Proceedings of the
44th IEEE Conference on Decision and Control, and
the European Control Conference 2005
Seville, Spain, December 12-15, 2005

Control of Epileptic Seizures: Models of Chaotic Oscillator Networks

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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 discuss 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.**

I. INTRODUCTION

Epilepsy is the second most common neurological disorder after stroke, and affects at least 50 million people worldwide. 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 areas of the brain. 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 with epilepsy, 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. Approximately one-third of patients experience at least a 50% reduction of seizure frequency, but fewer than 10% become seizure free. This device works primarily by chronic intermittent stimulation of the left vagus nerve in the neck, although it is possible for the patient to activate the stimulator with a magnet, if he or she has a seizure aura sufficiently early to allow activation before mental impairment from the seizure. Deep brain stimulation (DBS), principally of thalamic structures, has also been reported to reduce seizure frequency in humans. (See the latest results in [2],[3],[4]).

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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]. Using new tools from signal processing developed in the 1980's, [8] reported the first application of nonlinear dynamics to clinical epilepsy. Subsequently, the existence of long-term preictal (before a seizure) 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 (between seizures) state to an abnormal (more ordered) ictal (during a seizure) state and back to a "normal" postictal (after seizures) 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].

The following unified dynamical view about epileptic seizures starts to emerge: Seizures result from a progressive recruitment of brain sites in an abnormal hypersynchronization. The onset of such recruitment occurs long before a seizure and progressively culminates into a seizure. 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. Auras could then be defined as the early stage of emerging activity in the thus defined preictal period. Reflex seizures may be viewed as results of input stimuli capable of inducing a fast preictal dynamical recruitment.

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

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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 growth of signals.

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. Indeed, adaptation bursts are caused by parameter drift and, when the adaptation is part of a feedback loop, their effect is exacerbated by simultaneous destabilization of the loop. A necessary precursor of adaptation bursts is a relatively long period of insufficient excitation, or alignment in some direction in the space of regressor signals. This is in striking similarity with the observed entrainment during preictal periods, by [16].

By incorporating an appropriate feedback structure in the original model by Iasemidis et al., 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. The power of this approach will be shown through analysis of data from simulation studies in networks of coupled chaotic oscillators with internal feedback.

There is a sharp distinction between our approach and the chaotic dynamical systems modeling approach found in the literature to date. We do not build a detailed model of the brain on the basis of which to try to detect and predict future bifurcations, nor do we attempt a generic pattern recognition scheme that usually provides no physical clues and interpretation of the underlying physiological mechanisms. At present, without any doubt, the complexity of the system (the brain) makes both approaches futile. For example, a detailed model as in [21], [22] is invaluable but could obscure the basic mechanisms of seizure generation. 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. At first glance, our analyzed oscillator model with feedback (i.e. with adaptation) may seem as a quite specialized structure. However, biological systems are specialized (optimized), and they are the results of adaptation (evolution). This modeling approach is also consistent with the concept of Highly Optimized Tolerance proposed by Carlson and Doyle [23], since optimization and feedback are the fundamentally impaired mechanisms in our proposed theoretical model for epilepsy.

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 to function "normally" with minimum intervention time-wise and power-wise. We envision that this technology will eventually enable a long anticipated new mode of treatment for epilepsy and other brain dynamical disorders, with neuromodulation, AEDs and electromagnetic stimuli as its actuators.

II. NETWORKS OF CHAOTIC OSCILLATORS

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 works 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 with each oscillator i $(i = 1, \ldots, N)$ described by the following equations

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

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, ϵ' are the generally asymmetric coupling strengths; in this example, we take $\epsilon = \epsilon'$. When the ϵ between two oscillators increases, their dynamical behaviors synchronize until they become nearly identical at high values of ϵ. As shown in [16], the STLmax traces (an approximate measure of steady state stability, see [10]) begin to converge for values of ϵ above 0.1 and the system loses its spatio-temporal chaotic behavior for stronger coupling ($\epsilon \simeq 0.25$). It is important to realize that the synchronization, which is a structural/network property, occurs while the temporal response of each oscillator is still chaotic. In this manner, chaoticity is progressively lost in

spatial coordinates while not being clearly detectable in the temporal coordinates of each individual oscillator. In the same reference, it is demonstrated that the STLmax traces from a typical EEG recording exhibit a similar pre-ictal synchronization pattern. (Note: For the sake of simplicity of presentation and simulation expedience, in the simulation data we produce and analyze next, we use the correlation coefficient between pairs of two signals, instead of a distance measure between STLmax profiles, to quantify the synchronization between the signals.)

