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Control of network output by synaptic depression

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Abstract

In a network of an excitatory and an inhibitory neuron, depression in the inhibitory synapse can produce two distinct oscillatory regimes. In one regime, the network has a short period cell-dominated solution; in the other regime, the solution has much longer period and is synapse-dominated. These regimes overlap to produce an interval of bistability. Neuromodulatory input that targets one of multiple parameters in the network can switch the network control between the intrinsic properties of cells and the dynamics of the synapses.

Keywords: Oscillations; Inhibition; Bistability

1. Introduction

Excitatory-inhibitory (*EI*) pairs of neurons are common elementary circuits in the mammalian brain. Such circuits are found in the neo-cortex [8], the visual cortex [2], the hippocampus [3], the olivo-cerebellar system [14], the nucleus reticularis thalami [11], and so on. Often, these circuits show rhythmic activity, generated by intrinsic properties or emerging from network interactions. Due to the ubiquity of *EI* circuits, it is important to obtain a good understanding of the processes that control their output. Synaptic depression is widespread in all neuronal circuits. Recently, this form of synaptic plasticity has been shown to be functionally relevant in several contexts

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[1,10,12,13]. In particular, Nadim et al. have shown that depression in reciprocally inhibitory networks can cause a switch between distinct modes of antiphase oscillatory activity. We address the existence of a switch mechanism and bistability of synchronous rhythmic activity in *EI* circuits that involve synaptic depression.

Our model consists of a reciprocally coupled pair of neurons: an oscillatory excitatory neuron E and a non-oscillatory inhibitory neuron I. We address the situation where the synapse from I to E is depressing and the synapse from E to I is strong and fast. We show that, depending on the maximal conductance, $\bar{g}_{\mathrm{inh}}$, of the depressing synapse, two distinct oscillation modes emerge. When $\bar{g}_{\mathrm{inh}}$ is small, the depressing synapse remains weak, the rhythm is fast and its frequency is controlled by the intrinsic properties of the E neuron. Alternatively, when $\bar{g}_{\mathrm{inh}}$ is large, the synapse is strong, the rhythm is slow and its frequency is controlled by $\bar{g}_{\mathrm{inh}}$ and the time courses of the depressing synapse. The two modes co-exist for an intermediate range of values of $\bar{g}_{\mathrm{inh}}$ if the intrinsic time constants of the neurons are much smaller than the decay and depression time courses of the synapse. This results in a network showing bistability of periodic orbits.

2. The model

The cells are represented using two-dimensional biophysical models. The two state variables are v, the voltage of the cell and w, a slow recovery variable. E has a fast excitatory synapse to I. We make the assumption that the synapse from E to I is strong enough so that I is coactive with E.

The coupling from I to E is a depressing, slowly decaying inhibitory synapse. This synaptic current is described using two variables s and d; the former models the effect of the inhibitory current on E; the latter models the dynamics of depression.

The equations describing the model are

$$\begin{aligned}
Cv_i' &= -1.5 - I_{\mathrm{Ca},i} - I_{\mathrm{leak},i} - I_{\mathrm{syn},e\to i},\\
w_i' &= [w_\infty(v_i) - w_i]/\tau(v_i),\\
Cv_e' &= -I_{\mathrm{Ca},e} - I_{\mathrm{leak},e} - I_{\mathrm{syn},i\to e},\\
\mathrm{w}_e' &= [w_\infty(v_e) - w_e]/\tau(v_e),\\
s_i' &= [d_i s_\infty(v_i) - s_i]/\tau_{s_i}(v_i),\\
d_i' &= [d_\infty(v_i) - d_i]/\tau_{d_i}(v_i),
\end{aligned} \tag{1}$$

