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Synchrony and frequency regulation by synaptic delay in networks of self-inhibiting neurons

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Abstract

We show that a pair of mutually coupled self-inhibitory neurons can display stable synchronous oscillations provided only that the delay to the onset of inhibition is sufficiently long. The frequency of these oscillations is determined either entirely by the length of the synaptic delay, or by the synaptic delay and intrinsic time constants. We also show how cells can exhibit transient synchronous oscillations where the length of the transients is determined by the synaptic delay, but where the frequency is largely independent of the delay. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Synchronous oscillations; Inhibition; Synaptic delay

1. Introduction

The synchronization properties of networks of inhibitory neurons has been considered in several modeling studies, [1–6,9–11], to name only a few. A number of mechanisms have been proposed to explain why a stable synchronous solution exists for mutually coupled inhibitory cells. In all of the above studies except [4], slowly decaying inhibition between the cells is a primary candidate. Rubin and Terman [6] also show that inhibitory cells can synchronize with fast decaying inhibition provided that each of the cells has a slow sag current. In prior work [4], we showed that cells could synchronize with fast decaying inhibition provided that the synaptic delay is sufficiently long and the cells are self-inhibitory.

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While self-inhibition is often used as a simplifying assumption in modeling studies, it often arises naturally in different network contexts. For example, in the pyloric system of the spiny lobster, there exist excitatory-inhibitory pairs in which the inhibitory cell pre-synaptically inhibits the excitatory cell's axon [5]. The removal of excitation, in this case, is effectively a self-inhibition.

The frequency of oscillations in inhibitory networks has also received attention. In particular, Chow et al. [2] show how network frequency can depend on different parameters in different regimes. For example, they show that a network of mutually coupled, self-inhibiting spiking neurons can have a frequency that is completely determined by the inhibitory time constant, by the intrinsic time constants of the cells or in some cases, by a combination of these two parameters. While not specifically addressed in [6,9], the frequency in those studies can also be related to the decay time constant of inhibition (or the sag current for the former study). These studies, though, model the burst envelope of a neuron and thus, in certain contexts, would also find frequency dependence on time constants of the active state of a neuron.

In this paper, we show that the frequency of the network can be completely determined by the length of the synaptic delay, provided that it is long enough. Moreover, we show that when the delay is in an intermediate range, the synaptic delay together with the intrinsic time constants of the silent state determine the network frequency. In the long delay case, the synchrony and frequency of the network are largely insensitive to heterogeneities between the cells in the network.

2. Model

We use biophysical conductance based equations to model a network of two mutually coupled, self-inhibitory cells. The equations for each cell are of the form

$$\varepsilon \frac{dv_i}{dt} = I_{ext} - g_l[v_i - E_l] - g_K w_i[v_i - E_K] - g_{Ca} m_\infty(v_i)[v_i - E_{Ca}],$$

$$- g_{syn} s_i(t-\tau)[v_i - E_{syn}] - g_{syn} s_j(t-\tau)[v_i - E_{syn}], \quad (1)$$

$$\frac{dw_i}{dt} = [w_\infty(v_i) - w_i]/\tau_\infty(v_i), \quad (2)$$

$$\varepsilon \frac{ds_i}{dt} = \alpha[1 - s_i]H(v_i - v_{th}) - \beta s_i H(v_{th} - v_i), \quad (3)$$

$$\varepsilon \frac{ds_j}{dt} = \alpha[1 - s_j]H(v_j - v_{th}) - \beta s_j H(v_{th} - v_j), \quad (4)$$

where $i \neq j$. The functions $m_\infty(v_i) = 0.5[1 + \tanh(v_i - mh)/mst)]$, $w_\infty(v_i) = 0.5[1 + \tanh((v_i - wh)/wst)]$ and $\tau_\infty(v_i) = 0.5[1 + \tanh(20[v_i - v_{th}])][\tau_R - \tau_L] + \tau_L$. The function $H(v)$ is equal to 0 if $v < 0$ and equal to 1 if $v > 0$. We note that the synaptic s_i and s_j variables, which are governed by first order equations, and sit in the v' equation of each cell, are delayed by a time τ. The values of the parameters that

