THEORETICAL CONCEPTS OF CONTROL WITH APPLICATIONS TO EPILEPSY

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Abstract: In an effort to understand basic functional mechanisms that can produce epileptic seizures, and strategies for seizure suppression and control, we explore some key features of theoretical models of networks of coupled chaotic oscillators that produce seizure-like events and bear striking similarities to dynamics of epileptic seizures. We show that a plausible cause of seizures is a pathological feedback in the brain circuitry. These results have interesting physical interpretation and implications for treatment of epilepsy. They also have close ties with a variety of recent practical observations in the human and animal epileptic brain, and with theories from adaptive systems, optimization, and chaos.

Introduction

Epilepsy is the second most common neurological disorder after stroke, and affects at least 50 million people world-wide. Approximately 60% of new onset epilepsy cases respond to existing antiepileptic drugs (AEDs) but 40% are pharmaco-resistant, with seizures that cannot be fully controlled with available medical therapy or without unacceptable side effects [1]. Surgical removal of the seizure focus is an important and effective therapeutic intervention for some patients with difficulty to control epilepsy, but is not possible in the large majority of patients because of multiple foci, or seizure foci located within non-resectable brain areas. Resective surgery is unlikely to ever replace chronic treatment as the primary mode of epilepsy management in the large majority of patients with epilepsy. Currently, AEDs are the principal form of chronic epilepsy treatment. However, in addition to the lack of efficacy for complete seizure control in at least one third of all patients, there also is substantial morbidity associated with the use of AEDs in many patients, especially when polypharmacy is required.

Electrical stimulation paradigms as a means of seizure control have the advantage of not producing the systemic and central nervous system side effects which are seen frequently with AEDs. Vagus nerve stimulation has been shown to reduce seizure frequency in some cases but less than 10% become seizure free. Deep brain stimulation (DBS) has also been reported to reduce seizure frequency in humans. (See latest results in [2],[3],[4]).

In parallel, seizure prediction has also attracted great interest through the years. Until recently, the general belief in the medical community was that epileptic seizures could not be anticipated [5], although clinical practice and scientific intuition gave evidence for the contrary [6, 7]. The first application of nonlinear signal processing to clinical epilepsy was reported in [8]. Subsequently, the existence of long-term preictal periods was shown using nonlinear dynamical analysis of EEG subdural arrays leading to the development of seizure prediction algorithms by monitoring the temporal evolution of the maximum Short-Term Lyapunov exponents (STLmax), e.g., [9],[10],[11]. In these studies, the central concept was that seizures represent transitions of the epileptic brain from its "normal" less ordered (chaotic) interictal state to an abnormal (more ordered) ictal state and back to a "normal" postictal state along the lines of chaos-to-order-to-chaos transitions. Seizure prediction can then be achieved by monitoring the dynamical behavior of critical brain sites to reveal "entrainment," or, in other words, a form of dynamical synchronization between sites. The application of this technique to epileptic patients with temporal and frontal lobe focal epilepsy has shown that epileptic seizures can be prospectively anticipated in the range of 70 minutes prior to their occurrence with sensitivity of 85% and false prediction rate of 1 false warning every 8 hours, [10]. Other research groups followed and also found marked transitions toward low-dimensional states and reduction of brain's complexity a few minutes before the occurrence of epileptic seizures [12],[13],[14],[15]. Therefore, seizures appear to be bifurcations of a neural network that involves a progressive coupling of the focus with the normal brain sites during a preictal period that may last from days to tens of minutes.

In search of a model and a mechanism to explain the observed behavior of the epileptic brain, [16] followed Freeman's approach of representing the brain as interconnections of nonlinear oscillators, e.g. [17]. It was postulated that brain sites (i.e., groups of neurons) might be viewed as diffusively coupled chaotic oscillators. An increase in the strength of coupling results in progressive synchronization between the oscillators. Further analysis showed that, in terms of entrainment, this model's behavior was consistent with the preictal behavior of the epileptic brain. However, even though this coupled-oscillator model can exhibit chaos-to-order-to-chaos transitions, changes in the employed diffusive coupling do not produce seizure-like explosive signal growth.

