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Spatio-temporal patterns of network activity in the inferior olive

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Abstract

We have built several networks of inferior olive (IO) model neurons to study the emerging spatio-temporal patterns of neuronal activity. The degree and extent of the electrical coupling, and the presence of stimuli were the main factors considered in the IO networks. The network activity was analyzed using a discrete wavelet transform which provides a quantitative characterization of the spatio-temporal patterns. This study reveals the ability of these networks to generate characteristic spatio-temporal patterns which can be essential for the function of the IO.

Keywords: Inferior olive; Spatio-temporal patterns; Subthreshold oscillations; Electrical coupling

1. Introduction

The architecture of the inferior olive (IO) and the cerebellar circuits of mammals has been investigated anatomically and physiologically in great detail. However, the

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functional role of this system is still unclear [4,1]. The IO has been proposed as a system that controls and coordinates different rhythms through the intrinsic oscillatory properties of the individual IO neurons and the nature of their inter-connections [3]. The IO cells are electrically coupled and display a characteristic behavior with subthreshold oscillations and spiking activity. Their axons transmit rhythmic excitatory synaptic input to both the cerebellar nuclear cells and the Purkinje cells of the cerebellar cortex. The phasic response of the Purkinje cells is transmitted as inhibitory inputs to the cerebellar nuclear cells. Thus, the nuclear cells are excited by the inferior olive cells and latter inhibited by the Purkinje cells. The nuclear cells also send an inhibitory feedback to the inferior olive closing this loop. In the experimental in vitro recordings of the IO cells, the effect of the inhibitory loop is absent. In the simulations shown in this paper, we will try to reproduce the IO networks of the experiments in the in vitro preparations [5].

In the following sections, we will show that networks of electrically coupled IO neurons with subthreshold oscillations and spiking activity have the ability to generate characteristic spatio-temporal patterns which can easily encode several coexisting rhythms.

2. The IO model

We have used a Hodgkin–Huxley model of the IO cells which can generate subthreshold oscillations as well as spiking behavior in the amplitude and frequency ranges reported for these neurons (see top panel in Fig. 1). The single neuron model was modified from the work of Wang [9] by including an additional *h*-current. We consider only one compartment to describe the membrane potential of the cells. The membrane voltage is given by

$$C_{\mathrm{m}} \frac{\mathrm{d}V}{\mathrm{d}t} = -(I_{\mathrm{active}} + I_{\ell} + I_{\mathrm{ec}}), \tag{1}$$

where I_{ℓ} is a leakage current, I_{ec} is the current of the electrical gap junctions ($I_{\mathrm{ec}} = g_{\mathrm{c}} \sum_i (V - V_i)$, where the index i runs over the neighbors of each neuron and g_{c} is the electrical coupling conductance), and

$$I_{\mathrm{active}} = I_{Nap} + I_{Kd} + I_{Ks} + I_h \tag{2}$$

is the sum of all the active ionic currents that we have considered in the model.

The equations and parameters used in this paper were the same as those specified in [9] with $\sigma = 1$. The equations and parameters used for the *h*-current were: $I_h = \bar{g}_h h(V - V_h)$, where $\bar{g}_h = 0.1\ \mathrm{mS/cm^2}$, $V_h = -43$ mV and $\dot{h} = 28.57(\alpha_h(1 - h) - h\beta_h)$ with $\alpha_h = 0.07 \exp(-0.1(V - 43)/20)$ and $\beta_h = 1/(1 + \exp(-0.1(V + 13)))$.

We built two-dimensional networks of up to 50×50 IO neurons connected with gap junctions among close neighbors. A square ensemble of 30×30 neurons was considered the minimum size to study the emergence of the patterns. Above this minimum, it was