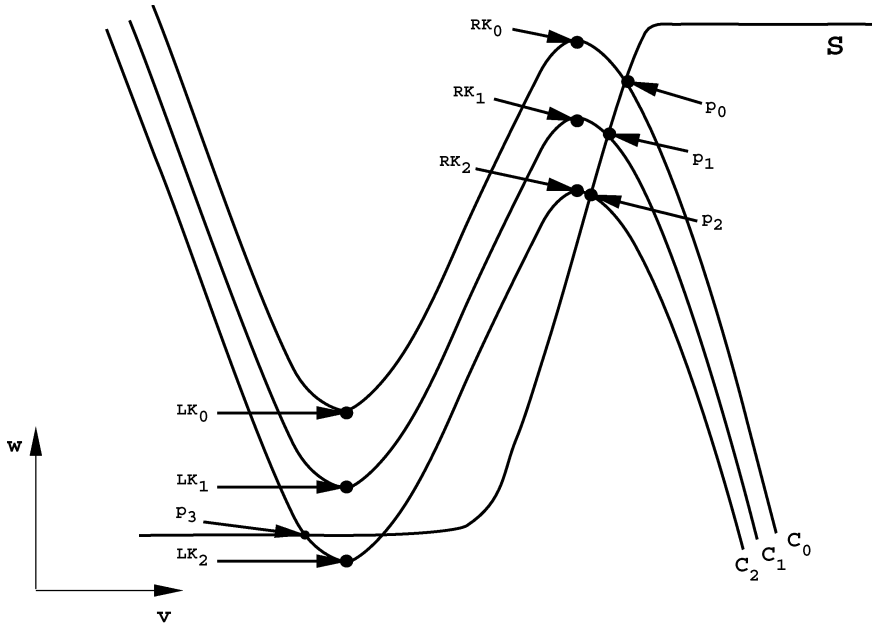

Fig. 1. The v- and w-nullclines together with relevant points on the v–w phase plane.

remained fixed throughout all simulations are: $g_l = 0.5$, $E_l = -50$, $g_{\mathrm{K}} = 2$, $E_{\mathrm{K}} = -70$, $g_{\mathrm{Ca}} = 1.9$, $E_{\mathrm{Ca}} = 100$, $\varepsilon = 0.01$, $E_{\mathrm{syn}} = -100$, $\alpha = 20$, $\beta = 20$, $mh = 1$, $mst = 14.5$, $wst = 5$, $v_{th} = 0$. For Fig. 2, $I_{\mathrm{ext}} = 20$, $\tau_{\mathrm{L}} = 2$, $\tau_{\mathrm{R}} = 1$, $g_{\mathrm{syn}} = 0.25$ and $wh = 12$. For Fig. 3, $I_{\mathrm{ext}} = 40$, $\tau_{\mathrm{L}} = 1$, $\tau_{\mathrm{R}} = 1$, $g_{\mathrm{syn}} = 0.2$ and $wh = -22$. For Fig. 4, $I_{\mathrm{ext}} = 50$, $\tau_{\mathrm{L}} = 1$, $\tau_{\mathrm{R}} = 1$, $g_{\mathrm{syn}} = 0.15$ and $wh = 12$.

There are three v-nullclines for each cell, each of which is cubic shaped. We denote them as the intrinsic, singly inhibited or doubly inhibited cubics, $\mathscr{C}_0$, $\mathscr{C}_1$ and $\mathscr{C}_2$ respectively, (see Fig. 1. for further notation). The w-nullcline for each cell is a sigmoid which we assume intersects the right branch of any cubic, and the left branch of only the doubly inhibited cubic $\mathscr{C}_2$. Thus in the absence of any synaptic connections, each cell would rest at the high-voltage fixed point p_0 of these equations. In the geometric analysis of this neural oscillator model, we use the smallness of ε to demarcate a fast and slow time scale. The silent and active states of the neuron correspond to slow activity (i.e. evolution near the left or right branch of a cubic), while the transitions between these states (branches) are fast.

3. Results

3.1. Long synaptic delay promotes synchrony

Suppose the two cells start some distance apart on the left branch of $\mathscr{C}_0$. If the synaptic delay is long enough, the cells will synchronize after the first few oscillations.