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Motivated by the analysis and results of burst phenomena in adaptive systems [18, 19, 20] we postulate the existence of a feedback action in the oscillators' network that enables the appearance of seizure-like behavior. By incorporating an appropriate feedback structure in the original model by Iasemidis et al., [16], we present a class of coupled oscillator models that exhibit more key aspects of seizure-like behavior. For example, changes in coupling do not cause seizures in the "normal" brain models, but do bring the "epileptic" brain models in an instability region where "seizures" may occur. Long-term dynamical entrainment is observed during "preictal" periods in the "epileptic" model and is interpreted as an indicator of pathology in the internal feedback of the network. At this point, we should emphasize that the models we present are not aimed at reproducing the exact output of the brain (e.g., EEG recordings). Instead, the objective is to capture the essential functional parts of the operation that leads to seizures and incorporate effective compensation strategies to prevent seizures. Thus, the analysis of the oscillator models provides guidance for developing novel control strategies for the suppression and control of epileptic seizures. In our approach, the observed seizures could relate to the burst phenomena in adaptive control, whose occurrence does not rely upon pathologies in the precise structure of the underlying system, but result from pathologies in the implementation of the general operational objectives of the system. The hypothesized pathological feedback in our models, as a way to reproduce the type of explosive growth observed during a seizure, is physiologically very relevant.

Based on the above, we envision a combination of the existing long-term prediction [10] and active real-time feedback control techniques into one technology for intervention and control of the transition of the brain towards epileptic seizures. The ultimate goal is to provide a seizure-free epileptic brain capable of functioning "normally" with minimum intervention time-wise and power-wise.

In this paper, we extend the results from [21], [22] to study the efficacy of various closed-loop control strategies to control seizures in oscillator networks. In particular, we present cases where predefined-stimuli-based closed loop control fails. This is consistent with clinical trials of electrical stimulation where simple stimulation strategies do not always work. In our framework, these cases are characterized by multiple pathological interconnections. However, the proposed closed loop feedback decoupling controller is consistently successful.

Networks of chaotic oscillators with feedback

The electrical activity at different brain sites has been observed to exhibit patterns of dynamics similar to the ones in coupled chaotic oscillators. In previous studies we have established that some form of generalized synchronization is a precursor to epileptic seizures. Guided by these physiological observations, it was postulated that such a phenomenon might be a fundamental property of networks of coupled oscillators. Indeed, similar synchronization patterns were demonstrated in chaotic oscillators interacting with a so-called diffusive coupling [16]. As an example of this class of models, we herein consider a system of N coupled Rössler-like oscillators. We then construct feedback around each pair of oscillators with the objective to de-correlate their outputs when excessive coupling occurs as a result of a change (input) in the network. Such inputs are translated into temporal changes of the coupling between the network oscillators. The equations for oscillator i, $i = 1, \ldots, N$ are:

$$\begin{aligned} \frac{dx_i}{dt} &= -\omega_i y_i - z_i + b_i + \sum_{\substack{j=1 \\ j\neq i}}^{N} (\varepsilon_{i,j}(x_j - x_i) + u^I_{i,j}) \\ \frac{dy_i}{dt} &= \omega_i x_i + \alpha_i y_i, \quad \frac{dz_i}{dt} = \beta_i x_i + z_i(x_i - \gamma_i) \end{aligned} \qquad (1)$$

where the intrinsic parameters $\alpha, \beta, \gamma, \omega$ are chosen in the chaotic regime, e.g., 0.4, 0.33, 5, 0.95, respectively. b_i are small constant bias terms, different for each oscillator, which ensure that the origin is not an equilibrium point (in our examples, b_i's have "random" values in $[-0.2, 0.2]$). ε are the time-varying coupling strengths; in this example, we take symmetric coupling. The model is solved with a fixed time step of 0.01sec. When the ε between two oscillators increases, their dynamical behaviors synchronize until they become nearly identical at high values of ε. In this manner, chaoticity is progressively lost in spatial coordinates while not being clearly detectable in the temporal coordinates of each individual oscillator. (Note: For simplicity in our simulations, we use the correlation coefficient, instead of a distance measure between STLmax profiles, to quantify the synchronization between the signals.)

