Bursting in Neurons with Fast and Slow Inhibition

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Abstract

$\mathbb{R}$ Collective oscillations abound in neural systems as hallmarks of behavioral patterns. They range from the characterisitic rhythmic movements of invertebrate motor responses to the oscillations at different frequency bands in the mammalian EEG. The study of neural oscillations assumes tremendous importance given their role in generating patterned behavior. Small neuronal networks in invertebrates called Central Pattern Generators directly control rhythmic activities such as swimming, heartbeat, breathing or walking. CPGs are networks often composed of a small number of neurons whose output is oscillatory. Individual neurons in CPGs may themselves be oscillatory and the network rhythm is patterned by the synaptic interactions between the neurons. Conversely, neurons in some CPGs are not endogenous oscillators and synaptic interactions are crucial in initiating and maintaining the network rhythm. Getting [1] and Harris-Warrick *et al.* [2] review the intrinsic and synaptic properties of several invertebrate CPG networks. Some well studied networks include the escape swim CPG in *Tritonia*, the gastric mill CPG in the lobster, the flight CPG in locust and the CPG controlling the heartbeat of the leech *Hirudo medicinalis*.

Several features of synapses contribute to temporal pattern genration in CPGs, such as the polarity (excitatory or inhibitory), ionic dependence and temporal characteristics (for example, the time course of multiphasic actions, where the synapse has both excitatory and inhibitory components). Circuit models with complex synaptic properties often show dramatic changes in network oscillations as the synaptic time course is varied. Most general

models of small neuronal networks [3–5] consider synaptic interactions with only a single time scale. However, several examples of synaptic interactions have multiple time scales. Pyramidal cells in the mammalian cortex can excite other cells with both fast and slow excitatory synapses, and some evidence suggests that the same inhibitory cell can provide fast and slow inhibition in the same target [**?**,**?**]. Invertebrate CPG circuits often have more complex synapses which have a fast excitatory and slow inhibitory component or vice versa [1], as well as mixed synapses of the same kind, which are crucial in determining the overall rhythm of the network [7]. What are the properties of networks of neural oscillators with mixed time scale coupling?

We study two identical oscillators coupled by both slow and fast inhibition, and show that the presence of multiple time scales in the coupling leads to varied behavior. We represent each oscillator by the following set of differential equations:

$$\begin{aligned}\frac{dv}{dt} &= -I_{ion}(v_i, n_i) - g_{ji}s_j(v_i - V_{syn}) \\ &\quad - g'_{ji}q_j(v_i - V'_{syn}) + I_{app}\end{aligned} \tag{1}$$

$$\frac{dn}{dt} = \frac{n_\infty(v) - n}{\tau(v)} \tag{2}$$

$$\frac{ds}{dt} = \frac{s_\infty(v) - s}{\tau_s} \tag{3}$$

$$\frac{dq}{dt} = \frac{q_\infty(v) - q}{\tau_q}, \tag{4}$$

where $I_{ion} = g_{Na}m^3_\infty(v)(v - v_{Na}) + g_K n^4(v - v_K) + g_L(v - v_L)$, represents the voltage activated currents (sodium and potassium) and the leakage current. n is the gating variable for the potassium current activation, s_j, is the probability of channel opening, and g_{ji} specifies the maximal conductance for the fast synapse, q_j does the same for the slow synapse. V_{syn}, V'_{syn} are the reversal potentials for the synaptic current. We assume that the sodium activation is instantaneous and achieves steady state immediately. These equations are a reduced version of the familiar Hodgkin-Huxley equations [8]. The functions $n_\infty(v)$, $s_\infty(v)$, $\tau(v)$, and q_∞ are the usual sigmoidal activation functions for the HH model.

We give the functional forms in Appendix A. The time scale τ_s is equivalent to the fast timescale of the spike mediated inhibitory synapse, while τ_q is the long timescale associated with the slow rise and fall of the slow inhibition. We take the slow inhibition to be one single aggregate process as the exact mechanisms of the slow synapse are not known [7,**?**].

