Qualitative validation of the reduction from two reciprocally coupled neurons to one self-coupled neuron in a respiratory network model

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Abstract The pre-Bötzinger complex of the mammalian brainstem is a heterogeneous neuronal network, and individual neurons within the network have varying strengths of the persistent sodium and calcium-activated nonspecific cationic currents. Individually, these currents have been the focus of modeling efforts. Previously, Dunmyre et al. (J Comput Neurosci 1–24, 2011) proposed a model and studied the interactions of these currents within one self-coupled neuron. In this work, I consider two identical, reciprocally coupled model neurons and validate the reduction to the self-coupled case. I find that all of the dynamics of the two-neuron model network and the regions of parameter space where these distinct dynamics are found are qualitatively preserved in the reduction to the self-coupled case.

Keywords Respiration • pre-Bötzinger complex • Central pattern generator • Bifurcation analysis • Bursting • Slow–fast decomposition

1 Introduction

The pre-Bötzinger complex (preBötC) of the mammalian brainstem is a heterogeneous neuronal network that generates the inspiratory phase of the respiratory rhythm [2, 3]. During synaptic isolation from the rest of the brainstem, the preBötC exhibits network-wide synchronous bursting [2]. This bursting rhythm persists under blockade of chloride-mediated inhibition [4–7]. Neurons within the preBötC are endowed with the calcium-activated nonspecific cationic (CAN) current [8] and the persistent sodium (NaP) current [9]. The CAN current [8, 10–12] and NaP current [9, 13–16] have both been found to be relevant to the rhythmicity of the preBötC. In modeling studies, sodium–potassium pumps were found to enhance the bursting rhythm [17]. We have proposed a model of a preBötC neuron that included the NaP current, CAN current, and sodium–potassium pump [1]. To facilitate analysis, that model considered a self-coupled neuron. However, preBötC neurons do not naturally make autaptic connections. Further, the effects of spike

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asynchrony for reciprocally coupled neurons can be subtle. For instance, in reciprocally coupled, intrinsically tonic neurons, spike asynchrony can expand the range of external input for which the two-cell network bursts [18]. It is not obvious that the reduction to a self-coupled model neuron will fully capture the behavior of the two-neuron network. In this work, I present computational analysis for two identical, reciprocally coupled model neurons and qualify the differences from the self-coupled case.

2 Model

In Dunmyre et al. [1], we introduced a model of a single self-coupled neuron where the dynamics depended on both the NaP and CAN currents, as well as a sodium–potassium pump. Here, I do focus on the same basic model but instead consider two model neurons reciprocally coupled via excitatory synapses. For $i, j \in \{1, 2\}$, the dynamics for model neuron i are given by:

$$\dot{v}_i = -\{I_L(v_i) + I_{Na}(v_i, h_i, m_i) + I_K(v_i, n_i) + I_{NaP}(v_i, hp_i) + I_{CAN}(v_i, Ca_i) + I_{pump}(Na_i) - I_{app} + I_{syn}(v_i, s_{j \neq i})\} / C_m \quad (1)$$

$$\dot{h}_i = (h_\infty(v_i) - h_i) / \tau_h(v_i) \quad (2)$$

$$\dot{m}_i = (m_\infty(v_i) - m_i) / \tau_m(v_i) \quad (3)$$

$$\dot{n}_i = (n_\infty(v_i) - n_i) / \tau_n(v_i) \quad (4)$$

$$\dot{Ca}_i = \varepsilon_{Ca}(k_{IP_3, s_{j \neq i}} - k_{Ca}(Ca_i - Ca_{base})) \quad (5)$$

$$\dot{Na}_i = \alpha(-I_{CAN}(v_i, Ca_i) - I_{pump}(Na_i)) \quad (6)$$

$$\dot{hp}_i = \varepsilon_{hp}(hp_\infty(v_i) - hp_i) / \tau_{hp}(v_i) \quad (7)$$

