ranging from what makes the behavior of a system predictable, seismic prediction, prediction in materials and financial systems, non-linear brain dynamics of complex partial seizures and synchronization in complex networks. Didier Sornette discussed the nature and predictability of outlier events in complex systems and presented results which indicated that the probability distribution functions of seizure energies and inter-seizure intervals follow power laws and the probability of seizure occurrence follows an Omori decay law as a function of time since the last seizure [3]. Interestingly, seizure laws are qualitatively similar to those governing earthquakes, an analogy that if confirmed, would provide encouragement given the recent progress in the field of seismology based on the concept of inter-event triggering. Shane Haas drew parallels between prediction in the financial markets and the prediction of seizures. He discussed the Sharpe ratio, which is a measure of return per unit of risk, and other measures, provided insights to compare and validate the performance of different prediction or detection algorithms, and discussed the considerable data requirements, given typical seizure occurrence rates, to distinguish skill from luck and determine the “best” algorithm from a field of candidates. An important overall message was the need to frame realistic expectations. Walter Freeman summarized his observations on microelectrode recordings in a cat model of complex partial seizures created by a repeated strong electrical stimulation of the lateral olfactory tract. Evidence in this model of epilepsy implicates high level of activity among inhibitory interneurons in the initiation of a seizure [4]. He discussed the careful work necessary to delineate and identify the different types of activity observed in this experimental preparation and the subsequent determination of the role played by inhibition in seizure initiation. His presentation underscored both his argument that seizures are an expression of the failure of complex feedback control systems and the necessity for looking at multiple levels of organization within the brain and the interactions between these levels. Jürgen Kurths presented evidence that the major feature of organization of cortical connectivity is a very strong hierarchical structure, a clustered organization into functional communities (a network of networks) with highly connected hubs which facilitate the integration of multisensory information [5]. His main argument was that there is

considerable promise in approaching problems in neuroscience as problems in complex networks with rich synchronization phenomena [6] and that progress in understanding synchronization in neuronal networks and the role played by the network topology will be crucial to understanding normal and pathological brain activity.

Investigators described, in platform and poster presentations, multiple approaches to seizure detection and prediction which were either novel, for example approaches based on machine intelligence, or modifications or updates of previous methods. It is amply clear that the statistical issues underpinning the effort to detect, predict and control seizures need to be fully understood. The importance of thorough objective assessment and validation of the performance of prediction and detection algorithms was emphasized along with the role that experimental design and statistical tools play. There was one presentation each on testing the null hypothesis on seizure prediction and probabilistic forecasting. Seizure prediction in humans is almost universally performed with passive recording techniques. An alternate approach seeks to perform seizure prediction with active perturbation through electrical stimulation, and two updates were presented on this approach. Seizure detection was the goal of a few studies, including one on the hardware realization of a prosthetic device for this purpose. Seizure detection was also introduced into the seizure prediction competition for the first time in this series of workshops, though there was no clear winner for the seizure detection or prediction competition.

The iEEG is typically sampled by electrode contacts that are a few mm in diameter and are placed 1 cm apart (center-to-center interelectrode distance). The introduction into epileptology of high density micro-electrodes, such as those used in the field of brain computer interface (BCI), has provided considerably greater detail of the local field potentials, allowing the identification of “microseizures” (brief, small amplitude oscillations not recordable with conventional intracranial electrodes) and of high frequency oscillations (HFOs, > 100 Hz) whose significance is the subject of research and debate. Investigators discussed the observation of microseizures and HFOs in normal (control) and epileptic brains and separately the relationship between HFOs, fast ripple activity and epileptiform discharges. Other investigators looked at the use of time-frequency methods to characterize and understand seizure, the circadian modulation of neural activity in an animal model of temporal lobe epilepsy, and the role of large scale networks in the generation of seizure.

In addition to seizure prediction and seizure generation a third topic explored in this series of workshops is the control of seizures through the use of a device. Investigators presented work on modulating neuronal activity with polarizing low frequency electric fields in an animal model of epilepsy and modulating gamma activity with weak electric fields in a hippocampal slice and computational model. Another presentation evaluated the impact of low frequency sine wave stimulation in the rodent kindling model of epilepsy. Other researchers applied the concept of phase resetting to demonstrate that the effect of electrical stimulation on seizures is linked to the timing of stimulation and the level of neuronal synchronization of the activity. Additional studies presented also included an evaluation of patient initiated vagus nerve stimulation to abort a seizure and a comparison of just-in-time and open loop stimulation in a rodent model of epilepsy.

The importance of patients’ perspectives in shaping the direction of research in seizure detection, prediction and control materialized in this workshop in the form of a survey and a session to present the results. The survey was published on the IWSP4 website and completed by both epilepsy patients and caregivers since epilepsy impacts both. The results of the survey, presented by Susan Arthurs, revealed an overwhelming desire and need for prediction of seizures but reluctance for having devices implanted without considerably more information about them and assurance of success. The lead-time preferred by survey

respondents for prediction of seizures was 3 to 5 minutes, a duration which would allow for patient safety. Longer warning times were seen as being more stressful than helpful.