III. ADDING FEEDBACK TO THE NETWORK: A NATURAL COMPENSATION FOR CHANGES

Motivated by the adaptation burst paradigm [20], in the previous general oscillator network we construct feedback around each pair of oscillators with the objective to decorrelate 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 thus modified oscillator network is now described by the following equations:

$$\begin{aligned} \frac{dx_i}{dt} &= -\omega_i y_i - z_i + b_i + \sum_{\substack{j=1 \\ j\neq i}}^{N} (\epsilon_{i,j}(x_j - x_i) + u^I_{i,j}) \\ \frac{dy_i}{dt} &= \omega_i x_i + \alpha_i y_i, \quad \frac{dz_i}{dt} = \beta_i x_i + z_i(x_i - \gamma_i) \end{aligned} \quad (2)$$

We now consider a case that incorporates some coupling changes with time, while other coupling remain constant over time. While results from a simple 3-oscillator network case were presented in [24], here we consider a network model containing 13 oscillators, only some of which have abnormal feedback, that can exhibit very complex behavior. Its topology is shown in Fig. 1. We take $\epsilon_{5,7} = \epsilon_{7,5} = 0.3$ (constant) and $\epsilon_{3,4} = \epsilon_{4,3}$, $\epsilon_{6,10} = \epsilon_{10,6}$ to be linearly varying between 0.02 and 0.5 and back to 0.02, in 4000 simulation seconds. The model is solved with a fixed time step 0.01sec. The internal feedback signals $u^I_{i,j}$ are defined as follows:

$$u^I_{i,j} = k_{i,j}(x_i - x_j), \; k_{i,j} = PI_I\{\rho_{i,j} - c_*\} \quad (3)$$

As in adaptive control, the feedback gains $k_{i,j}$ are themselves produced by a Proportional-Integral (PI) feedback, while $\rho_{i,j}$ denotes the 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 estimation of the correlation is performed in an exponentially weighted fashion in order to simplify the model's simulation:

$$\begin{aligned} \rho_{i,j} &= m^2_{x_i x_j}/(m_{x_i x_i} m_{x_j x_j}) \\ \dot{m}_{x_i x_j}(t) &= -a m_{x_i x_j}(t) + a x_i(t) x_j(t) \end{aligned} \quad (4)$$

In all of our simulations we used a time constant of 200sec ($a = 0.005$). The PI_I feedback can be viewed either as a decoupling compensator or as an estimator of the network's oscillator coupling parameter $\epsilon_{i,j}$. It is restricted to produce signals in the interval [0, 1] and it employs limited integration as an anti-windup mechanism (e.g., see [25]). This guarantees that when the correlation between the two signals is below the threshold c_*, no feedback is generated.

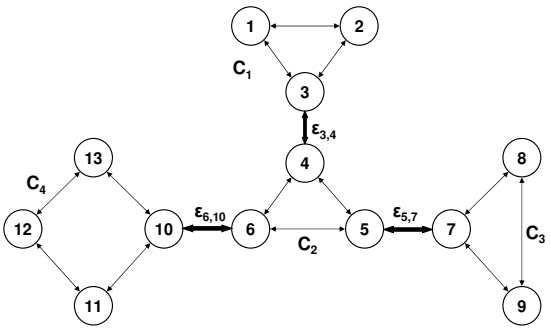

Fig. 1. Brain emulator as a network of coupled oscillators. The connecting lines indicate only non-zero coupling between the respective oscillators.

IV. PATHOLOGIC FEEDBACK IN THE NETWORK: A MECHANISM FOR SEIZURE GENERATION

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 $\epsilon_{i,j}$ 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 $\epsilon_{i,j}$ changes and corresponding parts of the system will exhibit adaptation bursts. For demonstration purposes, in our simulations we have modeled the normal PI_Is to have $K_p = 2.1$, $K_i = 0.0315$, whereas the pathologic PI_Is have an order of magnitude smaller values ($K_p = 0.21$, and $K_i = 0.00315$ –see below for more details). In the implementation of this model we use some additional high-level logic in order to emulate the pathological "brain's" recovery after a "seizure:" the model states x_i, y_i and z_i are reinitialized at the origin (x_i=y_i=z_i=0) as soon as their norm exceeds a large threshold value M_{xyz} (here 500). This reinitialization has a reasonable, quasi-physiological interpretation as high electrical activity might deplete critical neurotransmitters and thus deactivate critical neuroreceptors in a seizure participating neuronal network (passive mechanism). An alternative explanation is the release of neuropeptides in the brain as a result of seizures, which subsequently may contribute to the observed seizure recovery by initiating a feedback compensation intervention (active mechanism). Electrotonic coupling between neuronal axons may also account for coupling changes in the brain, and may thus constitute a better microscopic model for the type of coupling (diffusive) we consider in our networks herein.