$$\dot{s}_i = ((1 - s_i)s_\infty(v_i) - k_s s_i) / \tau_s \quad (8)$$

where ε_{Ca} , α , and ε_{hp} are small and cause Ca_i , Na_i , and hp_i to evolve on a separate timescale from v_i , h_i , m_i , n_i , s_i (see [Appendix](#)). Also, $I_L(v) = g_L(v - E_L)$, $I_{Na}(v, h, m) = g_{Na}m^3h(v - E_{Na})$, $I_K(v, n) = g_Kn^4(v - E_K)$, $I_{syn}(v, s) = g_{syn}s(v - E_{syn})$, $I_{CAN}(v, Ca) = g_{CAN}(v - E_{CAN}) / (1 + \exp((Ca - k_{CAN}) / \sigma_{CAN}))$, $I_{NaP}(v, hp) = g_{NaP}m_{p, \infty}(v)hp(v - E_{Na})$, $I_{pump}(Na) = \phi(Na) - \phi(Na_{base})$, where $\phi(x) = x^3 / (x^3 + k_{Na}^3)$. All remaining functions and parameter values can be found in the [Appendix](#). Integration of the model was performed by a C++ implementation of the CVODE routine from SUNDIALS [19], interfaced with MATLAB via the MEX compiler (The MathWorks, Natick, MA, USA). Absolute and relative tolerances were set to 10^{-6} .

The model was calibrated such that when $g_{NaP} = 0$ the model behaves similarly to the Rubin–Hayes model [17], that is, it can produce bursts featuring a period of depolarization block (e.g., Fig. 1a). When $g_{CAN} = 0$, the model behaves like the Butera model [20] because when g_{NaP} is varied the model produces quiescent solutions, square-wave bursting solutions, or tonic activity. Thus, the model may provide a good framework for understanding the interactions of the CAN and NaP currents. However, in Dunmyre et al. [1], for simplicity, we performed analysis on a self-coupled system (that is, $x_i = x_j$ for all $x \in$

Fig. 1 Example model output with $g_{\text{NaP}} = 4$, $g_{\text{CAN}} = 4$, and initial conditions $(v_1, h_1, m_1, n_1, \text{Ca}_1, \text{Na}_1, \text{hp}_1) = (v_2, h_2, m_2, n_2, \text{Ca}_2, \text{Na}_2, \text{hp}_2) = (-60, 1, 0, 0, \text{Ca}_{\text{base}}, 0, \text{Na}_{\text{base}})$. Model output for v_1 is shown in *red*, while model output for v_2 is shown in *black*. Initially, the solutions remain quite close together; note that even at $t = 11,000$ ms the traces are virtually indistinguishable in **a**. However, eventually the model neurons separate, though they still burst at roughly the same time, with essentially the same burst duration (**b**)

$\{v, h, m, n, \text{Ca}, \text{Na}, \text{hp}, s\}$). In this work, I compare the self-coupled system to a reciprocally coupled system of two model neurons that are identical to each other except for their initial conditions. When the homogeneous, reciprocally coupled pair is perfectly synchronized, it behaves precisely like a self-coupled neuron, hence the reduction to the self-coupled case leaves g_{syn} and k_{IP_3} unchanged. An important figure in Dunmyre et al. [1] shows the effect of modulating g_{NaP} , the conductance of the NaP current, and g_{CAN} , the conductance of the CAN current, for the self-coupled model neuron. To generate a similar figure, in Section 3 I vary g_{NaP} and g_{CAN} for the reciprocally coupled network. I demonstrate that all of the regions of qualitatively distinct dynamics are preserved, and no new dynamics are observed by reducing the reciprocally coupled pair of model neurons to a single self-coupled neuron.

3 Dynamics of reciprocally coupled model neurons

In this section, I qualitatively categorize the various dynamic regimes that arise from the two-neuron model given by Eqs. 1–8 and compare them against the self-coupled case. The first important observation is that spike synchrony between the model neurons is unstable. I illustrate this fact with simulation data. In Fig. 1, I begin a solution with identical initial conditions corresponding to the silent phase. Initially, the solutions behave as the self-coupled case (Fig. 1a), but eventually the voltage traces separate and spike synchrony is broken (see Fig. 1b).

