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A model for the evolution of the neuronal network in kindled brain slices

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HIGHLIGHTS

- Neurobiologically realistic model for epileptic brain slices dynamics.
- Dependence of network topology on kindling of epilepsy in brain slices.
- Hebbian learning as a mechanism for topological changes in epilepsy.
- Formation of modular clusters as an explanation of the origin of epilepsy.

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ABSTRACT

A biologically realistic neuronal network model for epileptic burst dynamics in chemically kindled rat hippocampal slices is proposed. The neuronal dynamics of hippocampus is incorporated through Hindmarsh–Rose (HR) neurons. Creation of new synapses or strengthening of existing synapses observed in the kindled brain slices is modelled through a hebbian learning mechanism that is switched on during kindling. The model reproduces a number of important features of kindling experiments. Prior to kindling, the neuronal network shows low activity oscillation corresponding to the normal or resting state of the brain. Subthreshold stimulation leads to a small growth in synapses that is not enough to elicit afterdischarge and the network reverts to the resting phase. At a critical threshold the network shows novel bistable bursting dynamics characterized by recurrent transition between a low 'normal' activity and a high 'bursting' activity as observed in experiments. Suprathreshold stimuli generate seizure states. For the four initial network choices, i.e., regular, small world, random and modular topologies, bistable dynamics and seizure states were observed for all. We observe that all topologies lead to seizure generation by the same mechanism of formation of modular clusters that fire simultaneously during population bursts. We believe that this computer model for focal epilepsy shall be useful in future epilepsy research.

1. Introduction

Epilepsy, a pathological state of brain characterized by a sudden generation of hypersynchronous activity by a network of neurons, is the fourth most common neurological disorder after migraine, stroke and Alzheimer's disease. It afflicts nearly 50 million people worldwide [1]. Epilepsy can be manifested by a generalized onset of the seizure spreading to the entire

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brain or a focal onset seizure originating from a particular region of the brain that remains confined to a small region [2,3]. There are various cellular mechanisms proposed for the development of seizure in an otherwise healthy brain: decreased synaptic inhibition, increased excitatory glutamate receptors, axonal sprouting and formation of new excitatory synaptic circuits [2]. Understanding the origin of epilepsy in the brain, therefore, remains a thrust area of brain research [1].

Epileptic seizure is always preceded by a pre-ictal period, during which there is a discernible change in the neuronal dynamics leading to seizures. Duration of seizure is called ictal period. Recent research focuses on studying and characterizing interictal period (time between two seizures) so that information about time of occurrence of seizures could be predicted [4]. Tools of non linear dynamics are being routinely used to characterize epilepsy and also to predict impending seizure. Many statistical models employ non-linear time series measures such as correlation dimension [5,6], and Lyapunov exponent [7,8] to identify patterns in the recorded brain signals indicative of an impending epileptic seizure. Tools from statistical learning theory such as support vector machines [9,10], Bayesian statistics [11–13], and artificial neural networks [14–16] have been used to construct efficient algorithms for seizure prediction. Stochastic models like Markov models and hidden Markov models have been proposed and used to explain and predict the existence of complex seizure patterns [17–19]. A number of recent works use complex network theory to link microscopic topology with macroscopic epileptic burst dynamics [20–23].

To understand the origin of various kinds of epilepsy experimentally, animal models have been used extensively to artificially generate epileptic state in the brain and then study the changes at both microscopic circuit level or at macroscopic dynamics level [24]. Two kinds of animal models have been studied extensively: *in vivo* and *in vitro*. The role of focus, initiation, paths of propagation and modulatory circuitry in *in-vivo* epilepsy has been studied [25]. For *in vitro* systems, a slice of hippocampus is kept alive neurobiologically for eliciting epileptic bursts. Further, these experimental eliciting of seizure generation, known as kindling, can be done by two methods: chemical [26–28], where inhibitory signals are suppressed through chemical injection thereby exciting the network continuously, or electrical, by application of monophasic or biphasic electrical pulses according to specific protocol that excites groups of neurons in certain frequency for a certain time [28]. The exact mechanism that synchronizes a cluster of neurons in kindled rat hippocampal slices is still unknown [29]. Depending on the method of slice preparation, in vitro hippocampal slices preparations from CA3 region may contain 1000 to 20 000 neurons [30]. Therefore, *in vitro* kindling models are also closer to the theoretical models that are studied through computer simulation of a tractable size of network, typically consisting of couple of hundred neurons [20,21,31].

