Variation of the Spiking Dynamics of a Hodgkin-Huxley Neuron with an Electrical Autaptic Connection Under Ion Channel Blocking

Elektriksel Öz-sinapstik Bağlantılı Bir Hodgkin-Huxley Nöronunun Ateşleme Dinamiklerinin İyon Kanal Bloklama Durumunda Değişimi

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***Abstract*—In this paper, we investigate how the blockage of potassium and sodium ion channels embedded in membranes affects the spiking dynamics of a Hodgkin-Huxley neuron model owing autaptic connection. We consider an electrical autapse expressed by its coupling strength and delay time. It is found that the spiking behavior of the neuron becomes more ordered with the increment of autaptic conductace regardless of the ion channel block level. Furthermore, it is obtained that the blockage of potassium and sodium ion channels influences differently to the spiking regularity of the neuron. Potassium ion channel blockage promotes regularity, whereas sodium ion channel blockage destroys.**

Keywords*—*electrical autapse; ion channel block; Hogkin-Huxley neuron model.

***Özetçe* —Bu çalışmada hücre zarında gömülü olan potasyum ve sodyum iyon kanallarının bloklanmasının öz-sinaptik bağlantıya sahip bir Hodgkin-Huxley nöronunun ateşleme dinamiklerinin nasıl etkilediği araştırılmıştır. Çalışmada, iletim gecikmesi ve kuplaj şiddetiyle tanımlanan bir elektriksel öz-sinaps durumu ele alınmıştır. İyon kanal durumuna bakılmaksızın, nöronun ateşleme davranışının öz-sinaptik iletkenliğindeki artışla daha düzenli hale geldiği tespit edilmiştir. Bunun yanı sıra, potasyum ve sodyum iyon kanallarının bloklamasının nöronun ateşleme dinamikleri üzerinde farklı etkilerinin olduğu tespit edilmiştir. Potasyum iyon kanal bloklamasının düzenliliği arttırırken, sodyum iyon kanal bloklaması ise düzenliliği bozmaktadır.**

Anahtar Kelimeler*—*elektriksel öz-sinaps; iyon kanal bloklama; Hodgkin-Huxley nöron modeli.

I. INTRODUCTION

Information processing within the nervous systems takes place in the presence of multiple sources of noise. One major source of noise is the voltage gated ion channels which act as a microscopic source of noise current that is injected into the cell [1], [2]. It is known that these ion channels switch randomly between open and close states. These properties of ion channels give rise to voltage fluctuations in the membrane potential [3]. Hence, voltage-gated ion channels embedded in neuronal membranes are of great importance in the generation and propagation of electrical signals. The channel noise depends closely on the number of ion channels, but its real effect is determined by the number of active ion channels participating in the generation of spikes [4]. Therefore, blockage of a given channel type is important to reveal the impact of specific ion channel type on the neuronal dynamics for a given membrane patch. Experimentally, it is showed that some neurotoxins such as tetraetylammonium (TEA) and tetratoxin (TTX) allow reducing the number of active (non-blocked) ion channels [5]. For a given membrane, by a fine-tuned addition of these toxins a certain portion of potassium- and sodium ion channels could be disabled or blocked and hence the number of working (active) ion channels can be reduced. It is also possible to examine the impacts of changing the number particular ion channels based on computational models. In literature, there are lot of studies that investigate the effect of channel blockage on the spiking dynamics of a single neuron or neuronal networks within different structures [6]–[13]. These studies revealed out that ion channel blockage have virtual effects on the dynamics of spiking activity. In the nervous system, the information processing (i.e. signal transmission) between neurons is carried out through synapses. Electrical and chemical synapses are two well-known synapse types. But, several decades ago, it is discovered that some neurons make connections with themselves once again instead of making connections with another neuron [14]–[16]. These types of synapses named as autapse by Van der Glosser in 1972 and found quite common in the nervous system, especially in different brain areas, contrary to expectations [17]. It is known that there are two type of autapse. One is electrical and the other is chemical [18]. Both experimental and computational studies showed that the autapse can change the electrical activities (thus, spiking dynamics) of neurons substantially [19]–[25]. In this context, it is

