Fast reciprocal inhibition can synchronize bursting neurons

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We study a pair of endogenously bursting neurons with fast non delayed inhibitory connections. We show that fast reciprocal inhibition, known to facilitate antiphase bursting, can stably synchronize bursting neurons. This contrasts with the classical view that reciprocal inhibition has to be slow or time delayed to establish in-phase synchronization. Through stability analysis, we reveal the emergent mechanism of in-phase synchronization and discuss its implications for various types of bursting neurons and networks.

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Reciprocal inhibition is the key component for functioning of various regulatory and neural networks such as central pattern generators (CPGs) [1–3]. CPGs are small polymorphic neural circuits governing various rhythmic activities including cardiac beating and locomotive behaviors such as walking, chewing, and swimming [3]. Switching between locomotion behaviors can be attributed to switching between various attractors of a CPG network. Each attractor is associated with a definite rhythm on a specific time scale. Such a multifunctional CPG contrasts to a dedicated CPG that is associated with a definite rhythm on a specific time scale. Such a bifurcation parameter of network

\[ CV_i' = F(V_i, h_i, m_i) − g_s(V_i − E_s)\Gamma(V_j − \Theta_{syn}), \]

\[ \tau_h h_i' = G(V_i, h_i), \quad \tau_m m_i' = R(V_i, m_i), \quad i, j = 1, 2, \]

where \( V_i, h_i, \) and \( m_i \) are the \( i \)th neuron nondimensionalized membrane potential and the gating variables for the fast sodium and the slow potassium currents in a reduced model of the leech heart CPG bin neuron [6]. The inhibitory synapses are instantaneous and described through the fast threshold modulation (FTM) concept [12], where the coupling function is given by \( \Gamma(V_j − \Theta_{syn}) = 1/[1 + \exp(−1000(V_j − \Theta_{syn}))] \). The synaptic threshold \( \Theta_{syn} \) is set to ensure that spikes within a burst cross it through, such as in Fig. 1(a). The FTM coupling is a remarkably good model of realistic fast synapses [2,11]. For instance, the rise time of the synapse in the leech heart CPG is comparable with the duration of a spike, and the synapse is nearly instantaneous [15]. The low level of reversal potential \( E_s = –0.625 \) makes the synapse inhibitory. We employ the level of \( \Theta_{syn} \) and the coupling strength \( g_s \) as two bifurcation parameters of network (1). Network (1) was shown to generate robust antiphase bursting via the hold-and-release mechanism [19], similar to synaptic release [2,4] in spiking cells. Observe that network (1) of two identical cells always possesses a symmetric solution \( \{ V_i(t) = V_2(t), h_i(t) = h_2(t), m_i(t) = m_2(t) \} \), corresponding to completely synchronous bursting and governed by the self-connected system known as autapse. This synchronous solution is unstable in the absence of coupling. In what follows, we will show that this synchronous bursting solution is stable and robust under quite general conditions on the inhibitory coupling. This makes the network bistable such that antiphase bursting and synchronous in-phase bursting coexist for the same parameter values (see Fig. 1). We also reveal the robustness of in-phase bursting with respect to transversal perturbations at its different phases by examining the shape of the attraction basin along the orbit. Figure 2 demonstrates that stable in-phase synchronization is a generic phenomenon for the two-cell network as it emerges from a wide range of

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different voltage values of both cells. This observation is reasserted by the computer-assisted verifications aimed to examine the robustness of in-phase synchronization against mismatch between the phases of the cells along the bursting orbit. Figure 3(c) shows the variations in the synchronization zone (shaded) as the cells enter the quiescent phase through tonic spiking. This is consistent with the results of Fig. 2 and confirms that in-phase synchronization is quite robust and hence achievable during the spiking phase of bursting. On the other hand, a little phase mismatch between the cells during the quiescent period will likely lead to antiphase bursting. In the rest of this Rapid Communication, we explain the synchronizing effect of fast nondelayed reciprocal inhibition through examination of the variational equations for transverse perturbations to the synchronous solution [16],

\[
C\xi' = F_1(V,h,m)\xi + F_h(V,h,m)\eta + F_m(V,h,m)\zeta + (S_1 + S_2)\xi,
\]

