Transitions between multistable states as a model of epileptic seizure dynamics

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Epileptic seizures are generally considered to result from excess and synchronized neural activity. Additionally, changes in amplitude and frequency are often seen in local field potential or electroencephalogram recordings during a seizure event. To investigate how seizures initiate, and how dynamical changes occur during seizure progression, we develop a neocortical network model based on a model suggested by Wilson [J. Theor. Biol. **200**, 375 (1999)]. We propose a possible mechanism for seizure initiation as a bifurcation, and suggest that experimentally observed changes in field potential amplitude and frequency during the course of a seizure may be explained by noise-induced transitions among multistable states.

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Neural synchronization occurs in a wide range of animals, from invertebrates to humans [1–3]. Since synchronization has been shown to play a role in processes ranging from simple sensory transduction [2] to perception and learning [3], and has also been detected in pathological conditions such as Parkinson's disease [4,5], understanding the mechanisms of synchronization may be a critical step in elucidating how neural systems work.

Epileptic seizures have long been considered to result from excess and synchronized brain activity [6], though some recent studies suggest that this picture may be an oversimplification [7]. Furthermore, changes in amplitude and frequency of electrical activity are often observed during seizure events in both human patients [8] and animal models [9]. Various computational models of seizure onset and progression have been developed [10,11], but many questions remain unanswered.

In this paper, we report a possible dynamical mechanism for seizure initiation, and for dynamical changes in electrical activity during seizure events. We develop a model of a neocortical network based on a nonlinear model suggested by Wilson [12] [Eqs. (1)–(4) below]. The effect of the potassium channel blocker 4-aminopyridine (4-AP), used experimentally to induce seizures [13], is simulated by decreasing the model's maximal K^+ channel conductance (g_K). We use phase reduction analysis [14] to demonstrate that the phase relationship of a pair of synaptically coupled neurons undergoes a bifurcation as g_K is varied. Multistability is observed in the stable fixed phase difference, and a dramatic increase in the activity of a larger network of neurons correlates with the bifurcation.

The dynamics of a single neuron is represented by a set of nonlinear ordinary differential equations [12],

$$C\frac{dV}{dt} = -m_\infty(V)(V-0.5) - g_K R(V+0.95) - g_T T(V-1.2) - g_H H(V+0.95) + I \quad (1)$$

$$\frac{dR}{dt} = \frac{1}{\tau_R}[-R + R_\infty(V)], \quad (2)$$

$$\frac{dT}{dt} = \frac{1}{\tau_T}[-T + T_\infty(V)], \quad (3)$$

$$\frac{dH}{dt} = \frac{1}{\tau_H}(-H + 3T), \quad (4)$$

where V is the membrane potential, and R, T, and H are the conductance variables for the K^+, Ca^{2+}, and Ca^{2+}-mediated K^+ hyperpolarizing currents, respectively. The following variables depend nonlinearly on the voltage V: $m_\infty(V) = 17.8 + 47.6V + 33.8V^2$, $R_\infty(V) = 1.24 + 3.7V + 3.2V^2$, $T_\infty(V) = 8(V+0.725)^2$. System parameters are given as follows: $C = 1.0\ \mu\mathrm{F\ cm^{-2}}$, $I = 0.7$ nA, $\tau_T = 14$ ms, and $\tau_H = 45$ ms. The first term in Eq. (1) represents the Na^+ current; the Na^+ channel dynamics is incorporated into $m_\infty(V)$ instead of using a conductance variable. In the model equations, V is scaled by 1/100 with respect to realistic membrane potential values in order to keep the constants in m_∞, etc., within a reasonable range. In the figures below, we rescale V by 100 (mV) in order to return to biologically realistic values. The model can be tuned to exhibit the behavior of the three major subtypes (regular spiking, bursting, and fast spiking inhibitory) of neocortical neurons by changing g_K, g_T, and g_H [12]. In this paper, we restrict ourselves to a single subtype, the regular spiking mode ($g_K = 26.0$, $g_T = 0.1$, and $g_H = 5.0$), which corresponds to the largest population of neocortical neurons [15]. Chemical synaptic coupling is modeled using an alpha function [16]:

$$\frac{df}{dt} = \frac{1}{\tau_{syn}}[-f + \Theta(V_{pre} - \Omega)], \quad (5)$$

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$$\frac{dS}{dt} = \frac{1}{\tau_{\text{syn}}}(-S+f), \tag{6}$$

where V_{pre} represents the voltage of the presynaptic neuron, $\tau_{\text{syn}}=0.5$ ms, $\Omega=-0.2$ mV, and the Heaviside function $\Theta(V_{\text{pre}}-\Omega)=1$ for $V_{\text{pre}}-\Omega>0$ and 0 for $V_{\text{pre}}-\Omega\leqslant 0$. The effect of synaptic coupling is incorporated into the dynamics of each neuron by adding the term $-Sg_{\text{syn}}(V-V_{\text{syn}})$ to Eq. (1), where g_{syn}, the synaptic strength, is set at 0.1, and V_{syn}, the synaptic reversal potential, is 0 mV, which mimics the effect of an excitatory synapse.