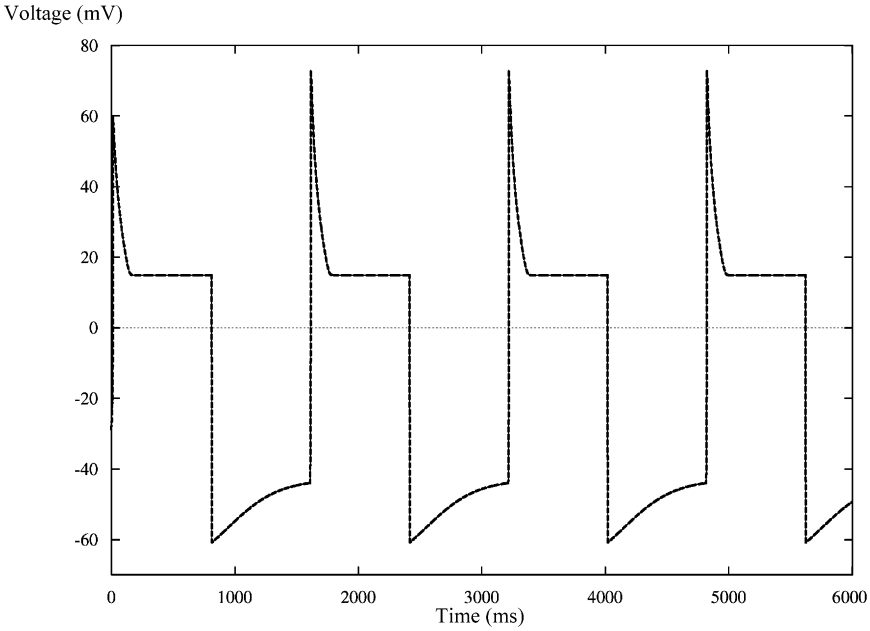

Fig. 2. For long delays, the period of synchronous oscillation is 2τ, with $\tau = 800$ ms. The cells remain in the active state, trapped by p_0 until inhibition is felt and they jump to the left. There, they remain in the silent state, trapped by p_3 until inhibition wears off, and the cells can jump up again. The duty cycle of the cells is 1/2.

If cell one jumps to the active state at $t = 0$ and cell two at $t = \Delta t$, then the mutual and self inhibition due cell one crossing the synaptic threshold will not be felt until time τ. If τ is sufficiently large, then on the time interval $(0,\tau)$, the cells will have traveled up the right branch of $\mathscr{C}_0$ and will be in a neighborhood of p_0. Since p_0 lies above the right knee of $\mathscr{C}_1$, at $t = \tau$, the cells will jump down to the silent state. Somers and Kopell [8] have shown that there is time compression across a jump of this sort which causes the cells to synchronize. At $t = 2\tau$ the inhibition due to both cells turns off and the cells again jump to the right. Either at this time, or a later time, the cells jump back up to the active state, and the process repeats. Thus if the synaptic delay is sufficiently long, the cells synchronize (see Fig. 2).

The same mechanism described here will also synchronize cells by post-inhibitory rebound. Indeed if the w-nullcline instead intersects the cubics along their left branches and not at all on the right branches, then a long enough delay will synchronize the cells. For example, suppose the cells start Δt apart on the left branch of $\mathscr{C}_0$. At $t = 0$, cell one jumps to the right branch and Δt later, cell two does. Now if the delay is long enough, then both cells will return to the silent state through the local maximum on $\mathscr{C}_0$ and the first inhibition will only be felt once the cells are again in their refractory state. The second inhibition will then cause the cells to jump left onto $\mathscr{C}_2$. If the delay is long enough, both inhibitions persist until the cells are sufficiently