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revealed experimentally that autaptic connections enhance the precision of spike times of neocortical interneurons [19]. Ikeda and Bekkers [16] suggested that autaptic connections, as a form of time-delay feedback, enable a self-control mechanism at a cellular level. Li et. al [20] reported that spiking activity of a stochastic Hodgkin-Huxley (HH) neuron alters substantially in the presence of autapse. In another study, it is shown that the presence of autaptic connections cause transition among different spiking patterns in a Hindmarsh-Rose (HR) model [21]. It is also demonstrated that the weak signal detection performance of a single HH neuron model is enhanced or suppressed in the presence of autapse depending its parameters [22]. Recently, it is demonstrated that the response of a single neuron to the subthreshold stimulus can be readjusted through autaptic connection [23]. In a recent study, Yılmaz et al. [24] demonstrated that spiking regularity of a single neuron or scale-free neural network can change in the presence of autaptic connections. More recently, we have analyzed how the firing regularity of a small-world (SW) neuronal network is affected in the presence of chemical autaptic connections and ion channel blockage [25]. In this paper, different from above studies, we investigate how the firing regularity of a single HH neuron change when it has an electrical autaptic connection and is exposed to ion channel blocking. To do so, we extend the previous study of Yilmaz et al. [25] by including the effect of ion channel blocking.

II. MODEL AND METHOD

Within this study, we use stochastic HH neuron model whereby the time evolution of the membrane potential is given as follows [22]:

$$C_m dV/dt + G_{Na} m^3 h(V - E_{Na}) + G_K n^4 (V - E_K) + G_L(V - E_L) + I_{aut} = 0 \quad (1)$$

where V is the membrane potential, $C = 1\mu F cm^{-2}$ is the membrane capacity and $E_{Na} = 50mV$,$E_K = -77mV$ and $E_L = -54.4mV$ are the reversal potentials for the sodium, potassium and leakage channels, respectively. G_{Na}, G_K and G_L denote sodium, potassium and leakage conductances, respectively [26]. While the leakage conductance is assumed to be constant, the sodium and potassium conductances defined as follows [6], [9]–[13]:

$$G_{Na} = g_{Na}^{max} m^3 h \qquad G_K = g_K^{max} n^4 \quad (2)$$

where $g_{Na}^{max} = 120mScm^{-2}$ and $g_K^{max} = 36mScm^{-2}$ are the maximal sodium and potassium conductances,respectively. m and n denotes activation and inactivation gating variables for the sodium channel, respectively, whereas the potassium channel includes an activation gating variable, n. In Eq. (2), the (two) scaling factors x_{Na} and x_K, which are confined to the unit interval, correspond to working (non-blocked, active) ion channels, to the overall number of sodium (N_{Na}) or potassium (N_K) ion channels, respectively [6], [7]. Stochastic behaviors of the gating variables obey the following Langevin generalization [27]:

$$dx/dt = \alpha_x(V)(1-x) - \beta_x(V) + \xi_x(t) \quad (3)$$
$$x = (m, h, n)$$

where α_x and β_x are the voltage-dependent rate functions for the gating variable x. We used same parameters as in [24]. In Eq. (3), $\xi_x(t)$ is an independent zero mean Gaussian white noise source whose autocorrelations have the following form [27]:

$$\begin{aligned} <\xi_m(t)\xi_m(t')> &= \frac{2\alpha_m\beta_m}{N_{Na}x_{Na}(\alpha_m+\beta_m)}\rho(t-t') \\ <\xi_h(t)\xi_h(t')> &= \frac{2\alpha_h\beta_h}{N_{Na}x_{Na}(\alpha_h+\beta_h)}\rho(t-t') \\ <\xi_n(t)\xi_n(t')> &= \frac{2\alpha_n\beta_n}{N_K x_K(\alpha_n+\beta_n)}\rho(t-t') \end{aligned} \quad (4)$$

Here corresponding ion channel numbers are calculated by $N_N a = \rho_{Na} S$ and $N_K = \rho_K S$ (S represents total membrane area) with an assumption of homogeneous sodium and potassium ion channel densities, $\rho_N a = 60\mu m^{-2}$ and $\rho_K = 18\mu m^{-2}$. In the model, the membrane area S globally determines the intrinsic noise level.

