Time-delay-induced phase-transition to synchrony in coupled bursting neurons

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Signal transmission time delays in a network of nonlinear oscillators are known to be responsible for a variety of interesting dynamic behaviors including phase-flip transitions leading to synchrony or out of synchrony. Here, we uncover that phase-flip transitions are general phenomena and can occur in a network of coupled bursting neurons with a variety of coupling types. The transitions are marked by nonlinear changes in both temporal and phase-space characteristics of the coupled system. We demonstrate these phase-transitions with Hindmarsh-Rose and Leech-Heart interneuron models and discuss the implications of these results in understanding collective dynamics of bursting neurons in the brain. © *2011 American Institute of Physics*.
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A large body of experimental work on brain activity has demonstrated that phase synchronization of neuronal oscillations is the basis for various percepts and actions, such as perceptual decision-making, attention and memory processes, awareness, sensory-motor, or multisensory integration. Synchronized neuronal oscillations can occur in neurons from a small brain region to a large-scale network of distributed brain regions. Synchrony in networks of spatially distributed neurons involves signal transmission time delays because of finite propagation speeds and axonal lengths. In recent years, many theoretical and computational studies of nonlinear oscillators reported various interesting effects of time-delays on phase synchrony. One of the important time-delay induced effects is a phase-flip transition leading to synchrony or out of synchrony. Here, we confirm and extend this time-delay induced effect in a class of multi-time scale dynamical systems such as bursting neurons. We find that phase-flip transitions are general phenomena and can occur in a network of coupled bursting neurons with a variety of coupling types. The transitions are marked by abrupt changes in both temporal and phase-space characteristics of the coupled system. We show that these phase-transitions occur in networks of different types of bursting neuron models and discuss the implications of these findings.

I. INTRODUCTION

Signal transmission time delays are the result of axonal conduction and chemical synaptic processes and are inherent in networks of neurons in the brain. While the chemical synaptic time delays are small (~2 ms), the axonal conduction delays, which depend on the distance between neurons in the brain, can reach upto tens of milliseconds.[1–3] Time delays comparable to time-scales of neuronal oscillations are known to have significant effects in the ensemble activity of neurons. Thus, in modeling studies of neurons and networks, the influence of time delays on the ensemble activity has received a great deal of attention recently.[4–16] In networks of coupled neurons, time delays have been shown to affect not only the amplitude dynamics generating instabilities,[8] oscillation death,[11,12] enhancement or suppression of synchronized oscillations,[4–6,17] or phase-coherent oscillations,[9] but also the phase dynamics leading the system to or out of synchrony.[13–16,18–21] This time-delay-induced phase transition, marked by a relative phase change from zero to π and a discontinuous change of the average oscillating frequency, was named as phase-flip bifurcation.[22] Such time-delay induced effects in phases and frequencies have not been systematically studied in different coupling types using multi-time scaled dynamical systems like coupled bursting neurons.

At the phase-flip bifurcation point, the ensemble activity of coupled periodic or chaotic oscillators changes from in-phase to out-of-phase (phase difference of π) oscillations (or vice versa).[22] This is accompanied by a discontinuous change in the average frequency of oscillations and also by a discontinuity in the largest negative Lyapunov exponent across a critical delay or coupling strength in time-delayed interaction.[19] The average frequency shows a nonlinear dependence with time-delay and coupling strength. A time-delayed interaction was identified to be the necessary condition for this transition. This phenomenon was observed in various dynamic regimes such as in oscillator death, periodic, quasi-periodic and chaotic oscillations.[19,22] Bursting neurons have distinctly different multiple time scales of oscillations: spike activity with fast time scale and burst activity (consisting of two or more spikes) with slow time-scales. How do bursting neurons respond to time-delayed interactions? Are there time-delay induced phase-flip transitions to or out of synchrony? What are the general characteristics of these

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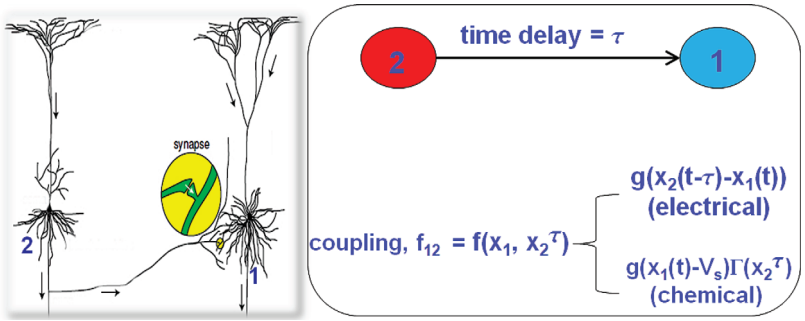

