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Synchronization with an Arbitrary Phase Shift in a Pair of Synaptically Coupled Neural Oscillators

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The phase dynamics of a pair of spiking neural oscillators coupled by a unidirectional nonlinear connection has been studied. The synchronization effect with the controlled relative phase of spikes has been obtained for various coupling strengths and depolarization parameters. It has been found that the phase value is determined by the difference between the depolarization levels of neurons and is independent of the synaptic coupling strength. The synchronization mechanism has been studied by means of the construction and analysis of one-dimensional phase maps. The phase locking effect for spikes has been interpreted in application to the synaptic plasticity in neurobiology.

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1. INTRODUCTION

The synchronization phenomenon [1–3] plays a key role in processing of signals and information in neural brain systems [4, 5]. Partial synchronization of neuronal ensembles underlies the formation of population rhythms of the brain (alpha, theta, and gamma oscillations) [6–8]. The synchronous activity of large ensembles of brain neurons is associated with pathologic processes, in particular, with epileptiform activity [9]. On the local dynamic level, the synchronous activation of a pair of neural oscillators with a small phase shift between the interacting neurons is responsible for long-term changes in the efficiency of signal transmission between them [10, 11]. This phenomenon in neurobiology is called synaptic plasticity. Synaptic plasticity is thought to underlie learning and cognitive functions in the brain. It is noteworthy that the plasticity effect can have phase-selective properties (spike timing dependent plasticity), which means the dependence of the parameters of a neural network on the relative phase of spikes [12].

In the classical works on the interaction of neural oscillators [3, 13–15], the investigation of synchronization is reduced to analysis of simple phase equations [3, 13–15]. In particular, the calculation of the phase response curve for various external actions made it possible to reveal stable phase locking regimes [15] and to establish their relation with the type of bifurcation in the oscillator model [16, 17] and with the presence of resonance [18, 2]. The coupling strength between neurons determining the appearance of certain collective dynamic regimes, is the main control parameter in most works. The depolarization level determining the neuron excitation threshold and the frequency of pulse activity is another important parameter. This parameter specifies the position of the working point of a neuron self-sustained oscillator. It is also worth noting that the level of neural depolarization in neurobiology can be controlled both by its own cellular dynamics and by extracellular factors whose role has been actively studied in recent years [12, 19–22].

In this work, we propose a model of a pair of synaptically coupled biological spiking neural oscillators capable to establish a stable phase locking regime with various phase shifts. A representative feature of this model is the dependence of the steady-state phase on the applied current determining the neuron depolarization level, which can be controlled in biological neurons by means of, e.g., extracellular signals. In this case, the relative phase is independent of the coupling strength between the neural oscillators. Furthermore, an anticipated synchronization regime is possible in the model under certain conditions. In this regime, the phase of the slave oscillator aticipates the phase of the master oscillator, predicting the beginning time of the next period [23]. We note that the classical approach in works on anticipated synchronization [24] implies the existence of a negative feedback loop with the delay of the slave oscillator to itself. In our case, the anticipated synchronization regime is possible in oscillators with various depolarization parameters.

2. MODEL

We consider a system of two Hodgkin–Huxley neurons [25] coupled by an excitatory unidirectional nonlinear connection describing the kinetics of chemical synapse:

$$C\frac{dV_1}{dt} = -\sum I_{\text{ion},1} - I_{\text{app},1},$$

$$C\frac{dV_2}{dt} = -\sum I_{\text{ion},2} - I_{\text{app},2} - I_{\text{syn}}, \quad (1)$$

$$I_{\text{syn}} = \frac{g_{\text{syn}}(V_2 - V_{\text{syn}})}{1 + \exp-(V_1 - \theta_{\text{syn}})/k_{\text{syn}}}.$$

Here, subscripts 1 and 2 mark the master (presynaptic) and slave (postsynaptic) neurons, respectively; C is the specific membrane capacitance; V_1 and V_2 are the membrane potentials; and t is the time. The dynamics of the membrane potential of each neuron is determined by three ion currents I_{ion}, sodium, potassium, and ohmic leakage, as well as by direct depolarizing current. The instantaneous active ion currents depend on the state of gate variables whose dynamic equations are not presented here for the sake of brevity (see, e.g., [25, 26]). The action of the master neuron on the slave one is described by the synaptic current I_{syn} in the equation for the potential of the slave neuron. The reversal synaptic potential for the excitatory connection is $V_{\text{syn}} = 0$. This means that the postsynaptic neuron in the resting state ($V_2 \approx -70$ mV) acquires a negative synaptic current. This gains the rate of increase in the membrane potential and, therefore, the spike generation probability. The choice of the parameters of the threshold synaptic function specifying its shift ($\theta_{\text{syn}} = 0$) and steepness ($k_{\text{syn}} = 0.2$ mV) ensures the short-term response of the postsynaptic neuron only to the top of the presynaptic pulse. The action of the subthreshold fluctuations of the membrane potential of the master neuron is cut off.