Results from a simple 3-oscillator network case [21], and a network with 13 oscillators [22] were presented earlier. In this work, we consider the network topology shown in Fig. 1 where abnormal feedback can occur between oscillators 3-4, 4-5, 4-8 and 3-8. In the following simulations, we consider different values of $\varepsilon_{3,4}$, $\varepsilon_{4,5}$, $\varepsilon_{4,8}$ and $\varepsilon_{3,8}$ (all time-varying). The internal feedback signals $u^I_{i,j}$ are defined as follows:

$$u^I_{i,j} = k_{i,j}(x_i - x_j),\ k_{i,j} = PI_I\{\rho_{i,j} - c_*\} \qquad (2)$$

The feedback gains $k_{i,j}$ are themselves produced by a Proportional-Integral (PI) feedback, while $\rho_{i,j}$ denotes the exponentially weighted correlation between two signals and c_* is a threshold parameter (here taken as $c_* = 0.1$). The PI_I notation signifies that the considered PI feedback is part of the internal network of the "brain". The PI_I feedback can be viewed either as a decoupling compensator or as an estimator of the network's oscillator coupling parameter $\varepsilon_{i,j}$. It is restricted to produce signals in the interval [0, 1] and it employs limited integration as an anti-windup mechanism. This guarantees that when the correlation between the two signals is below the threshold c_*, no feedback is generated.

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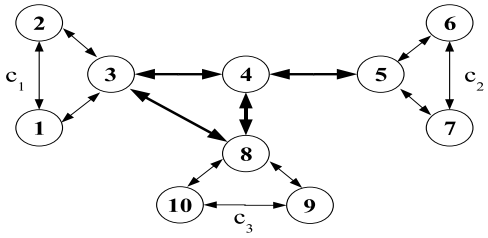

Figure 1: Brain emulator as a network of coupled oscillators. The connecting lines indicate only non-zero coupling between the respective oscillators. $c_1 = 0.08$, $c_2 = 0.07$, $c_3 = 0.05$

The assumption that in the "normal brain" correlations in the network have to exist and lie within "normal" range lead us to assume that the existing PI_Is in the "normal brain" should follow changes in $\varepsilon_{i,j}$ and, in a short time, compensate for them. On the contrary, in the pathologic "epileptic brain", we expect that the PI_Is would not be able to compensate for such $\varepsilon_{i,j}$ changes and corresponding parts of the system will exhibit adaptation bursts. As it turns out, a simple PI compensator is sufficient to decorrelate the oscillators, as long as its bandwidth is not too high. (For its tuning we followed [23], although a working solution can easily be obtained by simple trial-and-error). During its operation, the PI that emulates the internal feedback in the brain (PI_I) generates an output that attempts to cancel the effect of excessive diffusive coupling ε in the oscillator network and maintain the correlation between two signals below the given threshold c_*. Our underlying assumption is that "the pathology of the epileptic brain is that its intelligent controller does not provide the necessary feedback action to compensate for the increase in the oscillator network coupling." That is, an improperly tuned internal feedback controller may cause feedback correction that gets out of phase with the change in the oscillator network coupling, resulting in a negative effective coupling coefficient, and produce high amplitude divergence (instability resembling "seizures" illustrated in Fig.2). A precursor to this scenario is an abnormal increase in coupling and synchronization that is not removed quickly enough by the internal compensation mechanism. Implicit in this theoretical analysis is the dependence of seizures on the variations of the coupling ε. Thus, while the "epileptic" oscillator network is susceptible to seizures due to its pathologically high values of effective coupling, the exact onset of seizures depends on the inputs that caused variations to the network coupling.

