Intrinsic desynchronization properties of neurons containing dendritic rapidly activating K-currents

Vicente Charcos Lloréns, Erik Fransén*

Dept. of Numerical Analysis and Computer Science
Royal Institute of Technology, SE-100 44 Stockholm, Sweden

*To whom correspondence should be addressed
Email: erikf@nada.kth.se
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Abstract

In this work, we investigate the role of the potassium A-current (K_A) in linking network synchrony to cellular excitability and firing frequency. We present an analysis of the notion of synchrony and we describe its conceptual and modeling implications. At full synchronization, K_A enables a control over the timing, or even a supression, of spikes. For completely desynchronized activity, we show how K_A affects fast changes in amplitude of the summed EPSPs as well as amount of depolarization caused by the input. Simulations at intermediate levels of synchrony suggest that activity resulting from the interaction between cellular excitability and network synchrony could be altered through K_A modulation.

1. Introduction

Synchronous neural activity has been experimentally observed and discussed in a

multitude of functional contexts. Asynchronous activity, on the other hand, is seemingly involved in other functions such as working memory tasks. Furthermore, failures in synchrony regulation may have pathological consequences: enhanced synchronization, for instance, is characteristic of epilepsy and is associated in such cases to increased cell excitability. Therefore, there might exist a close relationship between modulation of synchrony and processing in the brain.

Several studies provide evidence for the participation of K_A channels in regulating excitability and epileptic synchronization. In particular, Castro *et al.* [2] show that heterotopic pyramidal neurons in hippocampus, which are prone to epileptic hyperexcitability, fail to express the A-current. Moreover, the study indicates that synaptic changes cannot explain their experimental observations and that "a hyperexcitability linked to excitatory/inhibitory neuro-transmission imbalance has not been reported." Furthermore, modulators such as acetylcholine, which is known to influence K_A and the cell integrative properties, also affect synchronization [4]. In addition, Hess *et al.* mention a role of K_A channels "in regulating the excitability of neurons and the pattern of activity in a neural network." Hence, K_A channels represent a plausible and particularly interesting mechanism relating network synchrony to cell properties.

2. Model of network inputs to a dendrite

Synchrony is often interpreted as the level of coincident activity of neurons in a network. If all neurons fire simultaneously, the network is said to be synchronized. Deeper considerations that take into account the statistical properties of neural firing introduce correlations among neural trains of spikes as a measure of synchrony.

However, the presence of correlations does not always reflect synchronization, since different phenomena can produce similar correlations [1]. Moreover, it seems reasonable to assume that even asynchronous activity within groups of cells is correlated, because the synapses between the cells compromise the independence of firing. The above-mentioned spike-timing coincidence is a pre-synaptic concept, because it does not depend on how the network activity continues to propagate through synaptic connections. Conversely, a post-synaptic definition could be based on EPSP coincidence, *i.e.* on the timing between post-synaptic signals measured *e.g.* at the soma. At the cellular level, the difference between spike and EPSP coincidence results from the dendritic location and propagation velocities of inputs to a cell. Consequently, given a post-synaptic definition, synchronous activity favors EPSP summation, consistently with the commonly accepted idea of synchronization being efficient in producing spikes.

Synchrony has therefore been defined post-synaptically as the time-window of EPSP summation. The time-window is the *average* duration over which the EPSPs are distributed. The more simultaneous (statistically) the EPSPs, the narrower the time-window and the higher the synchrony. The degree of synchrony s (in %) is then determined by the ratio r between the length of the time-window (T_w) and the average firing period of the network (T_0): $s = 100 \times (1 - r) = 100 \times (1 - T_w/T_0)$. A ratio r close to 1 corresponds to EPSPs that are distributed over time. EPSP summation is then minimal, so the activity in the network is asynchronous. On the contrary, with significant EPSP summation, r tends to 0, corresponding to high levels of synchrony. Other ratios determine intermediate degrees of synchrony. For instance, when inputs whose frequency is 10Hz (average period of 100ms) generate EPSPs that are distributed, on average, within time-windows of 30ms, the inputs have a synchrony

of 70%. However, due to the inherent randomness of spiking, the actual EPSPs are not exclusively restricted to the average time-window, see Figure 1a. It is important to observe that, given this model, synchronization results in high but short depolarizations (strong coincidence within a narrow time-window), whereas desynchronization causes much lower but sustained depolarizations. Note that this model of synchrony only indicates average time-boundaries for EPSP summation, but it does not constrain the distribution of synaptic pulses within the time-window.

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One straightforward solution for modeling inputs with a certain degree of synchrony consists in merging all the inputs into one single population EPSP occurring within the time-window. The amplitude of the population EPSP can be adjusted to account for different population sizes. Further, by adjusting the time-constants of the population EPSP, the input can be restricted to the desired time-window, *i.e.* the desired level of synchrony. However, despite the simplicity of this solution, the representation of multiple synaptic events by a smooth population EPSP fails to express the high-frequency potential variations that actually occur within the time-window, see Figure 1b. These rapid variations —which result from the relationship between the number of inputs, their average frequency and the exact time-course of single EPSPs— might affect the firing of the cell and its mechanisms of excitability, especially rapid mechanisms such as K_A channels. As a result, the use of multiple synapses associated to the different presynaptic cells seems to be a better modeling alternative than population EPSPs. The distribution of these multiple inputs can be modeled by means of several probability functions, such as square or gaussian functions. From a computational point of view, a square function has been preferred in this project for simplicity reasons. The

consequence is that synaptic events are statistically equally distributed over the whole time-window. The actual generation of events satisfying these criteria (given degree of synchrony and uniform distribution) is discussed in the following section.

