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Conflicting effects of excitatory synaptic and electric coupling on the dynamics of square-wave bursters

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Abstract

Using two-cell and 50-cell networks of square-wave bursters, we studied how excitatory coupling of individual neurons affects the bursting output of the network. Our results show that the effects of synaptic excitation vs. electrical coupling are distinct. Increasing excitatory synaptic coupling generally increases burst duration. Electrical coupling also increases burst duration for low to moderate values, but at sufficiently strong values promotes a switch to highly synchronous bursts where further increases in electrical or synaptic coupling have a minimal effect on burst duration. These effects are largely mediated by spike synchrony, which is determined by the stability of the

in-phase spiking solution during the burst. Even when both coupling mechanisms are strong, one form (in-phase or anti-phase) of spike synchrony will determine the burst dynamics, resulting in a sharp boundary in the space of the coupling parameters. This boundary exists in both two cell and network simulations. We use these results to interpret the effects of gap-junction blockers on the neuronal circuitry that underlies respiration.

Keywords

Pacemaker neuron; Square-wave bursting; Synchronization; Bifurcation analysis

1 Introduction

The dynamics of a neural network depend on a number of biophysical mechanisms which may operate at distinct time-scales. For example, the action potential (or spike) is about one millisecond long, and is often considered the fundamental unit of neural signaling. Bursting, recurring episodes of the firing of a “burst” of action potentials followed by a period of quiescence, contributes to the dynamics of a neural network on a broader time scale, from hundreds of milliseconds to seconds.

The activity pattern of a given neuronal network also depends on signaling among neurons, primarily chemical and electrical coupling. Coupling influences network dynamics via direct biophysical mechanisms (e.g. reciprocal inhibition in a half-center oscillator) and through population effects (e.g. changes in spike synchrony as a function of synaptic kinetics). We investigated the dynamics of a simulated excitatory network of bursting neurons coupled with both excitatory synaptic coupling as well as electrical, i.e. gap-junction, coupling. Our results show that synaptic and electric coupling have different effects on burst dynamics and spike synchrony within the burst, which lead to dramatic changes in cell behavior when both of these couplings are present. In particular, we will show that when both coupling mechanisms are strong, there is no compromise in the preferred dynamics of one mechanism vs. the other. Rather, a preferred mode will always dominate, both in network as well as two-cell simulations.

Many previous studies have separately addressed the dynamics of electrical and synaptic coupling on so-called square-wave bursters. A series of papers by Sherman and Rinzel in the early 1990s studied the dynamics of modeled pancreatic beta cells coupled via gap junctions (Sherman and Rinzel 1991, 1992; Sherman 1994). These cells have a bursting mechanism similar to the one we are studying in this paper, and their studies focused on the dynamics of individual cells as well as networks. The work presented here is an integration and extension of those studies. While the ion channel mechanisms are distinct from the model presented here, both our model and the one they studied can be classified as “square wave bursters” with qualitatively similar dynamics (Bertram et al. 1995; Izhikevich 2000). We briefly summarize these papers and their relationship to the present study.

Sherman and Rinzel (Sherman and Rinzel 1991) found that the burst period of an electrically coupled network of bursters first increases and then decreases, as the electrical coupling was increased from zero. Later they studied the same phenomena in a pair of electrically coupled cells (Sherman and Rinzel 1992) and showed that when electrical coupling was increased from zero, the period of bursting increased (vs. that at zero) and that the spikes during the burst were firing in anti-phase. Sherman performed a more detailed bifurcation analysis of two electrically coupled bursting cells and illustrated both qualitatively and geometrically how anti-phase spiking leads to longer burst periods (Sherman 1994). More recent work has shown that this weak coupling phenomenon is also

seen in models of dopaminergic neurons (Komendantov and Canavier 2002). The emphasis of all of these studies was on the dynamics of anti-phase spiking at weak coupling strengths and their effects on prolonging the burst period. Furthermore, none of these papers considered the distinct roles of electrical vs. synaptic coupling on the stability and topology of the in-phase and anti-phase spiking solutions and their relationship to bursting.

