Desynchronization of neural activity in a network model.

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Abstract

Electric brain activity during seizures is often associated with hyperactive and synchronous bursts of activity. We investigated different protocols of electric stimulation in a model network as potential seizure control mechanisms. Our network consisted of a chain loop of cells with excitatory synapses, representing a neocortical microcircuit. Random fluctuations of the membrane potential in each neuron simulated activity originating from other areas. Overall depolarizing and hyperpolarizing currents were not effective in stopping synchronized activity in the network. An electric current proportional to the inverted field potential was an effective desynchronizing stimulus in smaller networks.

Introduction

A major goal in epilepsy treatment is to control high levels of activity and synchronous oscillations of underlying neural networks in the brain. Several studies have investigated electric stimulation as a possible therapy for seizure control [2, 4, 5, 8, 10, 14, 16, 19, 21]. With few exceptions, it can be concluded that direct stimulation to areas where epileptiform activity occurs is the most effective.

In a clinical setting, a large scale parametric study on the relationship between electrostimulation and seizure activity isn't always feasible or ethical. Electric stimulation in slices of brain tissue is studied under the assumption that the behavior of

small networks can provide insight into the activity of the intact brain. Simulated activity of neural networks provides an additional route to study aspects of synchronized network behavior and the relationship between seizure control and various paradigms of electric stimulation. Current simulation studies seek to explain how synchronous activity may be generated and sustained, by looking into intrinsic properties of individual neurons, local cortical networks, and thalamo-cortical loops, [e.g. 3, 6, 11, 12, 13, 20]. Recently Kudela et al [9] explored the relationship between open loop electrostimulation and recurrent bursting in a model of connected sub-networks.

In this study we simulate synchronized activity within a small network representing local epileptiform activity in the cortex microcircuitry before it propagates to a larger area. We examined different types of electrostimulation as a tool to stop population discharges by looking for desynchronization of the activities.

Methods

To study the effects of electrostimulation in a network, the following elements were included in our simulation: (1) model neurons connected within (2) a network that is capable of displaying synchronous activity, and (3) a method to stimulate electrically using different paradigms. The paradigms we examined are (a) depolarization, (b) hyperpolarization, and (c) field potential related currents. The model is implemented as a MatLab (The MathWorks Inc, Natick, MA) script file and C programs created from these scripts. The accuracy of simulation is 1/25 ms.

(1) Neural elements. The unit of our model network is a Hodgkin-Huxley type membrane model [7] representing one neuron. Each element consists of membrane capacitance (C) and ion channels. The total ionic current (I) is the sum of the individual

ionic currents: $I = i_{Na} + i_K + i_L$, where i_{Na} – sodium current; i_K – Potassium current; i_L – Leakage current.

(2) Network structure. Isolation of tissue components in *in vitro* experiments established that the microcircuitry of the neocortex is capable of generating and sustaining epileptiform bursts [1]. This indicates that seizure activity may arise in small networks before it is propagated to involve a larger area. Our model network was a chain loop of a small number of units (< 10) coupled via excitatory synapses. Activity in excitatory synapses was simulated by a depolarizing current (i_s) for a duration of 5ms. Because the distance between neighboring neurons was assumed to be small (< 100 um), synaptic transmission was responsible for the delay between activities of connected units, there was no extra delay representing the conduction over the axon. Additional activity from other areas in the brain was simulated by independent random excitatory and inhibitory activity (i_R) on each neuron. The small network could be considered as a set of neocortical pyramidal cells in layers II/III and/or layers V/VI that interconnect in a local microcircuit [15, 17].

(3) Electric stimulation. Current to mimic electric stimulation is added to the transmembrane currents.

(a) A depolarization is caused by an inward transmembrane current (i_D).

(b) A hyperpolarization is created by an outward transmembrane current (i_H).

(c) We calculate the extracellular field potential by assuming that the recording electrode is equidistant to all the neurons. Their contribution to the recorded field potential is proportional to the sum of their individual electric activities [18, 20, 21]. The summated potential was scaled and subjected to a bandfilter (0.5-70 Hz) to mimic the

effects of the impedances of the extracellular medium and the filters that are typically applied to EEG signals. The applied transmembrane feed-back current (i_{FB}) was inversely proportional to the processed field potential and applied to each of the network elements. The equation describing the membrane potential (V) of one network element in time (t) is:

$$C(dV/dt) + I + i_s + i_R + i_D + i_H + i_{FB} = 0$$

Results

The effect of electrostimulation was studied by starting synchronized activity with an initialization pulse in a simulation with a total duration of 700 ms. Different types of test current were applied during a 100 ms epoch starting at 500 ms after the start of the simulation. This allowed us to observe behavior of the network before, during and after the test current. A typical result of each stimulus paradigm on a synchronized network of five neurons is shown in Fig. 1A (depolarization), Fig. 1B (hyperpolarization), and Fig. 1C (EEG feedback). Each example shows the applied current in the upper panel. The following five panels show individual activity of each neuron in the network. The bottom trace in each column of Fig. 1 depicts the individual activities superimposed. This trace is to visually determine the degree of synchrony in the network. A depolarization initializes synchronous activity 1 ms after the start of the simulation. In the examples shown, the overall activity of the network is in synchronous mode at the start of the test current. In Figs. 1A and C several small intervals of 'spontaneous' desynchronizations, prior to the test current onset, can be observed.