To study how changes in g_{K} affect the behavior of a pair of coupled neurons, we applied phase reduction analysis [14] to the system. Using this method, a pair of weakly coupled limit cycle oscillators can be reduced to a system of one variable, and the stability of the phase difference between the oscillators can be determined. We consider the two neurons i and j as stable limit cycle oscillators. If the dynamics of neuron i is represented by $dX_i(t)/dt=F(X_i)+G(X_i,X_j)$, its dynamics can be reduced to the equation for the phase variable θ_i,

$$\frac{d\theta_i}{dt} = \omega + H(\theta_j - \theta_i), \tag{7}$$

assuming that both neurons have the same natural frequency ω, and with H given by

$$H(\theta_j-\theta_i) = \frac{1}{T_0}\int_0^{T_0} u(t)^T G(\gamma(t), \gamma(t+\theta_j-\theta_i))dt \tag{8}$$

[14], where G is the coupling between the oscillators, γ is the periodic solution of a single oscillator with period T_0, and $u(t)$ is the periodic solution of the adjoint equation of $dX_i(t)/dt=F(X_i)$:

$$\frac{du(t)}{dt} = -D_F[\gamma(t)]^T u(t). \tag{9}$$

Here, $D_F[\gamma(t)]$ is the Jacobian matrix and T represents the matrix transpose. We determined H by numerically solving the adjoint equation [17] for our system. The dynamics of the phase difference between the two neurons can be represented as

$$\frac{d\phi}{dt} = H(-\phi) - H(\phi), \tag{10}$$

where $\phi=\theta_i-\theta_j$. A fixed phase difference is thus any value ϕ_0 for which $d\phi/dt=0$. The slope of $d\phi/dt$ at ϕ_0 gives the stability of the phase difference, with a negative slope corresponding to a stable, and a positive slope corresponding to an unstable, phase difference. Here, we follow Pikovsky and others in considering that a fixed phase difference is indicative of synchronization between two oscillators [18].

Plots of $d\phi/dt$ as a function of ϕ are shown in Fig. 1. At normal g_{K} ($g_{\text{K}}=26.0$), the stable phase difference is small [filled circles, inset, Fig. 1(a)] but nonzero, so that the neurons are almost, but not exactly, in phase. In fact, two stable states coexist, one where neuron i fires first and neuron j fires shortly afterward, and vice versa. Since the two neurons are identical, this bistability is trivial in the sense that, if ϕ is stable, then so is $2\pi-\phi$. The time delay in firing between the two neurons corresponds to τ_{syn}. A similar "trivial" bistability was observed by Van Vreeswijk *et al.* in the Hodgkin-Huxley neural model with synaptic coupling [19].

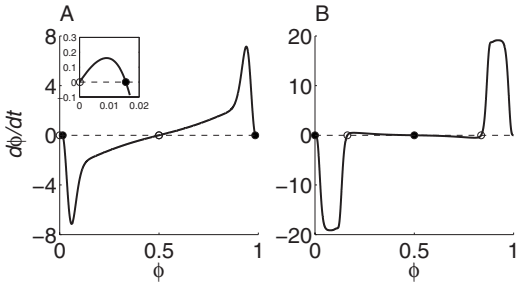

FIG. 1. $d\phi/dt$ at $g_{\text{K}}=$ (A) 26.0; (B) 0. Open and filled circles correspond to unstable and stable fixed points, respectively. Phase difference is normalized to [0,1]. The inset shows a blowup around $\phi=0$.

At high values of g_{K}, only the "trivial" bistability is observed. At $g_{\text{K}}\sim 5.0$, a subcritical pitchfork bifurcation occurs, as a result of which an antiphase firing pattern becomes stable (Fig. 2). Also, at $g_{\text{K}}\sim 5.0$, the "trivial" bistable states coalesce into a single stable branch (at $\phi=0$) corresponding to exactly in-phase firing. Thus, for low conductance, there exists a "nontrivial" bistability. These results were confirmed by numerical integration (fourth-order Runge-Kutta, $dt=0.01$ ms), using a variety of different initial conditions (data not shown).