In this work we investigate the combined effect of synaptic and electrical coupling on the dynamics of a simulated network of bursting neurons coupled with both excitatory synaptic (G_{syn}) and electrical, i.e. gap-junction (G_{gap}), coupling. Our results show that synaptic and electric coupling have opposing effects on both burst dynamics and spike synchrony within a burst. These opposing effects lead to dramatic changes in both cell and network behavior when both of these couplings are present. We then perform a quasi-steady state bifurcation analysis of a two-cell network in which both G_{syn} and G_{gap} were varied. Finally, we expand our two-cell results to network level simulations to assess the effect of varying G_{syn} and G_{gap} on network dynamics and network-level synchrony, including simulations of experiments in pharmacologically reduced electrical coupling. To assess changes in network synchrony, we introduce a metric that predicts the convergence of the bursting trajectory onto distinct periodic solution branches. In particular, we show that when both coupling mechanisms are strong, there is no compromise in the preferred dynamics of one mechanism vs. the other. Rather, a preferred mode will always dominate, both in network as well as two-cell simulations. Preliminary results of this work have previously appeared in abstract form (Wright and Butera 2006a, b).

2 Methods

Two-neuron simulations and bifurcation analysis of two-neuron simulation results were conducted with XPP/AUT (Ermentrout 2002). Network-level simulations ($N=50$) were conducted with NEURON (Hines and Carnevale 1997). Simulations were based on a previously developed model of an inspiratory neuron in the pre-Bötzinger complex (Purvis et al. 2007). Identical neuron models were connected with all-to-all excitatory synaptic (Butera et al. 1999; Purvis et al. 2007) and gap-junction couplings. Values of electrical and synaptic coupling are specified where needed, otherwise nominal parameter values were adopted from previous work (Purvis et al. 2007).

The voltage of each cell is described by following equation:

$$C_m \frac{dV_i}{dt} = - (I_{K_i} + I_{Na_i} + I_{NaP_i} + I_{leak_i} + I_{syn_i} + I_{gap_i})$$

where the currents are given by:

$$I_{K_i} = g_K n_i^4 (V_i - V_K)$$

$$I_{Na_i} = g_{Na} m_{\infty_i}^3 (1 - n_i) (V_i - V_{Na})$$

$$I_{NaP_i} = g_{NaP} p_{\infty_i} h_i (V_i - V_{Na})$$

$$I_{leak_i} = g_{leak} (V_i - V_{leak})$$

$$I_{syn_i} = G_{syn} \sum_{j \neq i} s_j (V_i - V_{syn})$$

$$I_{gap_i} = G_{gap} \sum_{j \neq i} (V_i - V_j)$$

Here the parameter g represents the maximal conductance of the appropriate current (Na , K , and NaP), while s , n and h are activation and inactivation variables.

The synaptic activation variable s can be found as:

$$\frac{ds_i}{dt} = \frac{(1 - s_i) H_i(V) - ks_i}{\tau_s(V)}$$

n and h , are described by the following equation:

$$\frac{dx}{dt} = \frac{x_{\infty}(V) - x}{\tau_x(V)}$$

where $x_{\infty}(V)$ is the steady state activation/inactivation curve and τ_x is the voltage-dependent time constant. The steady state activation/inactivation curves (m , n , h , p) and synaptic activation function $H(V)$ are modeled as sigmoids, with x representing m , n , h , p or H :

$$x_{\infty}(V) = \frac{1}{1 + \exp\left(\frac{V - V_x}{s_x}\right)}$$

while the time constant is modeled as follows

$$\tau_x(V) = \frac{\bar{\tau}_x}{\cosh\left(\frac{V - V_x}{2s_x}\right)}$$

V_x , s_x , and $\bar{\tau}_x$ for each current are as follows: $V_m = -34$ mV, $s_m = -5$ mV, $V_n = -29$ mV, $s_n = -4$ mV, $V_p = -45.1$ mV, $s_p = -5$ mV, $V_h = -53$ mV, $s_h = 6$ mV, $V_s = -10$ mV, $s_s = -5$ mV, $\bar{\tau}_n = 10$ ms, $\bar{\tau}_s = 5$ ms, $\bar{\tau}_h = 10000$ ms.

