Resonance and Selective Communication Via Bursts in Neurons Having Subthreshold Oscillations

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Abstract

Revealing the role of bursts of action potentials is an important step toward understanding how the neurons communicate. The dominant point of view is that bursts are needed to increase the reliability of communication between neurons (Lisman 1997). Here we present an alternative but complementary hypothesis. We consider the effect a short burst on a model postsynaptic cell having damped oscillation of its membrane potential. The oscillation frequency (eigenfrequency) plays a crucial role. Due to the subthreshold membrane resonance and frequency preference, the responses of such a cell are amplified when the intra-burst frequency equals the cell's eigenfrequency. Responses are negligible, however, if the intra-burst frequency is twice the eigenfrequency. Thus, the same burst could be effective for one cell and ineffective for another depending on their eigenfrequencies. This theoretical observation suggests that, in addition to coping with unreliable synapses, bursts of action potentials may provide effective mechanisms for selective communication between neurons.

Keywords: Frequency preference; Resonators; Doublet; Triplet; Hopf bifurcation

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1 Introduction

Understanding the nature of neuronal code is one of the most fundamental problems in neuroscience (Singer 1999): What is it in the spike train of a presynaptic neuron that is important for the postsynaptic one? Is the "information" encoded in the mean firing rate, in the interspike intervals, or in something else? Answering these questions is essential for our understanding of the functioning of the nervous system.

In this short paper we approach the problem by asking a simpler question – *What is the functional importance of generating a doublet, triplet, or a short burst of spikes instead of a single spike?* The prevailing answer to this question, influenced by the half a century history of treating neurons as spatio-temporal integrators, says that bursts increase reliability of communication between neurons. Indeed, sending a short burst of spikes instead of a single spike increases the chances that at least one of the spikes (or exactly one; see Lisman 1997) could avoid synaptic transmission failure. The timing of spikes within the burst does not play any role in this. Moreover, it is commonly assumed that the shorter the interspike interval, the better: If two spikes within a burst trigger the synaptic transmission, the combined postsynaptic potential is larger when the interval between the spikes is smaller, as we illustrate in Fig. 1a.

In this paper we argue that this classical view is only half of the story. The mechanism described above is indeed valid, but only for postsynaptic neurons exhibiting non-oscillatory PSPs, as in Fig. 1a. Such neurons are often called *integrators* in the com-
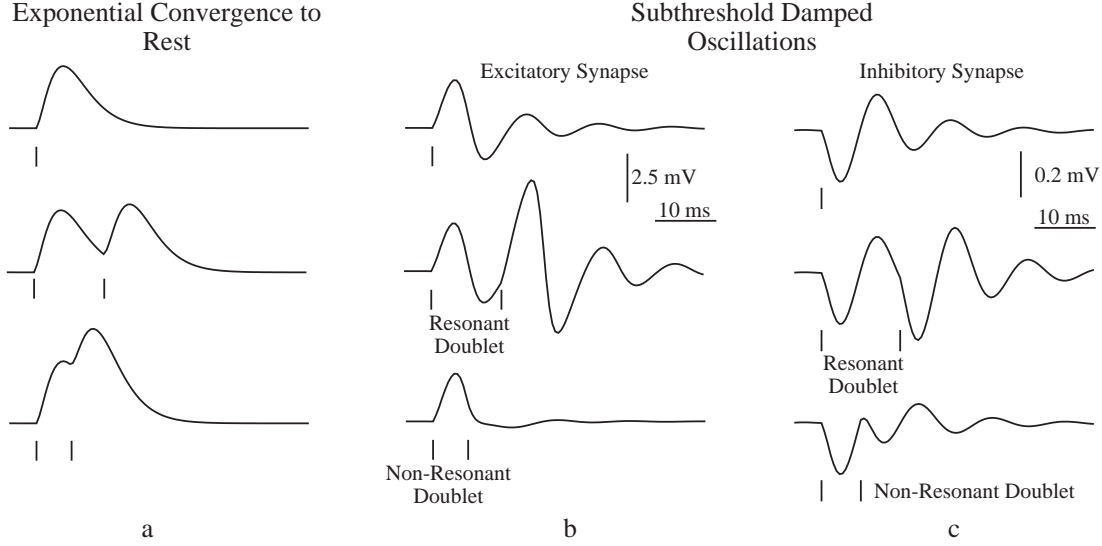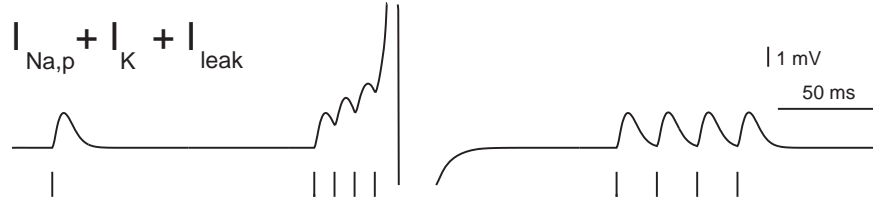
Figure 1: Illustration of exponential and oscillatory convergence of membrane potential to the rest state. a. Voltage variable in the Morris-Lecar (1981) system exhibits exponential (non-oscillatory) convergence to the rest state. The response of such a system is large when the two spikes arrive with a small delay. b. Voltage variable in the Hodgkin-Huxley (1952) model exhibits damped oscillation. Its response is large when the distance between the spikes is near the period of oscillation (resonant doublet). In this case the second spike "adds" to the first one. The model's response is diminished when the distance is half the period (non-resonant doublet). The second spike "cancels" the effect of the first one. c. The same as in b, but the doublet is inhibitory.