The applied currents $I_{\text{app},i}$ are constant and determine the depolarization level of neurons, as well as the dynamic regime (excitable, oscillatory, or bistable) [2, 27, 28]. The applied current unambiguously determines the spike generation frequency in the oscillatory and bistable regimes. For the set of parameters used in this work, a neuron is in the bistable regime at $5.5 < I_{\text{app}} < 8.7$ and in the oscillatory regime at $I_{\text{app}} > 8.7$ [28]. The parameters of the applied current in both oscillators corresponding to the ocillatory regime were chosen.

The relative phase in the case of coupled spiking oscillators is defined as the difference between the timings of spike generation by two oscillators divided by the period [2, 28, 29]:

$$\varphi(n) = \frac{t_2^{\text{ap}}(n) - t_1^{\text{sp}}(n)}{T_1}. \quad (2)$$

Figure 1 shows examples of (left panels) oscillograms of the membrane potentials of the system specified by Eqs. (1) and (middle panels) the corresponding dynamics of the phase calculated by Eq. (2). It can be seen that both the anti-phase synchronization regime (Fig. 1a) and in-phase oscillations (Fig. 1b) occur in the model depending on the parameters. Furthermore, the steady-state phase can be close to unity (Fig. 1c), which can be treated as anticipated synchronization. It is noteworthy that the anti-phase locking regime is atypical for the excitatory connection. Similar results were obtained for the Rowat–Selverston model [30] in [31, 32]. The fundamental feature of the result obtained in this work is the possibility of controlling the relative phase by means of variation of the depolarization parameter. We also note that a periodic excitatory action in this case reduces the frequency of the slave neuron. This counterintuitive effect was also observed in similar systems of coupled spiking oscillators [15]. Below, we examine the mechanism of control of the phase in a pair of pulse-coupled neural oscillators.

3. PHASE MAP

To test the stability of phase locking regimes demonstrated in Fig. 1, the phase dynamics of system (1) can be studied with the use of phase maps [29]. Briefly speaking, the phase difference φ_n between presynaptic and postsynaptic spikes is specified by means of the choice of the initial conditions for the slave oscillator at the limit cycle with the shift with respect to the conditionally chosen point of the beginning of the oscillation period, which corresponds to the maximum of the potential V. The phase of oscillations of the master neuron is chosen to be zero (at the point of the maximum of the potential). After the generation of the next pair of spikes, the phase difference φ_{n+1} calculated by Eq. (2) is renewed. This procedure is repeated for all values $\varphi_n \in [0, 1]$. The right panels in Fig. 1 exemplify the phase maps corresponding to the in-phase and anti-phase synchronization regimes. The intersections of the phase map curve with the diagonal specify the fixed points whose stability depends on the multiplier. It can be seen that one stable fixed point corresponding to the steady relative phase exists in each case. The phase map can be represented in the form

$$\varphi(n+1) = \varphi(n) + F[\varphi(n), T_1, T_2, g_{\text{syn}}], \quad (3)$$

where T_1 and T_2 are the periods of the oscillations of the master and slave oscillators, respectively, and F is the phase rearrangement function [33]. In view of Eq. (2), F can be represented in the form

$$F = T_2 - T_1 + \text{PRC}[\varphi(n), g_{\text{syn}}], \quad (4)$$

where PRC is the phase response curve of the slave neuron, which is determined by the dynamics of the neuron itself (by the type of the bifurcation of the limit

