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Subthreshold oscillations and neuronal input–output relationships

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Abstract

The difference between resonator and integrator neurons relies upon a frequency preference for the former, while the latter monotonically increase their spiking probability with the frequency of a periodic input. In model neurons where dynamics on multiple time scales are present (hence ubiquitously in real neurons) the concept of frequency preference can naturally be broaden to take into account preference towards temporally specific n-uples of presynaptic inputs. On the other hand, single neurons with dynamics on multiple time scales can detect specific temporal patterns as we discuss in this paper.
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1. Introduction

Traditionally, model neurons have been classified on the basis of their computational properties as integrators or resonators [3]. While integrator neurons are more likely to fire a spike when they receive high frequency inputs, resonator neurons show some preference to spikes with a certain interspike interval (*ISI*), in the sense that their firing probability is maximum when the presynaptic *ISI* has a certain non-zero value. This property depends on the kind of bifurcation of the stable equilibrium corresponding to the rest state the neuron is near to. In general, integrator neurons are close to a saddle-node bifurcation (whether off or on a limit cycle) while resonators are close to an Andronov–Hopf bifurcation. In the latter case the stable focus corresponding to the rest state is surrounded by an unstable limit cycle (subcritical Andronov–Hopf bifurcation) or by large amplitude trajectories which will eventually lead the phase point back to the stable focus (supercritical Andronov–Hopf bifurcation). In both cases a displacement of the current phase point from the stable focus might give rise to a small amplitude oscillation, eventually leading the phase point back to the stable focus, or a large amplitude oscillation, corresponding to a spike.

In this paper we focused our analysis in a simple model neuron near a supercritical Andronov–Hopf bifurcation. If we consider the response of the neuron to a pair of inputs (a doublet), the effect of the second input will depend upon its timing with respect to the first, and upon the amplitude of the first input. Indeed the first input will cause a subthreshold oscillation of the phase point, at a frequency that depends upon the amplitude of the oscillation, hence upon the input amplitude. The second pulse might push the phase point to regions of the phase space corresponding to large amplitude trajectories (i.e. spikes), or might as well push the phase point closer to the stable focus, resulting in a dampening of the subthreshold oscillations (e.g. [3, Fig. 7.22]). When more than a resonant variable is added to the model, the phase space around the stable focus might become very complex, and the frequency of oscillation might depend not only upon the amplitude but also upon the current phase. This scenario leads to complex input–output relationships, where single neurons might have evolved and developed so as to respond only to certain, precisely timed sequences of inputs. Neuronal preference in terms of temporal structure of incoming inputs has been known for a long time [6], nevertheless few theoretical efforts have been made for the identification of the minimal ionic mechanisms which can implement it.

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2. Model

We argue that the traditional notion of frequency preference can be naturally broaden to take into account n-uples of presynaptic inputs (Fig. 1). The neurocomputational property of frequency preference is based upon a resonance ionic mechanism. For instance, a model neuron with a K^+ activation variable or a Ca^{2+} inactivation variable could, with an adequate choice of the parameters, display a phase portrait close to an Andronov–Hopf bifurcation, and hence show resonant properties. Nevertheless real neurons display several amplifying and resonant variables acting on comparable time scales, hence it is reasonable to hypothesize that such an interaction might give rise to complex input–output relationships. We prove this hypothesis by injecting triplets of presynaptic spikes with different ISIs in a model neuron, and observing whether a triplet elicited a spike or not.

