



# Transitions between different synchronous firing modes using synaptic depression

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## Abstract

Bistability of different synchronous firing patterns arising in networks of pyramidal cells and interneurons which include depressing synapses is demonstrated. The firing modes differ in their frequencies, in the type of firing pattern and in their degree of synchrony. The network elements governing the frequency of each mode are identified and ways to transition between modes are discussed. © 2002 Published by Elsevier Science B.V.

*Keywords:* Synaptic depression; Bistability; Pyramidal cell; Inhibition

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## 1. Introduction

Networks of neurons that display different types of stable firing patterns have the advantage that they can code for different types of phenomena. For example, in region CA3 of the hippocampus, pyramidal cell firing during the theta rhythm may code for different locations within known environments [4] and during sharp wave bursts may also participate in the transfer of information from the hippocampus to the entorhinal cortex [7]. The network firing patterns may vary in the type of burst or spike profiles and may also vary in the degree of synchrony across the network [1]. It is important to identify networks and the neural mechanisms within these networks that allow for multiple outputs.

In previous work, we have analyzed different firing patterns in model networks of 2-compartment Pinsky–Rinzel pyramidal neurons [5] coupled to excitable interneurons [1,2]. In [2], we showed how the burst profile of a repetitively firing pyramidal cell could be changed from a complex burst to bursts with 4, 3, 2 or 1 spike by varying the

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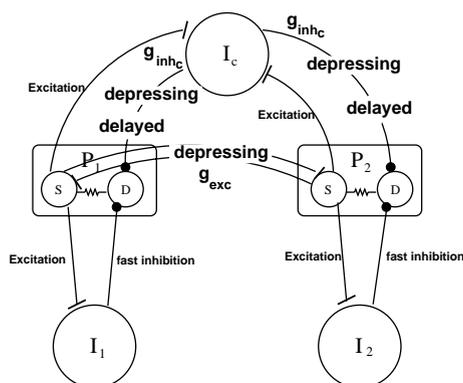


Fig. 1. Schematic of pyramidal cell—interneuron network with depressing synapses.

net level of synaptic inhibition arriving to the cell. In [1], we showed that different types of synchrony patterns exist in these networks and can be modulated as the strength and timing of synaptic inputs vary. In these papers, we studied the steady-state behavior of solutions for different but fixed values of the inhibitory and excitatory synaptic maximal conductances. We did not address how networks may transition between these patterns in a dynamic way.

In different work, we have investigated how synaptic depression can be used to create a switch between two distinct oscillatory modes [3]. In an ideal network of a repetitively firing excitatory cell reciprocally connected to an inhibitory cell through a depressing synapse, we showed that there is a fast oscillatory mode whose frequency is controlled by the intrinsic properties of the cells in the network, and a slow oscillatory mode whose frequency is controlled by the synaptic properties present between cells.

In this paper, we show how bistability of different synchronous solutions can arise in networks of pyramidal cells and interneurons in which some of the synapses are depressing. We consider a network consisting of two Pinsky–Rinzel pyramidal cells,  $P_1$  and  $P_2$ , with recurrent excitatory synapses between them, each reciprocally coupled to separate “local” interneurons,  $I_1$  and  $I_2$ , and both with reciprocal synaptic connections to a “common” interneuron,  $I_c$  (Fig. 1). The recurrent excitatory synaptic currents between the pyramidal cells and the slowly decaying, inhibitory current from the common interneuron display depression. The two different synchronous solutions are (1) a spiking mode in which the firing times of the pyramidal cells are perfectly synchronized and (2) a “burst-envelope” synchronous mode [1] in which the pyramidal cells burst at the same time, but the burst profiles are different. As in [3], the network frequencies are different in the two modes as are the network elements controlling the frequency. In the spiking mode, frequency is high and is controlled by a combination of the intrinsic properties of the pyramidal cells and the strength of the inhibitory synaptic currents from the local interneurons,  $I_1$  and  $I_2$ . In the burst-envelope synchronous mode, burst frequency is lower and is controlled by the inhibitory synaptic currents from the common interneuron.

