Emergent Bursting in Small Networks of Model Conditional Pacemakers in the pre-Bötzinger Complex

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Abstract. This paper summarizes some lessons learned from the computational study of bursting oscillations in small networks of model pre-Bötzinger complex (pBC) neurons.

1 Introduction

While a diversity of dynamic behaviors is observed across different isolated pBC cells, excitatory synaptic coupling promotes synchronized bursting oscillations, consisting of alternating *active phases* of repetitive spiking and *silent phases* of recovery without spikes, in pBC slice preparations. Simulations in networks of model pBC cells show that the dynamic range of bursting is further enhanced by heterogeneity (Butera, Rinzel and Smith 1999b). The focus of this work is on the dynamical mechanisms, based on the interaction of intrinsic cellular properties and synaptic dynamics, that explain these observations. The results presented here (see also Butera, Rubin, Terman, and Smith 2005) also include a novel classification of bursting and spiking activity patterns that emerges from the study of coupled pairs of model pBC cells. Further, the analysis shows that intrinsically bursting cells are not required for network bursting and characterizes how cells that are intrinsically quiescent or tonically active contribute to bursting in a heterogeneous pBC network.

2 Model and Dynamical Systems Analysis

Consider the following model (Model I of Butera, Rinzel, and Smith 1999a):

$$v' = -I_{NaP}-I_{Na}-I_K-I_L-I_{tonic\text{-}e}-I_{syn\text{-}e}-I_{app} \quad (1)$$

$$n' = (n_\infty(v)-n)/\tau_n(v) \quad (2)$$

$$h' = (h_\infty(v)-h)/\tau_h(v), \quad (3)$$

$I_{Na}=g_{Na}m_\infty(v)(1-n)(v-E_{Na})$, $I_K=g_Kn^4(v-E_{K)}$, $I_{NaP}=g_{Na}m_{\infty,P}(v)h(v-E_{Na})$, $I_L=g_L(v-E_L)$, with $x_\infty(v)=(1+\exp((v-\theta_x)/d_x)^{-1}$ and $\tau_x(v)= \tau_x/(\cosh((v-\theta_x)/(2d_x)))$ for $x \in \{h,m,m_P,n\}$. Eqs. 1-3 represent the dynamics of a single pBC cell with a persistent sodium current I_{NaP}. The external input currents in the model consist of an applied stimulus I_{app}, a background excitatory tonic drive $I_{tonic\text{-}e} = g_{tonic\text{-}e}(v-E_{syn})$, and an excitatory synaptic input $I_{syn\text{-}e}=g_{syn\text{-}e}\Sigma s_j(v-E_{syn})$, with summation over the synaptic conductances s_j

associated with presynaptic cells. A complete list of model equations and parameters are specified in the papers of Butera et al. (Butera et al. 1999a; Butera et al. 1999b).

To analyze the above model, note that $\tau_h(v)$ is large, and thus the inactivation h of I_{NaP} evolves much slower than the other variables in the model. This observation suggests the utility of a *fast-slow decomposition* (Rinzel 1987). In this approach, for a single cell, the *fast subsystem* is formed from the (v,n) equations of the model, with the *slow variable* h taken as a constant parameter. The structure of the important dynamic states of the fast subsystem is mapped out over a range of h values; that is, the *bifurcation diagram* of the fast subsystem, with bifurcation parameter h, is generated. This process yields the diagrams shown in Fig. 1. Next, the slow dynamics of h, as given in Eq. 3, is used to sweep the fast subsystem through the relevant dynamic states, which generates a prediction for the dynamics of the full model (Eqs. 1-3). The Butera model is a *square-wave burster* (Rinzel 1987), with activity onset promoted by the deinactivation of the inward current I_{NaP} and with gradual repolarization via the inactivation of I_{NaP}. Similar bursting can be achieved by other combinations of currents that result in an analogous bifurcation structure.