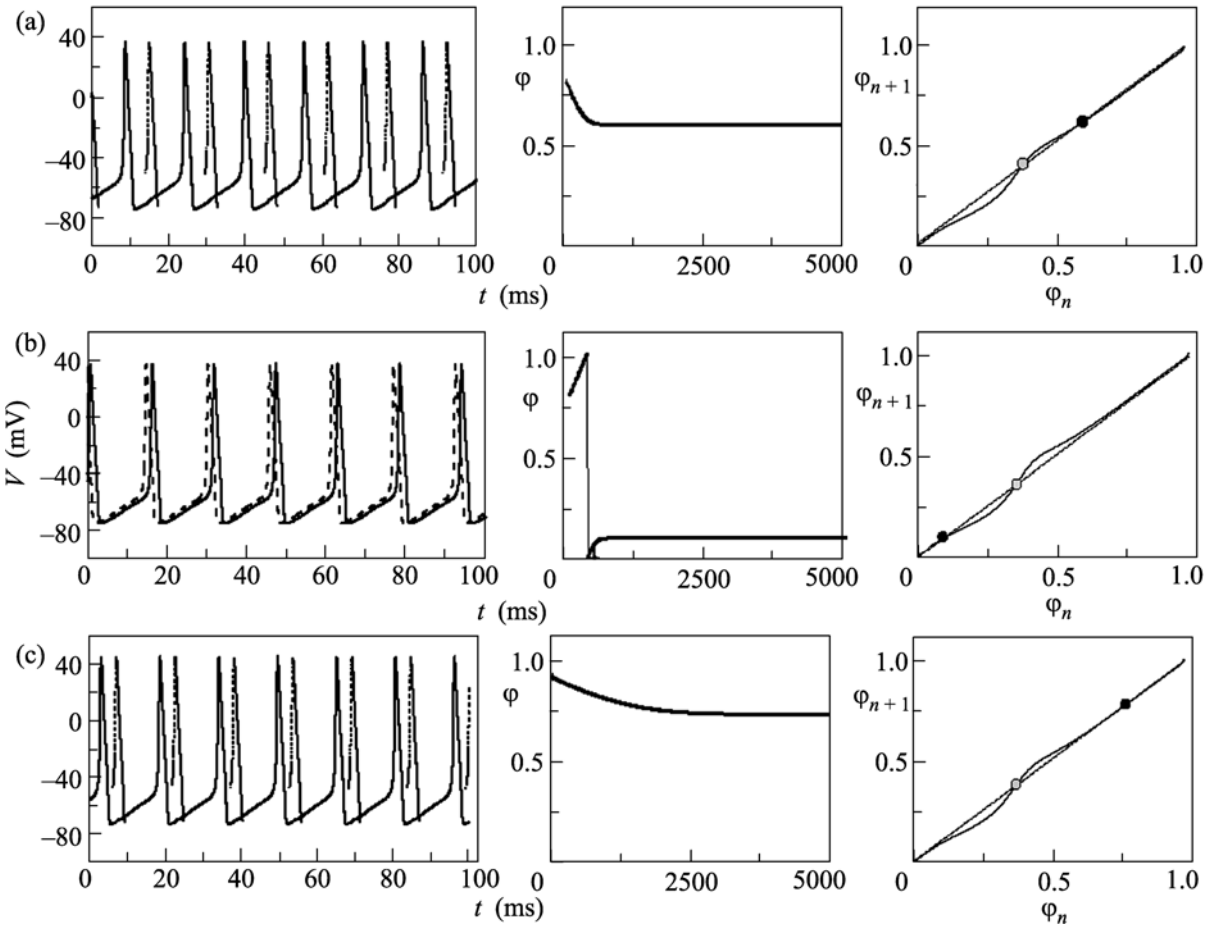

Fig. 1. Examples of the synchronization regimes in the model of a pair of synaptically coupled spiking neural oscillators specified by Eqs. (1): (a) anti-phase regime ($I_{app,\,1} = -8$ μA/cm^2, $I_{app,\,2} = -8.24$ μA/cm^2, $g_{syn} = 0.025$ mCm/cm^2), (b) in-phase regime with delay ($I_{app,\,1} = -8$ μA/cm^2, $I_{app,\,2} = -7.8$ μA/cm^2, $g_{syn} = 0.025$ mS/cm^2), and (c) in-phase anticipated regime ($I_{app,\,1} = -8$ μA/cm^2, $I_{app,\,2} = -8.02$ μA/cm^2, $g_{syn} = 0.025$ mS/cm^2). The left panels are the oscillograms of the membrane potentials after transient processes for the (dashed lines) master neuron and (solid lines) slave neuron. The middle panels show the time dependence of the relative phase. The right panels are the phase maps, where the closed and open circles are the stable and unstable fixed points, respectively.

