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Inhibitory inputs increase a neurons's firing rate

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Abstract

Neurons are typically thought of as receiving information primarily through excitatory inputs, with inhibitory inputs playing a gating or regulating role. In this paper we demonstrate that increasing the strength of inhibitory inputs to the Hodgkin–Huxley and FitzHugh–Nagumo models can induce them to fire faster. This result is counter-intuitive and important in neural network modelling where inhibitory inputs are often neglected.

Keywords: Inhibitory input; The Hodgkin–Huxley model; The FitzHugh–Nagumo model; IBF; The integrate-and-fire model; The IF-FHN model

1. Introduction

Why neurons in the cortex receive and emit stochastic rather than deterministic signals remains elusive, despite century-long research activity. The advantage of deterministic signal transmission over stochastic is obvious: it is much more economic and reliable. The stochastic part of a signal is usually thought of as 'noise' and is the part any system tries to get rid of. In stochastic resonance theory [15], noise is hypothesized to be useful, but an application of the theory to the neuronal system tells us that it only works inside a very limited parameter region and a carefully adjusted input signal is required [13]. In the present paper, we show that with Poisson type inputs and in certain parameter regions, increasing inhibitory inputs can actually increase firing rate of a neuron. The conclusions are numerically demonstrated both in

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the Hodgkin–Huxley (HH) and FitzHugh–Nagumo (FHN) models. As in the literature [10,3,9], we assume that a neuron receives inputs ranging from purely excitatory inputs to exactly balanced inhibitory and excitatory inputs. We term the phenomenon increasing-inhibition boosted firing (IBF).

A natural and interesting question is then why and when increasing inhibitory inputs to a neuron can boost its efferent firing rate. A full treatment of the HH and the FHN models with stochastic inputs is difficult, although this might not always remain 'a formidable task' [18]. In the present paper, we turn to the integrate-and-fire model (IF) and the IF–FHN model. Surprisingly the IBF phenomenon is observable for both models, which indicates that IBF is not due to complex, nonlinear mechanisms of biophysical models. Theoretical results for the IF model and IF–FHN model are developed, which elucidates the mechanism underpinning the IBF phenomenon.

The IF model is one of the most widely used model in (theoretical) neuroscience. It is an extremely simplified model and is linear (before resetting). Nevertheless, in the literature, a transparent and theoretical result on its input-output relationship is lacking. We apply theoretical results recently developed in [11] to the IF model and a simple relationship between input and output frequency is obtained. The formula enables us to prove that when input frequency is lower than a critical frequency, the output frequency is higher when the neuron receives a mixture of inhibitory and excitatory inputs than when it receives purely excitatory inputs. Moreover, the critical frequency is unique. For IF–FHN model, a model which is originally proposed to mimic the FHN model, we apply Kramer's formula [1] to prove that there is a critical frequency at which the efferent firing rate when the model receives purely excitatory inputs is equal to the rate with exactly balanced inputs.

Roughly speaking, the IBF phenomenon is due to a competition between two driving forces of neurons: stochastic and deterministic. Assume that a is the magnitude of EPSPs (excitatory postsynaptic potentials) or IPSPs (inhibitory postsynaptic potentials) and λ is the input frequency. When the neuron receives purely excitatory inputs, the deterministic force is proportional to $a\lambda$ and the stochastic force is $a^2\lambda$. For the exactly balanced input case, the deterministic force is 0 and stochastic force is $2a^2\lambda$. In general the deterministic force is more efficient in driving a cell to fire and therefore increasing inhibitory input reduces the firing rate of a neuron, in agreement with our intuition. However, when λ is small enough, the deterministic force of purely excitatory inputs is $a\lambda$ and the deterministic force plays a minor role in driving the cell to fire. In other words, now the noise term is more prominent. The noise term for the exactly balanced input case is $2a^2\lambda$, which is twice that for purely excitatory inputs, $a^2\lambda$. Therefore under these circumstances the neuron fires faster when inhibitory inputs increase, i.e. noise increases.

