Origins of Desynchrony in Seizures: Computational Model

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Abstract

Seizures have been assumed to be a manifestation of excessive synchrony since the 1950s. However, there has been little direct experimental evidence characterizing neuronal interactions during seizures. In CA1, we used electric fields to initiate seizures, and found from dual intracellular impalements that neurons desynchronize as seizures initiate and synchronize as seizures turn off. This is consistent with recent theoretical results [5]. We constructed a computational model that replicates the neuronal geometric variability and the electrically resistive properties of CA1, and observed changes from desynchrony to synchrony by varying the applied electric field.

Introduction

In the literature, the most common physical description of seizure dynamics suggests excessive synchrony or 'hypersynchrony' among neurons [6]. However, there has been very little quantification of the interactions between individual neurons necessary to characterize such synchrony.

We have conducted several experiments probing the nature of the interactions between neurons as a network transitions from nonseizure to seizure states in hippocampal CA1. We have demonstrated that electric fields can activate and suppress seizures *In Vitro* [3] and *In Vivo*. Using dual intracellular patch clamp techniques, we have found – contrary to expectation – that neurons *desynchronize* as they transition into seizure, and synchronize as seizures turn off.

These observations are consistent with recent theoretical work [5] demonstrating that sustained network activity is achieved in an asynchronous rather than a synchronous network of excitatory and inhibitory neurons. Two features of such asynchronous networks are important: 1) recurrent excitatory activity, required to maintain network activity, and 2) a balance between excitatory and inhibitory synaptic strength. For such networks, synchronization turned *off* network activity.

We have constructed a compartmental computational model, based on hippocampal pyramidal neurons, that exhibits desynchronous transitions. Our model includes electric field interactions, both from imposed and intrinsic electric fields. The goal of this modeling is to gain insights into the physical origins of the observed desynchronization, and to provide a simulation test bed for designing algorithms for electric-field feedback control of seizures.

Method

Electric fields modulate neuronal activity by polarizing neurons along their soma-dendritic axis [1,2,9]. The minimal requirement for model neurons to be affected by fields is therefore a two-compartment neuron. We have selected the lumped-parameter two-compartment Pinsky-Rinzel (PR) neuron [7] as the basic subunit in our network. Details appear in Appendix 1. We have embedded these neurons in a linear resistive array (Figure 1) and the imposed electric field is modeled by a potential difference between V_{top} and ground. The applied electric field serves as a global coupling parameter, while the intrinsic electric fields produced by neuronal firing provides local coupling. In addition, the neurons are coupled synaptically through their NMDA and AMPA channels.

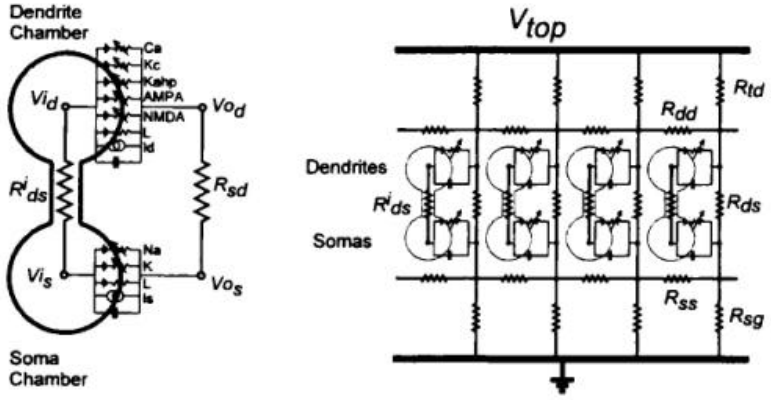

Figure 1: PR neuron diagram (left) and resistive network of PR neurons (right), after [4].

Results

Figure 2 shows activation of the network using piecewise-constant electric fields, including suppression of the network with a reversed field polarity. Such findings mimic our *In Vitro* and *In Vivo* experimental observations. For small parameter mismatch (near 1%) in the soma-dendrite lumped conductance and in the calcium conductance, the individual neurons in Figure 2 are seen to fire in synchrony.