putational neuroscience literature (as reviewed by Izhikevich (2000)), to distinguish them from *resonators* discussed next.
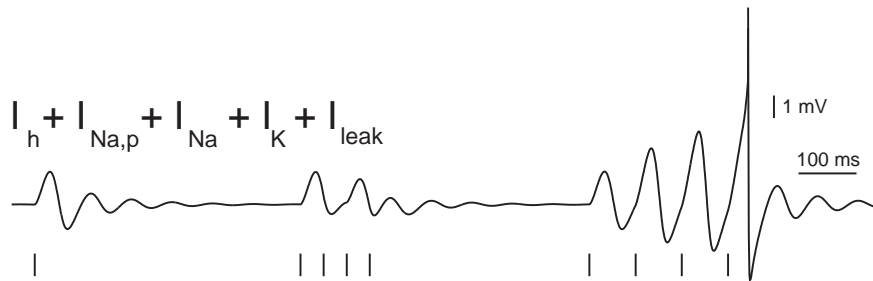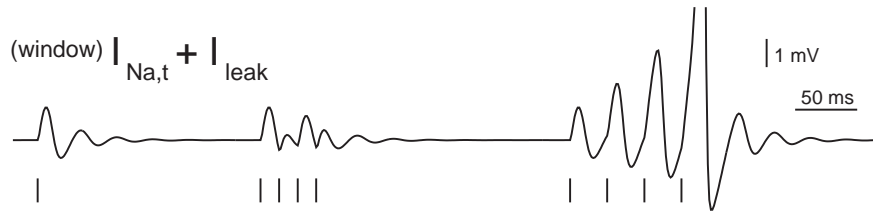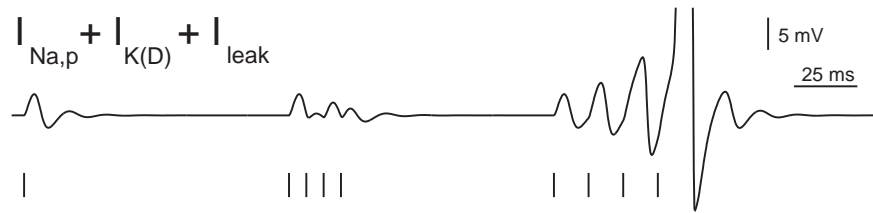
Many cortical (Llinas et al. 1991, Gutfreund et al. 1995, Hutcheon et al. 1996a,b), thalamic (Pedroarena and Linas 1997, Hutcheon et al. 1994, Puil et al. 1994), and hippocampal (Cobb et al. 1995) neurons exhibit oscillatory potentials, as in Fig. 1b and c. The responses of such neurons are sensitive to the timing of spikes within the burst. We illustrate this in Fig. 1b and c using the classical Hodgkin-Huxley model having fast synaptic conductances and in Fig. 2b using other conductance-based models. The first spike evokes a damped oscillation of the membrane potential, which results in an oscillation of distance to the threshold, and hence an oscillation of the firing probability. All of these oscillations have the same period – the *eigenperiod*. The effect of the second spike depends on its timing relative to the first spike: If the interval between the spikes is near the eigenperiod or its multiple, the second spike arrives during the rising phase of oscillation, and it increases the amplitude of oscillation even further, as in the middle trace of Fig. 1b. In this case the effects of the spikes add up. If the interval between spikes is near half the eigenperiod, the second spike arrives during the falling phase of oscillation, and it leads to a decrease in oscillation amplitude, as in the bottom trace of Fig. 1b. The spikes effectively cancel each other out in this case. The same phenomenon occurs for inhibitory synapses, as we illustrate in Fig. 1c. Here the second spike increases (decreases) the amplitude of oscillation if it arrives during the falling (rising) phase.