The above scenario provides us with the answer to the 'why' question. It is of equal importance to answer the 'when' question, since in parameter regions where the IBF phenomenon occurs the neuron might fire too slowly and has no physiological reality. For the IF model and in parameter regions used in the literature, this is truly the case. It is difficult to observe it if only numerical simulations are employed. This might also tell us that why the IBF phenomenon has never been reported in the literature. Nevertheless, for the IF–FHN model, there are physiologically reasonable regions of

(a,λ) in which increasing inhibitory inputs increases neuronal firing rate, as we have observed for the HH and the FHN models. We fully characterize the region for IF–FHN model. As we pointed out before, the nonlinear leakage in IF–FHN model ensures that it behaves very differently from the IF model.

The arguments above also indicate that increasing inhibitory inputs boosting neuronal firing rate is a universal phenomenon. Whether we could observe it or not in a physiologically plausible parameter region depends on neuronal parameters, or for real neurons, on the environment in which they operate. Since a neuron usually receives a massive excitatory and inhibitory input, we hope our finding could shed new lights onto the coding problem [12,15] and suggest another functional role of inhibitory inputs, or noise terms in signal inputs.

As a by-product, our results also alter another conventional view in theoretical neuroscience: increasing inhibitory inputs results in an increase of the randomness of output spike trains. In recent years, the issue has been extensively discussed [3,4]. A more general and biologically realistic principle is that the faster a neuron fires, the more regular its interspike intervals are. In terms of this principle, we demonstrate that in the parameter regions in which the IBF occurs, the efferent interspike intervals becomes more regular when inhibitory inputs increase.

Due to the space limit, here we mainly present numerical results of the IBF for the IF–FHN model and refer the reader to our further publications [10,14] on the HH model, the FHN model and theoretical approaches.

2. Models

For two given quantities $V_{\text{thre}} > V_{\text{rest}}$ and when $v_t < V_{\text{thre}}$, the membrane potential v_t satisfies the following dynamics:

$$\begin{cases} \mathrm{d}v_t = -L(v_t)v_t\,\mathrm{d}t + \mathrm{d}I_{\text{syn}}(t), \\ v_0 = V_{\text{rest}}, \end{cases} \tag{1}$$

$I_{\text{syn}}(t)$ is the synaptic input given by

$$\mathrm{d}I_{\text{syn}}(t) = \mu\,\mathrm{d}t + \sigma\,\mathrm{d}B_t, \tag{2}$$

with constants $\mu \geqslant 0$, $\sigma \geqslant 0$ and the standard Brownian motion B_t. Once v_t is greater than V_{thre}, it is reset to V_{rest}. More specifically we define

$$\mu = a\lambda(1-r), \quad \sigma^2 = a^2\lambda(1+r), \tag{3}$$

where $a > 0$ is the magnitude of EPSPs and IPSPs, λ is the input rate, r is the ratio between inhibitory inputs and excitatory inputs. In particular, when $r = 0$ the neuron receives exclusively excitatory inputs; when $r = 1$ the inhibitory and excitatory input is exactly balanced. Here for the simplicity of notation, we assume that the EPSP and IPSP size are equal and refer the reader to [16] for a more complete and biologically oriented formulation of synaptic inputs.

When $L(v) = L > 0$, a constant, the model is termed the IF model; when the leakage coefficient

$$L(v) = \gamma(v - V_{\text{thre}})(v - \alpha) + \frac{1}{\beta}, \tag{4}$$

with constants $\gamma > 0$, $\alpha > 0$, $\beta > 0$, the model is as proposed in [7,10] for mimicking the FNH model.

Unlike the IF model, for IF–FHN model the leakage coefficient is not a constant. When the membrane potential is between the resting potential $V_{\text{rest}} \sim 0$ and the threshold V_{thre}, the leakage coefficient $L(v)$ is positive. Hence the system will gradually lose its memory of recent activation. However, $L(v)$ is very different from L. $L(v)$ is larger when the membrane potential is close to the resting potential. The more the membrane potential is away from its threshold, the larger the decay is. This mechanism naturally prevents the membrane going too negative, a mechanism the IF model lacks and we have to set a lower bound for the IF model. The leakage coefficient vanishes when the membrane potential is close to the threshold. In other words, when the membrane potential is near resting potential, the model loses its memory rapidly. Incoming signals accumulate less effectively to increase membrane potential. When membrane potential is near to the threshold, however, the IF–FHN model behaves more like a perfect IF model. The IF–FHN model now has a very good 'memory' and in a sense 'waits' just below the threshold. As soon as some positive signals arrive, the neuron fires. Therefore, below the threshold, the IF–FHN model behaves as a combination of the *leaky* integrate-and-fire model and the *perfect* IF model.