FIG. 1. (Color online) Schematic of time-delayed neuronal interaction. Neuron 2 sends an action potential or a burst of action potentials to neuron 1 at time t, and neuron 1 feels it at later time $t+\tau$, where τ is the time delay. This delay in a chemical coupling is due to axonal conduction and synaptic processes, whereas time delay in electrical coupling is only due to axonal conduction. In modeling a time-delayed interaction from neuron 2 to neuron 1, the coupling term to neuron 1 can take the delayed input from neuron 2. The coupling function f_{12} depends on this delayed input, both for electrical and chemical synaptic couplings, where g is coupling strength, x_1, x_2 are potentials of neuron 1 and neuron 2, and $\Gamma(*)$ is 1 for positive $(*)$ and 0 otherwise. A part of the schematic was adapted from Izhikevich, Eugene M., *Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting*, figure 1.1, page 2, adapted, © 2006 Massachusetts Institute of Technology, by permission of The MIT Press.

transitions in excitatory and inhibitory neuronal networks? In this paper, we investigate into these questions using two bursting neuron models: Hindmarsh-Rose (HR) neuron[23] and Leech-Heart interneuron (IN).[24,25]

Here, we show that the phase-flip bifurcation can also occur in time-delayed coupled bursting neurons. But, in the network of these neurons, the phase-transition from synchrony to out-of-synchrony occurs with a different maximum relative phase, not π. The average frequency and the largest negative Lyapunov exponent show discontinuous changes at a critical delay and coupling strength. These results hold true in a variety of couplings: electrical, and excitatory and inhibitory synaptic couplings, and also in a network of three or more neurons. These results may help understand the mechanisms of a long-distance synchrony of oscillations underlying brain functions or dysfunctions.

II. METHODS AND RESULTS

A. Time-delayed coupled network model

We begin by formulating a general model for a network of neurons with time-delayed interactions. An example of a time-delayed interaction between two neurons is shown in Fig. 1. Consider a coupled system of N bursting neurons. Each neuron when isolated follows $\dot{\mathbf{X}} = \mathbf{F}(\mathbf{X})$, where $\mathbf{X}$ is an m-dimensional vector of dynamical variables such as membrane voltage and gating variables in Hodgkin-Huxley formalism, and $\mathbf{F}(\mathbf{X})$ is the velocity field. The coupled system is described by the following equations:

$$\dot{\mathbf{X}}_i = \mathbf{F}_i(\mathbf{X}_i) + \frac{\epsilon}{K_i}\sum_{j=1}^{K_i} A_{ij}\mathbf{H}(\mathbf{X}_i, \mathbf{X}_j, \tau), \quad i = 1, \ldots, N \qquad (1)$$

where subscript i in $\mathbf{X}_i$ and $\mathbf{F}_i$ represents i-th neuron. Here K_i is the number of connections to the i-th neuron, namely its degree and $1 \le K_i < N$, ϵ is the coupling strength, $\tau > 0$ is the net time delay—the time for the action potential to propagate along the axon connecting the pre-synaptic neuron j to the post-synaptic neuron i. The connection topology is given as $A_{ij} = 1$ if the neurons i and j are connected to each other and $A_{ij} = 0$ otherwise. The coupling function $\mathbf{H} : R^m \to R^m$ specify the manner in which the neurons i and j are coupled, with $\mathbf{H}(\mathbf{X}_i, \mathbf{X}_j, \tau)$ being a function of $\mathbf{X}_i(t)$ and $\mathbf{X}_j(t-\tau)$. For a three-variable neuron model, $\mathbf{X}_i = [x_i, y_i, z_i]^T$ and $\mathbf{H} = [g(x_i(t), x_j(t-\tau)), 0, 0]^T$, where g is a coupling function, and the superscript T denotes the transpose. If the neurons i and j are connected via a gap junction (electrical coupling), then the coupling function takes the form $g(x_i(t), x_j(t-\tau)) = (x_j(t-\tau) - x_i(t))$. For a coupling via a chemical synapse, it is $h(x_i(t), x_j(t-\tau)) = -(x_i(t) - V_{is})\Gamma(x_j(t-\tau))$, where the reversal potential V_{is} can set the threshold for excitation or inhibition, and $\Gamma(*)$ is 1 for positive $(*)$ and 0 otherwise. If $V_{is} > x_i(t)$ for all x_i and t, the coupling term is always positive and the synapse is excitatory, i.e., the input to ith neuron via coupling can enhance the activity of this neuron. On the other hand, if $V_{is} < x_i(t)$ for all x_i and t, the coupling term is negative and synapse is inhibitory, i.e., the input to ith neuron via coupling can suppress its activity. Usually, $\Gamma(*)$ is approximated by a sigmoidal function: $1/[1 + \exp\{-\beta(x_j(t-\tau) - \Theta_s)\}]$, where β determines the slope of the function and Θ_s is the firing threshold. Fig. 1 shows a time-delayed coupling setup with two neurons.

B. Neuron models

Both Hindmarsh-Rose neuron[23,26] and Leech-Heart Interneuron[24,25] models are known to produce bursting activity in extended ranges of system parameters. Here, to study the time-delay induced phase-transitions in a bursting activity, we have considered using them both. Three-variable HR neuron[26] is a phenomenological model although the original two-variable model[23] was constructed to describe snail's neuron dynamics. The IN neuron describes the electrical activity of neurons that control Leech's heart.