a. Exponential Decay to Rest

$I_{Na,p} + I_K + I_{leak}$

$|$ 1 mV

50 ms

b. Oscillatory Decay to Rest

$I_{Na,p} + I_{K(D)} + I_{leak}$

$|$ 5 mV

25 ms

(window) $I_{Na,t} + I_{leak}$

$|$ 1 mV

50 ms

$I_h + I_{Na,p} + I_{Na} + I_K + I_{leak}$

$|$ 1 mV

100 ms

Non-resonant Burst   Resonant Burst

Figure 2: Examples of subthreshold behavior in electrophysiological models of neurons. a. Neurons having exponential (non-oscillatory) decay to the rest state prefer high frequency of the input (vertical bars below the voltage traces). An input burst of four spikes is more effective when the interspike interval is small. b. Neurons having oscillatory potentials: A single spike (left) evokes damped oscillations of membrane potential with certain frequency (eigenfrequency). An incoming burst of pulses is not effective if its interspike frequency is half the eigenfrequency (non-resonant bursts in the middle). The burst is effective when the interspike frequency equals the eigenfrequency (resonant burst in the right). Action potentials are cut.

This mechanism is related to the well-known phenomenon of subthreshold membrane resonance, as reviewed by Hutcheon and Yarom (2000): Subthreshold response of the neuron depends on the frequency content of the input doublet, triplet, or a short burst of spikes. We say that the burst is *resonant*, if its interspike interval is near the eigenperiod of the postsynaptic cell, and *non-resonant* otherwise. A key observation is that the same burst can be resonant for one neuron and non-resonant for another depending on their eigenperiods. For example, in Fig. 3 neurons B and C have different periods of subthreshold oscillations: 12 and 18 ms, respectively. By sending a burst of spikes with interspike interval of 12 ms, neuron A can elicit a response in neuron B, but not in C. Similarly, the burst with interspike interval of 18 ms elicits response in neuron C, but not in B. Thus, neuron A can selectively affect either neuron B or C by merely changing the interspike frequency of bursting without changing the efficacy of synaptic connections.

1.1 Hopf Bifurcation and Resonance

We have used here the classical Hodgkin-Huxley model because it can easily exhibit subthreshold oscillation of membrane potential due to the interplay between transient sodium and potassium currents. Such oscillations can also occur, e.g., due to the alternating activation of persistent sodium and potassium (Hutcheon and Yarom 2000, Llinas et al. 1991) currents or h-current (Hutcheon et al. 1996a), an interplay between activation and inactivation of a window inward current, activation of low-threshold (Hutcheon et al. 1994) or P/Q type (Pedroarena and Linas 1997) calcium currents, or some combinations of the above currents, as we illustrate in Fig. 2. Thus, damped oscillations are ubiquitous in neural models. However, we fail to identify any "magical" set of channels that would *always* result in oscillatory potentials, since changing the maximal conductances and shapes of (in)activation curves can result in non-oscillatory potentials (unpublished observation).

Using dynamical system theory, one can show that damped oscillations *always* occur when neuron dynamic is near Andronov-Hopf bifurcation (Kuznetsov 1995). For example, the Hodgkin-Huxley model and all the models in Fig. 2 reside near Andronov-Hopf bifurcation. Taking advantage of this mathematical fact, we have shown analytically (see review by Izhikevich (2000)) that frequency preference, resonance, and selective communication are universal phenomena, which do not depend on the ionic mechanism or the details of equations describing neuron dynamics as long as the model is near Andronov-Hopf bifurcation.

