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A Paradigm for Epileptic Seizure Prediction Using a Coupled Oscillator Model of the Brain

Elma O'Sullivan-Greene, *GSMIEEE*, Iven Mareels, *FIEEE*,
Dean Freestone, *GSMIEEE*, Levin Kulhmann and Anthony Burkitt, *SMIEEE*

***Abstract*— This paper presents a novel theoretical paradigm for epileptic seizure prediction based on a coupled oscillator model of brain dynamics. This model is used to investigate prediction methods capable of tracking the synchronization changes that may lead to a seizure. Previous results indicate that state-space reconstruction of a coupled oscillator model from an EEG-like signal is ill-posed, therefore, monitoring system synchronization via the EEG signal is unlikely to give advanced warning of imminent seizure activity. Through simulation, it is shown that synchronization tracking may still be viable using an input probing stimulus to actively seek information from the coupled oscillator network.**

I. INTRODUCTION

Epilepsy is a neurological disorder characterized by recurrent seizures which are associated with "abnormally excessive or synchronous neuronal activity in the brain" [1]. The transitions from non-seizure to seizure states often occur with a synchronization of the recorded voltages on several electrodes of electroencephalography (EEG) data. This is thought to correspond with a synchronization of neural activity across different brain regions.

Over the past 34 years many methods, including synchronization measures, have been unsuccessfully applied to EEG recordings for seizure prediction [2]. Here we approach the epileptic seizure prediction problem with a very simplified coupled oscillator network.

Despite this simplicity, such networks exhibit EEG like behaviour from a measurement point of view. Our previous results [3] show that in the most ideal abstraction of the underlying problem, practical observability (assuming a finite precision EEG measurement instrument) is not an obvious property, even when the underlying system is observable in the normal sense (i.e. for ideal measurements). This may well explain why epilepsy prediction attempts based on passive observation of EEG signals fail, because the actual information cannot be gleaned from the EEG signal.

Because of the simplicity of our model, it is possible to explore active signal probing as a means to early-detection and prediction of epileptic events. This paradigm is explored using simulation studies.

The remainder of this paper provides a further background to the problem in section II, with details of the model described in section III. A paradigm for seizure prediction with the model, including supporting proof-of-concept simulations are presented in IV. Section V follows with a discussion and conclusions on the relevance of these findings in a clinical setting.

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The authors are with the Dept. of Electrical & Electronic Engineering, The University of Melbourne and the Bionic Ear Institute, Australia. {elmaog, i.mareels, levink} @unimelb.edu.au
{d.freestone, aburkitt} @bionicear.org

II. BACKGROUND

The reliable prediction of epileptic seizures would greatly reduce the burden of epilepsy for an estimated 60 million sufferers worldwide. Seizures manifest clinically in a variety of ways, including loss of consciousness and involuntary muscle contraction. In particular, the sudden and uncontrollable nature of the seizures is extremely debilitating for patients. The ability to predict seizures could revolutionize the treatment of epilepsy by facilitating strategically timed intervention [4].

The EEG measures the temporal fluctuations of electrical potentials recorded from the human brain. EEG is a non-stationary signal that can be considered quasi-stationary for periods in the order of 10s [5, p. 1200]. There are macroscopic, mesoscopic and microscopic scales of EEG measurement, measuring from the scalp, intracranial sources and small groups of neurons respectively.

Considering the EEG is a volume-conducted spatio-temporal average of neural activity, it is surprising that scalp EEG reveals coherent information in the form of frequently observable patterns related to specific states of consciousness such as attention, concentration, agitation and relaxation [5]. Simply by placing a pair of electrodes on a scalp, the unprocessed differential recordings clearly show several characteristic oscillations or $rhythms$ in the range 0.1-200Hz that are associated with various states of cognitive function.