where $I_{\mathrm{Ca}} = g_{\mathrm{Ca}} m_\infty(v)[1-w][v - E_{\mathrm{Ca}}]$, $I_{\mathrm{leak}} = g_{\mathrm{leak}}[v - E_{\mathrm{leak}}]$. All voltages are in mV, time constants in msec and conductances in nS. The functions m_∞, and w_∞ have the form $1/(1+\exp(-(v-x_1)/x_2))$. The function $\tau = \tau_{\mathrm{L}} + [\tau_{\mathrm{R}} - \tau_{\mathrm{L}}]h_\infty(v)$. Common parameter values for both cells are $E_{\mathrm{Ca}} = 0$, $E_{\mathrm{leak}} = -65$, $g_{\mathrm{Ca}} = 1.6$, $g_{\mathrm{leak}} = 0.3$, $C = 1$, $\tau_{\mathrm{L}} = 50$, $\tau_{\mathrm{R}} = 50$ and for m_∞, $x_1 = -50$, $x_2 = 4$. For w_∞ of the E cell we used, $x_1 = -53$ and $x_2 = 1$; for the I cell we used $x_1 = -64$ and $x_2 = 6$.

The excitatory synaptic current from E to I is given by $\bar{g}_{\mathrm{exc}} s_e (v_i - E_{\mathrm{exc}})$ where $g_e = 0.1$ and $E_e = 0$. The variable $s_e = 1/(1 + \exp(-(v_e - x_1)/x_2))$ with $x_1 = -53$ and $x_2 = 1$. The inhibitory current from I to E is of the form $\bar{g}_{\mathrm{inh}} s_i (v_e - E_{\mathrm{inh}})$. $s_\infty(v_i) = 1/(1 + \exp(-(v_i - v_{\mathrm{thresh}})/x_2))$ with $v_{\mathrm{thresh}} = -64$ and $x_2 = 6$, $\tau_{s_i}(v_i) = \tau_\kappa + [\tau_\gamma - \tau_\kappa] s_\infty(v_i)$ with $\tau_\gamma = 1$, $\tau_\kappa = 2000$, $d_\infty(v_i) = 1/[1 + \exp(v_i - v_{\mathrm{rec}}]$ with $v_{\mathrm{rec}} = -65$, and $\tau_{d_i}(v_i) = \tau_\beta + [\tau_\alpha - \tau_\beta] d_\infty(v_i)$ with $\tau_\alpha = 1000$ and $\tau_\beta = 100$.

Note that d recovers towards 1 whenever I is silent and decays towards 0 whenever I is active. s decays towards 0 whenever I is silent and is reset to the current value of d whenever I becomes active. Only the variable s directly affects the behavior of E. However, since s quickly approaches d when I is active, d influences the behavior of E during the active phase. The extent of recovery of d depends on the ratio of τ_{L} and τ_{R}, and on the time constants τ_α and τ_β.

3. Results

The main result of this paper is that for a range of parameter values, (1) displays two distinct, stable periodic solutions. One of the solutions is a high frequency, low amplitude solution whose period is controlled by the time constants of the E cell; namely, τ_{R} and τ_{L}. The other solution is a low frequency, high amplitude solution whose period is controlled by the time constants of the depressing synapse; namely, τ_α and τ_β. The cell-controlled solution exists if $\bar{g}_{\mathrm{inh}}$, the maximal conductance of the depressing synapse, is small enough, while the synapse-controlled solution exists if this conductance is large enough. We show that there is a range of values of $\bar{g}_{\mathrm{inh}}$ for which both solutions exist, thereby producing bistability of periodic solutions.

In the bistable range, the dynamics of the depressing synapse are of crucial importance in determining to which solution a given initial condition is attracted. The synapse-controlled solution is characterized by the fact that the synapse has a chance to recover on a cycle-by-cycle basis. Thus the value of d, which is bounded between 0 and 1, never becomes too small. Alternatively, the cell-controlled orbit is characterized by the fact that the synapse does not have a chance to recover on a cycle-by cycle basis. In this case, the value of d remains small. The extent of recovery of the synapse is directly dependent on the time constants τ_α and τ_β and therefore on the ratio of the time that I spends in the silent versus active phase. Since I is silent when E is, the extent of recovery can directly be related to the amount of time E spends in the silent state. In short, if E spends little time in the silent state, then the synapse depresses, while if it spends a lot of time in the silent state, then the synapse recovers.