Seizure control in oscillator networks

In addition to generating a functional model for the normal brain operation, the above network structure provides a test-bed and insight for implementation of feedback control strategies for the operation of the epileptic brain. A natural goal for a seizure control scheme

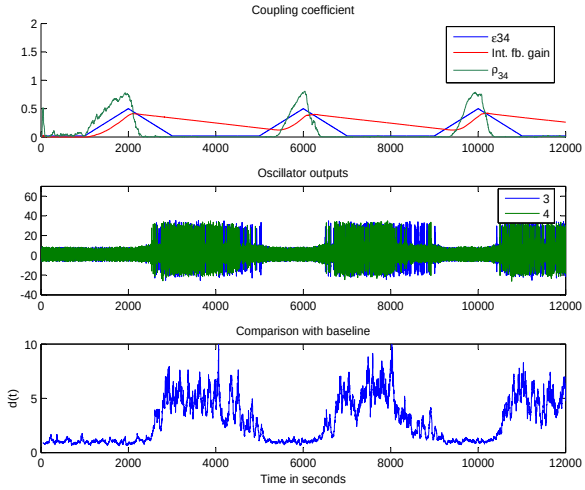

Figure 2: Uncontrolled "brain" response for pathological oscillator pair 3-4. With a reduced internal feedback gain for the PI_I between 3-4, the controller can no longer follow the coupling changes closely. Signal growth from instability bursts appears soon after the coupling estimate exceeds the actual value of coupling. Notice the significant increase in signal correlation between the pathological sites that precedes the "seizures" that is similar to the entrainment observed in actual epileptic EEG. Panel Legends (top to bottom): I. Coupling coefficient (blue), its feedback estimate by the internal PI(red) and approximate correlation signal (green). II. Oscillator outputs 3,4. III. "Seizure" intensity measure $d(t)$.

would be the disruption of correlation-synchronization-entrainment patterns observed prior to seizures. However, it would not be helpful at all if seizures are prevented, while the patient is rendered unconscious, in pain, or any other dysfunctional condition. Since seizures are chronic and typically not terminal for the patient, what is needed for their treatment is the equivalent of an epileptic brain pacemaker. The hypothesis-driven simulation experiments that we presented in [21], addressed this line of research, i.e., successful control of oscillator networks that could eventually guide us on the choice of suitable stimulation methods to prevent seizures with minimal intrusion. In particular, we considered the following control strategies: open and closed loop discrete control, closed loop continuous control (using predefined stimuli) and closed loop feedback decoupling, and showed the inability of discrete control with seizure detection to control bursts in oscillator networks. In this paper, we study the efficacy of various closed loop control strategies in controlling "seizures" in oscillator networks by considering more complex network topologies and oscillator coupling configurations. In the following, we assume that the external stimulation, denoted by u_i^E, enters the oscillator network in an additive manner, i.e.,

$$\frac{dx_i}{dt} = -\omega_i y_i - z_i + b_i + \sum_{\substack{j=1 \\ j\neq i}}^{N} (\varepsilon_{i,j}(x_j - x_i) + u_{i,j}^I) + u_i^E \quad (3)$$

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while y and z are as in (1). Fig. 3 shows a functional block diagram of the internal feedback and closed loop external controller.