As it turns out, despite the model's highly nonlinear nature, a simple PI compensator is sufficient to decorrelate the oscillators, as long as its bandwidth is not too high. (For its tuning we followed [26], 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_*. From the feedback point of view, PI_I destabilizes the oscillator network to maintain its chaotic behavior and counteract the stabilizing effect of the diffusive coupling. 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." This is then equivalent to "the internal feedback controller is not properly tuned and its feedback correction may get out of phase with an input that caused the change in the oscillator network coupling, resulting in a negative effective coupling coefficient of the combined network of oscillators and the PIs (whole brain)". If the effective coupling (i.e., the one caused by the coupling change and the corresponding internal feedback compensation) is large enough, it may destabilize the chaotic states of the network and produce high amplitude divergence (instability resembling "seizures"). A precursor of 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.

Our overall hypothesis also provides a model for the operation of the "normal" brain as follows: a) system in spatiotemporal chaos, b) stimulus enters the system, changes ϵ, and enables spatial coupling, c) spatial coupling produces spatial correlations, possibly storing the information about the stimulus and/or initiating action upon this information, d) spatial correlations also activate an internal compensating feedback mechanism, e) compensation removes (or assimilates) the stimulus effect, f) the system returns to spatiotemporal chaos.

Simulation examples that illustrate the above hypotheses are shown in Fig. 2, 3. The first figure shows the response of the oscillator network with a well-tuned internal feedback PI_I("normal brain"), producing a feedback gain that tracks the changing network coupling coefficient reasonably well. For this simulation the PI_I has a transfer function $2.1 + 0.0315/s$. Fig. 3 shows a network with a detuned PI_I ("epileptic brain"), its output reduced to 10% of the normal case. The PI_I estimates the increase of the network coupling relatively well until the network coupling drops too rapidly. At that point the internal feedback gain of the PI_I attains a large value, as it tries to estimate and follow the rapid change in ϵ, that destabilizes the oscillator network and its output grows in time. The "seizures" persist until the wrong value of the feedback gain from PI_I is dissipated. Entrainment similar to a real seizure is also noticed before the "seizure" which is hypothesized to be due to the inability

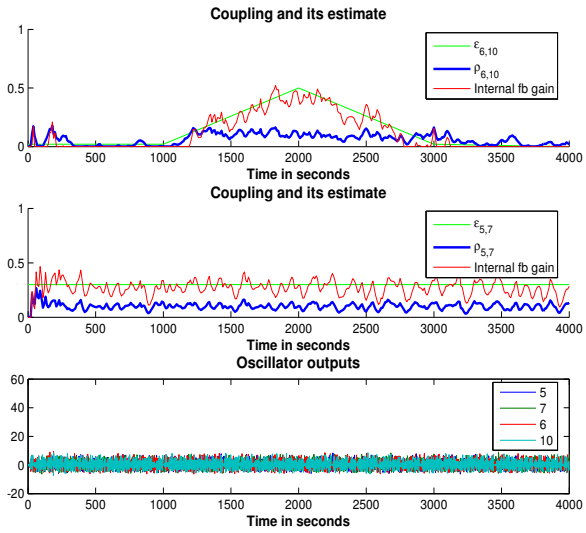

Fig. 2. Uncontrolled "brain" response for oscillators 5-7 and 6-10. "Normal brain network" behavior where signal correlations between sites remain low throughout the operation. (Similar for oscillators 6-10 and 3-4). Panel Legends (top to bottom): Coupling coefficient (green) and its estimate by internal PI feedback (red), and approximate correlation estimate (blue) for: I.Oscillators 6-10, II.Oscillators 5-7. III.Output of oscillators 5-7 and 6-10.