Other parameter values include the reversal potentials, $V_{Na} = 50$ mV, $V_K = -85$ mV, $V_{syn} = 0$ mV, $V_{leak} = -58$ mV; the membrane capacitance, $C_{ms} = 21$ μ F; the conductances $g_K = 11.2$ nS, $g_{Na} = 28$ nS, $g_{NaP} = 2.8$ nS, $g_{leak} = 2.8$ nS; synaptic constant $k = 1$.

Simulations were run for at least 160 s of simulation time. To eliminate initial transient network activity, results from the first 60 s of all simulations were discarded. When

classifying the type of synchrony observed in paired simulations, we considered bursts to be in-phase if the traces of both cells were essentially identical during the entire burst. Any phase difference during the burst was considered anti-phase synchrony. Simulation data were analyzed using custom MATLAB scripts.

When analyzing network synchrony over the time course of a single network-wide burst, a spike deviation index (SDI) was used to calculate the degree of spike-level alignment in firing times. The calculation of SDI can be summarized as follows. For each spike in the simulation, a value $d(i,t)$ exists which is a measure to how closely in time the other neurons in the simulation fired to the spike in neuron i at time t . Assuming there are N neurons in the network, let t_j be the spike time in neuron j that is closest in time, forward or backward, to the reference spike in neuron i . $d(i,t)$ is the standard deviation of the $N-1$ t_j values calculated for the reference spike in neuron i that fired at time t . The spike deviation index (SDI) is the average of $d(i,t)$ calculated for each spike in each neuron of the simulation. This metric was not intended to be a rigorous definition of spike-level synchrony, but rather to easily distinguish at a population level in-phase synchrony (SDI is near 0) from splay-phase synchrony (SDI is on the order of many milliseconds), which is analogous to anti-phase synchrony in the two-neuron case.

3 Results

3.1 Synaptic and electric coupling modulate burst duration through distinct dynamic mechanism in paired-cell simulations

To analyze the effect of synaptic and electric coupling on square-wave bursters, we varied the parameters for synaptic (G_{syn}) and electric (G_{gap}) coupling in two-cell and 50-cell networks. All cells in the simulations were identical. The key findings for two-cell simulations are shown in Fig. 1, where the top portion of each panel show the membrane voltage profile, the middle portion show the single burst, and the bottom portion show the bifurcation diagrams of the system.

Figure 1(a–c) shows simulations with a fixed G_{syn} (3 nS) and varying G_{gap} . For $G_{\text{gap}}=0$, the burst initially starts with the two neurons firing action potentials in-phase, but this synchrony is eventually lost within the first few action potentials of the burst (Fig. 1(a)). Increasing G_{gap} from zero to 0.5 nS results in an increase in burst duration, with spikes within the burst remaining in anti-phase (AP). Further increase in G_{gap} shortened the burst duration and made the two neurons fire action potentials in-phase (IP) during the burst (Fig. 1(c)). Therefore, in a paired-neuron scenario, spike synchrony within a burst is anti-phase when G_{gap} is less than some critical value. For larger values of electric coupling, the spike synchrony changes to in-phase.

Panels D through F of Fig. 1 illustrate the results of simulations with a fixed G_{gap} and varying G_{syn} . Increasing G_{syn} in this scenario leads only to progressive increases in burst duration associated with a loss of in-phase spike synchrony. Unlike varying G_{gap} , no decrease in burst duration was observed.

3.2 Increased electrical coupling promotes a transition from AP to IP bursting, but increased synaptic coupling promotes a transition from IP to AP bursting

To understand the dynamical mechanisms of synaptic and electric coupling, we conducted a quasi-steady state bifurcation analysis of the two-neuron model employing the technique of fast-slow decomposition (Rinzel 1985; Bertram et al. 1995; Izhikevich 2000), using the slow variable h as a bifurcation parameter. The variable h accounts for the slow inactivation of an excitatory (depolarizing) persistent sodium current in our neuron model and is responsible for burst termination (Butera et al. 1999). This form of analysis is comparable to that used in

previous studies of square-wave bursters for both single cells as well as pairs of coupled cells that have electrical coupling (Sherman 1994; De Vries et al. 1998).