The HR neuron dynamics is described by the following set of equations:[26,27]

$$\begin{aligned} \dot{x} &= y - ax^3 + bx^2 + z + I_{ext} \\ \dot{y} &= c - dx^2 - y \\ \dot{z} &= r[s(x - x_0) - z] \end{aligned} \qquad (2)$$

where x is the membrane potential, y is the fast current (recovery variable), and z is the slow current also known as

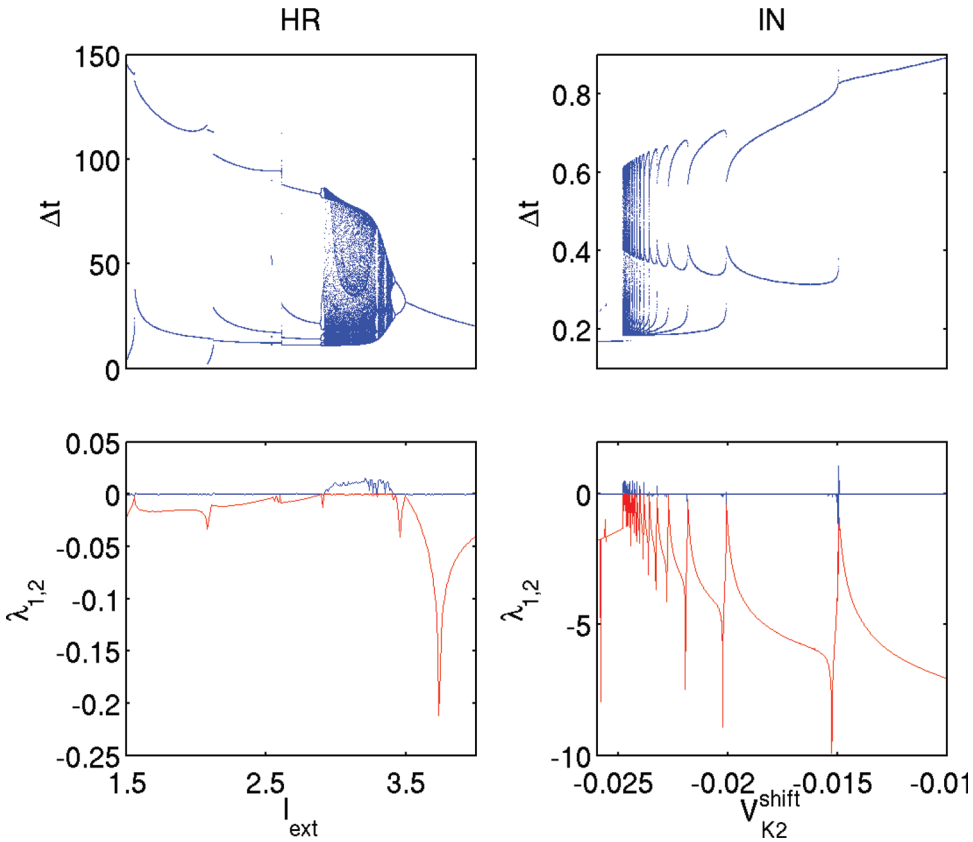

FIG. 2. (Color online) Bifurcation diagrams (upper panel) and first two Lyapunov exponents (lower panel) for Hindmarsh-Rose (HR) neuron (left panel) and Leech-Heart Interneuron (IN) neuron (right panel) models. These results help us understand the qualitative behaviors of single neurons. Here, the bifurcation diagrams are obtained by computing the times Δt between successive spikes, including the time intervals between bursts of spikes. As the parameter, external current to a neuron (I_{ext}) is decreased from 4.0 to 1.5, HR neuron goes through a series of transitions: from period 1 to chaos via period-doubling cascade and back to periodic behaviors. The maximum Lyapunov exponent (lower left, blue) shows that the HR system is chaotic approximately for the range $2.92 < I_{ext} < 3.40$. In the case of IN neuron, as the parameter, V_{K2}^{shift}, is decreased from –0.01 to –0.025 volt, it goes through a series of period-adding bifurcation.[31,32] There is a chaotic (or many period) regime around –0.024 volt, which belongs to one attractor state. There is another period-1 attractor at and around this parameter value. This region shows bistability of chaotic attractor and period-1 attractor (see Fig. 3).

adaptation variable. Here, $a=1.0$, $b=3.0$, $c=1.0$, $d=5.0$, $s=4.0$, $r=0.006$, $x_0=-1.60$, and I_{ext} is the external current input. r is the ratio of fast/slow time scales. This system exhibits a multi-time-scale spike-burst chaotic behavior for $2.92 < I_{ext} < 3.4$, as shown in the bifurcation diagram and Lyapunov exponents (Fig. 2, left panel).