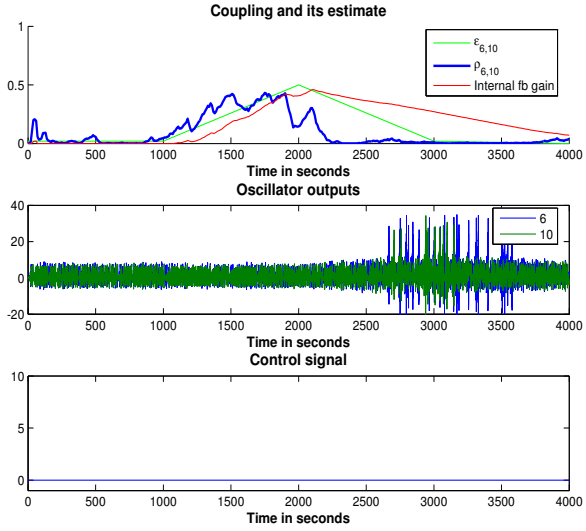

Fig. 3. Uncontrolled "brain" response for oscillators 6-10. "Uncontrolled epileptic brain network" behavior. Here, the overall gain of the internal feedback is reduced to 10% of the one in the "normal brain". The controller can no longer follow the coupling changes closely. Signal growth from instability 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. The response of the oscillators 5-7 and 3-4 remains similar to the "normal" case. Panel Legends (top to bottom): I. Coupling coefficient (green) and its feedback estimate by the internal PI(red); approximate correlation signal (blue). II. Outputs from each of the 2 oscillators. III. Applied external control signal (stimulation).

of the detuned (pathological) internal controller PI_I to track the changes in the oscillator network coupling, thus allowing correlations between two oscillator outputs to increase.

V. 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. Our current experiments with epileptic rats show the ability to affect the brain's dynamical entrainment by means of external electrical stimulation and/or drug intervention. At this point, it is not possible to assess whether electrical stimulation may provide complete seizure prevention or may be used as an add-on to AED treatment. Questions of whether the release of chemical substances during a seizure is an essential factor for recovery of brain's normal operation (resetting), and whether total suppression of seizures by external intervention would then affect the long-term brain's function cannot be answered yet.

A natural goal for a seizure control scheme 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. A good parallelism here can be drawn with the treatment of heart attacks (shock therapy) versus arrhythmias (pacemakers). 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 present next, address 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 the following, we assume that the external stimulation, denoted by u_i^E, enters the oscillator network in an additive manner. That is, for the ith oscillator,

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

$$\frac{dy_i}{dt} = \omega_i x_i + \alpha_i y_i, \frac{dz_i}{dt} = \beta_i x_i + z_i(x_i - \gamma_i) \qquad (5)$$

Fig.4 shows a functional block diagram of the internal feedback and closed-loop external controller.

A. Discrete Control

A first strategy for an external controller that could control the route of the epileptic brain towards seizures is the stimulation of the brain in an open-loop mode, e.g. with impulsive, sinusoidal, square or other signals, as is proposed in the literature and already applied in clinical trials, e.g., [2]. We refer to it as *open-loop discrete control* because the external controller generates a predefined stimulation sequence independent of the state of the brain, and the stimulation sequence is applied at discrete time intervals. It attempts to suppress seizures by a "shock" type of therapy that hopefully also resets the brain operation. Our computer simulations with the models described above show that this type of control input to the "focus"(one of the pathological

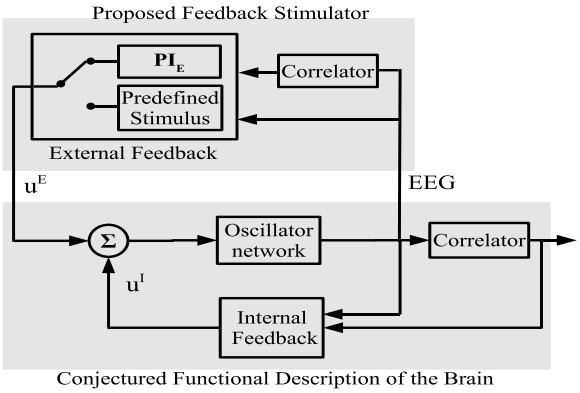

Fig. 4. Functional block diagram of the proposed internal feedback structure and closed-loop seizure control mechanisms.

oscillators) can indeed prevent a "seizure" provided that the stimulation has sufficient power and begins early enough prior to the "seizure". This indicates a second strategy for an external controller, that is a "shock" therapy combined with a long-term early seizure prediction scheme, referred to as *closed-loop discrete control*. The main simulation results (Fig. 5, 6) illustrate that seizure suppression is achieved with early warning but fails when the stimulation is applied close to the seizure onset. Systematic analysis along the same lines indicates that delaying the initiation of stimulation decreases the ability to suppress the upcoming seizure. Also, the earlier the warning, the less power is required, although there is a lower stimulation threshold below which the "seizure" is not suppressed. This emphasizes the need for an early seizure warning (and not simply a seizure detection) component in an effective and efficient (economical) seizure control system.

