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Regulating firing rate of networks of pyramidal cells

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Abstract

In a minimal network model consisting of two pyramidal cells and one interneuron, we show how excitation and inhibition cooperate to produce firing rate changes in pyramidal cells that are consistent with observed place cell firing in region CA3 of the hippocampus. We show that inhibition from a common interneuron can synchronize networks of pyramidal cells with no direct connections. Moreover, recurrent excitation together with common inhibition can modulate burst profiles of synchronously firing cells from complex bursts to bursts with multiple spike to single spikes.

Keywords: Inhibition; Excitation; Place cells

1. Introduction

The firing patterns of pyramidal cells in region CA3 of the rat hippocampus are believed to exhibit both a firing rate code [4,15] and a phase-based temporal code [6,10] which determines the animal's location in known spatial environments. There is active interest in determining the neural mechanisms that underlie the generation and reproduction of these codes, however, much is left to be understood. While the anatomy of the hippocampus is fairly well known, the functional interactions among pyramidal cells and interneurons has not been fully determined. Thus it is unclear whether changes in pyramidal cell firing rate, for example, result from changes in excitation or inhibition or both.

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In this paper, using a minimal network model consisting of two pyramidal cells and one interneuron, we show how excitation and inhibition cooperate to produce firing rate changes in pyramidal cells that are consistent with the observed firing patterns of place cells as a rat runs on a linear track. In particular, we show how the firing rate of place cells can increase either linearly [4] or in a Gaussian-like manner [3] as the rat passes through the place field. The results that we present depend on a dynamic balancing act between excitatory and inhibitory input to the pyramidal cells.

In previous work (reviewed in the Model section below), using the 2-compartment pyramidal cell model of Pinsky and Rinzel [7], we showed how inhibition arriving during a burst can change the burst profile and interburst (spike) interval of a repetitively bursting cell. Specifically, we showed that as the maximal conductance of fast inhibitory input to the dendrites of the pyramidal cell increases, the pyramidal cell firing changes from complex bursts, to bursts with multiple spikes to single spikes.

Here, we address the question of what effect recurrent excitation has on networks of pyramidal cells which receive inhibition from a common interneuron. Recurrent excitatory connections in CA3 are anatomically dense, albeit mathematically sparse. Previous modeling studies have shown that fast, recurrent excitation can synchronize burst firing of pyramidal cells [7,12]. We show that inhibition from a common interneuron can synchronize networks of pyramidal cells with no direct connections. Moreover, recurrent excitation together with common inhibition can modulate burst profiles of synchronously firing cells from complex bursts to bursts with multiple spike to single spikes.

Our motivation to study the dual effects of excitation and inhibition is to develop a model for place cell firing that is consistent with the functional model of associative memory developed by Recce [8] and with our biophysical model of phase precession [2]. Recce [8] proposes that synchronously firing assemblies of place cells code for the same spatial location and that recurrent excitation drives the recruitment, and thus the recall, of the location memory. We have proposed that the timing of inhibitory input to place cells controls the phase precession phenomena [2].

2. Model

The minimal network model that we consider consists of two pyramidal cells and one interneuron (Fig. 1). Each of the pyramidal cells is described by the 2-compartment model of Pinsky and Rinzel [7], while the excitable interneuron is modeled using the Morris-Lecar equations [5]. A pyramidal cell consists of a soma compartment, capable of producing fast sodium spikes, and a dendrite compartment, capable of producing a broad calcium-based depolarization. Pinsky and Rinzel [7] show that depending on the level of applied current to the soma and the relative strength of the electrotonic coupling between compartments, the cell can exhibit complex bursts, spike doublets and single spikes. The complex burst results from the interaction between the soma and dendrite compartments. Namely, the soma initially fires a sodium spike which back propagates to the dendrite instigating a large scale calcium event. The dendritic, calcium-based depolarization then supports further depolarized