Fig. 1a shows a cell-controlled, high frequency orbit. The period of this orbit is 77 msec. We note that τ_β is chosen to be significantly less than τ_α. Since the duty cycle of the cell is small, it is clear that the synapse does not have enough time to recover in the silent state. As a result, both d and s remain small through the oscillation. Thus the synaptic current given by $\bar{g}_{\mathrm{inh}} s(v - E_{\mathrm{inh}})$ is small and only minimally affects the rhythm. Therefore the period is cell-controlled and is close to the intrinsic period of E.

Fig. 1b shows a synapse-controlled, low frequency orbit. The period of the orbit is 3,230 msec. The parameter values are exactly as in Fig. 1a, except that the cells started

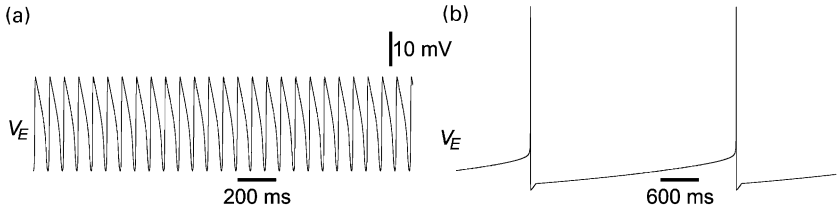

Fig. 1. Simulation results demonstrating the cell- and synapse-controlled solutions. (a) Voltage traces of the E cell in cell-controlled mode shows high-frequency oscillations. (b) Voltage traces of the E cell in synapse-controlled mode shows oscillations with much lower frequency and larger amplitude.

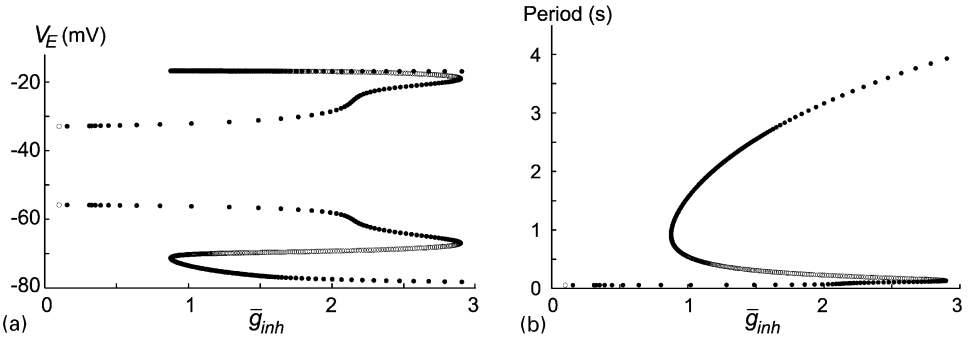

Fig. 2. Bifurcation diagram of the full system as the maximal conductance $\bar{g}_{\mathrm{inh}}$ of the depressing synapse is changed. Filled and white circles denote stable and unstable oscillations, respectively. (a) Bifurcation of the maximum and minimum values of the membrane potential of the E neuron on the periodic orbit. The inner and outer stable branches denote the cell- and synapse-controlled regimes, respectively. (b) Bifurcation diagram of the oscillation period. The lower and upper stable branches of the diagram denote the cell- and synapse-controlled regimes, respectively.

with different initial conditions than in that figure. Now at $t = 0$, we set s to a large value (i.e. close to 1) and started E in its silent state. Since s is large, so is $\bar{g}_{\mathrm{inh}} s(v - E_{\mathrm{inh}})$. Moreover, s decays slowly since τ_κ is large. This strong slowly decaying inhibition prohibits E from firing too quickly. While E remains silent, d now has a chance to recover towards 1. Thus the stronger the inhibition, the more chance d has to recover. E ultimately fires when s becomes small enough. At this time, s is renewed to the current value of d which had the chance to become large. Both of these variables depress while E is in the active state, but the amount of depression is not enough to counteract the strong recovery that had resulted from the previous silent cycle. Thus, when E returns to the silent state, s is still large and the process repeats. The period of this orbit is controlled by τ_κ, the time constant of inhibitory decay.