Much of the seizure prediction work to date has involved applying linear and non-linear techniques to both scalp and intracranial EEG data in attempts to track synchrony across brain regions. Linear methods have included cross-correlation [6] and phase analysis based on the Hilbert transform [7], [8]. Several non-linear techniques have utilized the Takens/Aeyels Embedding Theorem [9] in an effort to reconstruct the state space, with low embedding dimensions of 7-16. Measures including correlation dimension [10] and Lyapunov exponents [11] were applied to these reconstructed state-spaces. All these approaches have failed to reliably predict seizures better than a random predictor [2].

In light of this failure to predict seizures as the onset of mass synchrony in the brain we used a coupled oscillator model to investigate what we may expect from a

low-dimensional signal extracted from a high-dimensional system. We found that the system observable in the EEG was of much lower order than the true underlying system [3], and here our approach to seizure prediction is tailored accordingly.

Our model abstracts the problem to the study of a simple network of linear oscillators (or mildly non-linear for e.g. Van Der Pol oscillator) with linear interconnection. Such a model neglects the complexities of biologically realistic neuron-dynamics and instead formulates the problem as a generic network of oscillators where an EEG-like measurement is made. Synchrony of coupled oscillators is undoubtedly a non-linear process, however, here we use essentially a linear model. This choice was based on our poor observability findings [3]. When the extent of information that an EEG-like output can reveal is limited in the linear case, non-linear efforts are unlikely to be more productive.

To represent seizure dynamics in terms of synchronization events, a model based on coupled dynamical clock subsystems was created as described in (1). Each sub-system represents a region of brain tissue that is oscillating at a certain frequency. As the EEG is the weighted sum of oscillating potentials in the brain, the output in this model is the weighted sum of many pendulum oscillations. This is quite a generic and scalable model. On a microscopic scale, each pendulum represents only a small group of neurons and the output measure would model depth-EEG recording from a micro-electrode. This model could equally apply up to the global macroscopic scales, where each pendulum represents a large area of brain tissue.

The model described in section (III) model also facilitates the inclusion of an input probe stimulus. The inclusion of an input probe stimulus follows recent developments in epileptic seizure prediction that have focused on an active response model rather than the traditional passive EEG measurement [12]. The active response paradigm involves measuring the EEG following a stimulus (e.g. electric pulse) to a brain region.

A very similar coupled-oscillator model was described by Wright et al. in 1985 to model state changes in the brain [13]. Their motivation for a generic model was that the existing brain models of the time where constrained by "simplified neuronal relationships and laws of interaction", whose "ideas are difficult to put to critical test, and each [model] necessarily ignores certain problems treated in the others". Mathematical models have developed considerably since this work, however, Wright's comments still stand, in that, these models are not yet at a level of sophistication suitable for parameter fitting to EEG for the specific purpose of seizure prediction.

III. A Coupled Oscillator Model

EEG recordings from brain tissue are modeled as the output measurement from a system of networked clocks. Each individual oscillator is modeled as a pendulum clock with the oscillatory motion of the pendulum described as

$$\ddot{x}_i + 2\zeta_i\omega_i\dot{x}_i + \omega_i^2 x_i = F, \tag{1}$$

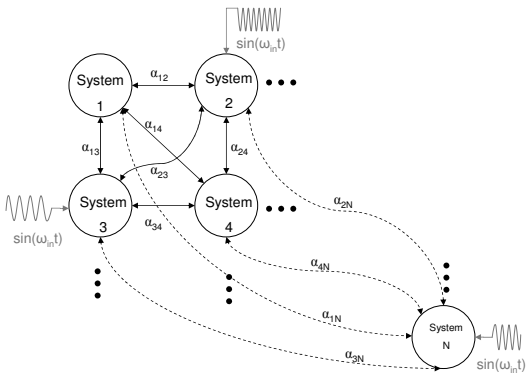


Fig. 1. The interconnection of N pendulum clock subsystems. α_{ij} is the coupling strength between sub-system i and j. The grey signals are inputs to the system.

where x is the angular position of the pendulum, ζ is the damping parameter, ω is the natural frequency of oscillation and F is the forcing term. F could take the form $\sin(\omega_{in}t)$ for an external input and $\sum_j \alpha_{ij}(x_i - x_j)$ for coupling of the position state from other pendulums. ω_{in} denotes any input frequency.