where \(\xi = V_1 - V_2\), \(\eta = h_1 - h_2\), and \(\zeta = m_1 - m_2\) are infinitesimal perturbations of the zero equilibrium state of Eq. (2), which represents in-phase synchronization. In Eq. (2), \(\{V(t), h(t), m(t)\}\) corresponds to the synchronous trajectory. The terms \(S_1 = -g_c(V - \Theta_{syn})\) and \(S_2 = g_c(V - E_0)\Gamma(V - \Theta_{syn})\) are due to the synaptic coupling. Note that \(S_1 \leq 0\) and therefore stabilizes the zero equilibrium state of Eq. (2). More precisely, \(S_1 < 0\) after the membrane potential \(V(t)\) goes over the synaptic threshold \(\Theta_{syn}\) as in the case of excitatory coupling [16]. Meanwhile, \(S_2 \leq 0\) due to \((V-E_0) > 0\) and positiveness of the partial \(\Gamma(V - \Theta_{syn})\) reaching the high peak at \(V = \Theta_{syn}\) and then rapidly decaying away from the threshold. Consequently, \(S_2\xi\) tends to destabilize the origin every time the membrane potential \(V(t)\) gets close to \(\Theta_{syn}\). In simple terms, the inhibition has a dual role in stabilizing and breaking in-phase synchronization as the terms \(S_1\) and \(S_2\) compete with each other to make the synchronous solution stable versus unstable. The overall out-
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FIG. 4. (Color online) (a) Largest transversal Lyapunov exponent, $L_{\text{max}}$, of synchronous bursting plotted against the synaptic threshold $\Theta_{\text{syn}}$ at $g_s=0.3$. Note two stability intervals where $L_{\text{max}} < 0$. (b) Dependence of averaged $\langle S \rangle$ of $(S_1 + S_2)$ on $\Theta_{\text{syn}}$. Observe the graph of $\langle S \rangle$ closely following that of $L_{\text{max}}$ within the physiologically relevant interval $[-0.025; 0.015]$ for $\Theta_{\text{syn}}$. It accurately predicts the critical threshold $\Theta_{\text{syn}} = -0.009$ beyond which in-phase synchronization breaks down. Insets (c,d) and (e,f) are similar to Figs. 3(a) and 3(b) and relate to the thresholds $\Theta_{\text{syn}}$ marked by the circle and the square in (b), corresponding to stable and unstable in-phase synchronization, respectively. When the spikes hit $\Theta_{\text{syn}}$ transversally [(c) and (d) and Figs. 3(a) and 3(b)], the impact of $S_2$ is weaker, so that $\langle S \rangle$ remains negative long enough to ensure stable in-phase synchronization. When $\Theta_{\text{syn}}$ touches spikes from below (e) and (f), the desynchronizing term $(S_2)$ lasts longer, thus making $\langle S \rangle$ positive and breaking in-phase synchronization down.

come depends on various quantitative factors including the coupling strength and the level of the synaptic threshold. Whenever the phase point, corresponding to the instantaneous state of one cell, gets close to the threshold $\Theta_{\text{syn}}$, the other cell receives a strong short-term desynchronizing kick due to $S_2$, which causes the divergence between the phase points. Once both rise above the threshold, the inhibition switches into a synchronizing role. Then the phase points receive a weaker though longer lasting synchronizing impact due to $S_1$, which converges the cells’ states, as illustrated in Figs. 3(a) and 3(b). The threshold value $\Theta_{\text{syn}}$ and the synaptic strength $g_s$ are two crucial factors determining the stability of the zero equilibrium state in variational Eq. (2), and, hence, the stability of in-phase synchronization. Note that the choice of $\Theta_{\text{syn}}$ affects the balance between the competing terms $S_1$ and $S_2$ and may reverse the overall contribution of the coupling from negative to positive and vice versa. That is, raising the threshold closer to the upper part of the spikes lowers the contribution of the stabilizing term $S_1$ and leads to antiphase bursting in the network (see Figs. 4 and 5).

It is worth noticing that the values of $\Theta_{\text{syn}}$ from the left interval of stability [see Fig. 4(a)] range from about $-0.038$ to $-0.036$. For these values, the threshold $\Theta_{\text{syn}}$ is placed below the minimum value of spikes and cannot intersect the bursting part of the trajectory and, hence, cannot account for the presence of spikes in the presynaptic cell. As far as the synaptic coupling between the cells is concerned, this location of the synaptic threshold $\Theta_{\text{syn}}$ implies an interaction that is similar to that between spiking (nonbursting) cells [2].

