



# Controlling the Spiking Activity of Autaptic Hodgkin-Huxley Neuron by Potassium Ion Channel Blocking

*Potasyum İyon Kanal Bloklama ile Öz-Sinaptik Hodgkin-Huxley Nöronunun Ateşleme Aktivitesinin Kontrolü*

Rukiye Uzun

Bülent Ecevit University, Engineering Faculty, Department of Electrical and Electronics Engineering, Zonguldak, Turkey

## Abstract

I investigated the spiking activity of autaptic Hodgkin-Huxley neuron with a tunable fraction of blocked potassium ion channels. I consider an electrical autapse expressed by its coupling strength and delay time. I showed that there exists a double coherence resonance induced by autaptic time delay at an intermediate autaptic conductance level, as well potassium ion channel blocking impairs this behavior at a certain extent at a specific range of autaptic time delay. In the light of the obtained results; I concluded that the reduction of the number of active potassium ion channels destroys the spiking regularity of a single neuron in the presence of electrical autapse.

**Keywords:** Autapse, Hodgkin-Huxley neuron, Potassium ion channel blocking, Spiking activity

## Öz

Öz-sinaptik bağlantıya sahip bir Hodgkin-Huxley nöronunun ateşleme davranışı, bloke edilmiş potasyum iyon kanallarının ayarlanmasıyla araştırılmıştır. Kuplaj şiddeti ve iletim gecikmesiyle tanımlanan bir elektriksel özsinaps durumu ele alınmıştır. Orta öz-sinaptik iletkenlik seviyesinde öz-sinaptik zaman gecikmesine bağlı olarak bir çift koherans rezonansının oluştuğu ve yanı sıra potasyum iyon kanallarını bloke etmenin bu davranışı özsinaptik zaman gecikmesinin belirli bir aralığında belirli bir ölçüde bozduğu gösterilmiştir. Elde edilen sonuçlar ışığında; aktif potasyum iyon kanallarının sayısındaki azalmanın, elektriksel öz-sinaptik bağlantı olması durumunda nöronun ateşleme davranışını bozduğu sonucuna ulaşılmıştır.

**Anahtar Kelimeler:** Öz-sinaps, Hodgkin-Huxley nöron, Potasyum iyon kanal bloklama, ateşleme davranışı

## 1. Introduction

Nervous system contains numerous noise source which has inevitable impacts on the information processing. Random switching between the opening and closing states of voltage-gated ion channels embedded in the neuron's membrane is one of them. This probabilistic behavior of ion channels leads fluctuations in the membrane voltage, and thus has vital impact on the spiking dynamics of the neuron (Steinmetz et al. 2000, White et al. 2000). It has been shown that the strength of the ion channels is mainly determined by the number of opened (i.e., active) ion channels near the threshold for spiking (Schneidman et al. 1998). Therefore, it is of great importance for evaluating the effect of the number of active ion channels, particularly for analyzing

the function of specific ion channel on spiking dynamics of the neuron (Ozer et al. 2009, Uzun et al. 2014). In this context, in the experimental studies, some neurotoxins such as tetraethylammonium and tetrodotoxin are used to control the number of active specific ion channels (Hille 2001). There are lot of numerical studies performed by computational neuronal models in the literature (Schmid et al. 2004a, Schmid et al. 2004b, Gong et al. 2008, Gong et al. 2011, Yilmaz et al. 2012, Uzuntarla et al. 2013, Uzun and Ozer 2015). For instance, Schmid et al. (2004a, 2004b) analyzed the spiking regularity of a single Hodgkin-Huxley neuron in the presence of potassium and sodium ion channels blockages. They found that the spiking dynamics of the neuron can be changed by either positively or negatively by blocking some portion of potassium or sodium ion channels. Uzuntarla et al. (2013) analyzed the effects of ion channels on the first response following stimulus onset in a scale-free neuronal network and showed that potassium ion channel

\*Corresponding Author: [rukiyeuzun67@gmail.com](mailto:rukiyeuzun67@gmail.com)

blocking has a healing effect whereas sodium ion channel blocking has destructive impact.