3. Correlated Poisson processes

By using correlated Poisson processes with a given degree of synchrony, we can account for the time-window of EPSP summation. A random variable $X$with a gamma distribution of shape parameter k and rate λ can be described, based on a Poisson process of same rate λ, as the waiting-time from a given spike until the k^{th} next spike. The case $k = 1$ corresponds thus to an exponential distribution. The probability of this waiting-time being t is:

$$\mathcal{P}(X = t) = \frac{\lambda^k t^{k-1} e^{-\lambda t}}{(k-1)!} \qquad \text{with} \quad t \geq 0, \quad k \in \mathbb{N}^*$$

The gamma distribution can be generalized to non-integer shape parameters $\alpha \equiv k$ and especially to the case $0 < \alpha \leq 1$:

$$\mathcal{P}(X = t) = \frac{\lambda^\alpha t^{\alpha-1} e^{-\lambda t}}{\Gamma(\alpha)} \qquad \text{with} \quad t \geq 0, \quad \alpha > 0 \quad \text{and} \quad \Gamma(\alpha) = \int_0^\infty t^{\alpha-1} e^{-t} dt$$

An interesting property of the gamma distribution is that if X_1 and X_2 are independent gamma variables $\gamma_{X_1}(\alpha_1, \lambda)$ and $\gamma_{X_2}(\alpha_2, \lambda)$, then $X_1 + X_2$ is $\gamma_{X1+X_2}(\alpha_1 + \alpha_2, \lambda)$. Therefore, by sequentially generating random numbers from $n \geq 1$ independent gamma variables $X_1, \ldots, X_n$ with distributions $\gamma_{X_i}(\alpha_i, \lambda)$ so that $\alpha_1 + ... + \alpha_n = 1$, we obtain n $\gamma(1, \lambda)$ variables, *i.e.* exponential variables. Provided that these exponential variables describe interspike intervals, this procedure produces n correlated Poisson processes. This technique suggests a method for modeling the firing of correlated neurons[1] with,

[1] This idea was proposed by Bruce Knight and is described in Jonathan D. Victor's website at

in addition, the possibility to obtain post-synaptic events that are statistically equally distributed over a time-window of a certain average duration. The solution consists in using a set of n spike generators firing sequentially[2], with delays from one another given by n gamma variables of shape parameters summing to unity. In order to restrict the spikes to the proper time-window, the shape parameters are chosen so that $\alpha_1 = \cdots = \alpha_{n-1} = r \times 1/n$ and $\alpha_n = 1 - (n-1) \times r/n$, with a common rate parameter that we set to 12Hz. The advantage of this method is that it extends the synaptic inputs over the time-window while preserving the representation of neural spiking as Poisson processes. In practice, however, the numerical generation of gamma variates with $\alpha < 1$ is a rather difficult task. Thus, although mathematically feasible, it gives rise to computational problems, almost unavoidable for high number n of synaptic inputs. An alternative model that has been used in this work is the use of exponential variables instead of gamma for the generation of delays between consecutive neurons. Their rate $\lambda_i = 1/T_i$ is set so that $T_1 = \cdots = T_{n-1} = r \times T_0/n$ ($T_0 = 1/12$) and $T_n = T_0 - (n-1) \times rT_0/n$. This method does not result in Poisson processes for the spiking of each of the spike generators, although it guarantees the average frequency of 12Hz and the randomness of spiking.

4. K_A effects on cell response

Biophysical multicompartmental neuronal simulations were performed using the NEURON simulation package. The study uses a model adopted from Migliore *et*

http://www.users.med.cornell.edu/~jdvicto/jdvunso.html

[2] Note that, in the context of this study, the order in which presynaptic neurons fire is unimportant; only the resulting series of spikes as perceived by the post-synaptic cell matters.

al. [3] and studied six different published K_A channels described by Hodgkin-Huxley dynamics. Presupposing the case of neurons connected in a network, the effects of K_A were studied in terms of spike production, and not only as suppression of EPSPs. For perfectly synchronous activity, modulation of K_A modifies its transient effect, partly because of its fast inactivation. Thus, K_A is able to affect the timing of the firing response or even suppress it, see Figure 2b. On the other hand, highly asynchronous activity results in a sustained depolarization with superimposed noise. The degree of K_A activation at the depolarized level determines the possibility of K_A to affect the fluctuations and thus the cell response, see Figure 2b. Furthermore, we note that intermediate synchrony-levels cannot be studied as a simple superimposition of two sets of fully synchronized inputs and fully desynchronized inputs. Such an input pattern does not reflect the proper time-distribution of spikes and, therefore, does not reflect the correct interplay between summed EPSPs and K_A activation and inactivation kinetics. All levels of synchrony considered, the conclusion is that both the amplitude and the steepness of changes in excitability (measured in number of spikes) induced via K_A modulation are different at different degrees of synchrony. Because of these differences, cell firing and network synchrony are not trivially related to each other. Instead, their relationship depends heavily on K_A and its modulating mechanisms. As a result, we argue that studies focused on the response of a cell in a network and more particularly studies of synchrony should not neglect this interdependence.