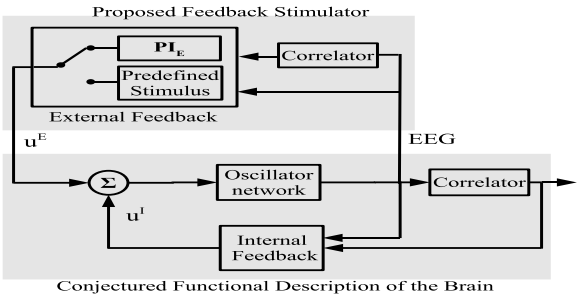

Figure 3: Functional block diagram of the proposed internal feedback structure and closed-loop seizure control mechanisms.

Closed loop continuous control

The closed-loop continuous control (see Fig. 3) involves continuous feedback during the intervals of high susceptibility to seizure. In this strategy, the controller produces a stimulus sequence continuously as long as measures of the brain state exceed a threshold. In our simulations, the level of correlations is used as a measure of the "brain" state. Other options include the T-index of STLmax for different sites.

The continuous feedback can be of two types: a) predefined stimuli; we use biphasic pulse inputs of various frequencies, and b) decoupling control. The predefined stimulus-based control is of two types: a) unidirectional or "focus" stimulation where the stimulation is applied only to one of the pathological oscillators, and b) bidirectional stimulation, where, opposite control inputs are applied to the oscillators in a pathological pair. The feedback decoupling controller, which is inspired from adaptive control, is turned on automatically and the feedback signal is $u_i^E = \sum_{j \neq i} C_{i,j}(x_i - x_j)$, the same form as the hypothesized internal feedback PI_I. The external controller gains $C_{i,j}$ are viewed as the manipulated variables and are updated using a PI control/estimation strategy (PI_E in Fig.3).

We use the following measure to quantify the efficacy of a control scheme in controlling seizures. Suppose there are P oscillators in the network which can exhibit seizures. Let $x_{b,i}$, $i = 1,\ldots,P$ be their seizure free outputs, and $x_{c,i}$ be their controlled outputs. Define $d_i(t) = \sigma^2_{x_{c,i}}(t)/\sigma^2_{x_{b,i}}(t)$ where $\sigma^2_{x_i}(t)$ is the variance of a window of data till time instant t, and $d(t) = (1/P)\sum_{i=1}^{P} d_i(t)$. Thus $d(t)$ can be considered a measure of "seizure" intensity with respect to a seizure free oscillator network. Fig.2 shows $d(t)$ for uncontrolled bursting oscillators; notice that $d(t)$ increases during seizures.

The predefined-stimulus-based controllers can be successful in mitigating seizures in certain simple cases. One such example is the case of the network with two pathological feedbacks between oscillators 3-4 and 4-5. The coupling profiles are shown in Fig.4, panel I. A large deviation from the "baseline" is seen for the uncontrolled network, which exhibits seizures (panel II). For the above configuration, it was possible to control seizures using the unidirectional, bidirectional and feedback decoupling controllers (panels III-V). On the other hand, the predefined stimuli had considerable effect on the amplitude of the oscillators and required greater control stimulation energy than the feedback decoupling controller. We next simulated more complicated network configurations to study the efficacy of these closed loop controllers.