On the other hand, information transmission within the nervous system is performed by synaptic connections between neurons. In general, synapses are classified as electrical and chemical. But several decades ago, Van der Loss and Glasser (1972) explored a special kind of synapse that connected a neuron to itself and named this type of synapses as autapse. Autapse is classified as chemical and electrical, and it is confirmed that electrical autapse can alter the dynamics of neuron more sensitively and effectively than the chemical (Ma and Tang 2017). Experimental studies reveal that autapse is quite common, contrary to expectations (Lübke et al. 1996, Bekkers 1998, Bacci and Huguenard 2006, Branco and Staras 2009, Flight 2009, Rusin et al. 2011). Besides these experimental studies, numerical studies have shown that autaptic connections play important roles on the spiking dynamics of the neurons (Bacci and Huguenard 2006, Li et al. 2010, Wang et al. 2014, Qin et al. 2014, Yilmaz and Ozer 2015, Yilmaz et al. 2015a, Yilmaz et al. 2015b, Wang and Chen 2016, Wang and Gong 2016, Yilmaz et al. 2016, Uzun and Ozer 2017a, Uzun and Ozer 2017b, Uzun et al. 2017). For example, Li et al. (2010) demonstrated that, at certain characteristic frequencies, the spiking dynamics of a single neuron are weakened by the delayed feedback which manifests itself by the occurrence of bursting firings and multimodal interspike interval distributions. Wang et al. (2014) analyzed the effect of autapse on the mode-locking spiking pattern of a single HH neuron exposed to a periodic stimulus. They found that the mode-locking pattern can be augmented or deteriorated depending autapse parameters. Yilmaz and Ozer (2015) presented that the weak signal detection performance of a stochastic HH neuron is closely related to autapse parameters. In a recent study; Yilmaz et al. (2016) demonstrated that spiking regularity of a single neuron can be improved via autapse. More recently, we analyzed the spiking dynamics of a single HH neuron which has a chemical autaptic connection, in the presence of ion channel blocking (Uzun and Ozer 2017a). We reported that at different ion channel blocking levels, the spiking dynamics of the neuron do not change for too small coupling strength whether it increases after a certain coupling strength' value. Apart from these studies performed at single neuron level, there are also many studies conducted at neuronal networks modelled with different network structures in the literature (Qin et al. 2014, Yilmaz et al. 2015a, Yilmaz et al. 2015b, Wang and Gong 2016, Uzun and Ozer 2017b, Uzun et al. 2017).

In this paper, different from the aforementioned studies, I investigate how the spiking regularity of a single autaptic HH neuron is affected as the active potassium ion channels embedded in the membrane is changed. To do so, I extend the previous study of Yilmaz et al. (2016) by including the impact of potassium ion channel blocking.

## 2. Models and Methods

In the presence of autapse and potassium ion channel blocking, the time evaluation of the membrane potential of a single stochastic HH neuron is given as follows (Hodgkin and Huxley 1952, Fox 1997, Schmid et al. 2014a, Schmid et al. 2014b, Wang et al. 2014, Yilmaz et al. 2016):

$$C_m \frac{dV}{dt} + g_{Na} \chi_{Na} m^3 h (V - E_{Na}) + g_K \chi_K n^4 (V - E_K) + g_L (V - E_L) + I_{aut} = 0 \quad (1a)$$

$$\frac{dx}{dt} = \alpha_x(V)(1-x) - \beta_x(V)x + \xi_x(t) \quad x = (m, h, n) \quad (1b)$$