Rinzel and Frankel [9] studied a similar model with slow inhibition alone. Note that for $1/\tau_q \ll 1$, the oscillators become a singularly perturbed dynamical system. Upon taking the singular limit $\tau_q \to \infty$, q_j can be treated as a parameter. The fast variables $\{v_i, n_i\}$ have a stable rest state for large values of q_j. This rest state destabilizes via a subcritical Hopf bifurcation at $q_j \sim 0.106$. Since the period of the membrane oscillations is much smaller than the variation of q_j, the averaging theorem [10] simplifies the dynamics of the coupled neurons [9,11,12]. Averaging over the fast variables, only the synaptic activation variables remain. This procedure drastically reduces the number of dimensions of the problem. The averaged equations for the slow subsystems are:

$$\dot{\bar{q}}_i = \bar{q}_\infty(\bar{q}_j) - \bar{q}_i, \;\; i \neq j. \tag{5}$$

The subcritical Hopf bifurcation of the rest state of each neuron implies that the neurons are bistable for a small range of q_j. For multiple oscillatory branches, the slow variables must be averaged over each oscillatory solution. Note that the steady states of Eqn. 5 are analogous to an input-output transfer function, denoting the response of $q_j(\{q_i\})$. We show the steady states of $q_1(q_2)$ in Figure 1.

FIGURES

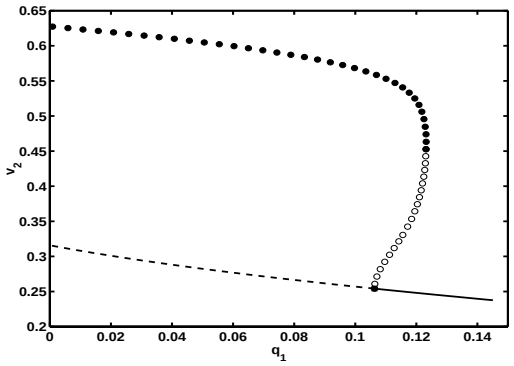

FIG. 1. Bifurcation diagram for the modified Hodgkin-Huxley equations driven by an unidirectional, slow inhibitory synapse. q_1 is the activation variable of the slow synapse from cell 1 onto cell 2. Solid lines indicate stable rest states, dashed lines indicate unstable rest states, open (filled) circles denote maximum amplitudes of unstable (stable) oscillations. The square at $q_1 = 0.106$ is the point of a subcritical Hopf bifurcation.

Rinzel and Frankel used a clever graphical construction to study the stable steady states of Eqn. 5. Figure 1 represents the steady states for a network with a unidirectional connection, cell 2 inhibiting cell 1. By plotting the steady states of $q_1(q_2)$ and $q_2(q_1)$ on the same graph, we can obtain the steady states of the network with reciprocal inhibition. The intersections of the two steady state curves are the steady states of the network. We see 4 intersections of the steady state curves (Figure 2: cell 1 at rest and cell 2 active, its symmetric counterpart, with cell 2 at rest and cell 1 active, both cells active and both at rest. The latter two states being intersections of unstable branches are unstable. Therefore, the network is bistable, with either cell 1 or cell 2 active and the other at rest. A strong current pulse to the active cell can switch the network between the two states.

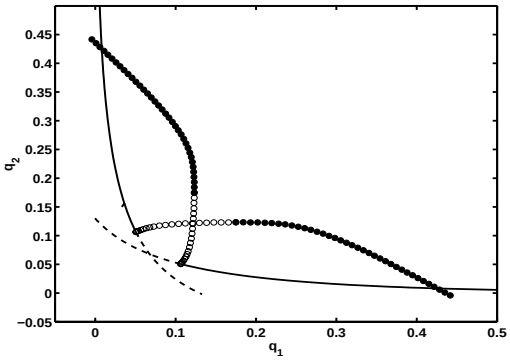

FIG. 2. Steady states of the averaged equations for the slow variables.Solid lines indicate stable rest states, dashed lines indicate unstable rest states, open (filled) circles denote maximum amplitudes of unstable (stable) oscillations. The intersections of the curves are the steady states for the equations.