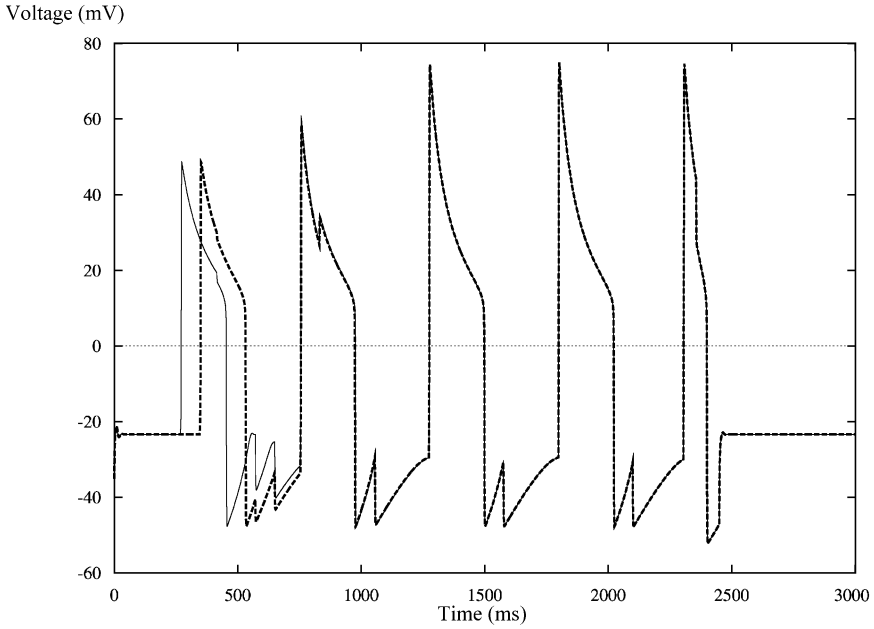

Fig. 3. Synchronization through post-inhibitory rebound. The cells start synchronized, trapped at the left, intersecting critical point of $\mathscr{C}_0$. After $t = 250$ ms, c_1 is given 5 mV of input and a short time after that c_2 receives the same. The cells desynchronize and then the voltage input is removed. If the delay is long enough, both cells will not be able to jump back to the active state until inhibition is removed. On this up-jump they will become more synchronous due to Fast Threshold Modulation. At $t = 2250$ ms, the delay was reduced to 50 ms. The cells were not able to move below LK_0 when the inhibition turned off, so they became attracted to the intersecting critical point of $\mathscr{C}_0$, where they remained in the silent state for the rest of the simulation. This shows that long delays are crucial for synchronous oscillations in this type of network.

close to the fixed point p_3 on the left branch of $\mathscr{C}_2$. When the inhibition is removed, the cells now jump up together and are compressed in time due to Fast Threshold Modulation [8] (see Fig. 3).

3.2. Frequency control for long synaptic delays

The choice of delay can affect the frequency of oscillation for synchronous neurons. For sufficiently long delays, the period of oscillation is equal to 2τ. Suppose at time $t = 0$, the synchronized cells jump to the right branch of $\mathscr{C}_0$ and travel up. For long delays, we showed above that the time spent in the active state is τ. When they jump back to the silent state at time τ, they land on $\mathscr{C}_2$ and travel down towards p_3. Since the delay was assumed to be sufficiently long, they become trapped by p_3. They remain there until the inhibition turns off, which is τ time after they jumped down onto the left branch of $\mathscr{C}_2$. So, the cells spend τ time in the silent state, before jumping back to the right branch of $\mathscr{C}_0$ and repeating the process. Thus the period of the cells is

2τ. This result holds if the delay is longer than the intrinsic refractory time of each neuron.

Both the synchrony and the network frequency persist in the presence of cell heterogeneities. For example, even if the cells evolve in the silent and/or active state with somewhat different rates, provided the delay is long enough, the cells will always jump between the silent and active states at the same time. The reason is that the fixed points on the left and right branches prohibit the cells from jumping up or down unless there is change in the inhibitory input. While their trajectories will not be identical, their jumping times will be $O(\varepsilon)$ close. Moreover the period will remain at 2τ.

3.3. Frequency control for intermediate synaptic delays

For intermediate delays, the cells' refractory time also contributes to the frequency determination. Assume, as for long delays, the cells jump onto the right branch of $\mathscr{C}_0$ at $t = 0$, travel up that branch, and jump down onto the left branch of $\mathscr{C}_2$ when the inhibitions activate. Again, the cells remain active for time τ. For intermediate delays, when the inhibitions turn off, the cells jump onto the left branch of $\mathscr{C}_0$, where the travel down, reach LK_0, and repeat the circuit. For this case, we call the total time that the cells spend on the left branch of any cubic the refractory time. Therefore, the total period of the oscillation is τ plus the refractory time.

There is a fairly clear cut off between what we mean by intermediate delay and long delay. There is a maximal time that any cell can spend on the left branch and still jump up from LK_0 on $\mathscr{C}_0$; namely the time from the w value of p_0 on the left branch down to LK_0. If the delay is larger than this time, then the cells will be in the long delay case. Otherwise they will be in the intermediate or short delay case. See Kunec and Bose [4] for complete analysis of the short delay dynamics.

3.4. Constant frequency of transient oscillations

For various choices of the time constants, different interesting behavior can be observed. For example, transient synchrony can be achieved through a balance of the delay and the rate constants on both branches of the cubics. In particular, the cells can oscillate for any finite number of times before becoming trapped at the high-voltage fixed point p_2.