## 2. Model

The equations and parameter values for the Pinsky–Rinzel model [5,6], for the interneurons [2] and for the dynamics of the non-depressing synaptic currents [1] have been previously described. In the voltage equations for  $P_1$  and  $P_2$ , post-synaptic currents of the depressing synapses are modeled by  $-g_x s_x (V_{\text{post}} - V_x)$  where  $V_{\text{post}}$  is the post-synaptic voltage,  $x = \text{exc}$  for recurrent excitatory currents between  $P_1$  and  $P_2$ , and  $x = \text{inh}_c$  for the inhibitory currents from  $I_c$ . Maximal conductance values are  $g_{\text{exc}} = 3.5$  and  $g_{\text{inh}_c} = 0.5$  mS/cm<sup>2</sup>. The reversal potentials for excitatory and inhibitory synaptic currents are  $V_{\text{exc}} = 0$  and  $V_{\text{inh}} = -80$  mV, respectively. The gating variables,  $s_x$  for the depressing synaptic currents obey equations of the form

$$s'_x = \frac{d_x - s_x}{\alpha_x} H_\infty(V_{\text{pre}} - V_\theta) - \frac{s_x}{\beta_x} H_\infty(V_\theta - V_{\text{pre}}),$$

$$d'_x = \frac{1 - d_x}{\rho_x} H_\infty(V_\theta - V_{\text{pre}}) - \frac{d_x}{\delta_x} H_\infty(V_{\text{pre}} - V_\theta),$$

where  $V_{\text{pre}}$  is pre-synaptic voltage. The Heaviside function,  $H_\infty$ , is used to enforce the synaptic threshold at  $V_\theta = -10$  mV. The constants  $\alpha_x$  and  $\beta_x$  are the time constants of activation and decay of the synaptic currents, respectively, and  $\rho_x$  and  $\delta_x$  are the recovery and depression time constants, respectively. In this model for a depressing synapse, when pre-synaptic voltage crosses threshold, the gating variable  $s_x$  approaches the value of the depression variable  $d_x$ . If the synapse is fully recovered,  $d_x = 1$ , but it depresses with a time constant  $\delta_x$  once pre-synaptic voltage is above threshold. When pre-synaptic voltage drops below threshold,  $s_x$  decays to zero with time constant  $\beta_x$  while  $d_x$  recovers back to 1 with time constant  $\rho_x$ . Both the excitatory and inhibitory synaptic currents activate fairly quickly ( $\alpha_{\text{exc}} = \alpha_{\text{inh}_c} = 0.5$  ms) and the excitatory current also decays quickly ( $\beta_{\text{exc}} = 2$  ms). Values of the other time constants are given in the text. There is a delay of 20 ms in the common inhibitory current from  $I_c$  to  $P_1$  and  $P_2$  which is modeled as a time delay in the value of  $s_{\text{inh}_c}$  in the appropriate post-synaptic current term.

## 3. Results

### 3.1. The high frequency, perfectly synchronized spiking solution

When the recurrent excitatory synapses between the pyramidal cells and the common inhibitory synapse from  $I_c$  to  $P_1$  and  $P_2$  are depressed, then the network displays a stable, perfectly synchronized spiking solution. In this case, the frequency of the network is determined by the properties of a single  $PI$  subcircuit. Specifically, since the excitatory synapse is depressed, the net level of inhibition from the local interneurons to the pyramidal cell is large. The effect, as shown in [2], is that the slow dendritic, potassium after-hyperpolarization current, which, in part, controls the cell's interburst interval, stays small, thereby allowing the subcircuit to fire at a relatively high frequency