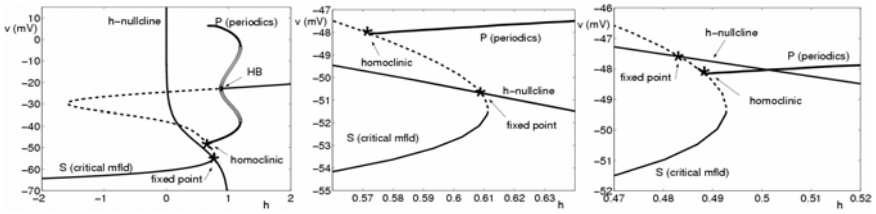

Fig 1. Bifurcation diagrams from a fast-slow decomposition of Eqs. 1-3 for different values of $g_{tonic\text{-}e}$. Left: Solid curves denote stable features, the dashed curve consists of unstable fixed points, and the curves of open circles show the maximum and minimum v along an unstable family of periodics, formed in a Hopf bifurcation (HB). The stable family P of periodics terminates in a homoclinic orbit, with a homoclinic point on an unstable part of the fixed point curve S. Finally, the h-nullcline, along which h'=0, is shown, and a stable fixed point for the full system (Eqs. 1-3), corresponding to quiescence, occurs where this nullcline intersects a stable part of S. Left panel used with permission from J. Best et al. (2005), SIAM J. Appl. Dyn. Syst. 4, 1107-1139. Middle: A zoomed view for larger $g_{tonic\text{-}e}$ shows that the fixed point has moved to an unstable part of S, yet lies below the homoclinic point. Thus, the full system is predicted to show bursting oscillations. Right: For still larger $g_{tonic\text{-}e}$, the fixed point lies above the homoclinic point. Thus, the full system is predicted to show tonic spiking.

3 How synaptic coupling promotes bursting

Increasing $g_{tonic\text{-}e}$ can switch the Butera et al. model from quiescence to bursting to tonic spiking (Butera et al., 1999a). Interestingly, even though the synaptic coupling between pBC cells is also excitatory, introducing synaptic coupling between two tonically active pBC cells can switch them back to burst mode. More generally, as $g_{syn\text{-}e}$ is raised from zero, the range of $g_{tonic\text{-}e}$ over which pBC cells burst initially

expands and then contracts. Moreover, changes in $g_{tonic\text{-}e}$ and $g_{syn\text{-}e}$ induce complex variations in burst characteristics (Butera et al. 1999b).

The key to these results (Best et al. 2005) is the observation that both $g_{tonic\text{-}e}$ and $g_{syn\text{-}e}$ affect the bifurcation structure of the pBC cell's fast subsystem. Consideration of a single self-coupled cell gives a first approximation to the effect of $g_{syn\text{-}e}$. Note from Fig. 1 that the fast-slow decomposition predicts a transition from bursting to tonic spiking when the fixed point of the full system intersects the homoclinic point of the fast subsystem. Increasing $g_{tonic\text{-}e}$ promotes spiking by moving the fixed point to smaller *h* values, such that it may overtake the homoclinic point (Fig. 2). Increasing $g_{syn\text{-}e}$, however, pushes the homoclinic point to smaller *h* values, such that a larger $g_{tonic\text{-}e}$ is needed to attain the bursting-to-spiking transition (Fig. 2; Best et al. 2005). These findings can also be cast in terms of I_{NaP}. Specifically, an elevated $g_{tonic\text{-}e}$ allows the cell to spike with lower I_{NaP} availability and to reach lower voltages on each spike, such that the deinactivation of I_{NaP} on each spike downstroke can balance out its inactivation on each spike upstroke, promoting tonic spiking. Excitatory synaptic coupling also allows for spiking with lower I_{NaP}. However, the synaptic input curtails the downstroke of each spike, such that a net inactivation of I_{NaP} still occurs on each spike and eventually spiking terminates.

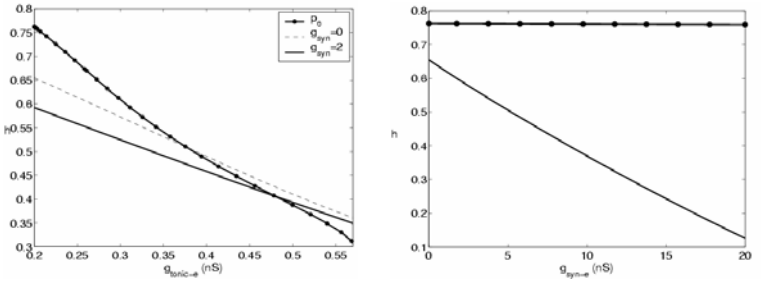

Fig. 2. The parameters $g_{tonic\text{-}e}$, $g_{syn\text{-}e}$ have different effects on the fast subsystem bifurcation structure. Left: As $g_{tonic\text{-}e}$ increases, both the curve of fixed points (p_0 ; solid dotted curve) and the curve of homoclinic points (solid or dashed) move to smaller *h*, but the fixed points overtake the homoclinic points. Left panel used with permission from J. Best et al. (2005), SIAM J. Appl. Dyn. Syst. 4, 1107-1139. Right: As $g_{syn\text{-}e}$ increases, only the homoclinic points (solid) move to smaller *h*, while the fixed points (solid dotted) remain unchanged.