The Leech-Heart Interneuron model has the following equations of motion:[25]

$$\begin{aligned}\dot{v} &= -2[30\ \mathrm{m}^2(v+0.07)+8(v+0.046)\\ &\quad + 200f^3(-150,0.0305,v)h(v-0.045)]\\ \dot{h} &= 24.69[f(500,0.0333,v)-h]\\ \dot{m} &= 4[f(-83,0.018+V_{K2}^{shift},v)-m],\end{aligned} \tag{3}$$

where v is the membrane potential, h and m are membrane channel gating variables. h is associated with fast ionic current such as flow of sodium ions and m is the slow gating variable. $f(a,b,v)=1/[1+\exp(a(b+v))]$ is a Boltzmann function which describes the kinetics of activation/inactivation of ionic currents. V_{K2}^{shift} is an experimentally accessible bifurcation parameter that is a deviation from the average potential $v=-0.018$ V corresponding to the semi-activated potassium channel at $f=1/2$. IN neuron has periodic and chaotic (or high-period periodic) states as shown in the bifurcation diagram and Lyapunov exponents (Fig. 2 right panel). Typical phase-space portraits and corresponding potential time series of burst activity for both of these neuron models are shown in Fig. 3. IN neuron is bistable—period 1 (shown in Fig. 3 with red) and chaotic state (or high period periodic state, shown in blue) coexist around $V_{K2}^{shift} \approx -0.024$ V. Both of these oscillators show the spike-burst activity (multi-time scale dynamical behaviors) in a wide range of bifurcation parameters. There are two distinct time-scale of oscillations and the trajectories in the phase-space move slowly in one region whereas they move fast in the other region. The y–z plane along the firing threshold $x=-1$ approximately separates these two regions in the HR neuron, and $v \approx -0.04$ V approximately separates in the IN neuron case. Different time scales of oscillations can also be seen in voltage traces: slow motion when the membrane potential is below the firing threshold and fast when it is above [voltage traces in Fig. 3 (lower panel)]. In non-delayed coupled systems consisting of these bursting neuron types, synchrony in individual bursts can be easily achieved through coupling of individual neurons as a precursor to a complete synchrony,[27] and by varying coupling strengths, or modifying connections of neuronal subnetworks.[28]

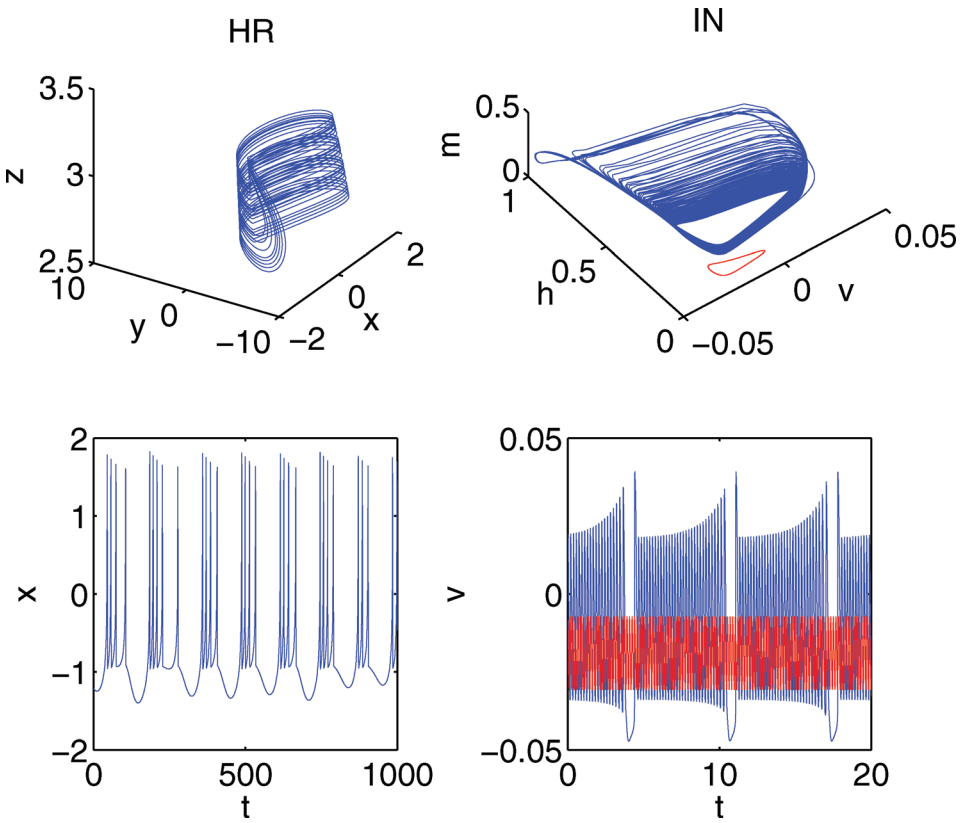

FIG. 3. (Color online) Bursting activity of HR (left panel) and IN (right panel) neurons. The first row of 3D-plots shows chaotic (blue) and periodic (red) attractors (phase space plot of three-variables) of the systems and the second row shows membrane potential time series (blue trace for chaotic time series, red trace for periodic time series).