Mathematical models of epilepsy, studied rigorously through computer simulation, on the other hand, look to reproduce specific experimental results and then try to propose a possible underlying mechanism. Such neural network models for epilepsy have been proposed using binary neurons [31,32] or realistic neurons [20,21,33], and are found to give useful insights in understanding the role of neuronal dynamics, circuit, control parameters etc. Further, such models can act as surrogate models for hypotheses testing and even suggesting new designs for experimental study of epilepsy [34]. Both deterministic and stochastic models, which could be further divided into microscopic and macroscopic models have been proposed and studied. Deterministic models of epilepsy, at microscopic level, use system of ordinary differential equations which could be conductance based neuron model such as Hodgkin–Huxley (HH) neuron model [35], Hindmarsh–Rose (HR) neuron model [36], Morris–Lecar (ML) neuron model [37,38] or Fitz–Hugh–Nagumo (FHN) neuron model [39], or more complex compartmental neuron model [40–45]. Cressman et al. [46] used micro scale deterministic model of modified excitatory and inhibitory HH neurons to investigate conditions under which seizure like activity can be obtained from persistent neural activity. Vincent et al. [45] showed that by changing extracellular potassium, activity of brain slice switches between regular and epileptiform activity. Oberheim et al. [47] showed that glutamate release from glia cells synchronizes the activity of adjacent neurons, which is then manifested in the form of epileptic seizure. Further, multi-compartment based neuron modelling was used to investigate the mechanism involved in epilepsy in CA1 hippocampal pyramidal cells [48–50]. It is observed that gap-junction between axons of pyramidal neurons may play an active role in the epileptic seizure with focal hippocampal origin. Another study revealed that NMDA conductance can explain epileptiform activity observed in conditions of low extracellular magnesium ion in hippocampal slices [51,52].

Epileptic dynamics has been generated by inhibition [53], by weak excitatory synapses [54] as well as by pathological reduction of excitatory synaptic transmission [55]. In a computational model of CA3 hippocampus neural network using Hindmarsh–Rose (HR) neurons, it has been shown that evolutionary rewiring through a genetic algorithm generates a synchronized state leading to seizure and the process is independent of initial graph topologies [21]. Vincent et al. [45] developed a computer model for electrically kindled rat hippocampal slice *in-vitro*, in which inhibitory and excitatory neurons are present in the ratio $1:3$. This model reproduces epileptic bursting and seizing behaviour of 4-AP *in-vitro* animal model for fixed synaptic topology with variable excitations. Epilepsy could be induced in a network, independent of its topology, by changing either synaptic strengths, or number of synapses per neurons, or proportion of local versus long-distance connection [20,56].

Methods of complex network, specifically the characterization of evolving networks, are particularly useful in understanding epileptic brain network [1]. By using a network of realistic neurons on different topology and 'complex network' framework, [21] showed that neurons can synchronize within a cluster leading to globally synchronous bursts through entrainment of distant areas. It has been observed that networks with few long range connections such as small world, scale free and random networks could be synchronized far easily than the network having just nearest neighbour connectivity [57]. Further, there exists modular structure in the brain, i.e., member within clusters are strongly connected to each other than to the members outside the cluster [58–61].

In this work, we attempt a realistic neural network model that generates epileptic behaviour by closely replicating the kindling mechanism in the epileptic hippocampal slices. The neuronal dynamics is modelled by Hindmarsh–Rose neurons