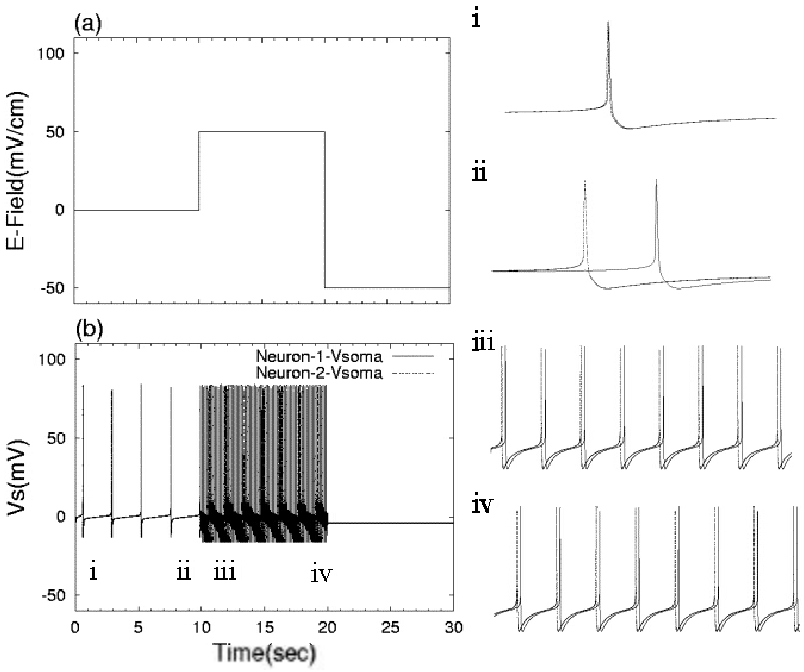

Figure 2: Tracing of two coupled PR neurons with low potassium (Electric field = 0, ±50mV/cm). The two PR neurons can be synchronized with +50mV/cm (see blowup graphs on the left panel).

Next, we employed a parameter-free estimator of phase locking to examine the synchrony transitions in these neurons. Following [8], we used the amplitude of the first Fourier mode of the distribution of the relative phase ? (t) between the neurons to calculate a synchronization index ?, where $g^2 = \langle \cos\Psi(t) \rangle^2 + \langle \sin\Psi(t) \rangle^2$ and "<>" denotes time-average. This index varies from 0 to 1 for unsynchronized and synchronized activity, respectively (see Appendix 2 for a description of ? (t) and ?).

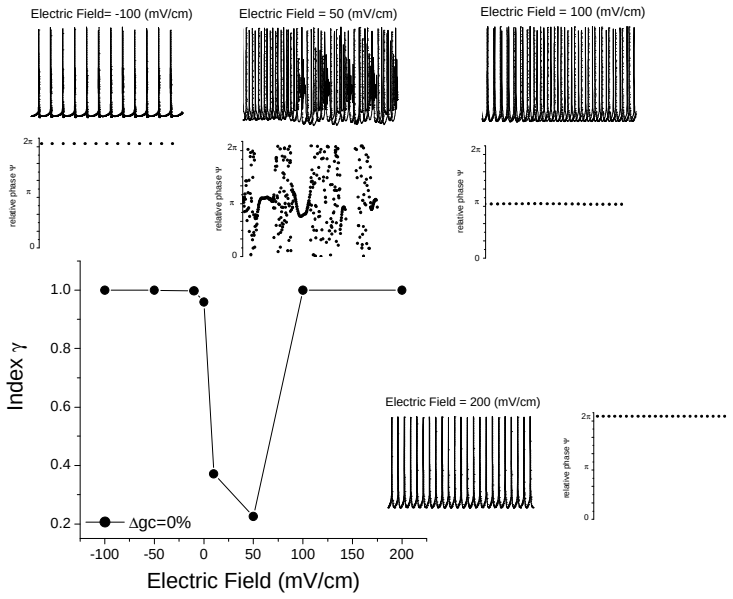

Figure 3: Synchronization index as a function of electric field. Parameters for each neuron are identical, but initial conditions differ by 10^{-13}.

In Figure 3 all parameters are identical, but the initial conditions of each neuron are different by approximately 10^{-13}. For weak activating fields (50 mV/cm), the synchronous state destabilizes as indicated by the pervasive phase slips. As the strength of the activating electric field increases, the neurons first synchronize in anti-phase (relative phase = p); at stronger fields, synchrony is identical (relative phase = 0 or 2p).

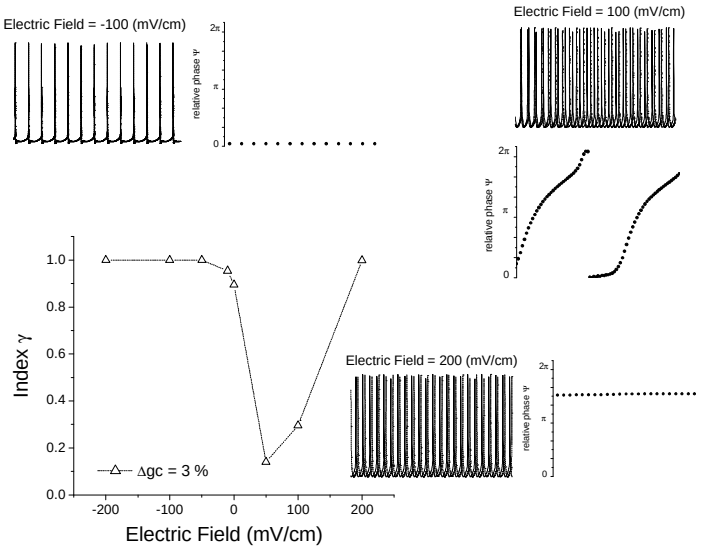

Figure 4: Synchronization index as a function of electric field. The internal conductance in each neuron is different by 3%; initial conditions differ by 10^{-13}.