With no electrical coupling (Fig. 1(a)), two sub-critical Hopf bifurcations corresponding to anti-phase (AP, red) and in-phase (IP, black) spiking, as shown before (Sherman 1994; De Vries et al. 1998). Both periodic branches originate from Hopf bifurcations in the increasing h direction (right) with unstable periodic orbits. At a limit point (saddle node of the periodic solutions), the AP and IP solutions continue in the decreasing h direction (left), and both branches terminate at the equilibrium solution branch. Bursting occurs within this region of bistability, where both periodic and equilibrium solutions coexist. The region of bistability is necessary for the existence of square-wave bursting (Bertram et al. 1995; Izhikevich 2000).

When G_{gap} is zero, the region of bistability consists of the stable AP branch and the lower portion of the equilibrium solution branch of the z-shaped curve (Fig. 1 (a)). Since the IP branch is unstable in this region, the bursting trajectory follows the stable AP branch resulting in anti-phase solutions (Sherman and Rinzel 1992).

As G_{gap} increases, the position of the IP branch does not change, but the whole AP branch is shifted to the left, extending the region of bistability; an increase in G_{gap} has the opposite effect on stability of periodic branches. The left part of the IP branch gains stability (Fig. 1(b), black thick portion) while the left part of the AP branch becomes unstable (Fig. 1(b), thick red portion). As G_{gap} increases even more, the entire AP solution branch loses stability and shifts to the left. As a result, the burst trajectory follows the fully stable IP branch (Fig. 1(c), thick black portion). Taken together, these results suggest that an increase in G_{gap} promotes a transition from anti-phase spiking to in-phase spiking.

Varying G_{syn} with a fixed value of G_{gap} has a qualitatively different effect on the dynamics of a two-cell network. As shown in Fig. 1(d–f), an increase in G_{syn} affects neither position nor stability of the AP branch. However, as G_{syn} increases, the IP branch loses the stability of its left region (Fig. 1(d–f), thick black portion), making the AP branch the only available stable periodic solution to coexist with the stable equilibrium solution.

The bifurcation diagrams presented in Fig. 1(d–f) demonstrate that for a viable range of h values, the bursting trajectory converges to the IP branch if it is available and stable. For example, in the bifurcation diagram shown in Fig. 1(d), the burst trajectory follows the IP solution. As G_{syn} increases, the bursting trajectory no longer interacts with the IP branch, and converges to the AP periodic branch on the left (Fig. 1(f)). These results suggest that an increase in G_{syn} promotes a transition from in-phase spiking to anti-phase spiking.

While the stable solution in Fig. 1(d–f) is anti-phase, we note that the burst always starts out nearly in-phase and converges to the anti-phase solution as the burst progresses. The speed of convergence (within the burst) appears to increase with higher synaptic coupling strengths as the coupling increases from Fig. 1(d–f). This same phenomenon is noted in the network simulations presented later in this manuscript (see raster plots in Fig. 4).

3.3 Range of synchronous burst durations is enhanced by synaptic coupling

The results shown in Fig. 1 suggest that synaptic and electric coupling have different effects on the burst duration of a two-cell network. To see the combined effect of both coupling types, we systematically varied parameters G_{gap} and G_{syn} . Figure 2 shows bifurcation diagrams for several consecutive values of electric and synaptic coupling. G_{syn} increases from left to right and G_{gap} increases from bottom to top.

For each fixed value of G_{syn} , the entire AP branch shifts to the left as G_{gap} increases (highlighted column of Fig. 2). As a result, the region of bistability between the AP and the equilibrium branch initially increases. This increase in the size of the bistable region correlates with longer bursts. However, an increase in G_{gap} also changes stability of both periodic branches, with the AP branch losing stability and the IP branch gaining stability. For a sufficiently large value of G_{gap} , the AP branch becomes entirely unstable and the IP branch becomes fully stable. This shift in stability causes the bursting trajectory to switch from the AP to the IP branch. Since the IP branch has smaller range of bistability, this transition leads to shorter bursts.