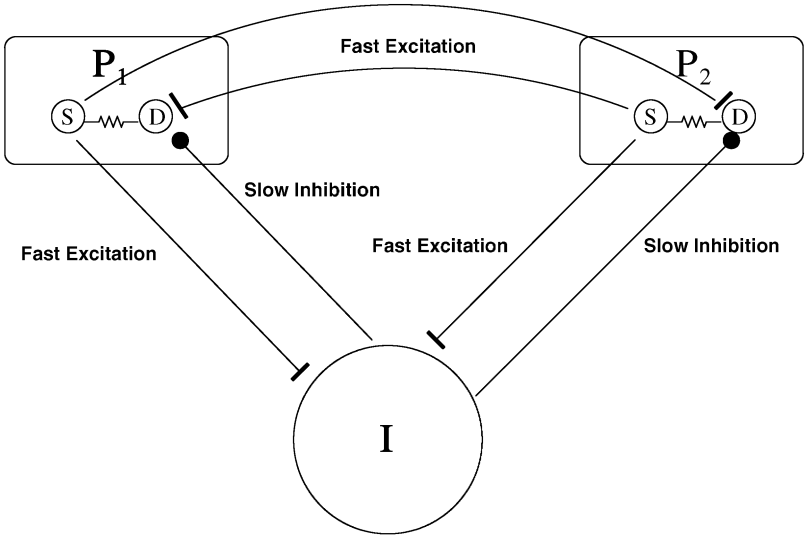

Fig. 1. Anatomy of three-cell network.

activity in the soma. If the calcium event is too large, the soma is overdriven, thus losing the ability to spike and resulting in a complex burst.

In our network, the soma compartment of each pyramidal cell sends fast excitatory input to the excitable interneuron that is sufficient to make it fire. The interneuron makes an inhibitory synaptic connection on the dendrite compartment of each pyramidal cell. For some of our results, the pyramidal cells make fast, AMPA-mediated excitatory connections to the dendrite compartments of each other. The dynamics of each synapse are governed by single first order differential equations with individual parameters for the rise and decay time constants. The model equations and parameter values are as in [1] except that we reduce the decay time constant of the inhibitory synaptic current from the interneuron to each pyramidal cell ($\beta = 0.1$) and increased the somatic applied current in each pyramidal cell ($I_s = 0.75\ \mu A/cm^2$). In the simulations shown here, the maximal conductance of the inhibitory current g_{inh} is set to 0.7 (mS/cm^2) and we vary the maximal conductance of the recurrent excitatory current g_{exc}.

The results presented here build on our prior work [1] where we showed how inhibitory feedback to a pyramidal cell can modulate its burst profile. We considered a single pyramidal cell connected to an interneuron as in Fig. 1. In that two-cell network, the leading sodium spike of a burst causes the interneuron to fire, thereby sending a hyperpolarizing current to the dendrites. We showed that as the maximal conductance of this inhibitory input g_{inh} is changed, the burst profile changes. Specifically, if g_{inh} is small, then the burst profile of the pyramidal cell is still complex, but the interburst frequency of the cell increases. If g_{inh} is large, then the pyramidal cell exhibits single spikes at high frequency. If g_{inh} is at intermediate values, then the

pyramidal cell has bursts with 4, 3 or 2 spikes (as g_{inh} is increased). The reason that these patterns occur is straightforward. When inhibition is weak (g_{inh} small), it is not strong enough to prevent a full dendritic calcium event, and a complex burst arises. When inhibition is too large, on the other hand, the leading somatic sodium spike backpropagates to the dendrite, but the full dendritic calcium event is completely suppressed. Thus, there is not sufficient depolarizing current to initiate any further sodium spikes. For intermediate values of g_{inh}, the dendritic calcium event is only partially blocked. This allows the soma to become sufficiently depolarized to have a second sodium spike, which again back propagates to the dendrite. If this second spike causes enough calcium to enter the cell, then a third sodium spike can be generated and so on. In [1], we used phase plane methods to show exactly how this occurs and additionally to show why there is an increase in interburst frequency with increasing g_{inh}.