Now consider a mixed synapse with fast and slow components. The fast component has a time scale comparable to the time scale of the oscillations and cannot be eliminated by averaging. We show the time course of the two cells for $g_{12} = g_{21} = 0.3$ in Figure 3, with all the other parameters fixed. The spikes within the burst are anti-phase and the amplitudes are slightly unequal. The initial conditions set both cells at rest. A constant current I_{app} is applied to both cells to model an external stimulus. An additional small, brief current pulse is applied to one cell as a small perturbation to break the symmetry.

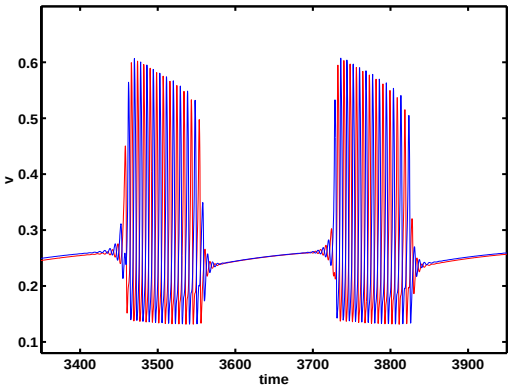

FIG. 3. Numerically integrated trajectories for Eqns. 4 shows a synchronous bursting solution with antiphase spikes.

If the current pulse is too high or long, the network settles into an *on-off* state, in which either cell 1 or cell 2 spikes with a large amplitude, while the other oscillates about the rest state with very small amplitude, as it is strongly inhibited by the spiking cell. These *on-off* fixed points are small perturbations of the original fixed points for slow mutual inhibition which persist (as they should according to invariant manifold theory). The synchronous bursting solution is a new stable solution for mutual inhibition with mixed time scales. We have numerically confirmed that the burst solution is stable. Brief current pulses (pulse widths less than τ_q) do not affect the bursting solution. Longer pulses switch the network to an *on-off* state depending on the cell to which the current pulse is applied. The network can also be switched from the *on-off* state to a bursting state.

Extensive numerical simulations show that the synchronous bursting solution has $q_1 \sim q_2$, *i.e.* the slow variables remain close. We recall a similar dynamics for the slow variables for coupled square wave bursters, and use the same geometrical method [13,14] to analyze bursting in Eqns. 4. Since the slow variables q_i are of $\mathcal{O}(\infty/\tau_f)$ close, we can treat them as identical. Therefore, we can construct a one parameter bifurcation diagram for the coupled fast subsystem (Figure 4).

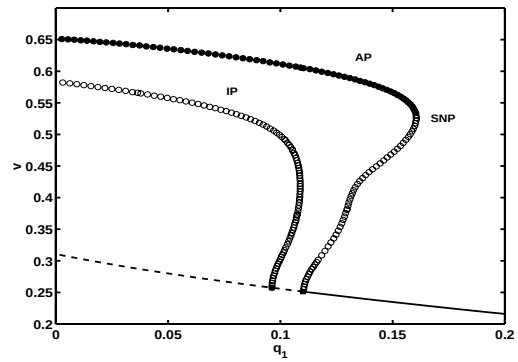

FIG. 4. Bifurcation diagram for the fast subsystem of Eqns. 4. The symbols are as before. The parameter values have been slightly shifted to move the in-phase Hopf bifurcation to $q_1 = 0.096$. AP denotes the anti-phase branch, IP denotes the in-phase branch and SNP denotes the Saddle Node of Periodics.

