Synaptic plasticity based model for epileptic seizures[☆]

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ARTICLE INFO

ABSTRACT

In this paper, a new dynamic model describing the epileptic seizure initiation through transition from interictal to ictal state in a brain predisposed to epilepsy is suggested. The model follows Freeman's approach where the brain is viewed as a network of interconnected oscillators. The proposed nonlinear model is experimentally motivated and relies on changes in synaptic strength in response to excitatory spikes. This model exhibits a threshold beyond which a bifurcation toward a short-term plasticity state occurs leading to seizure onset. A resulting explanatory assumption is that when considering epilepsy, brain regions are characterized by abnormally low thresholds toward short-term synaptic plasticity. It is shown by simulation that the proposed model enables some experimentally observed qualitative features to be reproduced. Moreover, a preliminary discussion on the impact of the underlying assumptions on the fundamental issue of seizure control is proposed through an EEG based feedback control scheme.

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1. Introduction

Epilepsy is the second most common neurological disorder after stroke. It affects approximately 50 million people around the world. Unfortunately, only 60% of cases respond to available antiepileptic drugs (AEDs). Besides the lack of efficiency of AEDs, they may induce unacceptable side effects and even lead to a substantial morbidity level, especially when polypharmacy is required (Iasemidis, 2003). This situation has triggered increasing interest in the seizure prediction paradigm (Sackellares, 2008) since an early anticipation of seizures may give us time to intervene therapeutically in a much less aggressive manner (Sackellares, 2008). The ability to perform early prediction of seizure onset relies on the assumption that a gradual transition takes place, steering areas of the brain from one state to another. Moreover, electroencephalogram (EEG) based prediction needs this gradual transition to produce some specific *signature* of the recorded signals. Although it is now widely accepted that all epileptic seizures do not fit this optimistic assumption (Sackellares, 2008), successful signal processing based prediction tools have been developed.

Besides such data processing based achievements, a deeper insight into the mechanisms involved can be obtained through dynamic phenomenological models. Such models may provide specific characterization that makes it possible to enlarge the subset of cases for which prediction is efficient and/or increase the anticipation time for the already successful situations. Deriving a simple and functional dynamic model that represents the onset of epileptic seizures is the aim of the present contribution.

The modeling approach proposed here follows Freeman's suggestion (Freeman, Kozma, & Werbos, 2001) according to which, the brain can be viewed as a network of nonlinear oscillators of relatively low dimension (Andrzejak et al., 2001; Babloyantz & Destexhe, 1986). Using this paradigm, it has been suggested (da Silva et al., 2003) that these oscillators show two attractors referred to respectively as normal steady state and paroxysmal state. The transition from the first to the second attractor explains the ictogenesis. Based on these ideas, a signal generator has been developed (da Silva et al., 2003) by identifying the attractors from recorded data and constructing ad hoc blocks (burst generators, transition firing, etc.) leading to simulated signals that fit astonishingly well to the true recorded EEG signal. A similar approach has been adopted in Traub and Bibbig (2000). These schemes however do not propose any conjecture as to the precise mechanism that lies behind the bifurcation occurrence.

Starting from this critical point of view and the commonly admitted idea that seizures reflect an abnormal hyper-synchronization between neuron activities (Iasemidis & Sackellares, 1996; Sackellares, 2008; Schelter et al., 2006; Schindler, Leung, Elger, & Lehnertz, 2007b), the authors of Chakravarthy, Sabesan, Iasemidis, and Tsakalis (2009b); Chakravarthy, Tsakalis, Sabesan, and Iasemidis (2009a) suggest a simple and attractive model for ictogenesis with implications on seizure control. According to this

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model, epileptic seizures result from badly compensated increases in the synaptic strengths. More precisely, while such sudden increases (i.e. enhancing synchrony) are suitably *attenuated* in a normal brain, thanks to *correctly tuned compensators*, they induce positive feedback (bursting) in brains predisposed to epilepsy that are characterized by *de-tuned* compensators.

This interpretation, while quite suitable to explain the experimentally observed bursts (Litt et al., 2001) that occur during the preictal period remains insufficient to explain the fundamental difference between transient bursts and the established relatively long-term seizure. In this paper, a qualitative difference is conjectured that involves the presence of low synaptic threshold for the development of seizures.

The dynamic model proposed in this paper is based on the following conjectures:

(1) The brain can be viewed as a network of interconnected oscillators (Freeman et al., 2001).
(2) Seizure onset reflects an abnormal synchronization level between neuron activities (Sackellares, 2008).
(3) In the absence of pathologies, there is a balance between synchronization and desynchronization disorders (Schnitzler & Gross, 2005).
(4) Synaptic strengths which support oscillator interconnection show dynamic behavior which differs according to the frequency and amplitude of an excitation signal (Gonzalez-Burgos, Krimer, Urban, Barrionuevo, & Lewis, 2004; Thomson, 1997; Varela et al., 1997) and may exhibit several attractors (Buonomano, 2000; Buonomano & Merzenich, 1995; Goldman-Rakic, 1995; Hempel, Hartman, Wang, Turrigiano, & Nelson, 2000; Matveev & Wang, 2000).
(5) The normal steady state and the short-term plasticity state may be viewed as two different attractors for the dynamic synapse strength. Based on experimental observations (Thomson, 1997) reporting that "*Once initiated by a brief high frequency spike train, facilitation (strength) was maintained at lower frequencies*". One may then conjecture that the high frequency spike train gradually increases the synaptic strength (see point (4) above) beyond a threshold where a transition is fired to the short-term plasticity attractor, contrary to the normal state. Once this occurs, despite the existence of a low frequency spike train, the strength retains its high value. Again, experimental evidence suggests that thresholds are involved in the synapse dynamics (Wasling, Hanse, & Gustafsson, 2002). This conjecture can be viewed as a particular instantiation of the two-attractors concept described above (da Silva et al., 2003) but applied to an interconnected network rather than to a single neuron.
(6) Regions in a brain predisposed to epilepsy are characterized by abnormally low synaptic thresholds from which transition to short-term plasticity is fired.
(7) Seizures may be initiated by a spike train as suggested by Hempel et al. (2000). This signal acts as input to the synaptic strength dynamical system (see conjecture 4 above) with sufficiently high frequency to enhance (in brains predisposed to epilepsy) an increasing-in-mean sequence in the synaptic strength causing transient bursts during the preictal phase. When the synaptic strength is beyond the threshold, transition occurs and short-term plasticity with high coupling is achieved. Synchronization is then accelerated giving rise to seizure onset.

In what follows, simple mathematical models of the above conjectures are proposed. These models are then assembled in order to produce a seizure occurrence scenario that qualitatively reproduces experimentally observed features. For the sake of simplicity, Rössler-like oscillators are used although specifically

identified oscillators (such those used in da Silva et al. (2003)) would provide better resemblance with experimental EEG signals. Synchrony indicators have been computed according to the multichannel approach proposed in Muller, Baier, Galka, Stephani, and Muhle (2005). These indicators have been used for EEG recording analysis in Schindler, Elger, and Lehnertz (2007a); Schindler et al. (2007b).

The paper is organized as follows: First the basic equations of the oscillator network are given (Section 2). In particular, it is proposed that the connections between oscillators involve a scalar representing the synaptic strength. A dynamic model for this parameter is then given and its experimental foundation is discussed (Section 3). The measure of synchrony proposed in Muller et al. (2005) and used in the current paper is recalled in Section 4. In Section 5, simulations are provided to assess the ability of the proposed model to qualitatively exhibit seizure onset scenarios. The sensitivity of the scenario features (duration of the preictal phase, amplitudes of bursts, etc.) are then discussed. Finally, an EEG based control strategy is proposed that relies on the underlying conjectures that may help attenuating seizure amplitudes.

2. Model of an oscillator network

Let us consider a model of a region in the brain constituted of N identical interconnected subregions of neurons. Subregion i is represented by a Rössler nonlinear oscillator that is governed by the following system of ordinary differential equations:

$$\dot{x}_i(t) = -\omega y_i(t) - z_i(t)$$
$$+ \sum_{j=1, j\neq i}^{N} \left[\varepsilon_{ji}(\eta) \cdot (x_j(t) - x_i(t)) \right] + x_d(t - \tau_i) \quad (1)$$

$$\dot{y}_i(t) = \omega x_i(t) + \alpha y_i(t) \quad (2)$$

$$\dot{z}_i(t) = b + z_i(t) \cdot \left[x_i(t) - \gamma \right] \quad (3)$$

where x_i is the variable that represents the contribution of subregion i to the EEG recording, that is:

$$V_{\text{EEG}} = \sum_{i=1}^{N} \lambda_i \cdot x_i \quad (4)$$

while y_i and z_i represent internal states of the oscillator that are necessary to produce the oscillations with a suitable degree of complexity (Andrzejak et al., 2001; Babloyantz & Destexhe, 1986). The coefficients λ_i' reflect the relative positions of subregions w.r.t. the recording sensor. The term: $\varepsilon_{ji}(\eta) \cdot (x_j(t) - x_i(t))$ represents the coupling effect of subregion j on subregion i. The coupling factor $\varepsilon_{ji}(\eta)$ is considered to be of the following form:

$$\varepsilon_{ji} = \varepsilon_{ji}^{\min} + \varepsilon_{ji}^{0} \cdot \eta \quad (5)$$

where $\varepsilon_{ji}^{\min}$ and ε_{ji}^{0} are some constant values and the scalar η denotes the synaptic strength in the region of interest. Under normal conditions, desynchronization is assumed to be enhanced through the terms:

$$x_d(t - \tau_i); \quad i \in \{1, \ldots, N\}$$

which represent the effects on the oscillator i of a dedicated desynchronization signal x_d, delayed by an amount of time τ_i that depends on the subregion. For a large number of neurons, the stochastic distribution of the delays (τ_i's) guarantees a high level of desynchronization between neurons under normal conditions. In our simulations, a simple sinusoidal desynchronization signal is used together with equally distributed delays:

$$x_d(t) = A_d \sin\left(\frac{2\pi t}{T_d}\right); \qquad \tau_i = \frac{2i\pi}{N}. \quad (6)$$