Discussion

IWSP4 brought together investigators from multiple backgrounds, laboratories, and countries working on seizure prediction and related problems to share their work, exchange ideas and form collaborative projects. The different sessions facilitated a common understanding of the problem and an evaluation of the status of the field. The debates helped highlight open problems in the field, brought to the fore the existence of important epistemic limitations, and clarified opposing perspectives on these open problems. The active participation of students and junior investigators as well as investigators from both academia and industry in the different sessions including the patient perspectives, technology and industry sessions bodes well for the future of this and related fields. The debates and patient perspective survey are being prepared for publication as manuscripts and the workshop proceedings are being prepared for publication as a book.

IWSP4 demonstrated that more comprehensive and sophisticated approaches are being employed to better understand seizure generation and fulfill the objective of predicting seizures. The emphasis on more rigorous hypothesis testing and validation of claims of prediction and seizure control are now widely recognized as necessary if substantive progress is to be made. The different presentations, discussions, debates and seizure prediction competition support the now accepted assessment that the challenge of predicting seizures is substantial. While some of the approaches presented may hold promise for seizure prediction they remain to be fully tested.

The ISPG may be considered a major innovative factor for research in epilepsy and it may serve as a “blueprint” for initiatives to better understand and manage other brain disorders. Important for the systematic development of this and related areas of inquiry is a clear definition of the problem, metrics to evaluate progress including testing on gold standard data, forums to exchange information, and training of students, fellows and faculty in interdisciplinary research and support for their research activities. Equally important is the ability to propose innovative solutions and develop, test and commercialize them with appropriate support for these efforts. Progress has been made towards some of these goals and the availability, for example, of icEEG data through freely available databases such as the University of Freiburg EEG database (<https://epilepsy.uni-freiburg.de/freiburg-seizure-prediction-project/eeg-database>) and the Flint Hills Scientific ECoG database (<http://www.fhs.lawrence.ks.us/PublicECoG.htm>) has lowered the barrier for entry into this field. The proposed creation of a large international human and animal EEG database supported by NIH will also facilitate access to data and further decrease the barrier to work in this field. Enhanced inter-group collaboration and integration of research efforts should contribute to advancement in an efficient manner including an economical use of resources. Progress in seizure prediction through definition of a pre-seizure period, detection of seizure precursors and improved understanding of seizure dynamics and seizure generation are expected to have broad implications for the treatment of epilepsy. Materialization of automated seizure prediction, detection and control will improve quality of life, lead to a greater understanding of how seizures are generated, and advance clinical epileptology.

Workshop Participants

The names and affiliations of workshop participants can be found on the workshop website. The organizing committee, advisory committee, keynote speakers, speakers, chairs, and

poster competition judges were (in alphabetical order): Ralph Andrzejak, Universitat Pompeu Fabra; Susan Arthurs, Alliance for Epilepsy Research; James Baxendale, University of Kansas; Gregory Bergey, Johns Hopkins University; Marom Bikson, The City College of New York; Andrew Bogaard, University of Michigan; Anatol Bragin, University of California; Paul Carney, University of Florida; Piotr Franaszczuk, Johns Hopkins University; Walter Freeman, University of California; Mark Frei, Flint Hills Scientific, LLC; Bruce Gluckman, Pennsylvania State University; Jeff Goodman, New York State Institute for Basic Research; Jean Gotman, Montreal Neurological Institute; Nina Graves, Medtronic, Inc.; Shane Haas, MIT alumnus; John Harris, NeuroVista Corporation; Leon Iasemidis, Arizona State University; Pedro Irazoqui, Purdue University; John Jefferys, University of Birmingham; Christophe Jouny, Johns Hopkins University; Stiliyan Kalitzin, Epilepsy Institute of the Netherlands (SEIN); Levin Kuhlmann, University of Melbourne; Jürgen Kurths, Potsdam Institute for Climate Impact Research; Bruce Lanning, ITN Energy Systems; Michel Le Van Quyen, Hôpital de la Pitié-Salpêtrière, INSERM; Klaus Lehnertz, University of Bonn; Jean-Marc Lina, Ecole de Technologie Supérieure; Brian Litt, University of Pennsylvania; Fernando Lopes da Silva, University of Amsterdam; John Milton, Claremont Colleges; Piotr Mirowski, New York University; Florian Mormann, California Institute of Technology; Milton Morris, Cyberonics; Tay Netoff, University of Minnesota; Ivan Osorio, University of Kansas; Yun Park, University of Minnesota; David Putz, Ad-Tech Medical Instrument Corporation; Shriram Raghunathan, Purdue University; Pooja Rajdev, Purdue University; J. Chris Sackellares, Optima Neuroscience, Inc.; Björn Schelter, University of Freiburg; Catherine Schevon, Columbia University; Steven Schiff, Pennsylvania State University; Andreas Schulze-Bonhage, University Hospital Freiburg; Ali Shoeb, Massachusetts Institute of Technology; Ivan Soltesz, University of California; Didier Sornette, ETH Swiss Federal Institute of Technology; Sridhar Sunderam, Pennsylvania State University; Yang Tang, Case Western Reserve University; Taufik Valiante, Toronto Western Hospital; Demetrios Velis, Epilepsy Institute of the Netherlands (SEIN); Steven Weinstein, Cornell University; Richard Wennberg, University of Toronto; Gregory Worrell, Mayo Clinic; Hitten Zaveri, Yale University.

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