cycle appearing) and by the existence of subthreshold resonance properties [2, 16, 18]. In particular, the transition to the oscillatory regime in the Hodgkin–Huxley model occurs through the Andronov–Hopf bifurcation. Therefore, this oscillator has a second-type phase response curve. Theoretical results indicate that the phase response curve is a linear function of the coupling strength [3, 15]

$$\mathrm{PRC}[\varphi(n), g_{syn}] = g_{syn} f[\varphi(n)]. \quad (5)$$

This is also confirmed in neurobiological experiments [34]. Moreover, the phase response curve at weak interaction certainly determines the next phase value at the periodic action of the master oscillator [35]. Otherwise, it is necessary to take into account phase permutations induced by not the last, but several preceding spikes [36]. At the same time, the experimental results indicate that the contribution of preceding spikes to the phase shift is insignificant [37]. Thus, the form of the phase map is determined by the phase response curve with the gain equal to the coupling strength and the linear shift equal to the difference between the periods of the slave and master oscillators, which determines the frequency detuning. This fact is illustrated in Fig. 2, which shows the function F plotted numerically for model (1) at various detuning values and coupling strengths.

It can be seen that the vertical shift of the phase rearrangement curve is a linear function of detuning. The establishment of a stable phase locking regime with a value corresponding to an increasing segment of the phase response curve is impossible. The other values of the phase

$$\varphi^* = f^{-1}\left(\frac{T_1 - T_2}{g_{syn}}\right) \quad (6)$$

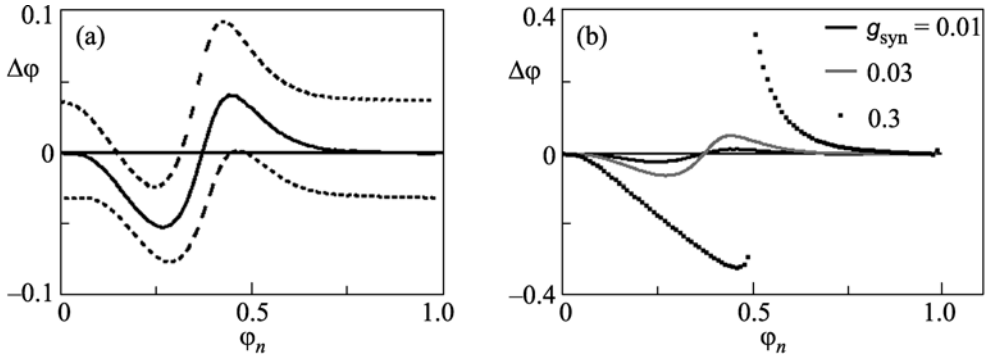

Fig. 2. Phase rearrangement curves at various (a) depolarization levels of the master neuron determining detuning ($I_{app,\,1}$ = 8 μA/cm^2, $I_{app,\,2}$ = 7.3, 8, and 8.7 μA/cm^2 for the upper, middle, and lower plots, respectively, at g_{syn} = 0.025 mS/cm^2) and (b) coupling constants for g_{syn} = 0.01, 0.03, and 0.3 mS/cm^2 and $I_{app,\,1} = I_{app,\,2}$ = 8 μA/cm^2.

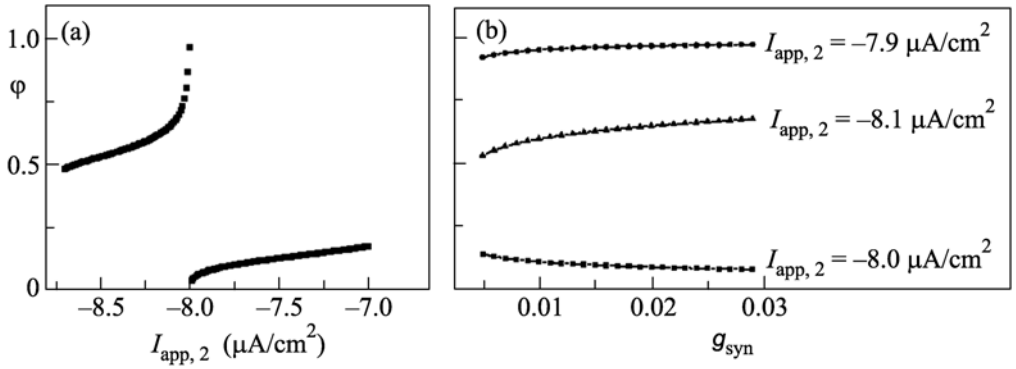

Fig. 3. Coordinate of the stable fixed point versus (a) the depolarization level and (b) the coupling strength at various depolarization levels $I_{app,\,2}$.