3. Results

3.1. Synchrony induced by common inhibition

With no recurrent excitatory connections between pyramidal cells ($g_{\mathrm{exc}} = 0.0$), the common inhibition provided by the interneuron can synchronize pyramidal cell firing. By varying the maximal conductance g_{inh} and the decay rate β of the inhibitory synaptic current, we obtain synchronous firing of complex bursts, of bursts with multiple spikes and of single spikes (Fig. 2a, other simulations not shown). The modulation of the burst profile with varying g_{inh} is obtained as described in the Model section and in [1]. Synchronization depends on adjusting the decay rate of inhibition. In particular, synchronizing complex bursts depends on weak g_{inh} and small β while to synchronize single spikes, both g_{inh} and β need to be larger. As in other studies obtaining synchrony with slowly decaying inhibition among cells [11,13,14], in our network the slowly decaying inhibition provides for a time compression of dendritic voltages during the silent phase of the burst cycle. In [1], we showed that dendritic voltage needed to increase past a certain level (what we called V_{d}^{*}) in order for the soma to fire and initiate a burst. In the present case with two pyramidal cells, the slowly decaying inhibition forces the dendritic voltages to pass through V_{d}^{*} closely in time. For complex burst synchronization, where the duration of the silent phase is long, a relatively slower decay rate of inhibition is needed as compared to the single cell case.

Since synchrony is induced during the silent phase of bursting, the same mechanism synchronizes firing of the different burst profiles. The burst dynamics in the active state are relatively unimportant for synchrony. In contrast, synchrony through recurrent excitation is induced during the active state of the neuron. In a network of Pinsky–Rinzel cells, this tends to promote complex burst synchronization, as opposed to singlet or doublet burst synchronization. The reason is that dendritic excitation promotes the full calcium event which underlies the complex burst, but which needs to be suppressed for singlet or doublet burst firing.

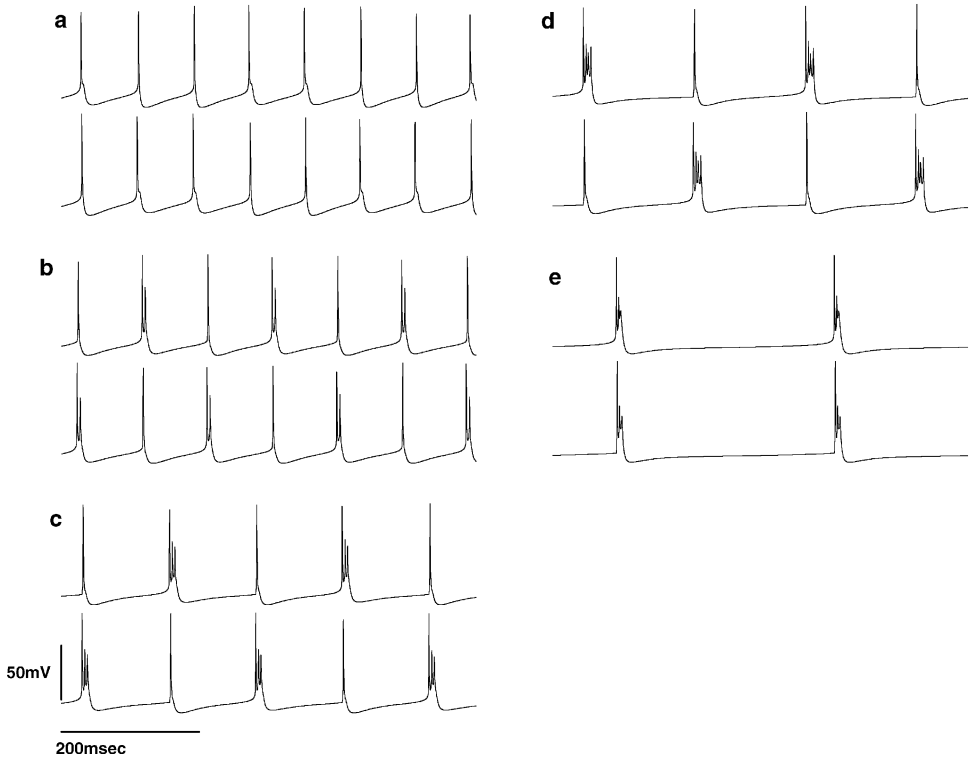

Fig. 2. Soma voltages of synchronized pyramidal cells (P_1 = top traces, P_2 = bottom traces) with varying g_{exc} (see text for values).