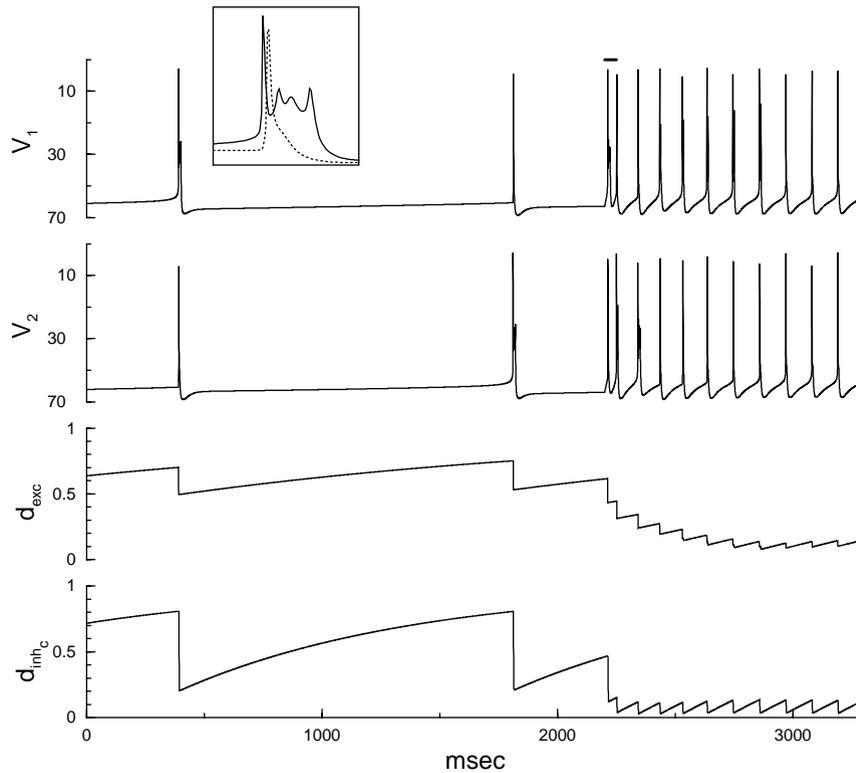


Fig. 2. Somatic voltage in  $P_1$  and  $P_2$  (top two traces), excitatory synaptic depression variable  $d_{exc}$  (third trace) and inhibitory synaptic depression variable  $d_{inh_c}$  in the low frequency, burst-envelope synchronous firing mode (up to 2000 ms) (Inset: close-up of first burst profiles in  $P_1$  (solid) and  $P_2$  (dashed)) and in the high frequency, synchronous spiking mode (beyond 2500 ms). Transition between two modes achieved by application of a 50 ms applied current pulse ( $3 \mu\text{A}/\text{cm}^2$ ) at 2200 ms (heavy bar, top trace).

of about 10 Hz. This frequency is independent of the time constants of depression and recovery of both the excitatory and inhibitory synapses, provided that they remain depressed. By choosing the time constants for recovery  $\rho_{exc}$  and decay  $\delta_{exc}$  of the excitatory synapses as 2000 and 2 ms, respectively, and for the inhibitory synapse as  $\rho_{inh_c} = 1000$  and  $\delta_{inh_c} = 2$  ms, we can ensure that the synapses remain depressed while the network oscillates at 10 Hz. The value of  $\beta_{inh_c}$ , the time constant of decay of the common inhibitory current, is, importantly, not relevant for this firing mode.  $I_c$  fires with each  $P_1$  and  $P_2$  spike, but since its synapses back to the  $P$ 's are depressed, it has little effect on the rhythm.

This spiking solution is perfectly synchronized. We show in [1] that perfect synchrony is possible between  $PI$  subcircuits if excitation is not too strong and if it targets the soma compartment of each pyramidal cell. In Fig. 2, from 2500 ms onward, the top two traces show perfectly synchronized spiking. The two bottom traces show

the excitatory depression variable ( $d_{\text{exc}}$ ) and the common inhibitory depression variable ( $d_{\text{inh}_c}$ ) in a depressed state oscillating between 0 and 0.18.