C. Results

In order to study the effect of time-delay and coupling strength in synchrony of bursting neurons, we simulate the networks of time-delayed coupled neurons (≥ 2) using HR and IN neuron models as described in Secs. II A and II B. The simulated coupling types include electrical synapses (also known as gap junctions), and excitatory and inhibitory chemical synapses. Across all types of weak couplings and in both systems of coupled HR and IN neurons, we observe time-delay induced phase-flip bifurcations to synchrony or out-of-synchrony as time delay τ is varied. In the case of periodic or quasi-periodic spike activities (with no burst activities present), the coupled system of two neurons exhibits oscillations out-of-phase by π. However, with burst activities, the phase-shift across the transition is less than π both for spikes and bursts. Here, we present some representative cases in Fig. 4–6.

In Fig. 4, we consider the case of two bursting IN neurons identically coupled with a time-delayed inhibitory chemical synapse and initial conditions from the antiphase states. In the absence of time-delay ($\tau = 0$), these two identical neurons would oscillate in antiphase. If τ is changed significantly at non-zero coupling strength, then we start to see the changes in the relationship of two bursting activities. At $\tau = 0.2$ and $\epsilon = 0.25$, these two neurons are out-of-phase with each other. At this coupling strength, as τ is changed to 0.25, they get into in-phase and then at $\tau = 0.3$, they are out-of-phase again (shown in the first column of sub-figures). Similarly, at non-zero time delay also, running the system through coupling strengths, one can bring about the phase-transitions as shown in Fig. 4 (second column). For non-delayed inhibitory coupling, the stable in-phase synchronization coexists with antiphase bursting within a broad range of initial conditions and parameter values of the network.[29] For delayed coupling with small delays, this will be true also. In Fig. 5, we show that the phase-transitions can also occur even when the bifurcation parameter, such as V_{K2}^{shift} in the case of the interneuron model, of the individual system is changed at non-zero delay and non-zero coupling. Such phase-transitions to synchrony or to out-of-synchrony can also be observed with HR neurons and with an excitatory electrical coupling (Fig. 6). These transitions are seen with discontinuous changes in the largest negative Lyapunov exponent (Fig. 6, top panel), in oscillation frequencies (Ω_1, Ω_2 in Fig. 6, the second panel), in spike phase-difference ($\Delta\phi_s$, third panel), and burst phase-difference ($\Delta\phi_b$, third panel) at $\tau \approx 3.7$. The phase difference between the oscillations of two bursting neurons is defined as: $\Delta\phi = \langle|\phi_1(t) - \phi_2(t)|\rangle$, where $\langle.\rangle$ denotes the average over time and $\phi_{1,2} = \tan^{-1}\,[Y_{1,2}(t)/X_{1,2}(t)]$ with X and Y representing the variables projected onto the plane of fast variables for spike activity or onto the plane of one fast and one slow variable for burst activity. Here, the phase-difference is less than π. This is because of the multi-time scales inherent in the system. At the transition from in-phase to out-of phase, the oscillators are out of phase because of their motion over the fast manifold, i.e., one oscillator can be ahead or behind the other by a time interval of about an inter-spike interval. At this transition, two negative Lyapunov exponents avoid crossing each other.

We now consider three, four, and eight IN neurons in a network. We performed these simulations to see how the phase-transitions to synchrony as seen in two coupled