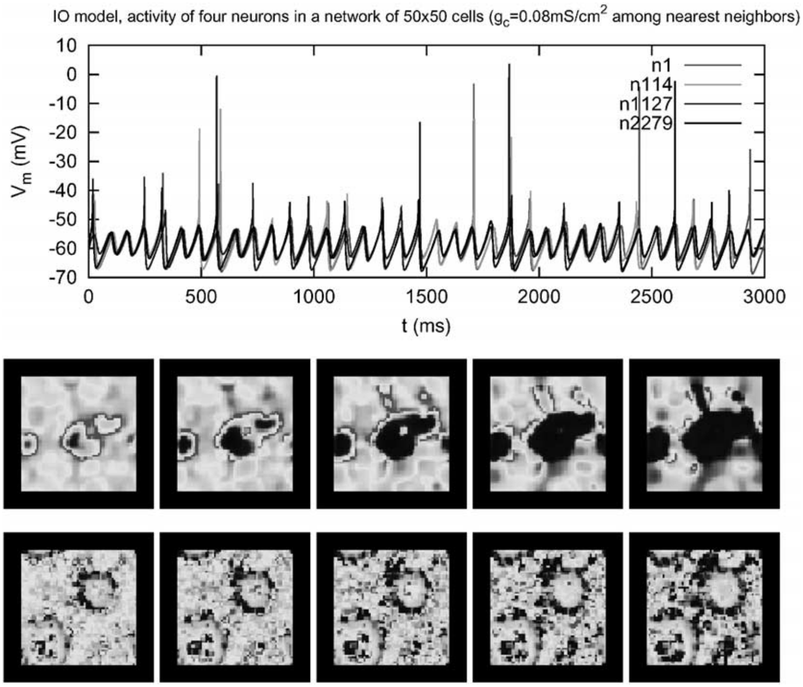

Fig. 1. *Top panel*: Time series of subthreshold and spiking activity for four IO neurons chosen randomly inside a 50×50 cell network. Note the small phase shifts in the quasi-synchronized subthreshold oscillations. *Middle panel*: Spatio-temporal patterns observed in the collective activity for the same network. *Bottom panel*: Several structures with different frequencies can coexist simultaneously in the network when several stimuli are present (see the text). Sequence goes from left to right. Regions with the same color have synchronous behavior. Light colors mean depolarized potential. Time between frames is 4 ms.

observed that the size of the network did not affect the topology and evolution of the patterns. Initial conditions were varied randomly up to 5% from a control value for all the dynamic variables. The simulations shown in this paper correspond to the networks with periodic boundary conditions to avoid border effects.

3. Results

3.1. Spatio-temporal patterns of spontaneous activity

Two-dimensional networks of IO model neurons connected with gap junctions among close neighbors are able to generate well-defined spatio-temporal structures as those shown in Fig. 1 (middle panel). In this panel, the sequence goes from left to right. Regions with the same color have synchronous behavior. Light colors mean depolarized potential, while dark regions represent hyperpolarized activity. The spatio-temporal patterns consist of propagating wavefronts of spiking activity that can remain bounded in a region of the network. The patterns arise from the small phase shifts in the quasi-synchronized subthreshold oscillations of each neuron (see the top panel in Fig. 1). The occurrence of a spike induces new phase shifts and fast propagating waves that shape the patterns within an almost synchronized subthreshold activity.

3.2. Patterns in the presence of stimuli

The simulations described so far implemented neurons with spontaneous spiking activity over the subthreshold oscillations. A major point of interest in this study was analyzing the response of the network to coherent stimuli that could induce different spiking frequencies in the IO neurons. Two different stimuli (constant current injections of 0.5 and 1.5 $\mu A/cm^2$) were applied to two different clusters of 36 IO neurons in a network of 50×50 cells. Under the effect of the stimulus, each cluster fired spikes with a different frequency. Coherent structures could be observed in the regions with stimuli that emerged over the spatio-temporal patterns of spontaneous activity. The spatial scale of the patterns evoked by a stimulus was greater when the frequency of response was lower (normal dispersion). Structures with different frequencies could thus coexist simultaneously in these networks (see the bottom panel in Fig. 1).

3.3. Factors shaping the spatio-temporal patterns

In summary, several factors that modulate the frequency of the spiking behavior and the nature of the spatio-temporal patterns were identified:

- The characteristic subthreshold oscillations and the spiking behavior of the IO cells (shaped by the properties of their ionic channels) are essential for the genesis of the spatio-temporal patterns in the network.
- Higher values of the electrical coupling conductance g_c among cells increased the synchronization level and diminished the frequency of the spiking behavior.
- A higher number of electrically coupled neighbors also decreased the frequency of the spiking behavior, but only for a strong enough coupling. In this case, the degree of synchronization among cells was higher although the frequency of the subthreshold oscillations remained constant under all these changes.
- The presence of regions with different stimuli could organize clusters of cells with different frequencies coexisting in the network at the same time. The spatial scale of the patterns evoked by a stimulus depends on the frequency of the response of the IO cells.