where  $C_m = 1 \mu F cm^{-2}$ ;  $E_{Na} = 50 mV$ ,  $E_K = -77 mV$ ,  $E_L = -54.4 mV$ ;  $G_L = 0.3 mScm^{-2}$ ;  $g_{Na}^{max} = 120 mScm^{-2}$ ,  $g_K^{max} = 36 mScm^{-2}$ ,  $\chi_K(\chi_{Na})$  is scaling factor which denotes the ratio of active (non-blocked) potassium (sodium) ion channels to the total potassium (sodium) ion channels embedded in the membrane. The smaller values of this factor, which is limited to the unit interval, denotes higher level of channel blocking for corresponding ion channels.  $m$  and  $h$  are the activation and inactivation gating variables for the sodium channel, respectively, whereas  $n$  is the activation gating variable of potassium ion channel. These gating variables change their position (to closed from opened, or vice versa) over time in response to the membrane potential as given by Equation (1b) in which  $\alpha_x$  and  $\beta_x$  denote the opening and closing transition rates.  $\xi_x(t)$  are zero mean Gaussian white noises of which the noise strengths are given by (Fox 1952):

$$\langle \xi_x(t) \xi_x(t') \rangle = \frac{2\alpha_x \beta_x}{N_j \chi_j (\alpha_x + \beta_x)} \delta(t - t'), \quad (2)$$

$$N_j = \rho_j S; j = Na, K; x = m, h, n$$

where  $N_j$  are the calculated total ion channel numbers by the assumption of homogeneous sodium and potassium ion channel densities, whereas  $\rho_{Na} = 60 \mu m^{-2}$  and  $\rho_K = 18 \mu m^{-2}$  are the corresponding ion channel densities.  $S$  is the total membrane area and adjusts the intrinsic noise level through  $N_j$ . In Equation (2),  $\chi_j$  is used to ignore the non-active channels, which has no effect at generating intrinsic channel noise. For more interpretations of these parameters, please see, e.g., the study by Uzun et al. (2014).

$I_{aut}$  gives the strength of autaptic current, which is modelled as the linear diffusive-type coupling form for electrical self-connections, as follows (Yilmaz et al. 2016):

$$I_{aut} = g_{aut} [V(t - \tau) - V(t)] \quad (3)$$

where  $g_{aut}$  is the autaptic conductance and  $\tau$  is the autaptic delay time.  $V(t - \tau)$  is the membrane potential of the neuron at an earlier time ( $t - \tau$ ).

The spiking activity of the neuron is quantified by the inverse of the coefficient of variation (CV), which denotes the spiking regularity, according to:

$$\lambda = \frac{1}{CV} = \frac{\langle ISI \rangle}{\sqrt{\langle (ISI)^2 \rangle - \langle ISI \rangle^2}} \quad (4)$$

Here  $\langle ISI \rangle$  and  $\langle (ISI)^2 \rangle$  represent the mean and the mean squared inter-spike intervals, respectively, whereas spike times are determined when the membrane potential crosses the detection threshold ( $V_{det} = 0mV$ ). It is worth noting that larger values of  $\lambda$  stand for more ordered spiking behavior. The numerical integration of Equations (1)- (3) are solved by standard stochastic Euler algorithm with a step size of  $10 \mu s$  and all the results are averaged over 20 different simulation realizations. All the algorithms were implemented by Dev-C++ and results were visualized using Matlab 2013a.