To study the effect of noise on the behavior of a pair of neurons, an independent Gaussian white noise term $\xi(t)$ was added to each dV/dt equation; the noise was defined such that $\langle\xi(t)\rangle=0$ and $\langle\xi(t)\xi(s)\rangle=D\delta(t-s)$, where D is the noise intensity. The stochastic differential equations were solved by the Heun method [20] with $dt=0.01$ ms. Transitions between the bistable states were observed for $g_{\text{K}}=0$, as illustrated by the "mean field" (average voltage from the two neurons) in Fig. 3. At normal g_{K} [Fig. 3(a)], transitions between the trivial bistable states are observed, which do not significantly affect the mean field. Since the spikes from the two neurons rarely coincide in time, the mean field has an amplitude half as large as the transmembrane potential of a single neuron throughout most of the simulated time series.

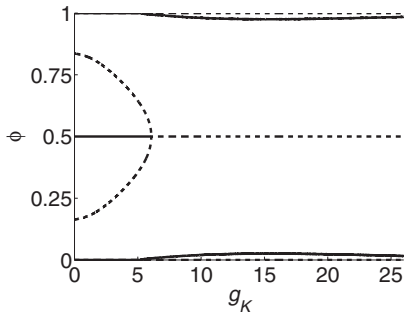

FIG. 2. Bifurcation diagram. Thick and thin lines represent stable and unstable fixed phase differences, respectively. Phase difference is normalized to [0,1].

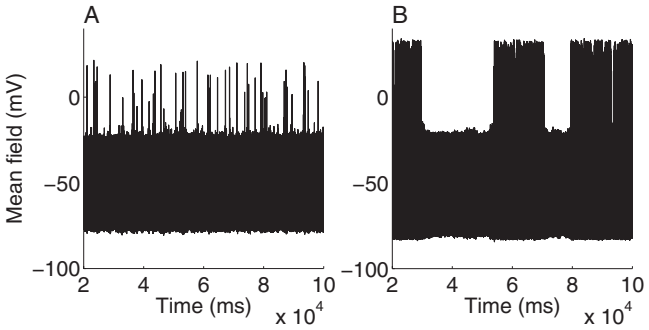

FIG. 3. Mean field for a pair of coupled neurons. g_K= (A) 26; (B) 0. $D=1.0\times10^{-4}$ in both cases.

The sharp spikes in the mean field correspond to the moments when the two neurons fire simultaneously. At $g_K=0$ [Fig. 3(b)], noise-induced transitions between in-phase and antiphase states were observed; these transitions significantly affect the mean field, in contrast to the case of normal g_K.

In order to investigate the role of decreased g_K on the activity of a larger array, we constructed a square lattice of 20×20 neurons with bidirectional nearest neighbor synaptic coupling. We suggest that the results of phase reduction analysis for two neurons can give a qualitative explanation of the network behavior. When g_K was decreased to zero [Fig. 4(a), 2.5×10^4 ms], to simulate the addition of 4-AP, a dramatic increase in the mean field amplitude was observed [Fig. 4(a)]. A raster plot [Fig. 4(b)] shows that, before the decrease in g_K, the neurons do not all fire in phase, which results in a small mean field amplitude. We suggest that this corresponds to the case of two neurons, in which a nonzero phase difference is stable, whereas the in-phase state is unstable. In contrast, after the decrease in g_K, where the in-phase state is stable, the neurons fire in phase, leading to large-amplitude mean field oscillations. These results, in a spatially extended array of neurons, are consistent with the result of phase reduction analysis for a pair of neurons.

We investigated the effect of noise on the network firing pattern by adding an independent Gaussian white noise term to each dV/dt equation. As in the case without noise (Fig. 4), a dramatic increase of the amplitude of the mean field was observed when g_K was decreased to 0 (data not shown). With $g_K=0$, we observed modulations in the amplitude and frequency of the mean field [Fig. 5(a)]. During the intervals when the mean field amplitude is relatively large, most of the neurons fire in phase [Fig. 5(d)]. On the other hand, when the amplitude is relatively small, some groups of neurons fire in phase with each other, but these small subpopulations are often out of phase with other subpopulations [Fig. 5(c)]. This suggests that there are similar noise-induced transitions between ''in-phase'' and ''antiphase'' network activities, analogous to the case of two neurons. We emphasize that both the ''in-phase'', large-amplitude network activity and the ''antiphase'', low-amplitude network activity occur during a simulated "seizure," i.e., when $g_K=0$.