To classify the dynamics of the two-neuron network, I use the scheme as described in Dunmyre et al. [1] to qualify the individual model neurons within the network as quiescent, bursting, or tonically active. First I allow a transient of 10,000 ms. I say that the model neuron spikes each time $v_i(t) = 0$ and $v_i'(t) > 0$. This condition is achieved by spikes but not by the sub-threshold oscillations observed in simulations. After the transient, I record the spike times for the next 9,999 ms. If there are no spikes after the transient, the model neuron is classified as quiescent. Otherwise, the algorithm records the times between spikes, also known as the interspike intervals (ISIs). Due to prolonged silent phases, bursting model neurons will have ISIs that have a very high standard deviation. On the other hand, tonic

activity produces ISIs with a relatively low standard deviation. If the ISIs of the model neuron have a standard deviation less than 10 ms, the algorithm classifies the model neuron as tonically active; otherwise, it is bursting. The threshold of 10 ms was chosen based on the self-coupled case [1]. Even though the solution in Fig. 1 does not have perfect synchrony, both model neurons burst at roughly the same time. The important feature of the preBötC is that the neurons burst synchronously; the neurons need not be perfectly synchronized as long as the active phases overlap sufficiently.

When both model neurons are classified as bursting, I consider a time window where each model neuron bursts exactly once. In this window, let F_1 be the time of the first spike of the first model neuron to enter the active phase, and similarly, let L_1 be the time of the last spike of the first model neuron to exit the active phase. Note that F_1 and L_1 need not correspond to the same model neuron. Let F_2 be the first spike of the second model neuron to enter the active phase, and let L_2 be the last spike of the second model neuron to exit the active phase. If $F_2 < L_1$, there is some overlap of the active phases; otherwise, the network is said to exhibit anti-phase bursting. I never observed anti-phase bursting in these simulations. When there is overlap in the active phases, I define the duration of the shared active phase as $S = L_1 - F_2$. Also, I define the total active duration as $T = L_2 - F_1$. I use the ratio $R = S/T$ as a measurement of burst synchrony; if $R > 0.4$, I declare the bursts to be in-phase; otherwise, the bursts are out-of-phase.

At each grid point of Fig. 2, the initial conditions for each neuron were drawn from a normal distribution corresponding to quiescence. Specifically, each neuron was

Fig. 2 Partitioning of parameter space based on resultant dynamics from a network of reciprocally coupled model neurons. Both model neurons start with slightly different initial conditions corresponding to quiescence, but otherwise all parameters are identical. *Dark blue dots* correspond to solutions where both model neurons remained quiescent. *Black dots* correspond to both model neurons having tonic activity. Model neurons with in-phase bursting are shown with *green dots*. The relatively few times when the model neurons have out-of-phase bursting, the dot is *colored light blue*. No out-of-phase bursts that were observed were anti-phase; their classification as out-of-phase seems to be a result of one model neuron exhibiting an extra spike before burst termination, which causes the total active phase to increase. Dots are *colored red* when both model neurons were bursting as defined by the standard deviation criterion, but the algorithm was unable to determine the phase relation. *Magenta dots* correspond to the situation where one model neuron is identified as tonically active and the other is classified as bursting. In each case, the bursting neuron is actually tonically active. These few errors in the automatic classification scheme are insignificant; they result from irregular ISIs during tonic activity, and are included so that the figure may be transparently reproduced. The boxed-dashed region marked * features bursts similar to Fig. 3c2. Reproduced from Dunmyre et al. [1], with kind permission from Springer Science+Business Media B.V.

initialized with $(v_i, h_i, m_i, n_i, Ca_i, Na_i, hp_i) = (N(-60, 5), N(1, 0.1), N(0.04, 0.1), N(0, 0.1), N(0, 0.0001), N(0.05, 0.01), N(0, 0.1), N(5, 0.1))$, where $N(x, y)$ is a normal distribution with mean x and standard deviation y . Even though some initial conditions drawn from the above distribution will not be physically relevant, the solutions quickly become physical. Note that qualitatively similar results are expected if, instead of drawing from the above distribution for each grid point, initial conditions were drawn once from the above distribution and then used for all grid points. I then used the above classification algorithm to partition the (g_{NaP}, g_{CAN}) parameter space based on the result of the integration. For sample model output from the various regions of Fig. 2, refer to Fig. 3. Regions II, *, III, and V have dynamically distinct bursting patterns. Region IV and region VI both contain tonically active solutions; the only distinction is that in region VI the CAN current is active in both model neurons, which causes the spiking to occur with higher frequency (see Fig. 3d2, f2). The boundaries of region * in Fig. 2 are where I have observed the existence of solutions with dynamics similar to Fig. 3c2. For (g_{NaP}, g_{CAN}) in region VI and above the dashed white line, there is bistability between bursting solutions and tonic solutions with low frequency (e.g., Fig. 3f2), which makes identifying boundaries of region * difficult. This bistability is also seen in the self-coupled case, but spike asynchrony makes the tonically active solutions more prominent here.