Once the membrane potential is above a certain value, $L(v) < 0$ and now it acts as an amplifier of incoming signal, rather than as a leakage. It will increase membrane potential until it arrives at its maximum value and then $L(v)$ becomes positive again.

In the sequence, we define

$$T(r) = \inf\{t : v_t \geqslant V_{\text{thre}}\}, \tag{5}$$

as the mean firing time for $r \in [0,1]$. For IF–FHN model a constant refractory period of $T_{\text{ref}} = 3.2$ ms is usually added to $T(r)$, which is approximately the refractory period of the FHN model [3].

3. Examples

We use the following set of parameters in simulations [3,8] for IF–FHN model

$$\gamma = 100, \quad \alpha = 0.2, \quad \beta = 2.5,$$

$v_{\text{thre}} = 1$ and $v_{\text{rest}} = 0$.

In Fig. 1 we see that when the excitatory input frequency is high ($\lambda = 5$ kHz), the output firing rate is a decreasing function of inhibitory input rate, in agreement with our intuitions. For example, when $r = 0, \langle T(0) \rangle + T_{\text{ref}} = 6.33$ ms and $r = 1, \langle T(1) \rangle + T_{\text{ref}} = 8.32$ ms. When the excitatory input frequency is around ($\lambda = 3.8$ kHz), the

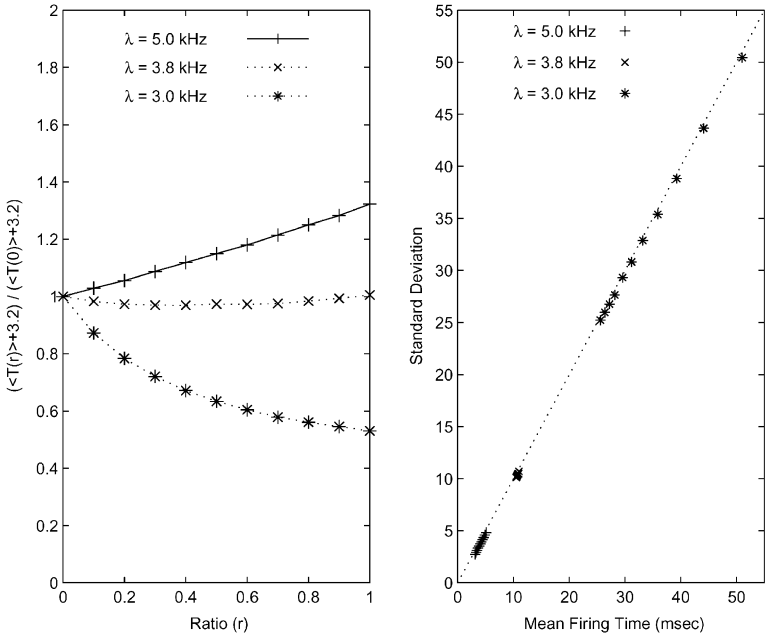

Fig. 1. $a = 0.1$. Left: when $\lambda = 5$ kHz, $\langle T(0)\rangle + T_{\text{ref}} = 6.33$ ms; $\lambda = 3.8$ kHz, $\langle T(0)\rangle + T_{\text{ref}} = 14.36$ ms and $\lambda = 3$ kHz, $\langle T(0)\rangle + T_{\text{ref}} = 57.17$ ms. Right: standard deviation of $T(r)$ vs. $\langle T(r)\rangle$. It is easily seen that the standard deviation is almost equal to $\langle T(r)\rangle$, namely the efferent spike trains are Poisson process.

output firing rate is almost a constant function of inhibitory input rate. For example when $r = 0, \langle T(0)\rangle + T_{\text{ref}} = 14.36$ ms and $r = 1, \langle T(1)\rangle + T_{\text{ref}} = 14.26$ ms. Further reducing the excitatory input rate shows the IBF phenomenon: *increasing inhibitory inputs increases neuronal firing rates*. For example when $r = 0, \langle T(0)\rangle + T_{\text{ref}} = 57.17$ and $r = 1, \langle T(1)\rangle + T_{\text{ref}} = 29.87$.