Figure 4 demonstrates the dynamical effect of a larger parameter mismatch. Here, the internal conductances between the dendrite and soma differ by 3%. In contrast to the previous case (Fig. 3), the neurons remain desynchronized and exhibit continuous relative phase slips at an activating field strength of 100 mV/cm. At 200 mV/cm, the neurons lock at a fixed relative phase.

Discussion

We have demonstrated that a computational model of CA1 that includes resistive properties exhibits phenomena similar to the activation and suppression of seizures with electric field observed in experiments. By explicitly including asymmetry, we find that the asynchronous state is more robust with respect to electric field stimulation. Nevertheless, sufficiently high field strengths synchronize the system.

Further explorations of the physical origins of asynchrony in such networks will provide a framework for a theory of epileptic seizures.

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Appendix 1: Equations

$$c_m \dot{V}_s = -I_{Leak}(V_s) - I_{Na}(V_{s,} h) - I_{K-DR}(V_s, n) + \left(\frac{g_c}{p}\right)\cdot(V_d + V_{DS} - V_s) + \left(\frac{I_s}{p}\right)$$

$$c_m \dot{V}_d = -I_{Leak}(V_d) - I_{Ca}(V_d, s) - I_{K-AHP}(V_d, q) - I_{K-C}(V_{d,} Ca, c)$$
$$-\frac{I_{syn}(V_d, S_i(V_s), W_i(V_s))}{(1-p)} + \left(\frac{g_c}{1-p}\right)\cdot(V_s - V_{DS} - V_d) + \left(\frac{I_d}{1-p}\right)$$

$$\dot{Ca} = -0.13\cdot I_{Ca} - 0.075\cdot Ca$$

Equation for gating variables ($h, n, s, c,$ and q) : $\dot{y} = \frac{y_\infty(U) - y}{t_y}$

U corresponds to V_s when $y = h, n$; V_d when $y = s, c$; Ca when $y = q$

$$\dot{S}_i = \sum_j H(V_{s,j} - 10) - \frac{S_i}{150}$$ (NMDA synaptic current weight)

$$\dot{W}_i = \sum_j H(V_{s,j} - 20) - \frac{W_i}{2}$$ (AMPA synaptic current weight)

Here, $H(x) = 1$ if $x \geq 0$ and 0 otherwise. Cell j synapses onto cell i

The summary of ionic currents is as follows:

$$I_{Leak}(V_s) = g_L(V_s - V_L)$$

$$I_{Leak}(V_d) = g_L(V_d - V_L)$$

$$I_{Na} = g_{Na} \cdot m_\infty^{\ 2}(V_s) \cdot h \cdot (V_s - V_{Na})$$

$$I_{K-DR} = g_{K-DR} \cdot n \cdot (V_s - V_K)$$

$$I_{K-C} = g_{K-C} \cdot c \cdot c\,(Ca) \cdot (V_d - V_K)$$

$$I_{Ca} = g_{Ca} \cdot s^2 \cdot (V_d - V_{Ca})$$

$$I_{K-AHP} = g_{K-AHP} \cdot q \cdot (V_d - V_K)$$

$$I_{syn}(= I_{NMDA} + I_{AMPA}) = g_{NMDA} \cdot S_i(t)\left(\frac{V_d - V_{syn}}{1 + 0.28 \cdot \exp(-0.062(V_d - 60))}\right)$$

$$+ g_{AMPA} \cdot W_i(t) \cdot (V_d - V_{syn})$$

V_s, V_d : soma and dendrite transmembrane potentials

V_{DS} : extracellular potential difference between outside the dendritic compartment and outside the somatic compartment

I_s, I_d : steady somatic and dendritic current injection

p : relative area of soma to dendrite

c_m : membrane capacitance

g_c : coupling conductance between soma and dendrite

Appendix 2: Relative phase and Index γ

The phase of each neuron is defined in terms of the times t_i for threshold crossings of the transmembrane soma voltage as follows:

$$\varphi_1(t) = 2p\left(\frac{t - t_k}{t_{k+1} - t_k}\right) + 2p\,k\,; \quad \varphi_2(t) = 2p\left(\frac{t - t_m}{t_{m+1} - t_m}\right) + 2p\,m\,.$$

The relative phase Ψ is defined as

$$\Psi(t_k) = \varphi_2(t_k) - \varphi_1(t_k) = 2p\left(\frac{t_k - t_m}{t_{m+1} - t_m}\right),$$ and ? is defined as in the text.

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