The results of the three stimulus paradigms can be summarized as follows.

1. The depolarizing current (Fig. 1A) causes a slight increase of activity in the individual neurons, and causes some desynchronization during the stimulus. However, immediately after the stimulus offset the network is in synchronous state.
2. A hyperpolarization of the neurons (Fig. 1B) stops the generation of action potentials during the application of the stimulus. The stimulus offset triggers the network's elements and creates synchronous activity.
3. The initial effect of the feedback current (Fig. 1C) is inhibition of the elements, followed by an excitation. Interestingly the activity (in action potentials/s) arising after the initial inhibition is slightly higher than before the stimulus onset. More importantly this activity is desynchronized, and the network remains to be desynchronized after the stimulus offset. This is a reproducible finding in the smaller networks we used in our simulation study.

Discussion

Our study demonstrates that EEG-like feedback current desynchronizes networks whereas depolarization and hyperpolarization do not desynchronize the neural activity. Our data agree with results from *in vitro* studies where electrostimulation was used to modify bursting behavior in populations of neurons. Gluckman and colleagues [5] found that adaptive field control, similar to our feedback current paradigm (Fig. 1C), is an effective inhibitor of seizure activity. Although the details of their experiment and findings differ from our simulation, the overall conclusion is similar. Nakagawa and Durand [16] found that hyperpolarization inhibits seizure like activity in hippocampal slices, but that population burst activity rebounds after stimulus offset (their Fig. 6). This finding is identical to the result following hyperpolarization (Fig. 1B). To our

knowledge, a depolarizing current pulse has not been tested as a desynchronizing stimulus in smaller networks. Simulations by Kuda et al [9], model propagation of epileptiform activity in a larger network. In this simulation, correctly timed depolarization can stop a propagating burst. In experimental models, the effects of a depolarizing current was used to evoke bursts in order to pace network bursting activity in cortical slices [8, 19].

One might hypothesize about the reason why EEG feedback is an effective desynchronizing stimulus. Clearly, it cannot be simply explained by inhibition caused by a hyperpolarization of the membrane (Fig. 1B). It seems that the inverted field potential creates the right 'dose' to stop synchronous firing of the neurons. In a population that is synchronously active, the field potential is proportional to each individual activity, and therefore the inverse of that activity may be an effective desynchronizing stimulus for the individual elements in the network. It is likely that high levels of synchrony between cells only arise in small populations, and as soon as larger populations are considered the cells spread over a larger distance and conduction delays destroy synchronous firing. Indeed in larger networks of sequentially coupled neurons, oscillations occur but the synchrony between neurons breaks down due to conduction and transmission delays. The activity pattern of larger networks wasn't visibly affected by an EEG feedback current.

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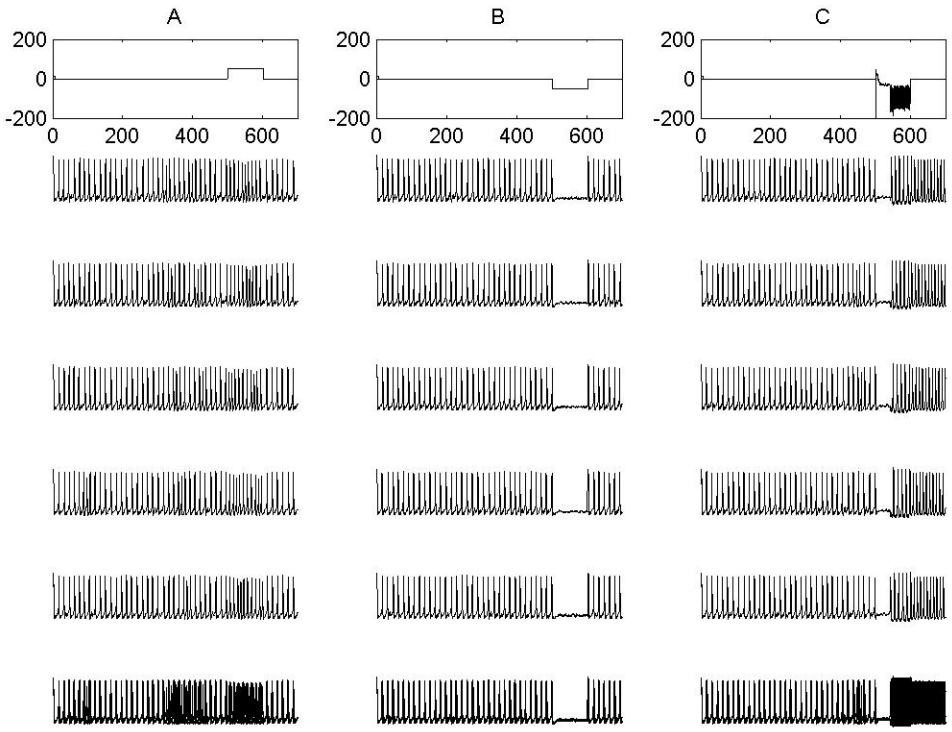

Figure 1

The effects of three different electrostimulation paradigms (A. Depolarization, B. Hyperpolarization, C. EEG feedback). Stimulus current in $\mu A/cm^2$ (upper panel) and activities of five neurons in the network (panels 2-6). The bottom trace shows the superimposed cellular activities. In the case of EEG feedback (C), the network remains desynchronized after stimulus offset.