Here, the synaptic coupling is always switched on when the system is on the bursting manifold and switched off when the system is on the quiescent branch of the solution. Stable synchronization observed in this interval is fragile as lowering the threshold closer to the quiescent part switches on the destabilizing term $S_1$ in a small vicinity of the quiescent part of the synchronous trajectory where the effect of $S_2$ becomes significant. Therefore, the synchronous solution receives a long lasting desynchronizing impact during the quiescent part and destabilizes. At the same time, the right physiologically relevant interval of $\Theta_{\text{syn}}$ corresponds to the spike interactions during the active phase of bursting and, therefore, to more robust synchronization. It is important to stress that the evaluation of the averaged synaptic term from the variational equations predicts the synchronization threshold rather precisely and serves as the necessary quantitative condition for stable in-phase synchronization. This calculation is particularly important for the bistable network where coexisting antiphase bursting typically dominates over in-phase synchronization such that it is easy to come to the wrong conclusion that in-phase synchronization is always unstable, relying only on numerical calculations from random initial conditions. Indeed, if one cell is initially in the spiking phase, whereas the other is in quiescence, fast nondelayed reciprocal inhibition between the cells leads only to antiphase bursting. However, if the cells start firing in the spiking phase, then the inhibition, instead of diverging them, will force the cells’ states to come together, resulting in stable synchronized bursting. Note that once antiphase bursting is achieved, it remains highly resistant to external voltage perturbations of either cell. On the contrary, a weak common inhibition applied to both cells can break the antiphase regime and make the cells burst together [19] so that the reciprocal inhibition between the cells could synchronize them.

The synchronizing effect of fast nondelayed reciprocal in-
hibitation is defined by the intrinsic property of the fast synaptic coupling to act differently on the synchronization trajectory, depending on whether the trajectory crosses or is above the synaptic threshold. This property is linked to the presence of the two competing terms \( S_i \) and \( S_j \) in the variational equations. In this context, it is generic and applicable to other Hodgkin-Huxley-type neurons, exhibiting different types of bursting. In support of this claim, we have examined the synchronization properties of network (1), composed of two coupled (i) Sherman pancreatic \( \beta \)-cell models [13], displaying square-wave bursting; (ii) Purkinje bursting cell models [20]; and (iii) FitzHugh-Rinzel elliptic bursters [14]. In all the three networks, we have observed stable and robust in-phase synchronization, which coexists with antiphase bursting. We have also verified the persistence of robust in-phase synchronization in network (1), after the synaptic FTM function was replaced by the Heaviside function [11] and by a precise dynamical model of fast synapses, wiring the heart beat central pattern generator of the leech [15]. In the latter case, the synapses are noninstantaneous yet fast so that the impact of inhibition on synchronization is identical to those of the instantaneous FTM coupling. We have also tested the robustness of in-phase synchronization with respect to mismatches in the synaptic strengths and the intrinsic parameters of the cells. Perfect synchronization is no longer possible in these cases, due to symmetry breaking, resulting in that the spikes within the synchronized burst do not coincide anymore. In all simulated cases this approximative (burst) synchronization has been verified to be robust for a mismatch in the synaptic strengths up to \( 5 \sim 10 \% \).

In summary, we present the general ability of fast non-delayed reciprocal inhibition to synchronize bursting cells. This synchronizing property is independent from the type of the individual bursting cell and the model of the fast non-delayed inhibition, be it the instantaneous FTM coupling or a dynamical synapse with the synaptic constants comparable with the duration of the presynaptic spike. The exact synergetic features that make stable in-phase synchronization possible are (i) the ability of fast inhibition to switch its impact from desynchronizing to synchronizing when the spikes cross the synaptic threshold and (ii) the presence of spikes in bursts. It is customary in biophysics to use relaxation oscillators as simplified models of bursting cells where the spikes are smoothed over and ignored. However, reciprocally coupled relaxation oscillators with fast non-delayed inhibition are impossible to synchronize [2,11]. In light of this, our result, that the addition of spikes to the individual cell model can reverse the role of fast inhibition from desynchronization to synchronization, is imperative for biophysical modeling of neuronal networks. It stresses the importance of full-scale detailed models of bursting cells versus simplified models such as relaxation oscillators. The two-cell network that we have studied is the fundamental building element of large realistic inhibitory networks. Our preliminary results show that such complex networks with fast inhibitory connections also possess the hidden property to produce the in-phase synchronized rhythm, provided that the individual cells are bursters, not spikers. A consequence is the enhanced multi-stability of complex neuronal networks, resulting in richer dynamical information capacity and spatiotemporal neuronal integration.

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