Neurons near an Andronov–Hopf bifurcation do not exhibit all-or-none firing behavior: medium amplitude depolarization cannot be unambiguously classified as spikes or as subthreshold oscillations. Nevertheless the region of the phase space corresponding to initial conditions leading to partial spikes is very narrow, hence their occurrence is highly improbable. Thus, a positive response to a presynaptic triplet was defined as the crossing of a threshold $V_{th} = -10\,\text{mV}$ with positive slope of the membrane potential variable within the 2 ms following the last spike of the triplet. We departed from a two-dimensional $I_{Na,p} + I_K$ model with low-threshold K^+ current near a subcritical Andronov–Hopf bifurcation, whose bifurcation diagram against a constant injected current is depicted in Fig. 6.16 of [3]. We added a hyperpolarization activated resonant h current to obtain a three-dimensional conductance based model:

$$C\frac{dV}{dt} = -(g_L(V - E_L) + g_{Na}m_\infty(V)(V - E_{Na})$$
$$+ g_K n(V - E_K) + g_h m(V - E_h) + I_{Syn}),$$

where

$$\frac{dn}{dt} = \frac{1}{1 + \exp((-45 - V)/5)} - n,$$
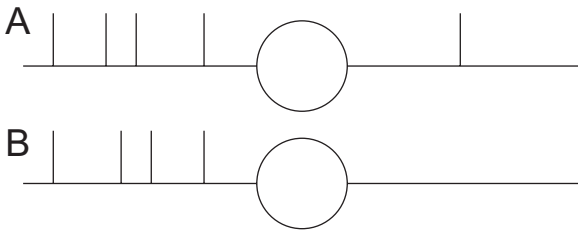
$$2\frac{dm}{dt} = \frac{1}{1 + \exp(60 + V)} - m$$

Fig. 1. Example of input–output preference relationship. The two input patterns are different permutations of the same set of ISIs, but the neuron responds only to input pattern A.

and

$$m_\infty(V) = 1 \Big/ \left(1 + \exp\left(\frac{-30 - V}{7}\right)\right)$$

having a leak current I_L, a persistent Na^+ current $I_{Na,p}$ with instantaneous activation kinetics, a relatively slower persistent K^+ current I_K, and a hyperpolarization activated I_h current. The parameters of the model have the following values: $C = 1\,\text{pF}$, $E_L = -78\,\text{mV}$, $g_L = 1\,\text{nS}$, $g_{Na} = 4\,\text{nS}$, $E_{Na} = 60\,\text{mV}$, $g_K = 4\,\text{nS}$, $E_K = -90\,\text{mV}$, $g_h = 2\,\text{nS}$, $E_h = 20\,\text{mV}$. The synaptic current is $I_{Syn}(t, V) = g_{Syn}r_i(t)(V - E_{Syn})$, where g_{Syn} is the peak synaptic conductance, $E_{Syn} = 62.5\,\text{mV}$ is the synaptic reversal potential, and the functions r_i represent the fraction of bound receptors at each synapse, modeled as described in [1]: $r(t) = 1 + (r(t_s) - 1)e^{(-(t-t_s))/\tau_r}$ if $t_s < t < t_s + t_1$, and $r(t) = r(t_s + t_1)e^{-\beta(t-(t_s+t_1))}$ if $t > t_s + t_1$. Here t_s is the time of the most recently detected presynaptic spike, and parameters $\tau_r = 1.128\,\mu\text{s}$, $\beta = 70.18\,(\text{ms})^{-1}$ and $t_1 = 4.176\,\mu\text{s}$ are the time constants of rise and decay of the synaptic conductance, and the duration of the rising phase. The model parameters were not chosen to match the values of their biological counterpart in any particular living neuron. Nevertheless we believe that this model neuron provides a valid prove-of-principle of the dynamical mechanism of pattern preference presented in this paper.

In general, response to synaptic inputs results in a deformation of the phase space. Even in the case of the widely used synaptic model where each presynaptic spike triggers a synaptic conductance with fixed reversal potential which is an alpha function of time, the time constants of rise and decay of the synaptic conductance are comparable with the time constants governing ion channels kinetics. Hence the dynamical response of the system cannot be qualitatively analyzed unless the system is cast into a higher-dimensional state space, which additionally complicates the understanding of the dynamics. In this case the values chosen for these parameters correspond to a very fast kinetics if compared to the other variables of the system, hence the synaptic conductances in this model can be considered as instantaneous current pulses which do not affect the vector field in the state space, but only displace the current phase point to the right along the V axis (see [3, Fig. 7.2]).