The range of G_{gap} values for which burst duration increases is larger for strong synaptic coupling (compare first and third column in Fig. 2). This is because synaptic and electric coupling have opposing effects on the IP branch, with strong electric coupling making it stable and strong synaptic coupling making it unstable. Since the IP branch is more unstable for larger G_{syn} (compare panels in bottom row Fig. 2), a larger value of G_{gap} is required to gain full stability of the IP branch (compare panels in highlighted row Fig. 2). As a result, when synaptic coupling is strong, the trajectory follows the AP branch for larger values of G_{gap} . Since the AP branch continues to shift to the left as G_{gap} increases, the region of bistability increases, which leads to longer bursts.

In contrast, varying G_{syn} while fixing G_{gap} has very small effects on the location and stability of the AP solution branch (highlighted row of Fig. 2), with a very small shift of AP branch to the left (compare two diagrams on the right in the highlighted row in Fig. 2). The more noticeable effect of G_{syn} is the change in stability of the IP branch. As seen from Fig. 2, an increase in G_{syn} makes the left portion of IP branch unstable. This effect is especially noticeable for smaller values of G_{gap} since, as discussed before, an increase in G_{gap} has an opposite effect on stability of IP branch. When the IP branch loses its stability, the bursting trajectory switches to the AP branch, whose stable portion extends further to the left. Therefore, the increase in burst duration can be fully attributed to the switch from the IP branch with a shorter range of bistability to the AP branch with a longer range of bistability.

As seen from two top rows in Fig. 2, synaptic coupling increases burst duration only for some range of electric coupling. For very strong values of G_{gap} , burst duration is minimally affected by changes in G_{syn} . For values of G_{gap} where a stable AP branch exists on the left of the knee (second row from the top in Fig. 2), further increase in G_{syn} eventually leads to a loss of stability of the IP branch and an increase in burst duration, as a result of the transition to the AP branch. However, for values of G_{gap} which result in a fully unstable AP branch (top row in Fig. 2), no value of G_{syn} leads to an increase in burst duration. Since G_{syn} does not affect the AP branch, it will remain unstable for any value of G_{syn} . Thus, the only available bistability region would be the one between the stable IP branch and stable equilibrium solution. As a result, the bursting trajectory always follows the stable IP branch. If G_{syn} is large enough for the IP branch to lose its stability, the trajectory is attracted to the equilibrium solution and bursting stops.

Thus, there is a composite effect of synaptic and electric coupling on burst duration. Since electric and synaptic coupling have opposing effects on the stability of the IP branch, strong synaptic coupling produces a larger range of burst durations. In contrast, electric coupling increases burst duration only for small and medium values of G_{gap} , where the AP branch has a stable part. For strong electric coupling, changes in synaptic coupling have a minimal effect on the burst duration.

3.4 Spike synchrony is largely determined by stability of the in-phase branch

Figure 2 shows that for some values of synaptic and electric coupling both AP and IP branches can be stable simultaneously (Fig. 2, second row). To examine the burst trajectory in this case, we plotted zoomed-in portions of the bifurcation diagrams in Fig. 3(a).

It is typically shown that a square-wave burster's trajectory follows a stable equilibrium solution until it reaches a “knee” of the z-shaped steady-state solution (Bertram et al. 1995). After the knee, the equilibrium branch becomes unstable and the bursting trajectory is attracted to the stable periodic branch. For lower values of G_{gap} , only the AP branch is stable at the knee, so bursting trajectory always converges to the AP solution (Fig. 3, bottom row). On the other hand, for higher G_{gap} (Fig. 3, two top rows) only the IP branch is stable, so trajectory converges to the IP solution. In cases when both periodic branches are stable, the solution always converges to the IP branch. For all panels in Fig. 3(a), the bursting trajectory converges to the IP branch if it is available and stable on the left of the knee. This indicates that the transition between the AP and IP branches is determined by stability of the IP branch on the left of the knee.

To quantify the transition between AP and IP bursting, we have constructed a metric (Fig. 3(b)) which represents the distance from the end of the stable branch of the IP solution to the knee of the steady-state solution ($h_{\text{stable}} - h_{\text{LK}}$). When the stable portion of IP branch reaches the knee, $h_{\text{stable}} - h_{\text{LK}}$ equals zero, at which point the system switches to IP bursting. The drop in bursting period, as G_{gap} increases, correlates with a drop of the value $h_{\text{stable}} - h_{\text{LK}}$ to zero (Fig. 3(c)). This metric is also valid when characterizing the G_{gap} -mediated increase in burst duration, since it became negative at the peak of burst length, around the transition from the AP to IP branch.