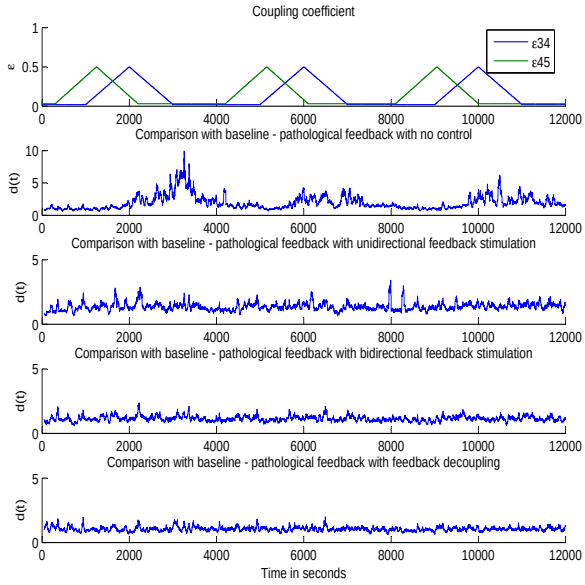

Figure 4: Network configuration with 2 pathological oscillator pairs: 3-4 and 4-5. It is possible to control seizures with unidirectional, bidirectional and feedback decoupling control. Notice the decrease in the deviations from the "baseline" by using the closed loop control, but larger deviations using unidirectional and bidirectional feedback control in comparison with feedback decoupling. Panel Legends (top to bottom): I. Coupling configurations. II-V. "Seizure" intensity $d(t)$ for the uncontrolled network, unidirectional feedback stimulation, bidirectional feedback stimulation and feedback decoupling controllers, respectively.

We consider the network setup with three pathological feedbacks between oscillators 4-3, 4-5 and 4-8. The coupling profiles are shown in Fig.5 (panel I). The large deviation from the "baseline" for the uncontrolled network exhibiting seizures in shown in panel II. Closed loop unidirectional control stimuli (corresponding to pathological pairs 4-3, 4-5 and 4-8) are applied to oscillator 4 ("focus"). We use biphasic pulse stimulation waveforms (period = 2 seconds) and tune their pulse-widths and power in order to select parameters that control the seizure. By using a straightforward technique to tune the control stimuli parameters, it was not possible to completely control the seizures. On the other hand, the feedback decoupling controller was successful in completely controlling the seizures. Note that the de-

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viation from the "baseline" by using unidirectional feedback stimulation is greater than that obtained using the feedback decoupling controller. This shows that unidirectional feedback stimulation may only (incompletely) mitigate, and not completely control, all seizures, unlike feedback decoupling.

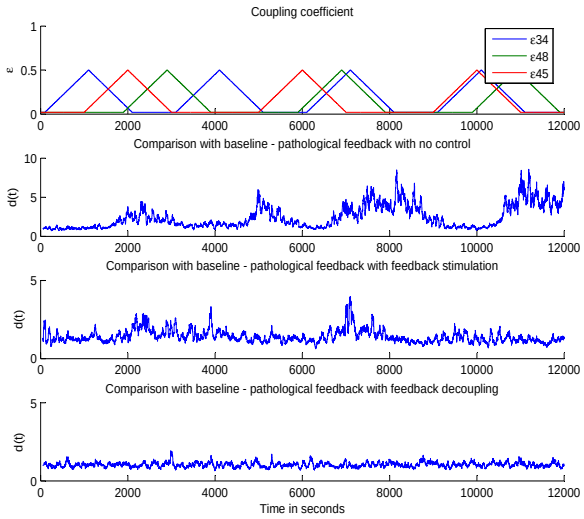

Figure 5: Network configuration with 3 pathological oscillator pairs: 4-3, 4-5 and 4-8. It is not possible to control seizures with unidirectional feedback control (panel III), whereas the feedback decoupling controller (panel IV) is successful. Panel Legends (top to bottom): I. Coupling configurations. II-IV. "Seizure" intensity $d(t)$ for the uncontrolled network, predefined-stimulus-based controller and feedback decoupling controller, respectively.

Next, we consider the bidirectional feedback stimulation to control a network with three pathological feedbacks: 3-4, 4-8 and 3-8. The internal coupling configuration is shown in Fig.6 (panel I). Notice the large deviation from the "baseline" for the uncontrolled network exhibiting seizures (panel II). Bidirectional feedback stimulation is applied between each of the pathological oscillator pairs. We use biphasic pulse waveforms (period = 2 seconds) and tune the stimuli pulse-widths and power (corresponding to 3-4, 4-8 and 3-8) to control seizures. It was not possible to use a straightforward tuning technique to control the seizures. On the other hand, in this case as well the feedback decoupling controller was successful in completely controlling all seizures. This is evident from panel IV which shows the deviation from the "baseline". Notice that the deviation using bidirectional stimulation is greater than that using feedback decoupling.