3. Results

This paper shows that n-uples of spikes with the same average frequency can elicit a postsynaptic spike depending upon the precise temporal structure of the n-uples. For visualization purposes triplets of spikes were considered. Fig. 2 shows the input–output preference relationship for increasing values of the injected current. The neuron was set at its only stable point, and its response to triplets with different ISIs was considered. Each triplet of spikes (t_1, t_2, t_3), corresponding to a pair of ISIs $(t_2 - t_1, t_3 - t_2) = (ISI_1, ISI_2)$, is represented with a black cell if a
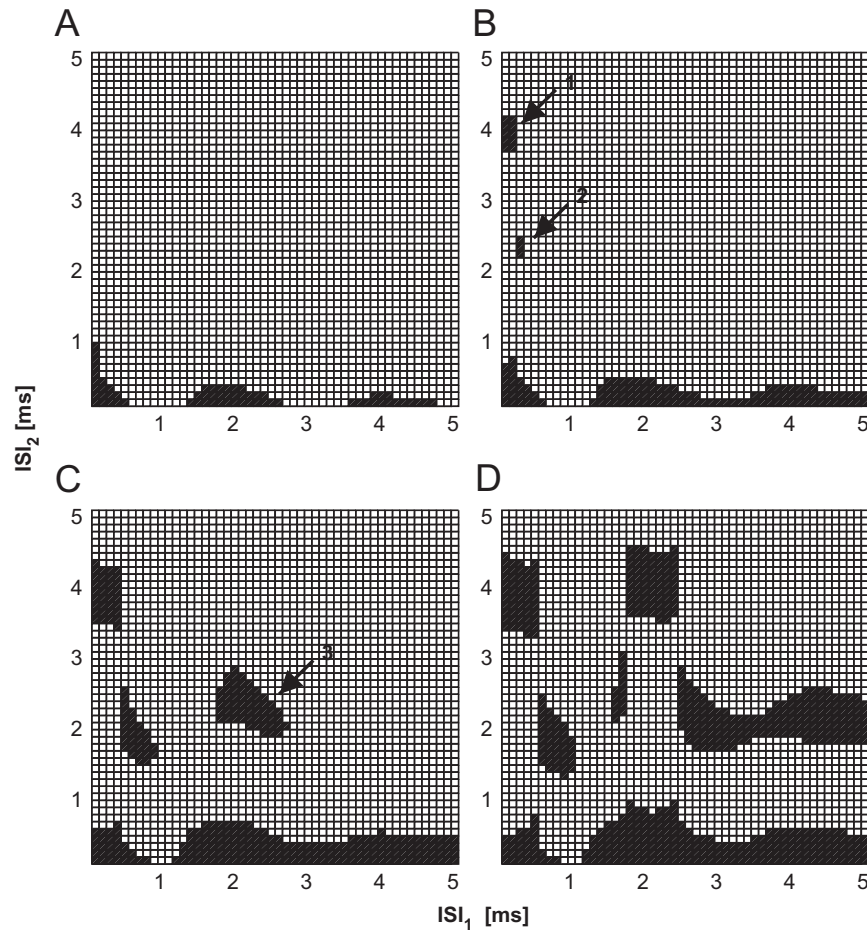
Fig. 2. Input–output preference relationship for the model neuron described in the text. Black cells correspond to triplets of spikes that fire the neuron. Panels A, B, C and D depict the preference relation for increasing values of the synaptic efficiency g_{Syn}: 4, 4.5, 5.5, 6 nS, respectively.

postsynaptic spike was observed after the third presynaptic pulse. In some cases postsynaptic spikes were observed before the third presynaptic pulse, but never in response to a single presynaptic pulse. Thus, the input–output preference relationship to triplets of spikes that we present here is not only shaped by the subthreshold ionic properties of the model neuron, but also by its refractoriness.