Fig. 3 Model output for both the self-coupled case as well as the case for a reciprocally coupled pair of model neurons. *a1–f1* (blue traces) represent the self-coupled case, while *a2–f2* (red and black traces) represent the reciprocally coupled case. Specifically, *a2* corresponds to model output from region II of Fig. 2, *b2* to region III, *c2* to region *, *d2* to region IV, *e2* to region V, and *f2* to region VI. Although it cannot be seen at this resolution, the spikes in *e2* are anti-phase. Note that all of the dynamics of the reciprocally coupled pair are observed in the self-coupled model case and vice-versa

The preceding classification algorithm can be used to partition the self-coupled case. In Fig. 4, I compare the differences between Fig. 2 and the partitioning for the self-coupled case. The primary difference between the self-coupled case and Fig. 2 is the location of region *. Bursting patterns seen in b1, b2, c1, and c2 of Fig. 3 require activation of the CAN current. Activation of the CAN current relies on sufficient increase of Ca_i . This Ca_i buildup is closely related to the spiking frequencies of solutions when they enter the active phase; higher frequencies lead to faster buildup. Asynchronous spiking may lead to lower spiking frequencies for the reciprocally coupled pair because each neuron receives the most synaptic input when it is in the trough between spikes. On the other hand, in the self-coupled case, the neuron receives maximal synaptic input when it is at the peak of a spike. The differences between these two cases is subtle and is outside of the scope of this work. Numerically, it is observed that the self-coupled solution spikes at a higher frequency than the solution for the reciprocally coupled pair. The spiking frequency is directly proportional to g_{NaP} ; therefore, in the self-coupled case, activation of the CAN current occurs for lower g_{NaP} than it does for the reciprocally coupled pair. This explains the difference in the location of region *. Also, the initiation of each burst requires sufficient deinactivation of the NaP current. The inactivation variable for the NaP current, hp , multiplies g_{NaP} in the definition of $I_{NaP}(v)$. Thus, increasing g_{NaP} shortens the silent phase between bursts, which explains the timing difference in c1 and c2 of Fig. 3. I also note that, in Fig. 4, the range of g_{NaP} for which there are square-wave bursting solutions of the reciprocally coupled pair (region II) seems to be smaller than the corresponding region for the self-coupled case. In general, introducing asynchronous spiking expands the range of external input and perhaps other parameters, for which square-wave bursting solutions are observed in traditional models featuring only the NaP current [18]. It has not been quantified whether g_{NaP} is one such parameter. Nevertheless, I have observed bistability between tonically active solutions and square-wave bursting solutions near the low g_{NaP} border of region VI, as well as in region

Fig. 4 Figure 2 with partitioning of the self-coupled case overlaid for comparison. *Yellow lines* indicate the boundaries of various regions of dynamics for the self-coupled case. Although positions of regions have shifted, all regions of activity in Fig. 2 are seen in the self-coupled case and vice versa. The most significant change is region *, which shifted to a much higher range of g_{NaP} due to the spike asynchrony. Reproduced from Dunmyre et al. [1], with kind permission from Springer Science+Business Media B.V.

II, which explains why the square-wave bursting region seems smaller for the reciprocally coupled pair.