Fig. 2 shows a bifurcation diagram which depicts how the network's period changes as a function of $\bar{g}_{\mathrm{inh}}$. The results shown were obtained using the differential equation solver XPP, together with the bifurcation continuation program AUTO (information on both XPP and AUTO is available at http://www.pitt.edu/~phase). There is a well defined region of bistability where both the cell- and synapse-controlled orbits exist.

The reason both can exist simultaneously has to do precisely with the fact that they are controlled by processes and parameters that are largely independent. For example, in the cell-controlled case, the value of τ_κ is largely irrelevant to the existence and stability of the periodic solution. Alternatively, in the synapse-controlled case, the network is insensitive to the time constant τ_L. In [4], we give a complete mathematical proof of how bistability can arise in *EI* networks that exhibit depression.

The mechanism for bistability that we show above is robust over a large set of parameter values. The cell-controlled solutions are largely insensitive to the decay time constant of the depressing synapse. In contrast, the synapse-controlled solution is insensitive to the intrinsic time constants of the *E* (or *I*) neuron. Thus, the existence and stability of each type of solution depends on the relative values of the intrinsic and synaptic time constants. For the cell-controlled orbit, in which the synapse remains depressed, it is important that τ_L is small relative to τ_α. Increasing τ_α expands the range of parameters for which the cell-controlled solution exists (i.e. the lower branch in Fig. 2b). For the synapse-controlled solution, it is important that τ_L is small relative to τ_κ. Increasing τ_κ gives the synapse more time to recover in the silent state, thus expanding the range of parameters for which the synapse-controlled solution exists to smaller values of $\bar{g}_{inh}$ (upper branch of Fig. 2b). By decreasing τ_α the cell-controlled solution can be destroyed, while decreasing τ_κ destroys the synapse-controlled solution.

4. Discussion

Both experimental and theoretical work have shown that brief perturbations (such as a short current pulse, short synaptic input or brief exposure to a neuromodulator) can induce long-lasting changes in neuronal networks. These changes may be in the membrane potential of neurons, patterns of activity [5], responses to input signals [7], phasing, firing frequency [6] or period of network oscillation [10]. Bistability in neuronal systems has been associated with a variety of functions, such as motor control, visual perception, memory and representation of temporal durations. In view of the wide range of behaviors attributed to neuronal bistability in its different forms, it is important to understand how bistability arises.

Due to the existence of two stable rhythmic orbits, the network that we have studied is capable of switching between distinct oscillation regimes. Thus, a brief synaptic or modulatory input to the network could evoke long-lasting changes in oscillation period. For instance, if the system is operating in the synapse-controlled regime, an excitatory input during the active phase of the *E* or *I* neuron may prolong the active state of the *I* neuron and thereby cause the *I* to *E* synapse to depress and switch the system to the cell-controlled regime. However, the same input during the silent phase of the synapse-controlled oscillation may be mostly ignored because the synapse cannot depress during this phase.

Our work also demonstrates that some parameters affect the oscillation period orbit only in the synapse-controlled regime, and not in the cell-controlled regime. For example, in the cell-controlled regime the network is largely insensitive to changes in

the decay time constant of synaptic inhibition. In contrast, in the synapse-controlled regime this parameter is important and determines the duration of the interburst phase. This allows the neuronal circuit to be primed (for example, by a modulatory effect that prolongs the decay time constant) for the change in control, without any apparent change in output, prior to the occurrence of a triggering event. Hence a neuronal circuit in the cell-controlled regime would switch to the synapse-controlled regime in two steps. A similar mechanism has been described in the endogenous burster R15 in Aplysia, where electrical activity changes from bursting to beating following a brief perturbation, but only in the presence of serotonin [9]. This procedure could be used as a safety mechanism, to prevent the system from accidentally switching from one activity mode to another, for example as a result of synaptic noise.

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