Suppose both cells start at LK_0. At $t = 0$, the cells jump to the right branch of $\mathscr{C}_0$ and travel up. At $t = \tau$, self and mutual inhibition turns on for both cells and both cells jump down to the left branch of $\mathscr{C}_2$. Assuming the delay is long but not too long, the cells travel below LK_0 before the inhibitions turn off and the cells jump back to the right branch of $\mathscr{C}_0$. This time, the cells are below the w-value of their original jump onto the right branch of $\mathscr{C}_0$. Therefore, the cells will not travel up and reach the same vertical height as the first time when the inhibitions activate. There now is a chance that when the inhibitions turn on, the cells will jump to the right branch of $\mathscr{C}_2$ and become trapped by p_2. However if the cells move fast enough to be above p_2 with a long enough delay, both cells *will* jump down onto the left branch of $\mathscr{C}_2$. Because the cells didn't reach the same vertical height before jumping down, as the first time, they

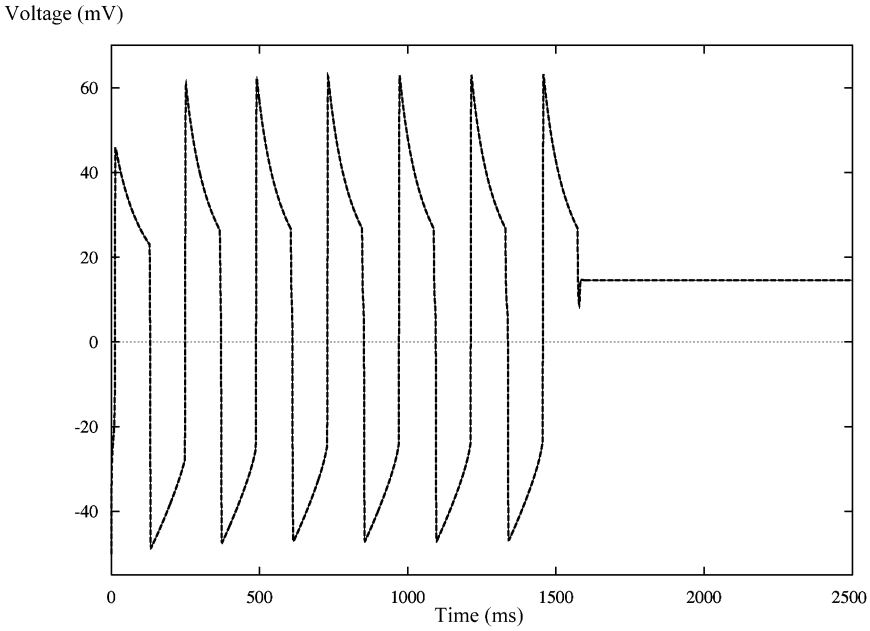

Fig. 4. Synchronous, transient oscillations before the cells settle into an on-state. Here $\tau = 117.3$. As the value of the delay is increased, the cells can be made to oscillate any finite number of times before moving to the on-state. However, the frequency of the synchronous, transient oscillation remains ~ 4 Hz despite the length of the delay (and, therefore, the number of transient oscillations) for this set of parameters.

will travel further down the left branch before the inhibitions turn off, again allowing the cells to jump up. This process repeats, causing the oscillations. However, each time the cells travel on the right branch of $\mathscr{C}_0$, they jump down from a lower w-value than the previous cycle. Eventually, they will not surpass p_2 at the moment the inhibitions turn on and become trapped, thus ending the oscillations. The frequency of these oscillations remain approximately constant because the reduction in w-values during each excursion up the right branch, before inhibition, is small (Fig. 4).

4. Discussion

In this paper, we have shown that the length of the synaptic delay is an important parameter to consider when determining the frequency of the synchronous solution of networks of inhibitory neurons. Indeed if the delays is sufficiently long, then it is the single parameter which determines the network frequency. In contrast to prior work with inhibitory neurons, we do not require the network frequency to be dependent on the decay time constant of inhibition. Indeed the long delay in some sense replaces the long time constant of inhibition.

The frequency results that we presented depend on the existence of the fixed points p_0 and p_3, but the synchrony results do not. Indeed if neither of these fixed points exist, then the network period is 2τ only for the range of delays that make the cells jump down above RK_1 and below LK_0. In delay parameter space, this implies that there exists disjoint intervals over which the period is 2τ. In between these intervals, the period is controlled by the delay and the time constants on the left and right branches. We note that synchrony can still be achieved without the fixed points as long as the cells have the opportunity to jump to and from the silent state at the same moment in time.

In our previous work [4], we show how other types of solutions such as anti-phase or n-to-1 solutions arise in the types of networks we have considered. There we present rigorous mathematical proofs for our results. We also show how the basin of attraction of various solutions is a function of the delay. The interested reader may find other results on inhibitory networks in [7].

Acknowledgements

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