3.5 Varying electrical and synaptic coupling strengths in a 50-neuron network alters burst duration and spike synchrony in a manner similar to the two-neuron network

Varying electrical and synaptic coupling strengths in a 50-neuron network reproduces the results obtained in our two-cell simulations. To measure the effect of synaptic and electric coupling on the spike synchrony within the burst, we calculated a synchronization deviation index (SDI) (see section 2) with a lower value corresponding to a higher level of synchrony.

For a given value of G_{syn} , increase in G_{gap} from zero causes the network burst duration to increase (Fig. 4(B1–B3)). However, beyond a critical G_{gap} value, the network burst duration quickly decreases and remains nearly unresponsive to further changes in coupling strengths (Fig. 4(B3–B4)). In contrast, we do not observe this type of complex thresholding phenomena when varying values of G_{syn} with a fixed value of G_{gap} (Fig. 4(C1–C3)). For each fixed value of G_{gap} , the burst duration abruptly increases as G_{syn} is increased beyond a critical value (Fig. 4(C2)).

Varying G_{gap} and G_{syn} also have significant effects on spike synchrony within each burst. As shown in Fig. 4(E1–E3), spiking activities produced by individual neurons in the network become more synchronized as G_{gap} is incremented from 0 nS to 2.0 nS. Furthermore, once G_{gap} is increased to 2.25 nS, the spiking activity of the individual neurons become completely synchronized (in-phase). On the contrary, an increase in G_{syn} with a fixed level of G_{gap} , results in an abrupt increase followed by a continuous yet gradual decrease in the SDI measure (Fig. 4(d)). The SDI measure never returns to its original value characterizing in-phase spiking activities (Fig. 4(F1–F3)). The abrupt change in burst duration occurs at the same level of G_{gap} where the switch in spike synchrony occurs (Fig. 4(C2, F2)). These observations are robust across a broad range of the parameter space (Fig. 4(d)).

Taken in its totality, the network level simulations serve as a validation of the effects of G_{gap} and G_{syn} on spike-synchrony and burst duration analyzed using the two-neuron model.

3.6 Effects of gap-junction coupling on spiking and spectral properties

It has been shown that gap-junctional coupling modulates inspiratory motoneuron and phrenic nerve activities in the transverse slice as well as the en-bloc preparations (Bou-Flores and Berger 2001). Specifically, a reduction in gap junction strength causes an increase in burst duration along with the emergence of a dominant intra-burst spiking frequency as observed in the spectrograms of hypoglossal nerve rootlet recordings from the transverse slice. Similar effects on bursting period and intra-spike frequency distribution were observed in phrenic nerve recordings. Since our model was originally developed to describe activity of inspiratory neurons, we used it to interpret the results of experimental findings above. To reproduce the effect of different concentrations of gap-junction blockers, we fixed G_{syn} and gradually decreased G_{gap} (Fig. 5).

Our results show that when G_{gap} is large the intra-burst spike frequency spectrum is flat, signifying the absence of a dominant spike frequency (Fig. 5(b), bottom right panel). This flat frequency histogram occurs when the network is firing with in-phase synchrony during the burst. As G_{gap} decreases below 2.25nS, the frequency spectrum starts to form a peak, indicating the emergence of a dominant frequency. The appearance of a dominant frequency coincides with the switch to anti-phase firing within the network during the burst and an increase in burst duration (Fig. 5(a), second Black Square from the top). Any further increase in G_{gap} preserves the dominant spike frequency (Fig. 5(b), top panels) but the burst frequency starts to decrease. These results, specifically the correlation of the presence or absence of a peak in the spike-frequency spectrum with the existence of in-phase spike synchrony, provide qualitative bounds on the strength of gap junctional coupling within the pre-Bötzinger complex when related to other experimental results using gap junctional blockers (see section 4).

