Special Issue on Epileptic Seizure Prediction

EPILEPSY is the most common neurological disorder after stroke, and affects almost 60 million people worldwide. Medications control seizures in only 2/3 of those affected, and another 7%–8% are potentially curable by surgery. This leaves fully 25%, or ~15 million people whose seizures cannot be controlled by any available therapy. Over the past ten years engineers and quantitative scientists have amassed evidence that seizures do not begin abruptly, as was previously thought, but develop over time, even hours before they cause clinical symptoms. This discovery leads to the exciting notion that there might be time to understand the physiological events that give rise to seizures and perhaps alter them before they can disrupt normal function. Collaborations between engineers, physicists, mathematicians, clinicians, neuroscientists, and industry are focusing on how to translate this work into therapeutic devices that can predict and modulate epileptic seizures, as well as how to explore these findings in the hope of understanding how seizures are generated in the brain and the underlying cellular mechanisms that drive this process. These collaborative efforts may eventually lead to triggering therapy, such as local electrical or magnetic stimulation, drug infusion, or cooling, by preventing the onset or limiting the spread of seizures. Work on these interventions is still early in its development, but a wave of gathering interest is propelling the field in a variety of directions, efforts that are mostly fueled by bioengineering technology.

This special issue provides a snapshot of the engineering science behind seizure prediction at a crucial stage. The excitement of initial "proof of principle" studies has already led to more carefully planned prospective and hypothesis-driven work. These efforts are arranged vertically, spanning methods designed to interpret complex human recordings in real-time all the way to theoretical studies on simple cellular systems. The papers included in this issue reflect this diverse body of work, and include a wide range of topics based upon two main areas: 1) techniques to understand, measure, and track precursor events leading up to seizures; and 2) applying these techniques to data from humans and animal models of epilepsy to develop practical, reliable systems for implementation in implantable warning and therapeutic devices. Studies of seizure detection have purposely not been included, despite some very worthy submissions. These papers will be published in subsequent issues of the IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING. The real challenge of seizure prediction, and the focus of this special issue, is developing methods to detect the unknown patterns that compose seizure precursors.

The papers in this issue are broken down into several categories, each of which evokes important questions related to seizure prediction. First, the overview paper by Lopes da Silva and colleagues, in their discussion of epilepsy as a "dynamical disease," synthesizes their insight into mechanisms underlying primary generalized (genetic) epilepsy within the framework of nonlinear dynamics. This vantage point is expanded to the rich history of seizure prediction using the dynamical approach, in the accompanying view of the field by L. Iasemidis, one of the founders of this approach. Four papers, by Hively, Notley, McSharry, and Rieke, focus on methods for improving and understanding seizure prediction techniques. Hively and Protopopescu apply phase-space dissimilarity measures to address the difficult problem of seizure prediction from scalp electroencephalography (EEG), a very hostile, noisy experimental environment. Notley and Elliott propose a method to improve upon the potentially prohibitive computational burden of correlation density calculations applied to seizure prediction. By demonstrating comparable performance from a linear and an established nonlinear seizure prediction method, McSharry and colleagues continue the debate as to which of these computational domains is best suited to identifying times of imminent seizure onset. Finally, in an important technical study, Rieke *et al.* demonstrate that the ability of their nonlinear method to distinguish preseizure from baseline segments is not due to changes in stationarity in the EEG as seizures approach. The technical details of this study, including the group's use of surrogates, are of interest.

In contrast, three papers from Chavez *et al.*, D'Alessandro *et al.*, and Iasemidis *et al.* push seizure prediction techniques forward into the clinical realm. Based upon an analysis of intracranial recordings from patients with *neocortical* epilepsy (originating outside of the middle temporal lobe), Chavez and his co-investigators describe a new finding of *decreased* synchrony at 10–25 Hz in the seizure onset zone about 30 min prior to seizures. They confirm these findings using measures of amplitude and phase coupling in this narrow frequency band. D'Alessandro and colleagues report a method focused on predicting seizures within a 10-min prediction horizon prior to seizure onset. This method selects a feature vector from a library of multiple quantitative parameters, processes signals from all implanted electrode sites, and fuses the subset of them chosen by a genetic search algorithm into an optimized, patient-specific algorithm. Iasemidis *et al.* report the first prospective seizure prediction algorithm (see Iasemidis invited paper in this issue for a definition). This on-line (and real-time) algorithm runs on continuous multichannel EEG data streams, and requires only the time of occurrence of the first seizure as input. The algorithm is based on progressive convergence of the maximum Lyapunov exponents of brain sites that are adaptively selected on-line via a zero/one global optimization methodology. Average seizure prediction time is over 70 min, with a sensitivity of more than 80% for clinical and subclinical seizures, and specificity values in the order of one false positive every 6 h.