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5. Discussion

Our modeling efforts suggest that synchrony should be defined post-synaptically and not based on firing correlations. In particular, we propose that synchrony can be represented as the average time-window of EPSP summation. In studies of synchrony we suggest to use multiple synaptic inputs rather than one smooth population synaptic input. The results in this work indicate that K_A provides means of altering in complex ways the relationship between synchrony levels in the network and spike frequency, which is usually considered to be trivial. Furthermore, assuming that there are other mechanisms imposing the firing frequency of the cell, we suggest that K_A can constrain the synchrony levels of the network activity to which the neuron tends to participate by preventing a cell to spike in concert with synchronous input.

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Vicente Charcos Lloréns has a M.Sc. in computer science with a major in biomedical engineering. He has a double degree from the Royal Institute of Technology in Stockholm and the Ecole Nationale Supérieure de Techniques Avancées in Paris. Material presented in this article was part of his Master Thesis. He is currently planning his career within the field of biomedical engineering, with a strong but not exclusive interest in research.

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Erik Fransén is an associate professor at the Department of Numerical Analysis and Computer Science at the Royal Institute of Technology, Stockholm, Sweden. He was a post doctoral fellow at the Department of Psychology at Harvard University during 1997-1998. He received his Ph.D. in Computer Science from the Royal Institute of Technology, Stockholm, Sweden in 1996. His research interests include mathematical modeling and biophysical simulation of neurons and networks of neurons. He studies the ionic basis of cellular and network properties of working memory.

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Fig. 1

a Time-window for EPSP summation. Three inputs whose frequency is 10Hz are synchronized at 70%. The time-window (dashed region) is therefore 30 ms long, and it is the average duration for the distribution of EPSPs. Note that both the occurrence of EPSPs at any time-window and the intervals between windows are random, reflecting the inherent unpredictability of neural firing. For clarity, EPSPs are superimposed and not summed.

b Membrane potential variations obtained with multiple (solid line) and population (dashed) inputs. The latter lead to smooth EPSPs that fail to express potential variations of higher frequency, especially important with rapid mechanisms such as K_A .

Fig. 2

a Regulation of the cell's response to multiple synchronous inputs by means of K_A modulation. A progressive change between firing and the loss of spikes is possible with the fast inactivation of K_A. The peak-conductance of K_A at the soma is given as indicative of K_A density.

b Asynchronous activity. Regulation of cell excitability through voltage-shifts of K_A dynamics with 1000 asynchronous inputs. The inputs produce a constant depolarization that changes the steady-state point with small superimposed noisy fluctuations. The modulation shift of K_A then determines the amount of K_A conductance around this new working point.

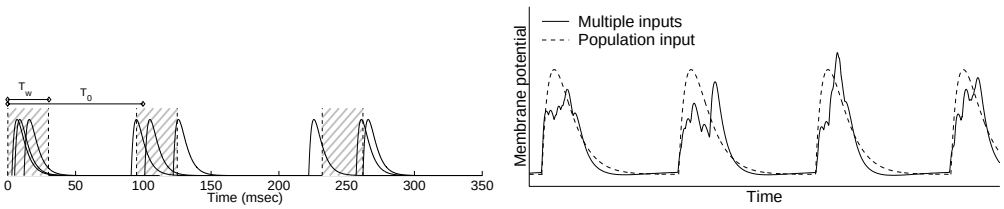

Figure 1: a (left), b (right)

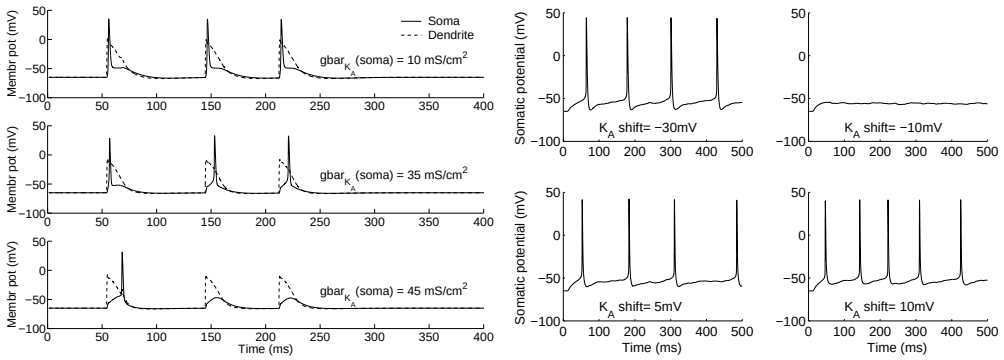

Figure 2: a (left), b (right)