We can use this picture to understand the nature of bursting geometrically. The fast inhibition now introduces a second Hopf bifurcation from the steady state which represents anti-phase oscillations of the two cells. The anti-phase Hopf bifurcation of the network is subcritical, similar to the subcritical Hopf bifurcation in a single cell driven by a slow unidirectional synapse. A network of HH cells with fast inhibition has spikes anitphase. Hence, the spikes within the burst are π radians out of phase. Initially, as the two cells are driven from rest by the external current, they begin to oscillate since the slow inhibition is zero. The activity of the cells causes the slow inhibition to increase and the cells track the stable periodic branch. As q_i crosses the saddle node of periodics point (where the stability of the periodic solution changes), the rest state becomes the only stable state and the oscillations terminate. Now the synaptic variables begin to decrease slowly as the voltage switches below the q_i nullcline and the cells track the steady state branch. Interestingly, the slow ramping of the control variable (in this case, the synaptic variable) causes the cells to track the steady state even when it has lost stability, due to a delayed loss of stability at the Hopf bifurcation [15,16]. A small noise term (uniformly distributed between $[-0.005,0.005]$) added to the voltage equations causes the cells to leave the rest state and jump to the unstable in-phase oscillation branch. As q_i begins to increase, the oscillators now track the stable anti-phase branch and the burst cycle repeats. This type of bursting, which starts at a subcritical Hopf point and ends at a saddle-node of periodics is termed type III bursting [17], and is characterized by slow ramping and small growing and damped oscillations prior to and after the burst (Figure 5).

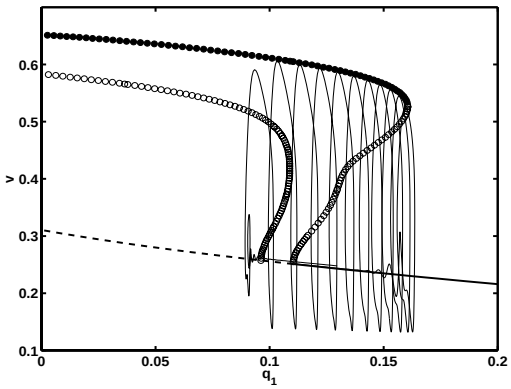

FIG. 5. A phase portrait of the bursting trajectory for cell 1 overlaid on the bifurcation diagram.

The burst solution is remarkable because it is not predicted by an analysis of the averaged equations. If we repeat the graphical construction in Figure 2, the only intersections of stable branches are the *on-off* states. Moreover, neither cell is an endogenous burster. Bursting is peculiar to the coupled network with mixed time scales. This network illustrates that synchronous solutions are possible in networks with inhibitory synapses, contrary to the usual dogma that inhibition leads to antiphase solutions. van Wreeswijk *et al.* also studied a model network of integrate and fire neurons (Type I oscillators according to the terminology of Section 3.3) and showed that fast, mutual inhibition led to synchrony in the network. However, their conclusions were based on the fact that the coupling strength was weak, and the methods of Section 3.3 apply [18]. Wang and Rinzel [4] studied the case of a network with slow inhibition which also synchronized. Terman *et al.* clarified the mechanisms of synchrony due to slow inhibition in relaxation oscillators. However, our model is remarkable in that it requires a mixed fast-slow inhibition for synchronization. The fast spike generating currents are as important as the slow averaged variables. Though, we have inferred the stability of the bursting solution numerically, we do not have a proof along the lines of Terman's [19] proof of a stable bursting solution for a square wave burster. The high dimensionality of the equations and the strong nonlinearity of the terms make any analytic progress difficult.

We can address some questions concerning the stability of these bursts by constructing a simplified, canonical form for the full equations. The bifurcation diagrams clearly indicate that the subcritical Hopf bifurcation governs the bursting dynamics. Thus we can study the dynamics of the network by considering the normal forms for a subcritical Hopf bifurcation. We can use a theorem of Hoppensteadt and Izhikevich [20] to show that the equations can be written as:

$$z_i' = (b_i + A_i v_j) z_i + d_i z_i |z_i|^2 + \sum_{j=1}^{n} c_{ij} z_j \tag{6}$$

$$+\text{nonlinear coupling terms} + \mathcal{O}(\varepsilon), \tag{7}$$

$$v_i' = \hat{\mu}(R_i + S_i |z_i|^2 + T_i v_i) + \mathcal{O}(\hat{\mu}\varepsilon), \tag{8}$$