An additional broadening of the burst region as $g_{syn\text{-}e}$ increases results from the fact that synaptic coupling induces spike asynchrony within the synchronized active phases of bursting pairs of coupled pBC cells. Spike asynchrony implies that while both cells are in the active phase, a cell receives strongest synaptic input during the downstroke of its spike. This input mitigates the downstroke, which prevents deinactivation of I_{NaP}, such that the cell is prevented from becoming tonically active. A full analysis of the coupled cell pair requires treatment of a system of two slow variables and is given elsewhere (Best et al. 2005; see also Butera et al. 2005). One outcome of this analysis was the discovery of four different modes of activity in the coupled pBC network, namely two types of bursting (symmetric and asymmetric) and two types of spiking (symmetric and asymmetric), with corresponding differences in burst characteristics. Examples of each pattern are shown in Fig. 3. The

nomenclature refers to the behavior of the slow variables h_1,h_2; in the symmetric case, h_1 and h_2 follow identical but phase-shifted time courses in the active phase, as seen in Fig. 3. The bottom line from this analysis is that the presence of synaptic coupling in networks of pBC cells can introduce a subtle variation in the availability of I_{NaP} across cells, even when the parameter values used for the cells are identical.

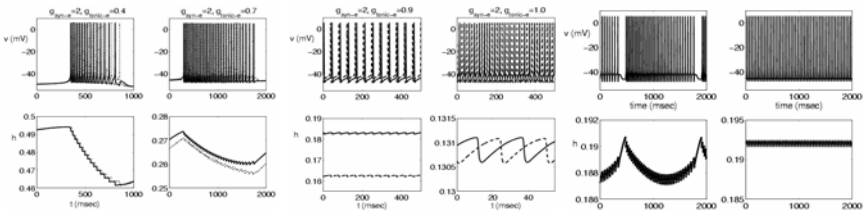

Fig. 3. Different solutions arising for a pair of synaptically coupled model pBC cells, each governed by Eqs. 1-3. For each solution, the top panel shows *v* versus time for both cells, while the bottom shows *h* versus time for both cells. From left to right: symmetric bursting, asymmetric bursting, asymmetric spiking, symmetric spiking (all in a pair of identical cells), bursting, and tonic spiking. The last two columns were generated with the same parameter values but different initial conditions, using a non-identical pair of cells (one cell shown).

4 Synaptic coupling in a heterogeneous network

With mild heterogeneity between the cells, the qualitative finding that different types of bursting and spiking solutions exist at different points in ($g_{tonic\text{-}e}$, $g_{syn\text{-}e}$) parameter space persists. One interesting new result is the existence of a parameter regime for which there is bistability between a bursting and a tonic spiking solution, with initial conditions picking which is observed (Fig. 3). If enough heterogeneity is introduced, the cells may behave qualitatively differently from each other, in the absence of coupling. What activity patterns emerge when the cells are synaptically coupled? The discussion in Section 3 shows that synaptic coupling does not necessarily yield a network behavior that averages the cells' intrinsic behaviors. In recent work, I derived sufficient conditions for network bursting to arise when a quiescent (Q) and a tonically active (T) pBC cell are coupled with synaptic excitation (Rubin 2006). First, the input from the T cell to the Q cell must be strong enough to recruit the Q cell into the active phase yet not strong enough to prevent the Q cell from exiting the active phase after a period of spiking. How strong an input is required depends on the rate of deinactivation of I_{NaP} for the Q cell (see below). Second, the synaptic input from the Q cell to the T cell will inactivate the I_{NaP} of the T cell, relative to its resting level in the absence of coupling. The most subtle point in the analysis is that *bursting requires the resulting additional inactivation to be sufficient such that, once the Q cell enters the silent phase and the synaptic input to the T cell wears off, the T cell cannot continue spiking and therefore falls silent as well.* This outcome requires a sufficiently rapid decay of synaptic input, in addition to sufficient inactivation of I_{NaP}. Finally, note that the T cell will eventually return to the active phase and re-excite the Q cell. The duration of the T cell silent phase sets the time available for

the deinactivation of the Q cell's I_{NaP} before synaptic input arrives and therefore determines, for a given strength of synaptic coupling, how fast a deinactivation is required for the Q cell to be activated again, maintaining the bursting oscillation.

This analysis (Rubin 2006) shows why intrinsically bursting cells are not needed for bursting in a heterogeneous network of synaptically coupled pBC cells. Like the other results discussed here, this finding carries over qualitatively to other models of the same burst class. Clearly, the biological relevance of this work will be enhanced by its extension to larger networks of cells, which is in progress (see also Rubin and Terman, 2002). However, the results of this analysis already suggest some principles that likely apply to synchronized bursting in a heterogeneous pBC population. In particular, intrinsically tonic cells within the network will enhance the robustness of bursting by preventing the network from falling completely silent, as long as these cells can induce a sufficiently strong synaptic excitation to recruit the other cells in the network. At the same time, robust bursting will require the presence of sufficiently many non-tonic cells such that when these cells enter the silent phase, the resulting withdrawal of excitation from the tonic cells will cause them to fall silent as well. Of course, the emergent activity patterns within a larger pBC network will depend on its synaptic connectivity architecture, which remains for future experimental elucidation. In the meantime, computational simulations and mathematical analysis represent powerful tools for exploring activity under a variety of network architectures and intrinsic activity pattern distributions.

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