4 Discussion

The results presented here demonstrate that manipulation of spike synchrony in more than one-way (electrical or chemical) leads to sudden changes in burst duration at the level of neuronal population. The two-neuron simulations are consistent with the 50-neuron simulated network. Such changes cannot be explained by a single well-defined biophysical mechanism, but only by considering the emerging dynamics of the spiking and bursting processes. A key factor in this change is the stability of the spiking mechanisms.

Individual aspects of these results have been reported in earlier studies. Previous work (Sherman and Rinzel 1991) noted that for a network of electrically coupled bursting pancreatic beta cells, a longer burst duration was obtained at levels of coupling lower than the highest levels of coupling possible. It was also shown that, in the two-cell case, weak coupling led to longer burst durations and anti-phase spiking (Sherman and Rinzel 1992). The detailed quasi-steady state bifurcation analysis for this effect of weak coupling was carried out in (Sherman 1994). In agreement with the work presented here, it was reported that for a range of very weak electrical coupling, the IP solution was unstable, with the bursting trajectory following an AP solution branch, thereby increasing burst duration. However, in contrast to our results, in Sherman's model the loss of AP solution stability occurred before the IP solution fully gained stability, resulting in the loss of the bistable region and the existence of quasi-periodic bursting. In our work, the stable portions of the IP and AP branches overlap for a significant range of electric coupling (see first column in Fig. 3(a)), so that the bursting becomes in-phase while the stable AP branch is still available in the bistable region. The slowing down of the stability gain of the IP branch via increased

synaptic coupling results in longer burst in our model, since the AP solution is still stable on the left of the knee. Thus, in our work, the increase in burst duration is not limited to the case of weak electric coupling, as in Sherman's work, but instead can occur at any value of the electric coupling, provided the cells are also coupled synaptically.

This effect of weak coupling has also been observed in models of mid-brain dopaminergic neurons (Komendantov and Canavier 2002). Experimentally, recent studies in the rat pre-Bötzinger Complex (upon which our model is based) have shown that blocking gap-junctions leads to desynchronization of motor nerve output from a more intact preparation than that modeled here (Solomon et al. 2003).

Previous research in two cell networks of cells similar to ours (Best et al. 2005) has identified two modes of bursting, termed symmetric bursting and asymmetric bursting that varied as a function of excitatory synaptic coupling. These modes were distinguished by the similarity (or difference) between the slow variable (h) trajectories during bursting of the two neurons. Their analysis did not consider the effects of G_{gap} and was carried out in its entirety over the AP branch, as the IP branch was always unstable. For the simulations shown here, our anti-phase solutions corresponded to their mode of asymmetric bursting, though at times the difference between the h trajectories was minimal. Our IP solutions always exhibited symmetric bursting. However, we suspect that, based on the geometry of the bifurcation diagrams, the effects shown here with G_{gap} would occur if our AP solutions occurred during symmetric bursting as well.

There are two interesting observations of these results that warrant a higher level of mathematical analysis. First, even when the anti-phase solution is the only stable spiking solution, why do the spikes during the burst start out nearly in-phase? This is not just observed in the two-cell simulations, but in network simulations as well. Such “transient synchrony” may not be easily explained by quasi-steady-state analysis techniques like those employed in this paper. Secondly, when both the in-phase and anti-phase solution branches are both stable, why does the in-phase spiking solution dominate?

In summary, we have shown that in a coupled network of square-wave bursters, the effects of synaptic excitation vs. electrical coupling are distinct. Increasing synaptic coupling generally increases the burst duration. Electrical coupling increases burst duration for low to moderate values, but at sufficiently strong values promotes a switch to highly synchronous bursts where further increases in electrical or synaptic coupling have a minimal effect on the burst duration. These effects are largely mediated by spike synchrony, and spike synchrony is largely mediated by the stability of the in-phase spiking solution of the quasi-steady-state model. When both coupling mechanisms are strong, there is no compromise between the “preferred” mode of spike synchrony and one form (in-phase or anti-phase spiking) will dominate, resulting in a sharp boundary in the space of the coupling parameters whether measured by spike synchrony or burst duration.