where $z_i \in \mathbf{C}$, $v_i \in \Re$, b_i, c_{ij}, d_i, and A_i are complex coefficients. R_i, T_i, S_i are real matrices, and $\hat{\mu} = \mu/\varepsilon$. Kuramoto [21] and Aronson *et al.* [22] have formally outlined the reduction procedure that transforms a vector field near a subcritical Hopf bifurcation to the z equation which can be used to calculate the coefficients for Eqns. 4. This reduction results in a canonical form for a subcritical Hopf bifurcation, where the bifurcation parameter v_i is fixed. If $\mu \sim \mathcal{O}(\varepsilon^{\|})$, $\hat{\mu} \ll \infty$, and v_i varies slowly and consequently, Eqn. 8 is singularly perturbed. The coupling terms must take into account that the synaptic interaction has nonlinear components that enter into the equation at $\mathcal{O}(\sqrt{\varepsilon})$. Note that the bifurcation parameter for z_i is the slow variable v_j, as for the slow synapses. Since the bifurcation is subcritical, the rest state and the oscillations are bistable for a range of v_i. Frankel and Kiemel [11] considered a model of slowly coupled oscillators, similar to the normal form equations, with coupling only via the slow variables and showed that the generic solutions are either phase locked or phase trapped ones. However, their model did not include the fast coupling terms and they did not study the case of singular perturbations, although they did correctly include the amplitude effects for weakly coupled oscillators.

As we increase the coupling strength associated with the fast inhibition, we see a qualitative change in the oscillations. The periodic bursting solution is no longer stable, and the oscillators irregularly alternate between episodes of antiphase spiking and in-phase bursting with anti-phase spikes. The length of the episodes appears to be chaotic. We expect the reduced equations, Eqns. 8 to have a similar transition to chaos.

A commonly observed feature in CPG networks is the lack of mutual, chemical excitation between cells. Excitatory chemical synapses are usually unidirectional. Instead, gap junctions or electrical coupling provide mutual excitation. One example of a mixed electrical and slow inhibitory coupling is in the cells of the somatogastric ganglion of the lobster,

which controls the rhythmic movement of internal teeth that masticate food in the animal's foregut [2]. Abarbanel *et al.* have studied a network of intrinsic bursters with electrical and instantaneous, inhibitory chemical coupling. We can extend our model by incorporating an electrical coupling term and leaving out the fast inhibitory synapse. The HH equations with mutual, electrical coupling have parameter regimes where both the in-phase and anti-phase solutions are simulataneously stable, which should lead to interesting dynamics for the network.

A model network of HH neurons with gap junctions replacing the fast inhibition also shows qualitatively similar behavior to the network with mixed inhibitory synapses. The synchronous bursting state persists, with somewhat enlarged stability boundaries. The spikes within the burst are in-phase, unlike in the network with fast inhibition. The duration of the active phase is shorter with 5-6 spikes per burst. Also, large gap junctional coupling does not lead to chaotic bursting behavior.

Most neurons in CPG networks are much more complicated than the simple Hodgkin-Huxley type model considered here, with additional slow currents and dendritic properties. The spatial effects of dendrites must be studied using coupled PDE-ODE systems, which makes analytic solutions very hard to come by, as dendritic proerties of neurons are not completely classified experimentally. The slow currents are more amenable to analysis. Two typical slow currents in CPG neurons are the "sag"current, which activates when the membrane is hyperpolarized, and the T-type calcium current, which allows the neuron to fire upon release from inhibition. Both these currents have slow activation variables, allowing the use of singular perturbation methods for analysis. These models are usually simplified by including only the slow currents, while the slow and fast synaptic interactions are retained, by implicitly assuming that the averaging fast, spike generating variables is legitimate [23–25]. While averaging techniques can reduce biophysical models such as the HH model to a Hopfield like description, it can also mask potentially interesting dynamical modes of the network. Averaged approximations are qualitatively accurate however, if interactions between neurons has only a single time scale.

Finally, we note that even though the CPGs operate autonomously, they are under the control of external influences through the influence of chemicals called neuromodulators [26]. These chemicals, such as acetylcholine, serotonin or adrenaline alter the intrinsic and synaptic properties of CPG neurons (as well as cortical neurons). This level of control renders the temporal patterns of CPGs labile, and several different temporal patterns can be established, without any extensive rewiring of the circuits. A simple example of neuromodulation in our model would be a chemical that altered the strength of the fast synapse, switching the network from a bursting to an *on-off* mode or changing the length of the bursts.

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