For low synaptic efficacies, only triplets with a sufficiently short ISI_2 can elicite a spike, thus the neuron acts mainly as an integrator. Nevertheless specific values for ISI_1 can prevent the neuron from firing in response to the third spike, regardless of its latency with respect to the second (excitation-induced depression). As g_{Syn} is raised to 4.5 nS, two new regions of preference in the (ISI_1, ISI_2) plane appear, marked in Fig. 2B with black arrows. The first cluster corresponds to triplets which elicit two postsynaptic spikes, one in response to the second pulse and another in response to the third. The interplay between the refractory current I_K and the hyperpolarization activated resonant current I_h results in a second postsynaptic spike if $ISI_2{\sim}3.9$ ms. Note that this interval is remarkably different from the resonant interval of the model neuron, which is around 2.1 ms. The second cluster comprises triplets whose first ISI is slightly subthreshold, and results in a wide oscillation which is exploited by a correctly timed third presynaptic spike.

When g_{Syn} is raised to 5.5 nS, the previously described favorite regions broaden and move in the (ISI_1, ISI_2) plane, and a new region marked with the arrow number 3 appears. This region corresponds to a group of resonant triplets with similar ISI_1 and ISI_2, thus reflecting the traditional notion of frequency preference. When g_{Syn} is raised to 6 nS, a complex topology of favorite triplets emerges. A short or a resonant ISI_1 will elicit a spike in response to the first doublet. At both sides of the resonant column of triplets, a single postsynaptic spike will be elicited if $ISI_2{\sim}2.1$ ms, which is the intrinsic frequency of subthreshold oscillations in this model. Nevertheless this row of favorite triplets shrinks and widens as ISI_1 is increased from 2.1 ms until 5 ms, reflecting the complex history-dependence of the input–output relationship exhibited by this model neuron. In addition to this there is a range of ISI_1 centered around 1.3 ms which will prevent the neuron to fire in response to a ISI_2 at the intrinsic frequency. There are two regions in the (ISI_1, ISI_2) plane which corresponds to two postsynaptic spikes. They

correspond to a short or a resonant ISI_1, followed by an ISI_2 around 4 ms, which is the post-spike favorite interval already discussed in the presentation of panel B.

4. Discussion

This work shows how complex input–output relationships can arise even in a very simple neuronal model: a triplet of inputs with a certain average frequency can elicit a postsynaptic spike, or not, depending upon the precise temporal structure of the triplet, as well as upon the amplitude of each of the inputs. This input–output preference relationship depends upon the parameters of the model neuron. Hence in the context of a network of such neurons with a certain distribution of parameters, a presynaptic spike train can elicit spikes in a different postsynaptic cell at different times [2], thus translating a temporal code into a spatiotemporal or purely spatial code. This observation is highly relevant in the context of large networks describing different layers of information processing. In the context of signal propagation, for instance, a large scale network of model neurons with different subthreshold dynamics might display signal propagation to one or another region of the network depending on the temporal structure of the external signal, or could convey different information to different regions. Recent modeling results have shown that neural signatures, i.e. cell-specific ISI distributions, can be part of a multicoding strategy of bursting neurons [4]. The model presented in this paper can distinctively react as a reader of these neural signatures.

This study focuses on intrinsic neuronal dynamics and neglects the realistic dynamics of synaptic transmission. Since the frequency of subthreshold oscillations depends upon oscillation amplitude, the input–output temporal preference relationship outlined above is expected to change when short term plasticity is added to the synapses. Synaptic conductances modeled as instantaneous current pulses do not alter the phase portrait of the system but only shift the current phase point to the right along the V axis; obviously the inclusion of a more realistic synaptic dynamics, with time constants comparable to ion channels kinetics, would lead to more complicated input–output relationships. Nevertheless we proved that a simple three-dimensional neuron has the computational capabilities for implementing the well known non-commutative summation observed experimentally [6].

Many neural systems encode sensory information using a small number of simultaneously active neurons. In fact many areas of the brain are surprisingly very sparsely active [7]. One of the proposed explanations to silent neural systems is the presence of sparse stimulus selectivities, i.e. smart neurons that only respond to very specific stimuli [5]. In this paper we have explained a simple dynamical mechanism for these preferred input–output relationships.

Acknowledgments

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