The above two cases are representative of a large number of cases wherein closed loop control using predefined stimuli are not sufficient to control seizures, while a similar feedback decoupling controller (PI_E) is successful in all cases. Furthermore, in comparison with control using predefined stimuli, the control input from PI_E needed to prevent seizures from occurring, a) is less interfering with the "brain" output patterns, b) uses lower amplitude/power control. Finally, for implementation purposes, the success of the closed loop strategy depends on how realistic is our postulated internal feedback structure, and if the critical site measurement and stimulation is available.

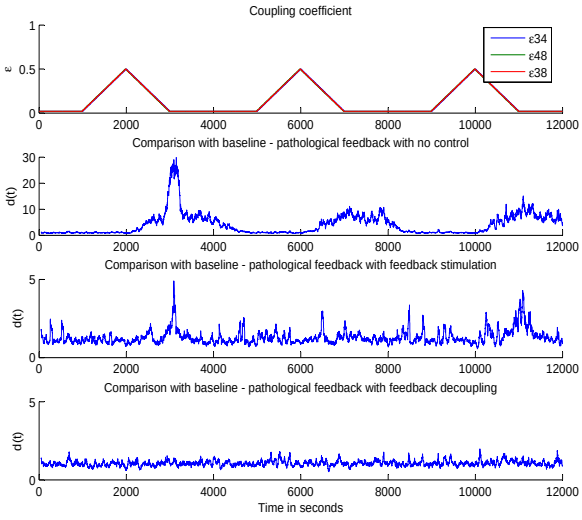

Figure 6: Network configuration with 3 pathological oscillator pairs: 3-4, 4-8 and 3-8. It is not possible to control seizures with bidirectional feedback control (panel III), whereas the feedback decoupling controller (panel IV) is successful. Panel Legends as in Fig.5.

Conclusions

Motivated by recent advances in the early detection of a preictal state, and consequently the prediction of epileptic seizures, we discussed the problem of controlling or suppressing seizures by means of feedback control. First, we improved previously proposed networks of chaotic oscillators as functional models of brain operation. We showed that by including internal feedback terms in such networks, many qualitative similarities with the observed dynamical behavior of the epileptic brain exist. In particular, when pathology causes de-tuning of the postulated internal feedback, the combined network exhibits "seizures", preceded by entrainment periods, similar to the ones observed prior to actual epileptic seizures. Although such a model has to be considered only an approximation to what really happens in the epileptic brain, it is developed on basic engineering principles and exhibits striking similarities with the observed dynamics before, during, and after seizures.

Resolving brain signals at the level of neuron firing is a highly nontrivial undertaking. Also, analysis of large-scale neuronal networks involves interconnected nonlinear systems with complex dynamics. Clearly, such models are very complicated and depend on many factors both internal and external to the system (brain). For example, the state of the subject (wake/asleep), sensory inputs, anatomy and physiology, will all play a role on the exact long-term brain behavior. A theoretical modeling approach is useful in addressing the basic dynamics of such

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physiological networks and allows the testing and refinement of control strategies for seizure control.

Based on this theoretical model, we previously presented three different seizure control strategies. Here, we studied the efficacy of unidirectional and bidirectional closed loop control in comparison with feedback decoupling control, in controlling "seizures". Our simulation results illustrate that simple tuning methods such as those used in clinical trials are not sufficient to obtain unidirectional and bidirectional stimulation parameters to control "seizures". The success of these methods depend on the network topology (number of pathologies) and coupling profiles. The best results on control of "seizures" in terms of deviation from the "baseline", and interference with oscillator outputs, were achieved with feedback decoupling control for all network configurations. The validation of this model is currently actively pursued with several animal models of epilepsy in our Laboratories at Arizona State University and collaborating sites at Barrow Neurological Institute, Phoenix, Arizona.

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