The unified model has not been calibrated to capture specific voltage traces; rather, it seeks only to qualitatively describe the bursting behavior of preBötC neurons. Numerically, it is found that the reduction from the two reciprocally coupled model neurons to the self-coupled case does not significantly impact statistics such as the burst period, which indicates that the self-coupled case indeed can inform us about the reciprocally coupled case and may help elucidate the bursting rhythm of the preBötC. A summary of some results from Dunmyre et al. [1] can illustrate how one can use insights from the self-coupled case to understand bursting in the reciprocally coupled case. Bursts are primarily initiated and terminated by the drift in the slow variables Ca_i , Na_i , and hp which, by virtue of geometric singular perturbation theory, can be treated as bifurcation parameters for the fast subsystem $(v_i, h_i, m_i, n_i, s_i)$. For low g_{NaP} , corresponding to region II, a burst is initiated when hp crosses a particular threshold corresponding to a fold bifurcation in the fast subsystem, and the burst is terminated when hp later decreases through a homoclinic bifurcation of the fast subsystem. Spike asynchrony modulates the hp coordinate of the homoclinic bifurcation differently from the self-coupled case; however, for the g_{syn} considered here and low g_{NaP} , decreasing hp will always terminate the burst. This accounts for the similarities in region II for both the self-coupled and reciprocally coupled cases.

I have already discussed how spike asynchrony requires higher values of g_{NaP} to cause a sufficient Ca_i buildup to ignite the CAN current. In the self-coupled case, when the CAN current turns on, the spike frequency dramatically increases, which causes Ca to build up even higher. Eventually Ca increases through a supercritical Andronov–Hopf bifurcation of the fast subsystem, leading to depolarization block. Meanwhile, the CAN activity has increased the Na variable, which corresponds to increasing the Ca coordinate of the homoclinic bifurcation that must be crossed to terminate the burst. Once in depolarization block, the self-coupled system stops spiking, and thus s decays, resulting in a decay of Ca . Decaying Ca crosses the homoclinic bifurcation of the fast subsystem before returning to spiking behavior. This mechanism generalizes to the reciprocally coupled case. Suppose neuron 1's CAN current is activated first. The activated CAN current causes neuron 1 to bombard neuron 2 with synaptic signals (s_1 is high), leading neuron 2's CAN current to ignite, which causes both s_2 and Na_2 to significantly increase. Elevated s_2 further elevates Ca_1 (and so also elevates Na_1); eventually, Ca_1 is high enough to put neuron 1 in depolarization block by crossing the Andronov–Hopf bifurcation of the fast subsystem. During depolarization block, $s_1 = 0$, so that Ca_2 decreases, and since Na_2 is elevated, neuron 2's burst terminates as Ca_2 decreases through the homoclinic bifurcation of the fast subsystem. When neuron 2's burst terminates, $s_2 = 0$, which causes Ca_1 to decrease and eventually terminate neuron 1's burst.

In Dunmyre et al. [1], we also provide analysis for the boundaries of the various regions of dynamically distinct activity. For instance, we identify the mechanism of crossing from region III to region IV by decreasing g_{CAN} . The mechanism involves the Andronov–Hopf bifurcation of the fast subsystem when Ca is treated as a bifurcation parameter. When g_{CAN} is decreased, the Ca coordinate of the Andronov–Hopf bifurcation increases, eventually blowing up for finite g_{CAN} . With the Andronov–Hopf bifurcation unattainable by Ca , the self-coupled cell has no way to enter depolarization block and hence terminate its burst. Thus, the g_{CAN} value for which this blowup occurs depends on g_{NaP} and can be used to approximate the boundary between regions III and IV. This will carry over into the reciprocally coupled case. If g_{CAN} is sufficiently low, such that the Ca_i coordinates of

Andronov–Hopf bifurcations of the fast subsystems are beyond the maximal attainable values of Ca_i , the system will cease to exhibit synchronous bursting because neither neuron will enter depolarization block, which is required for the other neuron's Ca_i to begin to decrease and eventually terminate the bursts. Similar insights from Dunmyre et al. [1] can be applied to the transitions between all of the regions of Fig. 2.

These arguments can be extended to the case when the reciprocally coupled neurons are not from the same region of Fig. 2. For instance, a reciprocally coupled pair consisting of a region III neuron and a region IV neuron may still exhibit bursting. For region III and region IV neurons, the CAN current of both neurons will eventually become activated. The region III neuron will go into depolarization block, and this sudden loss of synaptic output to the region IV neuron could cause it to suddenly return to the silent phase. Hence, the sudden loss of synaptic input to the region III neuron will cause its return to the silent phase.