To convert the characteristic equation (1) into a state space format, the states for clock system 1 can be labeled as x_{11} and x_{12} which are defined as follows: $x_{11} = x_1$ and $x_{12} = \dot{x}_1$. The time derivatives of the states are then $\dot{x}_{11} = x_{12}$ and $\dot{x}_{12} = \ddot{x}_1 = -2\zeta_1\omega_1 x_{12} - (\omega_1^2 - \alpha_{12})x_{11} - \alpha_{12}x_{21} + \sin(\omega_{in}t)$, where x_{21} is the 1^{st} state of system 2.

The resulting state space model for an interacting system of two pendulums is $\dot{\mathbf{x}} = \mathbf{A}\mathbf{x} + \mathbf{B}u$, where u is the input signal and the $\mathbf{A}$ and $\mathbf{B}$ matrices are as follows:

$$\mathbf{A} = \begin{bmatrix} 0 & 1 & 0 & 0 \\ -\omega_1^2 + \alpha_{12} & -2\zeta_1\omega_1 & -\alpha_{12} & 0 \\ 0 & 0 & 0 & 1 \\ -\alpha_{21} & 0 & -\omega_2^2 + \alpha_{21} & -2\zeta_2\omega_2 \end{bmatrix} \tag{2}$$

$$\mathbf{B} = \begin{bmatrix} 0 & 1 & 0 & 1 \end{bmatrix}', \tag{3}$$

where prime($'$) denotes transpose.

This can be extended to an $2N$ state system, where there are N interconnected pendulum clock subsystems, as illustrated in Fig. 1. Each subsystem is allowed to connect to all the others and $\alpha_{ij} \equiv \alpha_{ji}$ (symmetric coupling). Random graphs can be constructed by choosing $\alpha_{ij} \geq 0$ from a distribution of values.

The output state equation for a single recorded EEG channel can be described by $\mathbf{y} = \mathbf{C}\mathbf{x}$, where

$$\mathbf{C} = \begin{bmatrix} \delta_1\omega_1^2 & 0 & \delta_2\omega_2^2 & \dots & \delta_n\omega_{2N}^2 & 0 \end{bmatrix}. \tag{4}$$

The output is a convex combination of the frequency-scaled position states in the system ($\delta_i \geq 0, \sum_i \delta_i = 1$). The states are frequency-scaled with a corresponding natural frequency, ω_i, such that the transfer function, $G(s) = \mathbf{C}(s\mathbf{I} - \mathbf{A})^{-1}\mathbf{B}$, is normalized to 1 at DC. $\delta_i \geq 0$ indicates the relative contribution clock i makes in the EEG output signal.

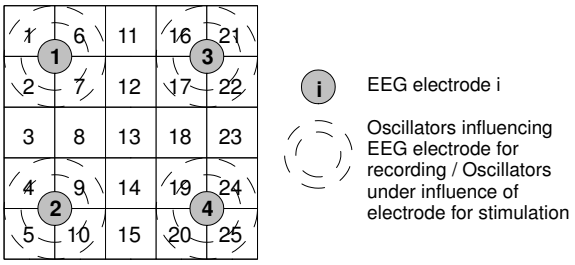


Fig. 2. The simulation experimental set-up for a network of 25 coupled oscillators with 4 EEG channels.

Even when this system is observable in the normal sense of the word, it turns out that the simple limitation of a finite precision measurement reduces our ability to distinguish all states drastically. EEG machine A/D resolution typically ranges from 14-24 bits [14], [15]. The distribution of the singular values of the observability matrix demonstrates that for all practical purposes observability is an illusion given the precision range of $2^{14} - 2^{24}$ levels in the measurement.

In that case, why is epilepsy even detectable as a synchronous event via large scale EEG measures on the cortex and scalp? These observability findings imply that the brain must be in an very advanced state of synchronization across a large area of cortex before it can be seen in the EEG. This underscores why seizure detection may be successfully completed from EEG signals and suggests that prediction based on large scale EEG measurements may be an elusive goal.