Clustering is a phenomenon in which multiple populations, each exhibiting in-phase synchronization, but not in phase with each other, emerge from a larger group of oscillators. Clustering has been observed in theoretical studies of

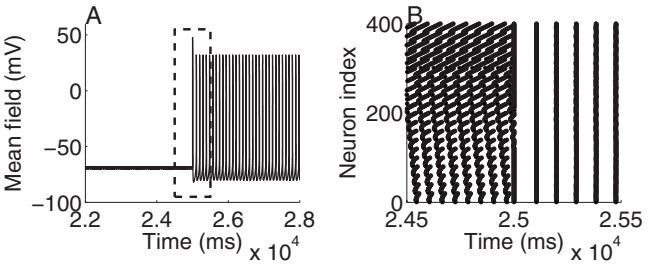

FIG. 4. (A) Mean field of network without noise. (B) Raster plot corresponding to the time interval represented by the dashed rectangle in (A).

coupled oscillators [22] and might play a role in neural systems [23]. To quantify the degree of clustering in the network, we measured the distribution of the phases of all the neurons. We defined the instantaneous phase of the ith neuron as $\phi_i(t)=2\pi(t-t_{i,n})/(t_{i,n+1}-t_{i,n})$, where $t_{i,n}$ is the nth spike time of the ith neuron and $t_{i,n}\leqslant t\leqslant t_{i,n+1}$ [18]. We calculate

$$R_m(t)=\left|\frac{1}{N}\sum_{k=1}^{N}\exp[im\phi_k(t)]\right|, \tag{11}$$

which can be used to detect the m-modal distribution of a circular (periodic) variable as follows [21]. For a given time t, a unit vector is assigned for each neuron with the phase $m\phi(t)$ in the Gaussian plane. Then the magnitude of the resultant vector, normalized by the total number of neurons, is represented by $R_m(t)$. For $m=1$, the magnitude of the resultant vector would be high (close to 1) in the case of a single cluster, in which the neurons exhibit in-phase synchronization, whereas, in the case of antiphase clustering, the two populations would form vectors with opposite directions, re-

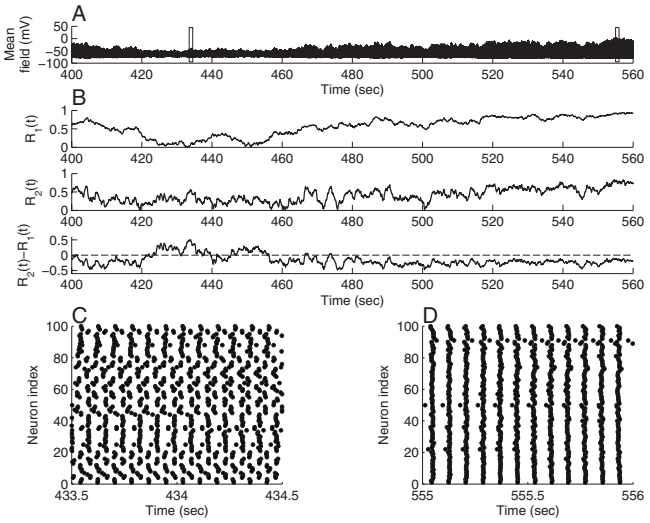

FIG. 5. (A) Mean field of network with $D=5.3\times10^{-4}$, $g_K=0$. (B) Measures for clustering. Top: R_1; middle: R_2; and bottom: R_2-R_1 as defined in the text. (C) Raster plot corresponding to the time interval enclosed by the left rectangle in (A). (D) Raster plot corresponding to the time interval enclosed by the right rectangle in (A).