Our simulations show that decreasing the strength of electrical coupling from a sufficiently high value (corresponding to in-phase spike synchrony) to a lower value (corresponding to anti-phases spike synchrony) causes a change in the intraburst spike frequency spectrum consistent with those recorded during gap junctional blocking experiments. In particular, the anti-phase spiking regime yields an intraburst frequency spectrum with a notable peak, while the frequency spectrum during in-phase spiking is relatively flat, indicative of synchronous network output. These results suggest that a strong non-zero value of electrical coupling may be present within the neonatal pre-Bötzinger complex.

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Fig. 1.

Bifurcation diagrams of two-cell network simulations. From top to bottom, Panels (a–c) illustrate the simulation results when G_{syn} is fixed at 3.0 nS, and (a) $G_{\text{gap}}=0$ nS, (b) $G_{\text{gap}}=0.5$ nS, and (c) $G_{\text{gap}}=1.5$ nS. Similarly, Panels (d) through (f) illustrate the results when G_{gap} is fixed at 0.7 nS, and (d) $G_{\text{syn}}=0.75$ nS, (e) $G_{\text{syn}}=1.5$ nS, and (f) $G_{\text{syn}}=3$ nS. Insets in each panel show the spiking profile that occurs within each burst. IP: *black*. AP: *red*. Bursting trajectory: *green*. Equilibrium solution: *brown*. For all diagrams x-axis represents h , and the y-axis represents membrane voltage (similar to axes on panels (a) and (d))

Fig. 2. Profiles of the bifurcation diagrams with coupling strengths being $G_{\text{syn}}=0, 1, 2$ nS and $G_{\text{gap}}=0.1, 0.5, 1, 1.5$ nS. The highlighted row and column shows the behavior of the bursting trajectory, and changes in the two periodic solution branches AP (*red*) and IP (*black*)

Fig. 3.

Panel (a) is a zoomed-in version of Fig. 2. Panel (b) illustrates the metric proposed to categorize the convergence of bursting trajectory. Panel (c) compares the change in burst duration (as the coupling strengths are varied) versus the switch in the sign of the metric ($h_{\text{stable}} - h_{\text{LK}}$). The black curve the boundary where $h_{\text{stable}} - h_{\text{LK}} = 0$. Note that G_{gap} is incremented in 0.1 nS in panel (c). The dashed line in Panel (a) represents the transition of ($h_{\text{stable}} - h_{\text{LK}}$) between positive and negative value. The value of ($h_{\text{stable}} - h_{\text{LK}}$) is positive for the sub-panels in the *bottom-right corner*; and negative for the sub-panels on the *top-left corner*. Accordingly, the bursting trajectory (*green*) for the three sub-panels in the *bottom-right* converges to the AP branch (*red*), and to the IP branch (*black*) for the *top left* five sub-panels

Fig. 4.

Effects G_{gap} and G_{syn} on burst duration (panel **a**) and spike synchrony (panel **d**). The Spike Deviation Index (SDI) color-coded in panel (**d**) is described in section 2. Panels (**b/e**) are raster plots of several periods of bursting (**b**) and a single burst (**e**) within the network for 4 sets of coupling parameters indicated by the *solid black boxes* in panels (**a/d**); the parameter sets are: $G_{\text{gap}}=0, 1, 2$, and 2.25 nS, with G_{syn} fixed at 2.25 nS. Panel (**c/f**) contain the same information for 3 sets of coupling parameters indicated by the *dashed black boxes* in panels (**a/d**); these parameters are: $G_{\text{gap}}=1.5$ nS, with $G_{\text{syn}}=0, 1.25$, and 3 nS

Fig. 5.

Panel (a) is identical to Panel (a) of Fig. 4, illustrating how burst duration changes with respect to changes in coupling strengths. Panel (b) demonstrates the appearance of a dominant intra-burst spiking frequency as gap-junctional coupling strength is varied. The x-axis runs from 0 to 60 Hz, showing the range of intra-burst spiking frequency. The y-axis shows the percentage of occurrences of a specific spiking frequency within a single burst. The coupling strengths used to generate the spike-frequency spectrum in Panel (b) correspond to the *solid black boxes* in Panel (a)