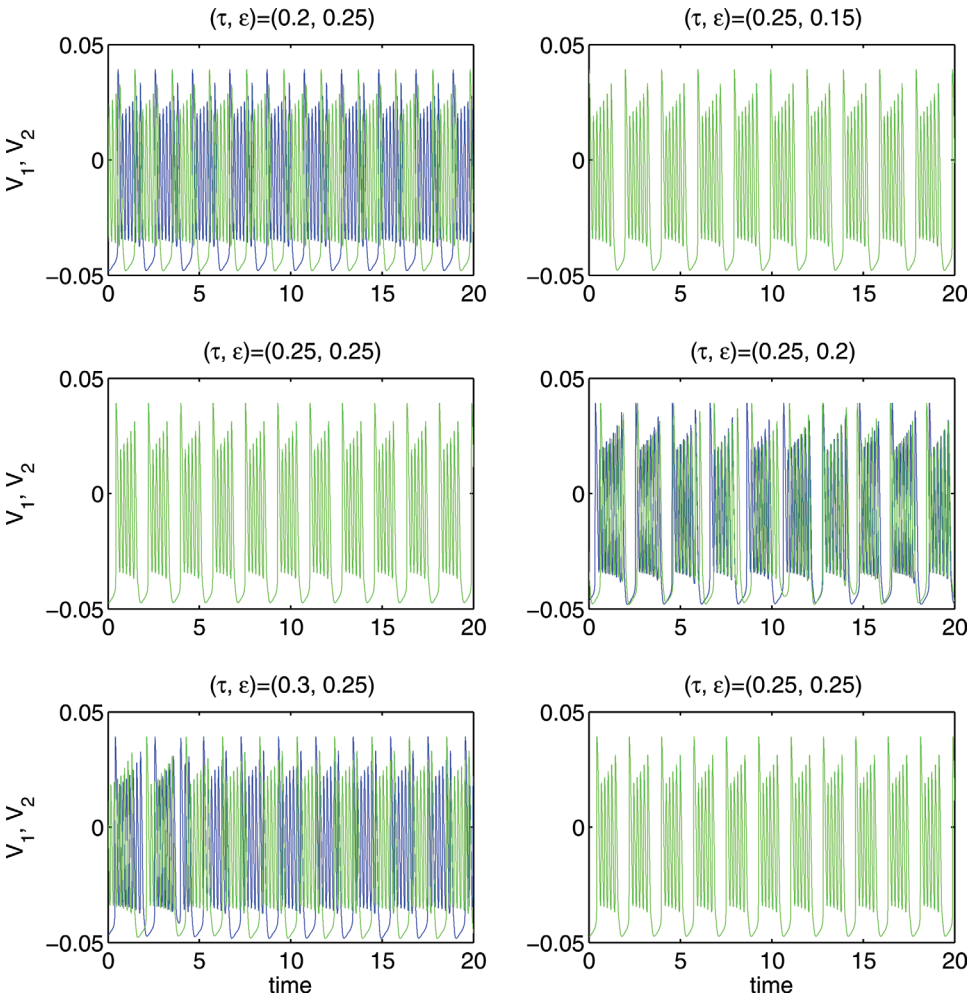

FIG. 4. (Color online) Time-delay induced phase-flip transitions in coupled bursting neurons. Two bursting Leech-Heart interneurons coupled with a time-delayed inhibitory chemical coupling undergo phase-transitions from out-of-phase state to in-phase and again to out-of-phase state as τ is changed from 0.2 to 0.25 and to 0.3 at fixed non-zero coupling (first column of plots). The system goes from in-phase state to out-of-phase and back to in-phase when ε is changed from 0.15 to 0.2 and to 0.25 at fixed non-zero time-delay (second column). In the absence of such a time-delayed interaction, these neurons would oscillate in out-of-phase bursts in a weakly coupled interaction.

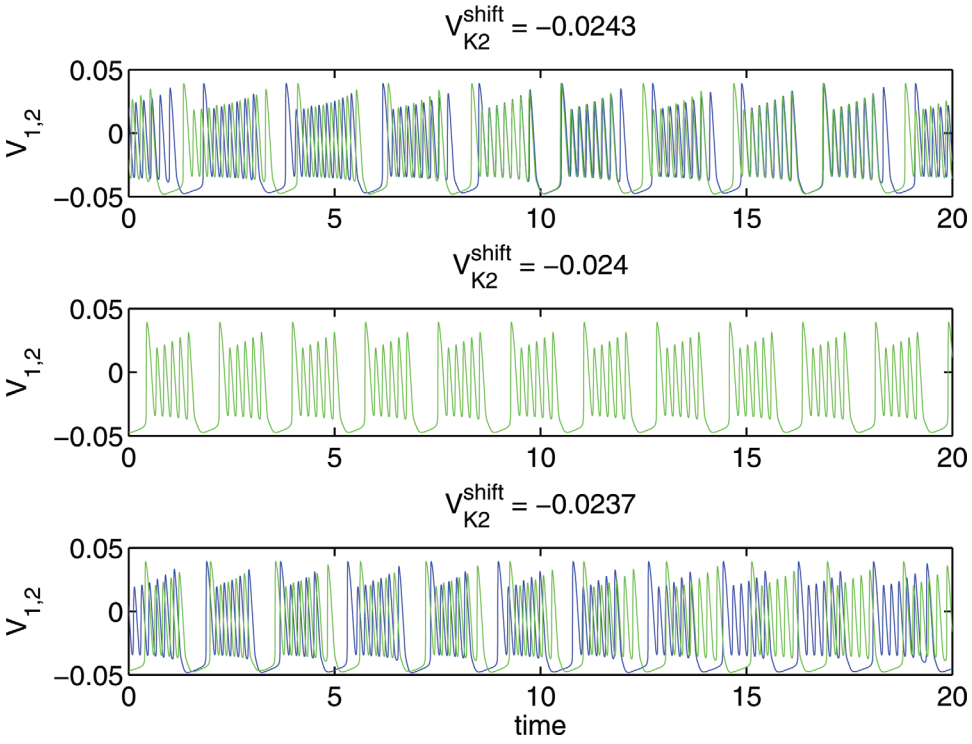

FIG. 5. (Color online) Time-delay induced phase-flip transitions in coupled bursting neurons by changing bifurcation parameters values. Two bursting Leech-Heart interneurons coupled with a time-delayed inhibitory chemical coupling undergo phase-transitions from out-of-phase state to in-phase and again to out-of -phase state as V_{K2}^{shift} is changed from –0.0243 to –0.024 and to –0.0237 at fixed $\epsilon = 0.25$ and $\tau = 0.25$ in all cases. In the absence of such a time-delayed interaction, these neurons would oscillate in out-of-phase in a weakly coupled interaction.