can be obtained by choosing the corresponding depolarization level. The inverse function f^{-1} is defined only in decreasing segments of f in Eq. (5) and, consequently, is single-valued and piecewise continuous. It is noteworthy that detuning was specified by means of change in the frequency of the slave neuron. However, a similar result can be obtained by means of the tuning of the frequency of the master neuron.

The possibility of obtaining stable locking regimes with various phases is demonstrated in Fig. 3. For each depolarization level (Fig. 3a) and each coupling strength (Fig. 3b), we calculated the phase map and found the coordinate of a stable fixed point as the point of intersection of the diagonal of the phase map curve from top to bottom. In the case of the intersection of $\varphi(n+1)$ and $\varphi(n)$ at small angles (the multiplier is close to unity), we additionally calculated the traces of the membrane potentials until the achievement of the stable phase locking regime. Stability was tested by introducing small phase shifts in both directions. According to Fig. 3, the key parameter responsible for the stable phase value is the depolarization level rather than the coupling strength. Figure 3a includes the phase interval where there is no stable locking regime (in other words, φ^* is piecewise continuous), as was found analytically (6).

However, in the case of strong connections, the function F itself can become piecewise continuous, as is shown in Fig. 2b for g_{syn} = 0.3. In the classical theory of phase synchronization of coupled oscillators, this discontinuity appears at a significant increase in the coupling strength. In this case, the phase response curve becomes descending in both segments [2, 18]; hence, an arbitrary stable phase can be established by means of the choice of detuning. The form of the limit cycle in the case of Hodgkin–Huxley biological neural oscillators significantly differs from a circle and isochrones are complex trajectories in four-dimensional space. This explains the presence of a small increasing segment in front of the break in line F at large coupling constants (see Fig. 2b, g_{syn} = 0.3). Nevertheless, an increase in the coupling strength can completely fill the phase range that cannot be reached only by the control of the depolarization level.

4. DISCUSSION

To summarize, we have presented a model of a pair of spiking Hodgkin–Huxley neuronal oscillators coupled by a unidirectional spiking chemical connection which simulates synaptic input. The mechanisms of spike phase locking of the slave neuron have been analyzed by the method of point maps. It has been shown analytically and numerically that, at weak interaction, a stable locking regime is established with various relative phases depending on the frequency detuning of the oscillators, which is specified by the external applied current. The steady-state relative phase in this case is independent of the coupling strength, which is an additional control parameter expanding the allowed phase range.

First of all, this effect is of interest as a fundamental nonlinear dynamic phenomenon in the synchronization theory consisting of the control of the phase shift in the stable phase locking regime owing to the depolarization-parameter-controlled tuning of the difference between the frequencies of the oscillators. This corresponds both to the classical concept of the phase dynamics of coupled oscillators and to modern studies of synaptically coupled spiking neurons [12, 38, 39].

Phase synchronization of two neural oscillators with an arbitrary phase shift can play an important role in the generation and propagation of information signals in living neuronal networks of the brain. In particular, two pacemakers can establish both negative (anticipated synchronization) and positive (synchronization with phase delay) phase shift. This phenomenon is of potential importance for large networks with numerous synchronized pairs controlling switching between signal propagation paths through the initiation of synaptic rearrangements [10, 11] owing to the adjustment of their depolarization levels. The result obtained in this work confirms the hypothesis of the possible effect of the active extracellular medium of the brain on the signal transmission process. The inclusion of extracellular factors, in particular, the dynamics of glial cells and extracellular matrix, results in the appearance of slow fluctuations of neuron depolarization levels. This in turn leads to fluctuations of phase relations.

Finally, we have shown that anticipated synchronization (Fig. 1c) is one of the stable phase locking regimes in a pair of neural oscillators coupled by a unidirectional synaptic connection. This phenomenon in neural networks of the brain can underlie the anticipation of key events in the environment at the formation of reflector sensorimotor reactions.

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