IV. A Paradigm for Seizure Prediction

A fully observably system would enable a reconstruction of the model to be estimated and tracked over time from the EEG. However, we find this unlikely to be feasible with the EEG signal. An alternative to parameter tracking and state-space estimation for seizure prediction is investigated in this section. In particular, we study what can be learned by probing the system with an input.

In our model we equate prediction of seizures with evidence of synchrony between many individual oscillators before synchrony is visible in our EEG electrode recordings. Synchrony is defined as sustained phase locking to a particular frequency and is computed as the least squares solution to the model

$$X(t) = A\cos(2\pi ft + \phi) + \mathrm{w}(t) \tag{5}$$

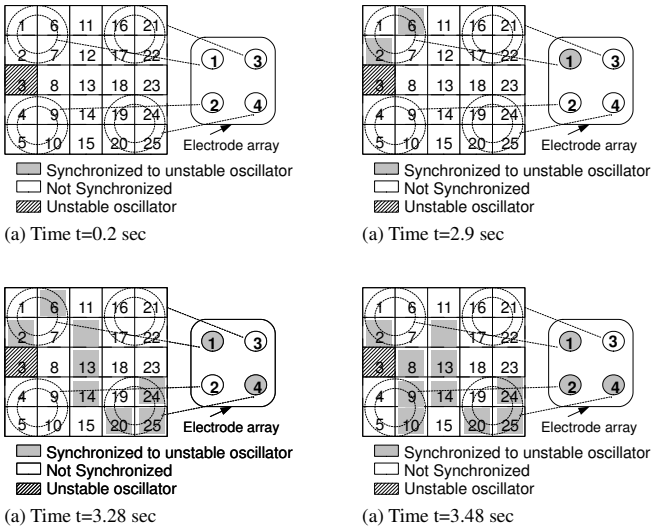
where f is the known frequency of the input stimulus, $\mathrm{w}(t)$ is zero mean white noise and the phase, ϕ and amplitude, $A = A(f)$, are estimated (see [16, Ch. 7] for the details of the least squares solution). $X(t)$ can be either (1) the EEG signal used to estimate the phase-locking response to our probe stimulus, or (2) the internal states of the model to determine phase for individual clocks to establish if predictions from the EEG data correspond to a true picture of the underlying system activity. This definition of phase synchrony is used as it is more robust than the Hilbert transform in the presence of noise and can be used on broadband signals without any ambiguities.

The simulated coupled oscillator network was configured as shown in Fig. (2). There are 4 electrodes each influenced by the individual oscillators in their immediate vicinity. The network was interconnected with coupling parameters α_{ij}, chosen uniformly in the range 0-0.01. The system's natural frequencies, ω_i, were randomly chosen from a uniform distribution spanning from 0.5 Hz-100Hz. To stimulate the case of synchronization build up throughout the network, the damping parameters, γ_i, were chosen uniformly in the range 0.001 to 0.01. The generation of a seizure was modeled by expanding (1) for a single clock in the network to include a non-linear element, creating a Van der Pol oscillator with system equation $\ddot{x} + (\epsilon x^2 + 2\zeta\omega)\dot{x} + \omega^2 x = F$. By allowing a negative damping parameter, ζ, in this non-linear clock an unstable (marginally stable) oscillator was formed which would slowly take over the entire network.

The prediction paradigm was centered on the knowledge that a stable coupled oscillator network (modeling the normal brain state) only has significant responses to input frequencies in close proximity to the system natural frequencies ($\omega_1 \cdots \omega_n$). Investigative probing can enable the collection of normal system responses, $A(f)$, with a library of natural frequencies found as the peaks in this spectrum. In general we hypothesize that the seizure state will exhibit a significantly altered response to probe stimuli. One likely alteration to the system response is that subsequent probing with the system frequencies should elicit a measurable response in the EEG, except when the network propagates into a seizure state. In the seizure state, individual oscillators are synchronized to the frequency of the unstable oscillator and are therefore non-responsive to any probing stimulus (of sufficiently low stimulation level for patient safety). Sufficiently low stimulation implies that we would be operating in the subthreshold region to avoid inducing a seizure. Subthreshold stimulations are routinely used in epilepsy surgery for mapping purposes.