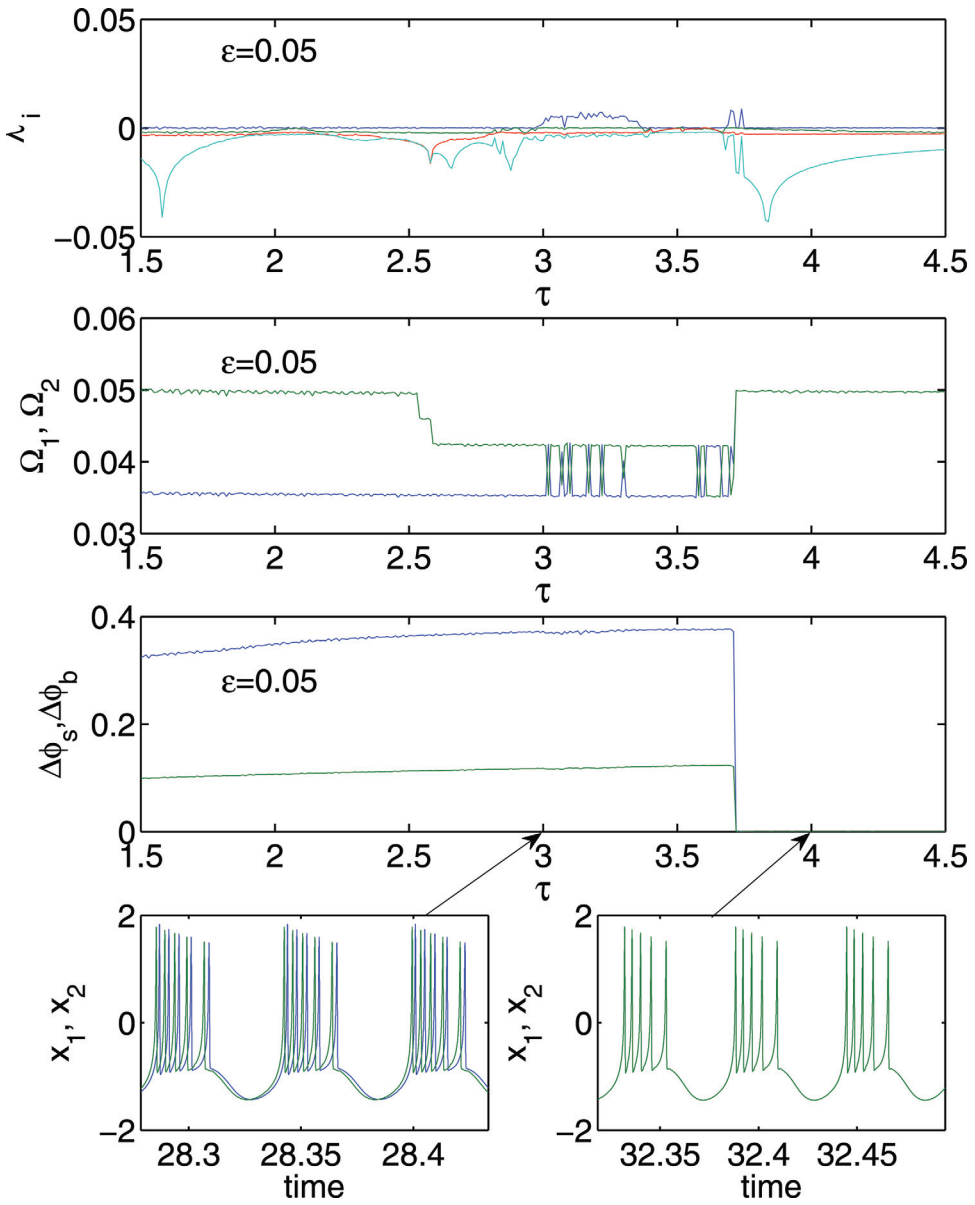

FIG. 6. (Color online) Characteristics of time-delay induced phase transitions shown with time-delayed electrically coupled HR neurons. The time-delay induced phase-flip transitions are marked by the abrupt changes in the largest negative Lyapunov exponent (λ), oscillation frequencies (Ω_1 and Ω_2), and relative phases between spikes ($\Delta\phi_s$) and between bursts ($\Delta\phi_b$). Unlike periodic and chaotic oscillators, bursting neurons can go from in-phase burst synchrony (as shown in the figure on the fourth row, right) to out-of-phase state (the fourth row, left) with phase-difference less than π near the bifurcation point.

neurons generalize a network consisting larger number of neurons. Fig. 7 in the top panel shows an example of four neurons connected in a ring with excitatory synaptic coupling. As time-delay τ changes from 0.25 to 0.30, the system goes from out-of-phase state to in-phase state. Here, the out-of-phase state is the most stable when the phase-difference between the nearest neighbor is $2\pi/N$, where N is the number of oscillators, and in this example it is 4. For a network of eight oscillators, this phase difference becomes $2\pi/8$. We have used the similarity function as described in Ref. 33 to find the phase-differences between neurons. Here, the neurons in the periphery close to each other in a ring topology have $\pi/2$ phase difference whereas off-diagonal neurons farthest from each other are out-of-phase by π. These network results extend the previous findings[19] from two oscillators. The phase-flip transitions can be demonstrated even in weakly coupled phase-oscillators.[34] Consistent with such finding, our results of weakly coupled oscillators indicate that the phase-flip transitions are primarily due to the intrinsic time-scales of the system and time delays in couplings. Thus, these results of phase-flip transitions in weakly coupled systems can be expected to remain robust to variations of number of nodes or the system size.