Discussion

Neurons exhibiting subthreshold oscillations have attracted much attention recently because they can exhibit frequency preference and resonance (see review by Hutcheon and Yarom (2000)). Most researchers are interested in how such neurons can contribute to synchronization and its role in neuronal processing (see review by Singer (1999)). Here we propose an alternative hypothesis on the importance of subthreshold oscillations – selective communication via short bursts of spikes. Indeed, neurons with subthreshold oscillatory potentials prefer rhythmic input with certain frequencies, i.e., resonant input, but bursting *is* such a rhythmic input. The same burst of action potentials can be resonant for some neurons and non-resonant for others, depending on their eigenfrequencies. By generating such a burst, a neuron can selectively affect some neurons, but not the others. This is the key to our hypothesis of selective communication. Incidentally, our hypothesis also provides an alternative interpretation of the functional importance of bursting activity.

There are many cells, including neocortical pyramidal neurons, that rarely exhibit subthreshold oscillatory potentials. Such cells would not show frequency preference to *incoming* bursts, but they can still communicate selectively with other neurons by *sending* bursts provided that the postsynaptic neurons have oscillatory potentials.

Methods

We have used the Hodgkin-Huxley (1952) model with original values of parameters except for $I = 5$, which
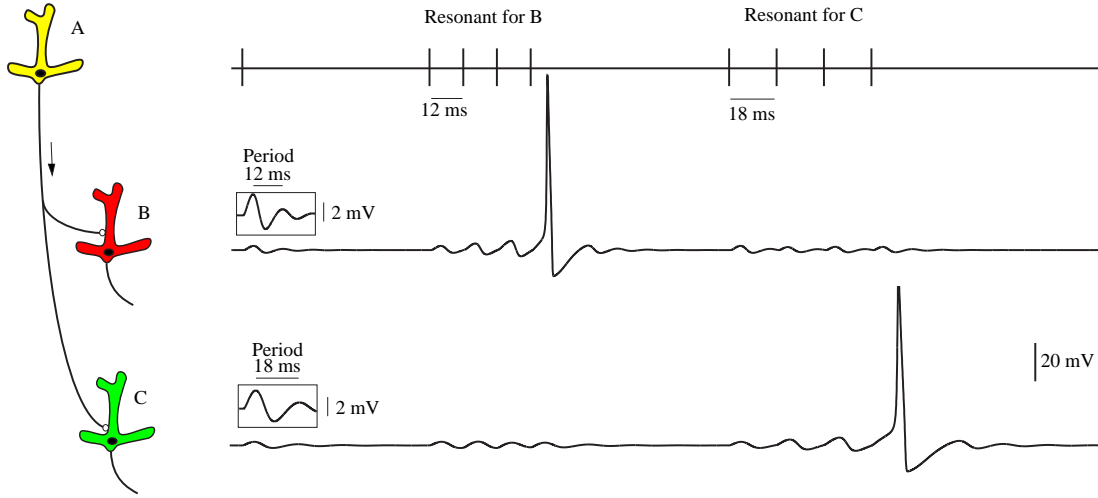
Figure 3: Selective communication via bursts: Neuron A sends bursts of spikes to neurons B and C that have different eigenperiods (12 ms and 18 ms, respectively. Both are simulations of the Hodgkin-Huxley model). As a results of changing the interspike frequency, neuron A can selectively affect either B or C without changing the efficacy of synapses.

makes subthreshold oscillation of membrane potential more pronounced. The synaptic conductance is modeled as the "α-function"

$$g_{\mathrm{syn}}(t) = \alpha t e^{-t/\tau}$$

where $t \geq 0$ is the elapsed time after spike, $\tau = 2$ ms and $\alpha = 0.015$ (in Fig. 1b,c and 3). To obtain the subthreshold oscillations with 18 ms period (the bottom trace in Fig. 3), we rescale time in the Hodgkin-Huxley model by the factor of 2/3, i.e., we multiply the right-hand side of the Hodgkin-Huxley 4-dimensional system by 2/3. All simulations are performed in MATLAB, The MathWorks Inc.

Acknowledgments

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