3.4. Wavelet analysis of the network activity

We have used the discrete wavelet transform (DWT) to characterize quantitatively the spatio-temporal patterns of the IO networks. This measure gives us a better insight than a mere visual inspection of the movies of the simulations (available under request from the authors). The coefficients of the DWT represent the resolution

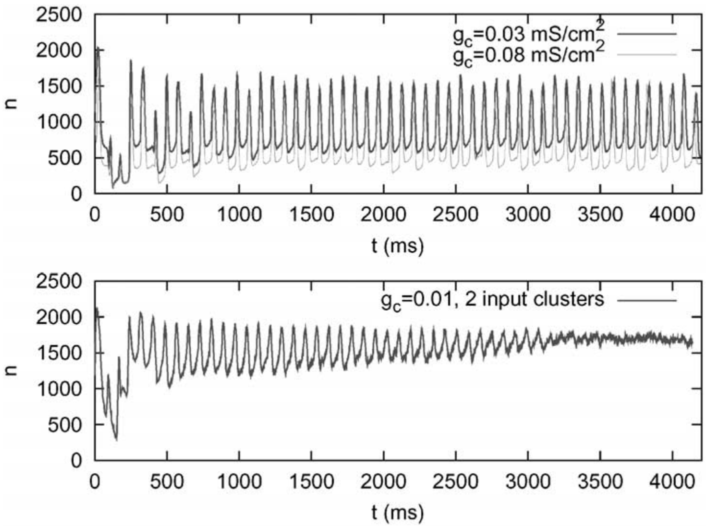

Fig. 2. Number of coefficients, n, of the two-dimensional DWT that are bigger than 1 for three different IO networks. *Top panel*: Networks without stimuli show a periodic pattern (traces show n for a network of 50×50 neurons with $g_c = 0.03\ \text{mS/cm}^2$ among nearest neighbors and for a network with $g_c = 0.08\ \text{mS/cm}^2$). *Bottom panel*: A network with several coexisting frequencies displays a more complex evolution of the coefficients whose shape characterizes the spatio-temporal patterns and shows the presence of multiple rhythms.

content of the data. A two-dimensional basis was generated by direct Cartesian product of the one-dimensional Haar basis [6]. We followed a compression-like technique to characterize the spatio-temporal patterns of activity in the IO networks. First, we calculated the two-dimensional non-standard DWT for each frame of network activity as described above. Second, we counted the number of coefficients, n, that were bigger in absolute value than a given threshold. The number of these coefficients provides a useful characterization of the patterns in which both the frequencies and the spatial extent can be discussed as shown in Fig. 2.

High values of n indicate the presence of complex spatial structures in the patterns, while completely synchronized networks produce a small number of coefficients. Fig. 2 shows the evolution of the number of coefficients for three different IO networks: a network with a small electrical coupling $g_c = 0.03\ \text{mS/cm}^2$, a network with high electrical coupling $g_c = 0.08\ \text{mS/cm}^2$ showing a high degree of synchronization (yet with evolving spatio-temporal patterns), and a network with several coexisting frequencies of spiking activity as the one displayed in the bottom panel of Fig. 1. The average higher value for n in the latter shows a more complex spatial structure of the patterns. The dominant frequency in the evolution of n corresponds to the subthreshold oscillations. The spiky waveform in the evolution of n shown in the bottom panel of Fig. 2 also indicates the presence of multiple spiking frequencies evoked by the stimuli in the network.

4. Discussion

The patterns observed in the simulations were very similar to those recorded in vitro in slices of IO neurons and reported in [2,8]. The model can include the effect of the inhibitory loop arriving from the cerebellar nuclei [7], absent in the in vitro experimental recordings. These simulations can help us to test hypotheses related to the role of subcellular and network processes in the genesis of neuronal spatio-temporal patterns as well as to understand how the IO oscillations can encode and control several simultaneous rhythms.

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