Finally, the last two papers in this issue focus on animal models of epilepsy. The paper by Paul *et al.* presents a seizure prediction method in an acute rat seizure model. Based upon

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residual subband wavelet entropy, this method tracks bursting in intracranial recordings that progresses to clinical seizures after infusion of a seizure-provoking chemical, pentylenetetrazole. The paper by Slutzky and colleagues examines intervention to control seizure-precursor-like events in rat hippocampal (middle temporal lobe) slices based upon chaos control. Though somewhat far removed from seizure prediction and prevention in humans, these studies are interesting, thought-provoking, and remind us of the important role of animal work in understanding seizure generation and control, while the pressures of a burning clinical need push this work into human trials and practical applications.

The papers in this special issue raise many questions and provide opportunities for excellent discussion and forward thinking. Some of these questions are far reaching and deal with the capability to intervene and control seizures in a timely fashion, as well as to understand the neurophysiological mechanisms underlying seizure generation. One can ask, are long prediction times more useful than short ones? Theoretically, the earlier the warning, the more effective and diversified (electric stimulation/drugs) the therapeutic intervention for seizure control can be, but the time horizon is not the only issue. In practice, we have to evaluate clinically the effects of a false alarm, and warnings have to be combined with a projection of when the next seizure will occur. From a signal processing perspective, we should strive for the longest warning time, at a given false alarm level, with seizure projection accuracy. How should we interpret the output of prediction methods? A vital point, raised by the different methods used to assess performance in this issue, is related to the statistics of prediction. Items such as block versus point-based statistics and the effect of prediction horizon (i.e., the expected time from a prediction declaration to seizure onset) on performance measures clearly need more attention. What is the utility of animal models? Does bursting in hippocampal slices relate to clinical seizures in some way, e.g., to seizure generation (Slutzky *et al.*)? Do acute seizure models in animals tell us anything about forecasting spontaneous seizures in human epilepsy, a chronic condition (Paul *et al.*)?

The more clinical oriented papers independently raise their own questions. Is prediction different in subtypes of the great heterogeneity of human epilepsy (*temporal lobe*: Iasemidis, D'Alessandro, McSharry, Notley, Rieke; *neocortical*: Chavez; *primary generalized*: Lopes Da Silva). How can we optimally select the set of parameters that are most relevant to seizure prediction? Will one set of parameters be good enough (e.g., Lyapunov exponents by Iasemidis *et al.*), or will multiple sets of parameters be required (e.g., D'Alessandro *et al.*, and Hively *et al.*)? Will multiple different parameters provide independent, irrelevant or redundant information about the process? Most seizure prediction methods have been applied to intracranial EEG recordings, both because of their higher fidelity and practical problems associated with externally worn devices. What is the potential role of seizure prediction from scalp versus depth recordings? (Hively *et al.*). Will prediction methods work if implanted electrodes miss the epileptic focus? These are vital issues at the cutting edge of the field and clearly show that much more interdisciplinary research is needed.

Finally, these papers raise questions about how seizure prediction methods will be linked to intervention to prevent clinical symptoms. The paper by Slutzky *et al.* begins to touch on this issue. Most investigators now agree that it is very difficult to prospectively predict the specific time of a seizure onset. Rather, seizure prediction methods will likely identify periods of time in which the probability of seizure onset is increased. In this scheme, the way treatment is applied may be guided by the prediction horizon (e.g., how far from the alarm is the seizure likely to occur) and the side effect profile associated with a particular therapeutic intervention. Of course, these questions and lines of thought appear to be valid now, but may become irrelevant later on with the upcoming new discoveries on the dynamics of the epileptic brain.

The Guest Editors would like to thank all who submitted manuscripts to this special issue on seizure prediction for their contributions, and to Jose Principe, Editor-in-Chief, for proposing and allowing them to participate in this important event. They expect that the field of seizure prediction will continue to move steadily forward, if the response to their call for papers is any indication of interest in this area. They also expect that it will continue to provide a wonderful example of the kind of intensely collaborative work between clinicians, and basic and quantitative scientists, which typifies modern Biomedical Engineering.

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