### 3.2. The low frequency, burst-envelope synchronous solution

When the depressing synapses in the network are in a non-depressed state then burst frequency is very low, about 0.6 Hz, and, while the bursts are nearly synchronized, their profiles are different. Specifically, one cell fires a complex burst and the other fires a single spike (see inset in Fig. 2). In this firing mode (Fig. 2 up to 2000 ms), the values of  $d_{\text{exc}}$  and  $d_{\text{inh}_c}$  recover to above 0.7 at the time of burst initiation. The interburst interval is sufficiently long for them to recover back to this value by subsequent burst firing. In contrast to the fast spiking mode, the length of the interburst interval, and thus burst frequency, is primarily controlled by  $\beta_{\text{inh}_c}$ . We have chosen  $\beta_{\text{inh}_c} = 5000$  ms to exaggerate the frequency difference between the two firing modes and thus highlight the dependence on this parameter. The slowly decaying inhibition, which is delayed so that it only acts during the interburst interval, slows the pyramidal cells' approach to firing threshold and thus dominates this low frequency solution.

The existence and stability of the burst-envelope synchronous solution is discussed in [1]. There, we show that although strong recurrent excitation between pyramidal cells causes them to fire at the same or nearly the same time, differences in each cell in the timing of recurrent excitation and inhibition from the local interneurons allows the leading pyramidal cell to fire a complex burst, but causes the follower cell to fire a single spike (as in inset in Fig. 2). When the strength of the recurrent excitation decreases, with local inhibition remaining strong, the burst profile of the leader pyramidal cell changes to bursts with 4, 3 or 2 spikes, and for low values of excitation, both cells fire single spikes. Thus, the burst-envelope synchronous firing and the perfectly synchronized spiking in the two firing modes are both stable firing patterns of this network when the common interneuron is removed and the synapses do not depress. Including depression of the recurrent excitatory synapses between the pyramidal cells allows the network to intrinsically transfer between these modes and including the common interneuron with its depressing synapse creates the bistable switch between the modes.

### 3.3. Transitions between fast and slow rhythms

The two firing patterns exist for a common set of parameter values thus implying bistability of solutions. There are several ways that the network can transition between these two modes. In Fig. 2, the transition from the slow bursting mode to the fast spiking mode is achieved by providing a short depolarizing current pulse to both of the pyramidal cells (heavy bar at 2200 ms). This pulse forces the cells to fire at a higher frequency thereby depressing both the excitatory and common inhibitory synapses. The switch between modes could also have been activated by supplying the current pulse to just one of the pyramidal cells, as recurrent excitation would force the other cell to also fire at high frequency. Depolarizing the common interneuron, forcing it to fire faster, would also switch modes, but not as quickly as in Fig. 2.

The reverse transition from the fast spiking mode to the slow bursting mode can be achieved by applying a sufficiently long, hyperpolarizing pulse to both pyramidal cells or to the common interneuron. In either case,  $I_c$  stops firing and the inhibitory synapse has a chance to recover. When the hyperpolarization is removed and  $I_c$  fires again, it produces a strong, long lasting inhibitory current that keeps pyramidal cell frequency low. We note that hyperpolarizing only one of the pyramidal cells would not activate this transition since the other pyramidal cell would continue to stimulate  $I_c$  and the inhibitory synapse would not be able to recover.

#### 4. Discussion

In this paper, we have shown how various synaptic mechanisms interact with intrinsic mechanisms of two-compartment pyramidal cells to produce multiple, stable synchronous firing patterns. These solutions differ in their frequencies, in the type of firing pattern and in their degree of synchrony. We have identified the network elements governing the frequency of each mode, and discussed ways to transition between the two modes.

These results may have implications for the action of neuromodulators on a network. We have shown that the high frequency spiking mode is largely independent of the common interneuron  $I_c$ . Therefore, neuromodulators that target  $I_c$  or its synapse could affect pyramidal cell firing without directly acting on the cells. For example, if the network is in the fast mode and the common interneuron is hyperpolarized, pyramidal cell firing will not change. Indeed, since the inhibitory synapse is depressed, its absence will only minimally affect the pyramidal cells. However, once  $I_c$  does fire, if its synapse has sufficiently recovered, it will immediately switch the network to the slow bursting mode.

Our results also demonstrate how a single network can participate in different neural coding activities. The different frequency firing modes would have different effects on downstream neurons which react to changes in firing rate. Moreover, the different types of synchrony could also be utilized by downstream neurons that detect differences in firing times. In this way, a single network can have many different uses within larger networks of neurons.

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