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Complex patterns in networks of hyperexcitable neurons

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ABSTRACT

Complex patterns in neuronal networks emerge from the cooperative activity of the participating neurons, synaptic connectivity and network topology. Several neuron types exhibit complex intrinsic dynamics due to the presence of nonlinearities and multiple time scales. In this paper we extend previous work on hyperexcitability of neuronal networks, a hallmark of epileptic brain seizure generation, which results from the net imbalance between excitation and inhibition and the ability of certain neuron types to exhibit abrupt transitions between low and high firing frequency regimes as the levels of recurrent AMPA excitation change. We examine the effect of different topologies and connection delays on the hyperexcitability phenomenon in networks having recurrent synaptic AMPA (fast) excitation (in the absence of synaptic inhibition) and demonstrate the emergence of additional time scales.

1. Introduction

Neuronal networks of the brain display complex spatio-temporal patterns [1]. These patterns result from the cooperative activity of the participating neurons, the synaptic connectivity and the network topology [2,3]. The dynamics of individual neurons depend primarily on the nature and properties of the participating ionic currents whose combined activity generates the neuron's effective intrinsic time scales. Synaptic connectivity can be electrical (gap junctions) or chemical [4]. The latter, in turn, can be excitatory or inhibitory and operate at different time scales within a relatively large range. Network topologies depend on the brain area and the level of organization and include ring [5,6] (and references therein) and small-world network [7–10] connectivities.

While realistic neuronal networks include both excitation and inhibition, there are several aspects of the network dynamics that can be addressed by first understanding the dynamics of recurrently excited networks [8–13] and then investigating how recurrent inhibition affects the resulting patterns [12]. One such aspect is that of the hyperexcitability of neuronal circuits, which is one of the hallmarks of epileptic brain seizure generation [14,15]. Various hypotheses have been put forward to explain the generation of abnormal recurrent excitation including the lack of enough inhibition (dormant interneuron hypothesis) [16–24] and aberrant axonal reorganization of principal cells (e.g., mossy fiber sprouting in the dentate gyrus)

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(recurrent excitation hypothesis) [25–35]. Regardless of whether the net imbalance between excitation and inhibition results from decreased inhibition or increased excitation, the study of recurrently excited networks is key to understand how the network patterns transition between "normal" to hyperexcitable.

Synaptic excitation constitutes a positive feedback effect, and therefore increasing levels of the maximal AMPA synaptic conductance (G_{ex}) are expected to produce an increase in the spike (or firing) frequency f_{spk} at a rate that also increases with G_{ex} (Fig. 1-a1). However, synaptic excitation does not operate alone, but its net effect depends on its interaction with the intrinsic properties of the postsynaptic cell. As shown by us and other authors [12,13,36,37], this can result in some unintuitive effects. In [12] we have investigated the mechanism of hyperexcitability in medial entorhinal cortex layer II stellate cells motivated by experimental findings in [23,38]. We used self-excited cells mimicking a population of recurrently excited cells synchronized in phase. We showed that the firing frequency is maintained constant or slightly decreases for increasing values of the maximal synaptic conductance (G_{ex}) within some relatively large range, above which an abrupt increase in firing frequency to a significantly large value occurs (Fig. 1-b1). The firing frequency gradually increases for values of G_{ex} above this abrupt transition. The interaction between the decay time of excitation and the effective intrinsic time scales generated by the persistent sodium and the hyperpolarization-activated currents is crucial for this phenomenon. Synaptic inhibition acts as a switch between the two firing frequency regimes. In [13] we have carried out a thorough comparative study of the classes of models that produce these two qualitatively different types of behavior, and we have extended our results to minimal, two-cell network models.

The goal of this paper is to extend our results to larger networks. Specifically, we examine whether the gradual and abrupt transition between low and high firing frequencies generated by the two classes of models described above persist in larger, recurrently excited networks. In addition, we examine the similarities and differences between the patterns generated by these two classes of models in these larger networks. Finally, we investigate the role of synaptic delays in stabilizing the network activity in the high-frequency regime at lower spike frequencies than those for instantaneous synapses. Synaptic delays have been shown to play significant role in the generation of network coherent activity [39–47].

We use two models that are prototypical for the two modes of transitions between low and high firing frequencies: the integrate-and-fire (IF) model and the so-called $I_h + I_{Nap}$ model. The IF model has passive subthreshold dynamics (no active ionic currents) and exhibits gradual transitions (Fig. 1-a1). The $I_h + I_{Nap}$ model has persistent sodium and hyperpolarization-activated (h-) currents and exhibits abrupt transitions (Fig. 1-b1). For simplicity we focus on networks with ring topologies where each cell is only connected to its nearest neighbors. Our results provide the basis for the investigation of networks with more complex connectivity patterns and more general model types.

2. Methods

Neurons are modeled using the Hodgkin–Huxley (conductance-based) formalism [48]. The current-balance equation in the subthreshold voltage regime is given by

$$C\,\frac{dV}{dt} = -I_L - \sum_j I_{ion,\,j} + I_{app}, \tag{1}$$

where V is the membrane potential (mV), t is time (msec), C is the membrane capacitance ($\mu F/cm^2$), I_{app} is the applied bias (DC) current ($\mu A/cm^2$), $I_L = G_L\,(V - E_L)$ is the leak current, and $I_{ion,\,j}$ are ionic currents of the form

$$I_{ion,\,j} = G_j\, m_j^a\, h_j^b (V - E_j) \tag{2}$$

with activation and inactivation gating variables m_j and h_j respectively, maximal conductances G_j (mS/cm^2), reversal potentials E_j (mV), and constants $a \geq 0$ and $b \geq 0$. All gating variables x obey a first order differential equation of the form

$$\frac{dx}{dt} = \frac{x_\infty(V) - x}{\tau_x(V)} \tag{3}$$

where $x_\infty(V)$ and $\tau_x(V)$ are the voltage-dependent activation/inactivation curves and time-constants respectively.

The models used in this paper do not contain a biophysical description of the spiking dynamics, which is usually generated by the interplay of a transient sodium and delayed-rectifier potassium currents [4]. Instead, spikes are added artificially once the voltage has reached a threshold value V_{th}. The artificial spikes have the form $60\,e^{-2(t-t_{spk})}$ for $t \in [t_{spk}, t_{spk} + \Delta_{spk})$ where t_{spk} is a given spike time and Δ_{spk} is the spike duration, which was set to be equal to 1 msec. The variables V and x are reset at $t = t_{spk} + \Delta_{spk}$ to V_{rst} and x_{rst} respectively. In the leaky integrate-and-fire (IF) model V_{th} is part of the mechanism for spike generation. In contrast, the persistent sodium/h-current ($I_h + I_{Nap}$) model (described below) describes the onset of spikes and V_{th} only indicates their occurrence.

For the (IF) model [4] the subthreshold dynamics are described by eq. (1) with $I_{ion} = 0$. We used the following parameter values: $C = 1$, $E_L = -65$, $G_L = 0.025$, $V_{th} = -50$, $V_{reset} = -70$. Additional parameter values are provided in the corresponding figures.

The $I_h + I_{Nap}$ model is an adaptation of the reduced model derived in [49] from the fully spiking model introduced in [50]. The subthreshold dynamics are described by eqs. (1)–(3) with a persistent sodium current and an h-current given