4 Discussion

In this work, I analyze a model of a small preBötC network where each model neuron includes the CAN and NaP currents, as well as a sodium–potassium pump. Previously, we simplified the analysis of the model network by considering a single self-coupled model neuron [1]. In this work, I validate the reduction of the pair of reciprocally coupled neurons (henceforth called the “network”) to a single self-coupled one. This reduction is only valid when both neurons are identical in all parameters except for initial conditions.

Perfect synchrony is at least a weakly unstable state for the network. However, it is not necessary for preBötC neurons to be perfectly synchronous; as long as the active phases have enough overlap, I consider the network to be synchronized. Indeed, almost all bursts observed in this network had sufficient overlap to be called synchronous bursts. To validate the analysis of the self-coupled model neuron, I reproduced an important figure from Dunmyre et al. [1] in the context of the network (Fig. 2). I partitioned the network parameter space into seven different regions containing distinct dynamics. All of the dynamics observed in the network are qualitatively observed in the self-coupled setting and vice-versa (Fig. 3). I also compared the boundaries of the regions in the network and self-coupled case. The regions for the network case are qualitatively similar to the self-coupled case (Fig. 4), which completes the validation of our reduction to the self-coupled case. Numerical exploration suggests that similar results are obtained when g_{syn} and k_{IP_3} are varied.

There are several ways to extend this work. In Dunmyre et al. [1], we elucidate how the self-coupled system produces bursts by understanding the bifurcation structures of the fast subsystem of the individual neuron. As discussed at the end of Section 3, the arguments made in Dunmyre et al. [1] can be extended to consider coupling of neurons from regions of Fig. 2. Precisely quantifying the effects of spike asynchrony on each neuron's three-dimensional slow subsystem is required to produce computational or analytic boundary curves for many of the regions of Fig. 2. It is also required, therefore, to explicitly describe the activity patterns of a heterogeneous pair of reciprocally coupled preBötC neurons, which is an important step in understanding the activity of large networks of preBötC neurons.

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Appendix: Function definitions and parameter values

In Eqs. 1–8, which were introduced in [17, 20], for each $x \in \{h, hp, m_p, n, s\}$, the function $x_\infty(v)$ takes the form $x_\infty(v) = \{1 + \exp[(v - \theta_x)/\sigma_x]\}^{-1}$. Also for each $x \in \{h, hp, m, n\}$, the function $\tau_x(v)$ is given by $\tau_x(v) = \bar{\tau}_x / \cosh[(v - \theta_x)/(2\sigma_x)]$. Table 1 shows the parameter values used for Eqs. 1–8. Many of these values were used in [17] or [20], though some were changed slightly to maintain appropriate dynamics in limiting cases of the present model. Values of g_{NaP} and g_{CAN} are discussed throughout the text so these parameters do not appear in Table 1.

Table 1 Common parameter values for Eqs. 1–8

Parameter	Value
α	$6.6 \times 10^{-5} \text{ mM pA}^{-1} \text{ ms}^{-1}$
C_{abase}	$0.05 \text{ }\mu\text{M}$
C_m	45 pF
E_K	-75 mV
E_{Na}	65 mV
ε_{Ca}	0.0007
ε_{hp}	0.001
E_{CAN}	0 mV
E_{syn}	0 mV
g_K	30 nS
g_L	3 nS
g_{Na}	160 nS
g_{syn}	2.5 nS
I_{app}	0 mV
k_{IP_3}	$1,200 \text{ }\mu\text{M ms}^{-1}$
k_s	1
k_{Na}	10 mM
k_{Ca}	22.5 ms^{-1}
k_{CAN}	$0.9 \text{ }\mu\text{M}$
Na_{abase}	5 mM
r_{pump}	200 pA
σ_{CAN}	$-0.05 \text{ }\mu\text{M}$
σ_h	5 mV
σ_{hp}	6 mV
σ_m	-8.5 mV
$\sigma_{m,p}$	-6 mV
σ_n	-5 mV
σ_s	-3 mV
$\bar{\tau}_h$	15 ms
$\bar{\tau}_{hp}$	1 ms
$\bar{\tau}_m$	1 ms
$\bar{\tau}_n$	30 ms
τ_s	15 ms
θ_h	-30 mV
θ_{hp}	-40 mV
θ_m	-36 mV
$\theta_{m,p}$	-40 mV
θ_n	-30 mV
θ_s	15 mV
E_L	-61 mV

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