3.2. Excitatory, inhibitory interactions conspire to modulate firing rate

We now add recurrent excitation between pyramidal cells (g_{exc} nonzero). Fig. 2 shows somatic voltage traces of the pyramidal cells as the value of g_{exc} is systematically increased. The systematic increase is used to model the recruitment of other co-active pyramidal cells together with their recurrent excitatory input. The first set of traces shows the cells synchronized in the single spike mode ($g_{exc} = 0$, Fig. 2a). As g_{exc} is increased, the cells change their firing pattern from single spikes, to doublets ($g_{exc} = 1.0$, 2b), to triplets ($g_{exc} = 2.0$, 2c), to quadruplets ($g_{exc} = 2.5$, 2d) and to complex bursts ($g_{exc} = 3.5$, 2e) without losing burst synchrony.

We note that the synchrony of firing in the doublet, triplet or quadruplet mode is in the burst envelopes, rather than in the spikes within these bursts. The relative timing of inhibition and excitation promotes the observed alternating pattern of spike firing. At each burst cycle, one of the two pyramidal cells fires first. This cell then depolarizes its own dendrites through electrotonic coupling, and through synaptic coupling, it also depolarizes the dendrites of the second pyramidal cell and the interneuron. Since

electrotonic coupling acts much faster than synaptic coupling, the feedback inhibition from the interneuron arrives at this pyramidal cell after the onset of the dendritic calcium event and, thus, merely modulates it. On the other hand, the inhibition arrives at the second pyramidal cell concurrently (or within a short time window) of the excitatory input, and is capable of blocking its dendritic calcium event. Thus, the second pyramidal cell fires only one spike. As described in [1], the interburst interval following a single spike is shorter than that following a complex burst, thus the second cell becomes the initiator of the next burst.

4. Discussion

We have shown that inhibition can be used to not only synchronize pyramidal cells, but can also work with excitation to shape the firing patterns of these cells. The primary targets of these synaptic currents and the electrotonic current between soma and dendrite compartments are calcium-based mechanisms. The timing of inputs to the dendrites are also important in determining the finer structure of spikes within a burst.

We note that inhibition is not necessary to evoke changes in firing rate and frequency. Indeed in the original Pinsky-Rinzel paper, they show how these changes can occur by changing the applied current to the soma. The reason that we chose to study the effects of inhibition is that we have used the changing role and timing of inhibitory input to produce new explanations for the phase precession phenomena found by O'Keefe and Recce [6] in previous work. In [2], we proposed that the phase precession phenomenon of hippocampal place cells could result from changes in control of interneuron networks in region CA3. Specifically, we showed that if interneuron firing is initiated by theta pacemaker input, then place cells don't fire, or fire without precession. Alternatively, if interneuron firing is initiated by place cells, then both the interneuron and the place cell phase precess. We also provided mechanisms which could account for the switch in control at the beginning and end of a place field. In [1], we showed that fast decaying inhibition arriving just before a pyramidal cell burst could delay it by over one theta cycle, and that fast decaying periodic inhibitory input could completely suppress firing.

Our results suggest neural mechanisms that account for the rate changes observed in place cell firing as the corresponding place field is crossed. For example, Mehta et al. [4] propose that firing rate increases linearly as the animal moves through the place field. This can clearly be achieved in our model if inhibition is kept constant and the net excitatory input to the dendrites of the pyramidal cell increases cycle by cycle. This increase can occur as more co-active place cells are recruited into the firing pattern. Burgess et al. [3] have alternatively proposed that firing rate within a place field is better described by a Gaussian envelope. In our model this can be achieved, for example, if both co-active place cells and interneurons are differentially recruited cycle by cycle, or if the excitatory synapses among co-active place cells are depressing.

In summary, the effects described above provide insight into how place cells may modulate their firing rate. Together with our prior results on how the timing of

inhibitory input can be changed [2,9], a consistent model for the phase precession and the firing rate changes of place cells can be obtained. Our results suggest that dynamic balances between excitatory and inhibitory input may be crucial in understanding coding schemes in other brain regions.

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