B. Continuous Control

Another control strategy is to employ *closed-loop continuous control* (see Fig. 4), which would involve continuous feedback, at least during the intervals of high susceptibility to seizure. In this strategy, the controller produces a predefined stimulus sequence continuously as long as measures of the brain state exceed a threshold. In our simulations of this control strategy, the level of correlations in (4) is used as a measure of the "brain" state. Other options include the T-index of STLmax for different sites. Results from the application of this strategy on the "brain network" are shown in Fig. 7, 8. The first shows the response to a pulse train stimulus to the "focus". The difference from the closed-loop discrete-time control is that here the pulse train is activated based on the monitoring of the brain state and stays active as long as needed for the measures of brain state to return to "normal" values. Fig. 8 shows the response to an alternative continuous control strategy, termed *decoupling control* and inspired from adaptive control. In this closed-loop continuous control scheme, the controller is turned automatically on as needed (intelligent) and its output is not a predetermined sequence of values but is a function of the "brain" state. In this scheme, the feedback signal is $u_i^E = \sum_{j\neq i} C_{i,j}(x_i - x_j)$, the same as the hypothesized internal

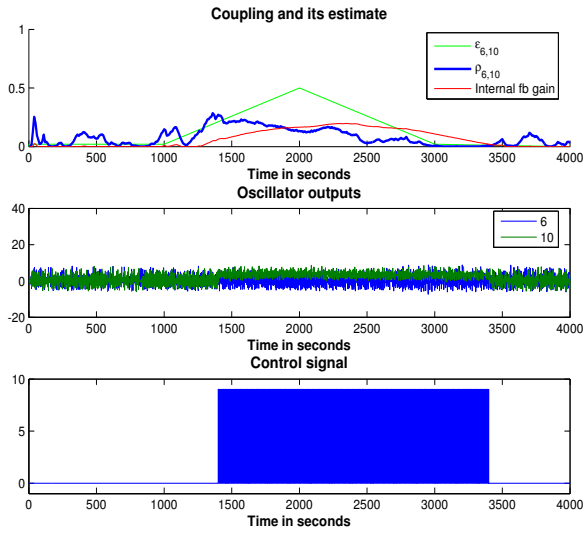

Fig. 5. Discrete control of the "epileptic brain network" by pulse-train stimulation. Emulating an early seizure warning (in reality issued by a prospective seizure *prediction* algorithm), the square pulse external stimulation is switched on in a discrete fashion as the coupling and the correlation between pathological sites increases. After activating the stimulation, the correlation returns to low values and remains low throughout the range of coupling change. However it appears that this kind of intervention, while it prevented the "seizure", has a considerable effect on the amplitude of the "brain" responses too. Thus, implications of this "treatment" on an actual brain must be carefully evaluated. Panel Legends as in Fig. 3.

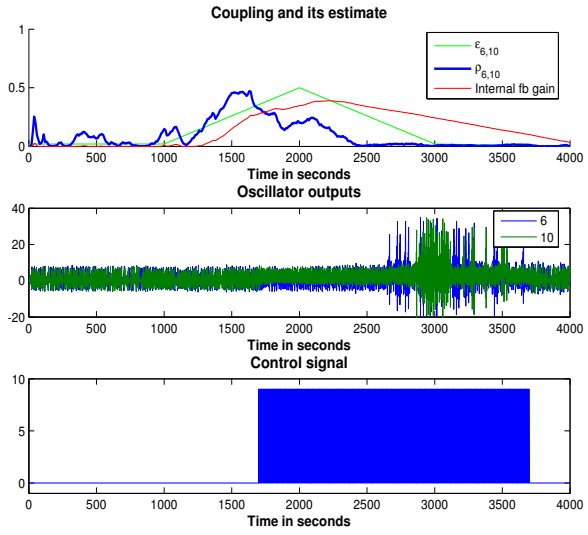

Fig. 6. Discrete control of the "epileptic brain network" by pulse-train stimulation. External stimulation, after an issue of a late warning (typically given by a seizure *detection* algorithm at the onset of a seizure), is insufficient to suppress the "seizure," even with large stimulation amplitudes. Panel Legends as in Fig. 3.

feedback PI_I. The external controller gains $C_{i,j}$ are now viewed as the manipulated variables and are updated using a PI control/estimation strategy(PI_E in Fig.4). This controller takes advantage of the hypothesized structural information about the system and, theoretically, it could completely decouple the two oscillators. The benefits of extracting and using more information for control are apparent from the simulation results of this strategy shown in Fig. 8: the stimulus needed to prevent seizures from occurring a) is less interfering with the "brain" output patterns, b) uses lower amplitude/power control. For implementation purposes, the success of this strategy depends on how realistic is our postulated internal feedback structure, and if the critical site measurement and stimulation is available. However, an advantage of continuous feedback is that, since control corrections are continuously updated, the requirements on model accuracy are less stringent than the ones for discrete control.