In Eq. (1) I_{aut}, which denotes to the strength of the autaptic current input, is modelled as the form of electrical diffusive type with the following linear coupling [24]:

$$I_{aut} = \kappa[V(t-\tau) - V(t)] \quad (5)$$

where κ is the autaptic conductance and τ is the autaptic delay time. $V(t-\tau)$ is the membrane potential of the neuron at an earlier time $(t-\tau)$. To measure the spiking activity of the neuron, we use the coefficient of variation of the inter-spike intervals (ISIs), represented by λ, which is given as follows [9]:

$$CV = \frac{1}{\lambda} = \frac{\sqrt{(<(ISI^2)> - <(ISI)>^2)}}{<(ISI)>} \quad (6)$$

Here $<(ISI)>$ and $<(ISI^2)>$ represent the mean and the mean squared inter-spike intervals, respectively. It is worth noting that CV takes smaller values as the spiking regularity of the neuron increases and vice versa. The numerical integration of equations of the stochastic H-H model is performed by the standard stochastic Euler algorithm with a step size of $10\mu s$ and in order to ensure statistical meaningful, each data on the figures is obtained by averaging the result over 20 different realizations.

III. RESULTS

In this paper, we pay attention to the effects of ion channel blockage on spiking regularity of a single HH neuron in the presence of an electrical autaptic connection. To this end, by extending Yilmaz et al.'s study [22], we investigate how CV alters with the potassium and sodium channel block (thus, the scaling factors x_{Na} and x_K) as a function of autaptic

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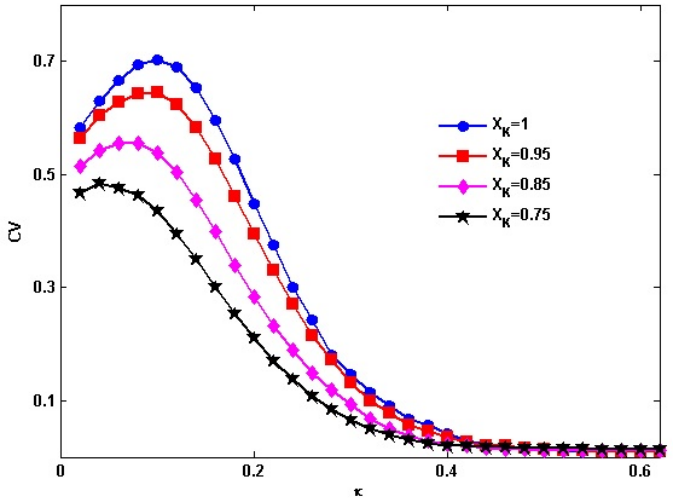
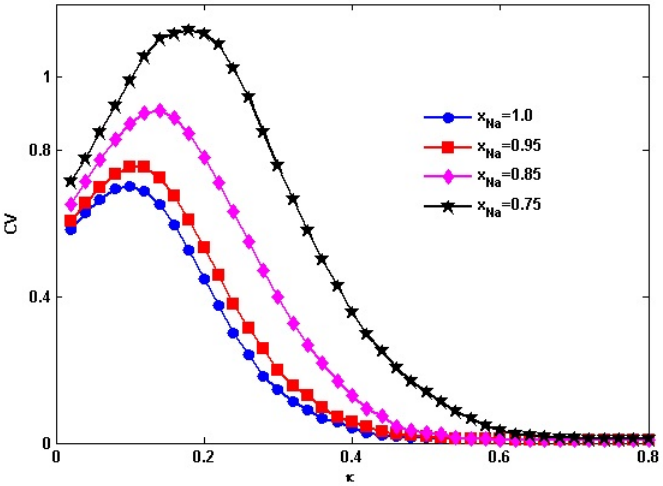