Let us define a *critical input frequency* λ_c as the quantity which satisfies

$$\langle T(0)\rangle = \langle T(1)\rangle. \tag{6}$$

The numerical results of Fig. 1 tell us that $\lambda_c \sim 3.8$ kHz when $a = 0.1$.

It has been widely reported in the literature that increasing inhibitory input to a neuron could increase the variability of its output [2,3,6,5]. Fig. 1 (right) shows standard deviation vs. mean firing time $\langle T(r)\rangle$. As we reported before [3], the standard deviation of $T(r)$ almost equals its mean. Therefore in the no IBF parameter regions, increasing inhibitory input induces an increase of its variability of output. However, in the parameter regions in which the IBF occurs, we see that now the coefficient of variation (CV) of $T(r)$ is a decreasing function of r rather than an increasing function of r, in contrast to conventional theory in the literature (Fig. 2).

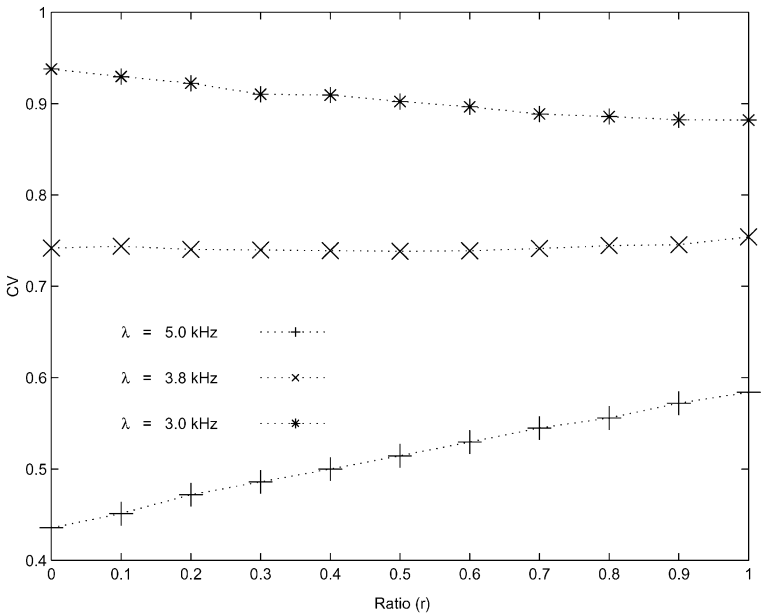

Fig. 2. Coefficient of variation (CV) of IF–FHN model. CV could be either an increasing or a decreasing function of r.

4. Discussion

We answer the following questions in the present paper [10,14]: why and when does increasing inhibitory inputs increase neuronal firing rates? For the IF model, we show that there is a unique input frequency λ_c at which the efferent firing rate of a neuron is identical when the cell receives purely excitatory inputs or exactly balanced inhibitory and excitatory inputs. For IF–FHN model, by Kramer's formula, we prove that when input frequency is low enough the model increases its efferent firing rate when inhibitory inputs are added to the model. Our results provide a theoretical foundation for the IBF phenomenon and might alter our traditional views on stochastic inputs of a neuron.

Finally, we point out that the mechanism of IBF described here is totally different from that in [17]. In [17] the authors consider a network of excitatory and inhibitory neurons and find that increasing the direct external inhibitory input to the inhibitory interneurons, without directly affecting any other part of the network, can, in some circumstance, cause the interneurons to increase their firing rates. It is essentially a network phenomenon, but the IBF phenomenon, as we have emphasized before, is observable for single neuron, no matter it is an inhibitory (interneuron) or an excitatory neuron. Furthermore, the IBF phenomenon cannot be observed, if the input is deterministic which is the case in [17]. The IBF is due to the ergodic property of a system driving by noise.

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