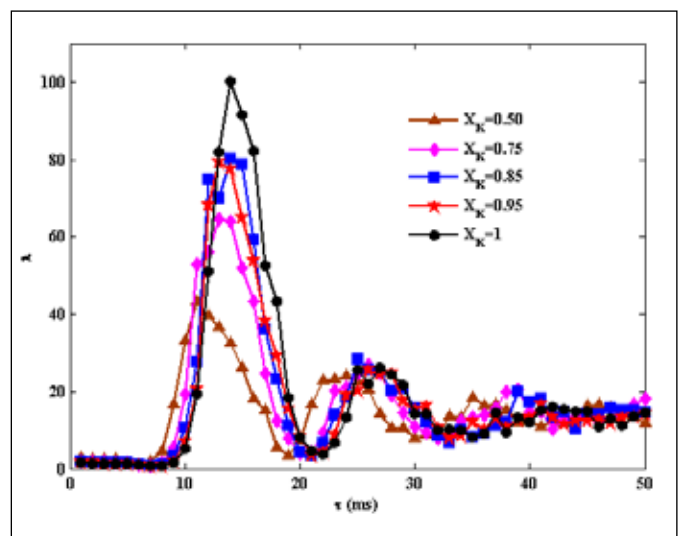
### 3. Results and Discussion

I investigated the impacts of potassium ion channel blocking on the spiking regularity ( $\lambda$ ) of an autaptic HH neuron by tuning autaptic time delay ( $\tau$ ) at an intermediate autaptic conductance level ( $g_{aut} = 0.5 mS cm^{-2}$ ) and a fixed membrane area ( $S = 6 \mu m^2$ ). To this end, I extended Yilmaz et al. study (2016) where they do not consider the ion channel blockage. Throughout the study, I set  $\chi_{Na} = 1$  to observe only the effect of the potassium ion channels embedded in the membrane. Yilmaz et al. (2016) have shown that at a fixed membrane area ( $S = 6 \mu m^2$ ), the neuron's spiking regularity exhibits a double coherence resonance (CR) induced by autaptic time delay. I also obtained similar results in the presence of potassium ion channel blocking for the same conditions (as given in Fig. 1). Fig. 1 displays the dependence of  $\lambda$  on  $\tau$  for various  $\chi_K$  where  $g_{aut} = 0.5 mS cm^{-2}$  and  $S = 6 \mu m^2$ . It can be clearly seen that for each  $\chi_K$ ,  $\lambda$  passes through peaks and dips upon increasing  $\tau$ , which quantitatively characterized the double CR. In addition, the decrement of  $\chi_K$  (that is, increasing potassium channel blocking) causes the peak of  $\lambda$  to move to smaller  $\tau$ . Moreover, as  $\chi_K$  decreases, the amplitude of  $\lambda$  reduces prominently at roughly range of 10

$< \tau < 20 ms$ . Out of this range, there is virtually no impact of the ion channel blocking on  $\lambda$ . One can conclude from this result that the spiking regularity of a single stochastic HH neuron can be controlled both by an electrical autapse and potassium ion channel blocking, at certain conditions, namely for specific values of  $\tau$  and  $\chi_K$ .

In addition, the obtained results can be explained as follows: autapse introduces different time scales to the neuron dynamics depending own parameters and thus, impacts the spiking dynamics (Yilmaz and Ozer 2015, Wang and Chen 2016, Yilmaz et al. 2016). On the other hand, a neuron has an intrinsic time scale which alters in the presence of ion channel blocking positively or negatively (Gong et al. 2011). Consequently, if the time scales do not match with each other, the spiking regularity deteriorates or vice versa. In our case, the intrinsic time scale varied by the decrease of the active potassium ion channels does not matches with the autapse, thus the spiking regularity decreases.

In conclusion, I analyzed by numerical simulations the impact of potassium ion channel blocking on the double CR induced by autaptic time delay in a single stochastic HH neuron. I obtained that in a range of autaptic time delay, the decrement of the active potassium ion channels (that is,  $\chi_K$  decreases) impairs the spiking regularity of the neuron. It is worth nothing that the obtained result is different from the results obtained previously in which the potassium



**Figure 1.** Dependence of  $\lambda$  on  $\tau$  for various  $\chi_K$  at  $S = 6 \mu m^2$  for an intermediate coupling strength ( $g_{aut} = 0.5 mS cm^{-2}$ ).  $\lambda$  exhibits a double CR upon  $\tau$ , regardless of  $\chi_K$ . In the range of  $10 < \tau < 20 ms$ , roughly, the decrease of  $\chi_K$  makes the amplitude of  $\lambda$  lower and also moves the peaks of  $\lambda$  to smaller  $\tau$ . Out of this range, there is virtually no impact of the ion channel blocking on  $\lambda$ .

ion channel effect does not considered in the presence of electrical autapse. Thus, I hope that this study may help to understand the joint role of potassium ion channel block and autaptic time delay in the information processing and transmission of real neurons.

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