III. CONCLUSIONS

In summary, we uncover a phenomenon of phase-flip bifurcation in networks of bursting neurons with a variety of time-delayed coupling types and topology. Unlike the previous findings in systems of periodic or chaotic oscillators, coupled bursting neurons undergo time-delay-induced phase transitions to asynchrony out of synchrony by a phase difference less than π. The transitions are marked by abrupt changes in the second negative Lyapunov exponent, average frequency, and relative phase difference. In the case of nearest neighbor excitatory coupling, oscillators next to each

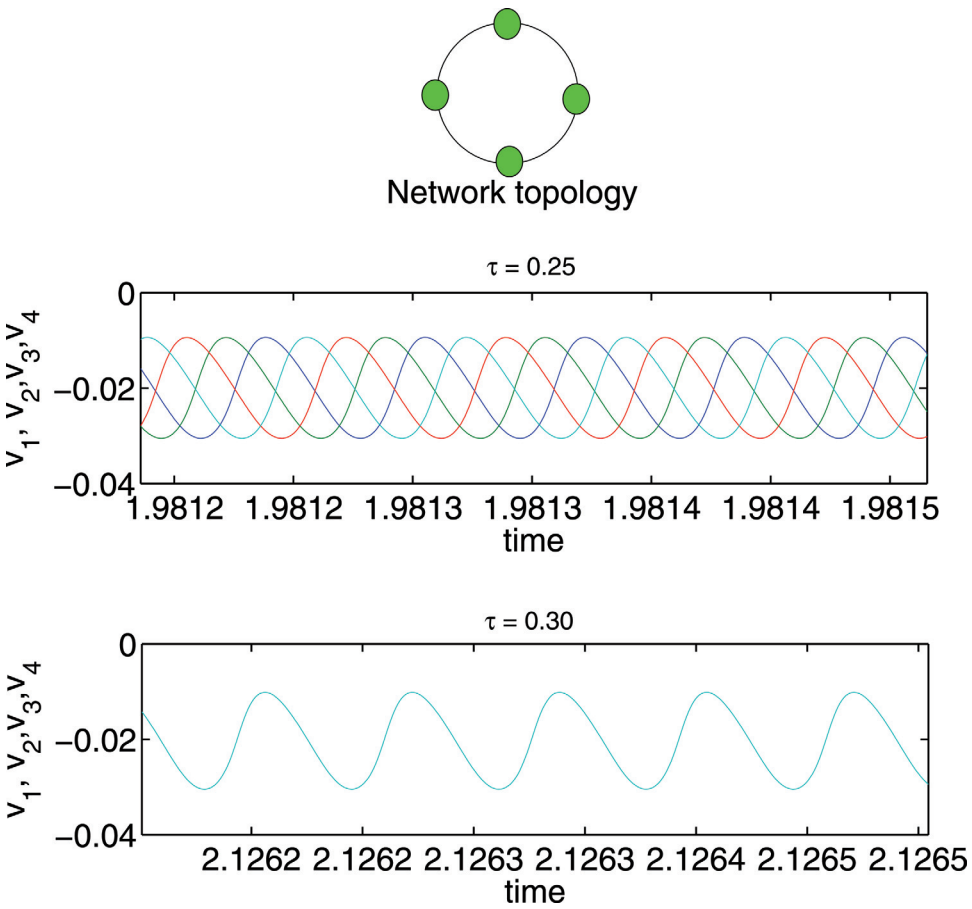

FIG. 7. (Color online) Network of four IN neurons in a ring topology and phase-transition to synchrony. By changing time-delay from 0.25 in synaptically coupled periodic neurons on a ring, we can drive the coupled system to phase synchrony. Across the critical delay (or coupling), the relative phase changes by $2\pi/N$ between nearest neighbors, where N is the number of neurons in the network.

other are at an equal phase difference around a circle: for three oscillators, the phase difference between neighbors is $2\pi/3$; for four, it is $2\pi/4$, which generalizes to N oscillators with phase difference of $2\pi/N$. Time-delays are unavoidable in spatially distributed dynamical systems like the neurons in the brain and can play significant roles in large-scale synchronized oscillations in the brain. Time-delayed coupling can, for example, induce synchronization between two cells with intrinsic antiphase bursting activities. Even in mutual inhibition among multiple neurons, synchrony of burst-spike activities can occur with time-delayed coupling. These time-delay-induced transitions may help explain the co-existence of various frequency rhythms in different parts of a large neuronal network.

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