Our approach to seizure prediction is to monitor when the response to probe stimuli, $A(f)$, is significantly altered from the library of normal responses. If we get such an altered response on several adjoining electrode stimulation sites we can infer that the underlying brain matter may be in a seizure state. We hypothesize that the early seizure state will exhibit an altered response in advance of the seizure state being visible as synchronization across EEG channels. This hypothesis is based on the knowledge that the signal at the EEG channel is a function of much fewer oscillators than are present in the system, thus an oscillation would have to be widespread across the network before it is visible at the EEG level.

Sample EEG signals generated from the coupled oscillator model are shown in Fig. (4). Simulation results providing proof-of-concept are illustrated in Fig. (3). In this simulation, a poor response to normally-resonant probe stimuli was found in advance of visible synchronization (seizure activity) at the EEG level. This paradigm acts as a predictor of very immediate seizures and could be considered a form of early



(a) Time t=0.2 sec (a) Time t=2.9 sec

(a) Time t=3.28 sec (a) Time t=3.48 sec

Fig. 3. The simulated time evolution of a synchronization (or seizure event) in the coupled oscillator model. Note that from t=0 seconds clock number 3 was unstable, by 2.9 seconds there was no longer a response to input probe stimuli in electrode one. However, it was not until t=3.48 seconds that synchronization to the unstable natural frequency was measurable in the majority of EEG electrodes. Prediction therapy time window = 3.48-2.9= 0.58 seconds.

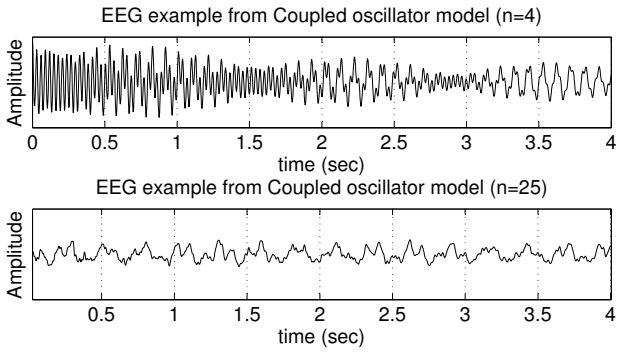


Fig. 4. Sample EEG signals generated from the coupled oscillator model. The upper-trace shows the EEG signal corresponding to electrode number 2 in Figure 3. This is the weighted sum of the states from 4 clocks (n=4). The trace becomes synchronized to the unstable oscillator at 3.48 seconds. The lower trace is an example of the weighted sum of all 25 clocks (n=25) in the "normal" (stable) system, illustrating the increase of signal complexity with model order.

detection. However, early detection could prove sufficient to provide a therapeutic window for seizure abating stimuli in an implantable seizure control device. Note the time of the therapeutic window was 0.58 seconds for this simulation, which was entirely dependent on the choice of damping and coupling parameters in the model. A realistic estimate of therapeutic window time in real brain matter would require clinical data from probe stimuli.

V. Discussion and Conclusion

We have provided, for a very simplistic abstraction of the real problem, a seizure prediction paradigm based on synchrony for use with EEG measurement using an input probe stimuli. While the therapeutic window following prediction may be small, strategically placed electrodes at the seizure focus may enable synchronous activity to be found and abated prior to the emergence of clinical symptoms of epilepsy.

For this paradigm to be a viable clinical option stationarity and repeatability issues need to be addressed. The EEG is inherently non-stationary, however, the EEG may remain quasi-stationary for periods long enough to build up a library of "normal" responses to stimuli. Also, it needs to be established if the real brain system responses to probe stimuli are repeatable to some degree. This last question could be rephrased as, can the brain response be approximated by a linear system for certain stimuli?

Our future work is to analyze data from evoked potentials in the epileptic brain to inform further model development. We hope that such development can in turn inform the experimental procedure of active EEG towards successful clinical seizure prediction.

VI. Acknowledgments

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