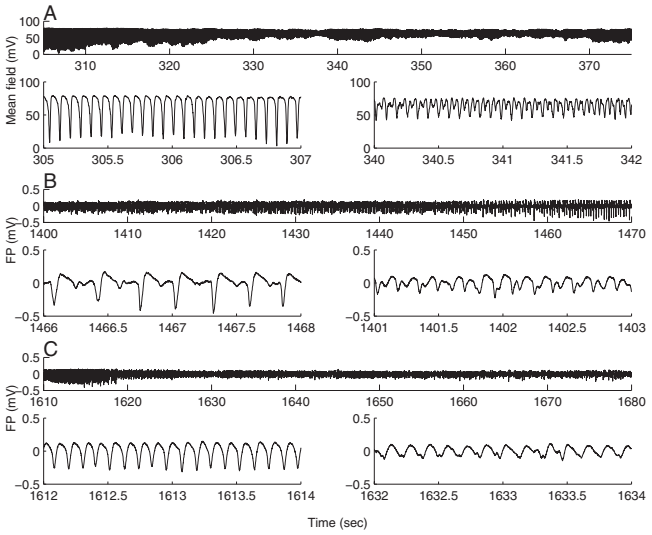

FIG. 6. Comparison between simulation and experiment. (A) Mean field from simulation. Note that the sign is inverted with respect to the previous figures for comparison with extracellular recordings. (B), (C) Extracellular field potential *in vivo* recordings from 4-AP-induced seizures in the rat neocortex. The bottom two graphs in each panel (A), (B), and (C) zoom in on intervals within the top graphs, showing examples of high-amplitude field potential spikes (left column), and low-amplitude activity (right column).

sulting in a small resultant vector. For $m=2$, two antiphase clusters would have vectors in the same direction, leading to a large resultant vector. Therefore, a relatively large positive value of $R_2(t)-R_1(t)$ is a signature of antiphase clustering. As shown in the bottom panel of Fig. 5(b), this occurs during the interval of lower-amplitude firing [compare Fig. 5(a), between 420 and 460 s, and the raster plot in Fig. 5(c)].

The transitions between mean field firing patterns observed in the network simulation captured the qualitative aspects of local field potential transitions observed in 4-AP-induced seizures in the rat neocortex. Figure 6(a) shows such a transition in the simulated mean field from our network model, in comparison with segments of field potential recording in the rat neocortex *in vivo* [Figs. 6(b) and 6(c)], following the focal injection of 4-AP [9]. Based on these observations, we suggest that neural activity during 4-AP-induced seizures may be caused by a bifurcation in the stable phase difference between neurons. Furthermore, our results suggest that changes in amplitude and frequency of the field potential, reminiscent of the transitions between so-called spike-and-wave patterns and low-voltage fast activity, seen in human patients [8] may be explained by noise-induced transitions among multiple stable states.

Several dynamical system models have been proposed to describe seizure dynamics [10,11]. Suffczynski *et al.* [10] have proposed a possible mechanism of seizure initiation where transitions between bistable states (epileptic and non-epileptic) are caused by noise. (In contrast, our model relates such transitions to shifts between firing patterns *during* a seizure.) Wendling *et al.* [11] have shown that various firing patterns of the electroencephalogram signal can be produced by tuning the synaptic "coupling strength." These models suggest different mechanisms from ours for the initiation and development of seizure dynamics. However, none of these models need be mutually exclusive. Since seizures can arise via a vast array of biological mechanisms, it is probably reasonable to assume that the underlying dynamical mechanisms of their onset and development can also fill a wide spectrum.

We conclude with a brief discussion of the limitations and shortcomings of the present model. All the synaptic connections in the model used here were bidirectional, for such a simple coupling scheme allows direct translation from the two-neuron phase reduction analysis to our larger array simulations. While the percentage of unidirectional excitatory synapses in the neocortex outweighs that of bidirectional excitatory synapses [24,25,28], it has been reported that, for a subtype of neocortical pyramidal neurons, the proportion of bidirectional connections is much larger than that expected from a random network; moreover, the synaptic strength is stronger in a pair of neurons with bidirectional synaptic coupling than unidirectional coupling [28]. These considerations lead us to consider a bidirectionally coupled array as a valid "first pass" model for our study of the effects of 4-AP on neocortical synchrony.

As further simplification, inhibitory neurons were not considered in the present model. Although a large percentage of neocortical neurons and synapses are excitatory [15] and disinhibition resulting from the blockage of GABA recptors by drugs such as bicuculline and picrotoxin can cause seizures [29], the activity of inhibitory neurons has also been shown to be an important contributor to synchronous neural firing during various seizures induced by other drugs, including 4-AP [30]. A critical next step will be to add inhibitory neurons to the present model.

The increase of extracellular potassium concentration has been observed during epileptiform activity [31]. Several modeling studies predict that the increase of extracellular potassium can play a role in transitions and synchronization in epileptic activity [26,27]. In the present model, however, changes in the concentration of extracellular potassium were not taken into account, again in order to develop a preliminary, simplified model capturing some basic features of the system's dynamics. In addition to the role of extracellular potassium, other complex effects, such as the role of astrocytes and the effects of long-range neocortical connections, will be addressed in future expansions of the current model. Despite its shortcomings, our synaptically-connected excitatory network model provides testable hypotheses of bifurcation and noise-induced transitions as potential mechanisms underlying key elements of neocortical seizure dynamics.

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