Şekil 1: The dependence of CV on autaptic conductance (κ) for different levels of potassium block (x_K) obtained by a fixed membrane area $S = 6\mu m^2$ and a certain autaptic time delay $\tau = 14ms$.

conductance (κ) for a certain autaptic time delay $\tau = 14ms$ and a fixed membrane area $S = 6\mu m^2$. Obtained results are given in Fig. 1 for potassium and in Fig. 2 for sodium ion channel block. We get each ion channel effect by alternating the density of one channel type (x_{Na} or x_K), while holding the other equal to one.

In case of potassium ion channel block (Fig. 1), there is two important findings. One is that CV reduces with the increment of autaptic conductance (κ) regardless of the level of potassium ion channel block (x_K). Namely, the spiking regularity of the neuron becomes more regular. This is also consistent with the results presented in [24] where the ion channel block was ignored. The other important finding is that CV diminishes with the augmented potassium block level (i.e., with the decrement of x_K) at low κ values (approximately $\kappa \leq 0.4$). That is to say, at smaller κ, the spiking regularity of the neuron (λ) becomes more regular with the decrement of x_K. But however, for $\kappa > 0.4$, CV takes a constant value, where the spiking regularity of the neuron is more regular, regardless of x_K. Autaptic connection introduces an additional new time scale into the spiking dynamics of the neuron depending its parameters in addition to neuron's intrinsic time scale which is determined by channel noise (thus depending both membrane area and active ion channel numbers) [22]. The neuron's spiking dynamic is determined by these times scales. At lower κ values, channel noise-induced time scale is more dominant on the determining the spiking dynamics of the neuron, thus the spiking regularity of the neuron enhances by decreasing x_K. This dominant behavior starts to disappear with the increment of κ and the autaptic activity-induced time scale start to become dominant (not shown).

Fig. 2 shows the variation of CV as a function of autaptic conductance (κ) for various sodium block. Here we take into consideration just $x_{Na} \geq 0.75$ that is guaranteed that the neuron fires spikes. As in the potassium ion channel blockage case, CV gets smaller with the increment of κ, regardless of the level of sodium ion channel block (x_{Na}). Besides, as x_{Na} decreases, the value of CV increases, namely the spiking regularity of the neuron deteriorates at lower κ values (approximately $\kappa \leq 0.6$). It is known that sodium channels are responsible for the initiation of spikes and therefore, the decrease of non-blocked sodium ion channels decreases spiking regularity of a neuron for a given membrane area in the absence of autaptic connections [9], [11]. If the neuron has an autaptic connection, the spiking regularity of the neuron exhibits similar trend as clearly seen from Fig. 2. But again, for $\kappa > 0.6$, CV takes a constant value as in potassium ion channel block. This is because of the time scales that is responsible for determining the spiking dynamics of the neuron.



Şekil 2: Variation of CV as a function of autaptic conductance (κ) for various sodium block (x_{Na}) by fixing $S = 6\mu m^2$ and $\tau = 14ms$.

In sum, the increment of the autaptic conductance induces more regular spiking trains regardless of the potassium or sodium ion channel block, namely CV decreases. On the other, the impact of ion channel block is more apparent at lower autaptic conductance values whereas it losses its influence at bigger autaptic conductance levels. Comparing the impact of potassium and sodium channel block, it can be seen that they have a quite change on the spiking dynamics of the neuron. For potassium ion channel block, the regularity of the spike trains becomes more regular, while for sodium ion channel block, it impairs. This is because the potassium and sodium ion channel blocks have different effects on the spiking dynamics of the neuron. These results show that ion channel block has a non-negligible impact on the spiking dynamics of the neuron owing an electrical autapse.

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