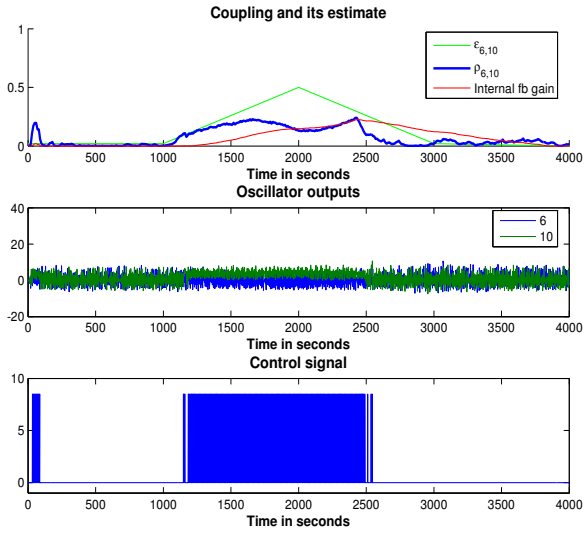

Fig. 7. Continuous control of the "epileptic brain network." Closed-Loop Continuous Control with pulse-train stimulation activated by a feedback signal when the correlation between two sites exceeds a threshold of "normality" (0.1). However, it appears that this kind of intervention, while it prevented the "seizure", it has a considerable effect on the amplitude of the "brain" responses too. Panel Legends as in Fig. 3.

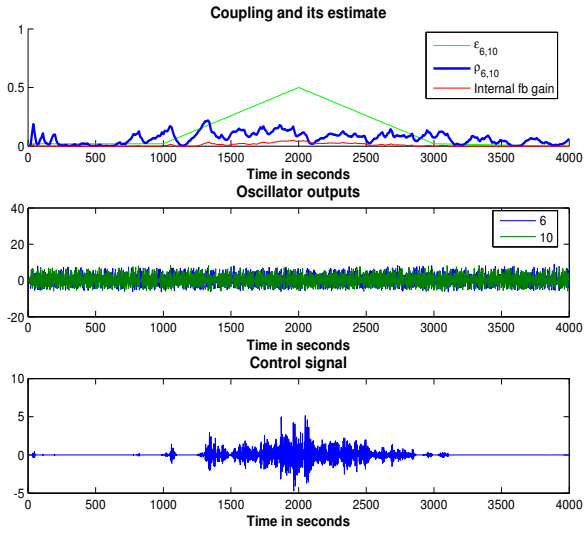

Fig. 8. Continuous control of the "epileptic brain network." Closed-Loop Continuous Control with PI feedback decoupling compensation. This is much closer to normal operation with respect to all measures, while utilizing lower stimulation signal power. Panel Legends as in Fig. 3.

VI. 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 approach is necessary to address the basic dynamics of such physiological networks. We believe that modeling approaches like the one proposed herein do exactly this. Such an approach is consistent with experimental observations and suggests interesting applications to the control of the epileptic brain by adjusting the brain's information processing mechanisms. The most important aspect of the proposed model is that it allows the testing and refinement of control strategies, and suggests alternative ones for seizure control. Our hypothesis for the normal and pathological operation of the brain suggests a method to suppress seizures by supplying external compensation to fix the pathology of the biological internal feedback.

Based on this theoretical model, three different seizure control strategies were tested, including the open-loop pulse-train stimulation that is currently used in clinical trials. Our simulation results illustrate the inefficiency and potential side effects of such a strategy. The best results on control of "seizures" were achieved by our novel method of closed-loop continuous feedback, that we have called "decoupling control". In addition to achieving the best results on seizure control, this method requires considerably less stimulation power to achieve the disentrainment or decorrelation of the brain-network sites, and with what appears to be minimal side effects (reduced interference with brain oscillator outputs) to avert impending seizures. 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, and the University of Florida, Gainesville, Florida.

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