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Effects of The Peak to Baseline Ratio on Phase Difference of The Coupled Hodgkin Huxley Neurons

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Abstract. Phase response curve (PRC) examines how weak perturbation effects spike time of neurons. Peak-to-baseline ratio is one of the most important specification of type II PRC neurons and it gives a brief explanation of PRC in terms of numerical sense. In this study, Hodgkin Huxley (HH) model neurons coupled via gap junction under three different applied currents were investigated in terms of PRCs, peak-to-baseline ratio and required time interval of minimum phase difference. Although the used three HH model neurons had same type of excitability and PRCs, the shapes and maximum and minimum peaks were varied. The close relationship between peak-to-baseline ratio and the required time interval of minimum phase difference of coupled neurons were found. To sum up, the results of our simulations indicated that the required time of minimum phase differences of two coupled HH neurons via gap junction were related to calculated peak-to-baseline ratios.

2010 AMS Classification: 65C20, 92B20, 92B25.

Keywords: Peak-to-baseline ratio, PRC, HH Model, phase difference.

1. Introduction

As is well known, the human brain is the most complex system in the universe. There are some 10^{11} neurons each of which can be connected to 10^4 other neurons exist [25]. The exact working mechanism of the brain is still unknown. Understanding mechanism of the complex neural network lies on learning behavior of a single neuron. Neuron fires, if certain threshold is achieved and this generates the basis of communication between nerve cells [13]. Single neuron is mathematically modeled by a set of differential equations and one of the most used neuron model is Hodgkin Huxley (HH) model since its discovery in 1952 [10].

In nature, a variety of the different systems in physics, chemistry, and biology also exhibit periodic activity and these systems can be mathematically modeled as nonlinear oscillators [17]. In the simplest form of HH Model, neurons periodically fire when the applied current reaches or goes above the certain value. The phase response curve (PRC) is one of the significant tools to investigate neuronal dynamics [4]. PRC describes how an oscillatory system response to a brief pulse that given in different phases. The shape of PRC also gives invaluable information about network synchronization, type of neural excitability and oscillatory stability [2, 3, 6, 24]. In the field of computational neuroscience, phase difference, phase locking and synchrony in neural systems have gained a great interest [15]. PRC is utilized to examine these behaviors of weakly coupled neurons [1, 7, 9, 14, 16, 18].

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Transmission of an electrical pulse that generates neural spike dynamics, has been represented in various conductance based neural models [8, 12, 19, 20]. Although neural dynamics described by only two coupled equations in Morris-Lecar (ML) model, HH equations have been used extensively to model currents observed in single neurons. Both type I and type II PRCs are observed in HH model neurons but peak-to-baseline ratio is existed at only type II PRCs. PRCs have been examined in several studies, but a few studies have been connected PRC with peak-to-baseline ratio [5, 23, 28]. It was firstly proposed by Robinson [28] in 2007. The relationship between peak-to-baseline ratio and firing frequency was investigated for Purkinje cell [23] and it was modified to examine firing rate [5]. We believe that this is the first study that shows a relationship between peak to baseline ratio and required time duration for the minimum phase difference of two HH neurons coupled via gap junction.

In this paper, firstly we stimulated HH model under three different applied currents, then their corresponding PRCs were found. Then, the required time interval of the minimum phase difference of two-coupled HH neurons with same applied currents was examined. Peak-to-baseline ratios were calculated from the three obtained PRCs and the relationship of peak-to-baseline ratio and the required time duration of coupled HH neurons was explored.

2. Models and Methods

2.1. **Hodgkin-Huxley Model.** In our study, to simulate the behavior of neuron, Hodgkin-Huxley (HH) model was selected. The HH model is actually the sum of currents of sodium, potassium and leak voltage gated channels. The model is adapted from [27] and it is given by four nonlinear differential equations:

$$C_m \frac{dV}{dt} = -(I_L + I_{Na} + I_K + I_{app}) + Iapp \tag{2.1a}$$

$$I_{Na} = g_{Na} m^3 h (V - V_{Na}) \tag{2.1b}$$

$$I_K = g_K n^4 (V - V_K) \tag{2.1c}$$

$$I_L = g_L (V - V_L) \tag{2.1d}$$

At Eq. 2.1, C_m represents membrane capacitance, I_{Na}, I_K and I_L imply currents of sodium, potassium and leak channels respectively. I_{app} denotes applied constant current. The maximum conductance of sodium ion, g_{Na}, gating variables, m and h, and sodium reversal potential, V_{Na} , are given in Eq. 2.1b, Eq. 2.1c and Eq. 2.1d. g_K and g_L indicate maximum conductance of potassium and leak ions, n shows gating variable and V_K and V_L are reversal potentials of corresponding ions. The conductance of g_{Na}, g_K and g_L are 40, 3, 0.1 μS and reversal potential of V_{Na}, V_K and V_L are 50, -100, -75 mV respectively. Gating variables n, m, and h were modeled as follows:

$$\begin{aligned} \frac{dn}{dt} &= \alpha_n(V)(1-n) - b_n(V)n \\ \frac{dm}{dt} &= \alpha_m(V)(1-m) - b_m(V)m \\ \frac{dh}{dt} &= \alpha_h(V)(1-h) - b_h(V)h \end{aligned} \tag{2.2}$$

As mentioned above the HH model is composed of four coupled nonlinear equations, the first one represented by voltage, V, at Eq. 2.1a, the other three are given by Eq. 2.2. The forward and backward rates of activation and inactivation variables of used currents are $\alpha_m(V)$, $\alpha_h(V)$, $\alpha_n(V)$, $b_m(V)$, $b_h(V)$ $b_n(V)$, satisfying:

$$\begin{aligned} \alpha_m(V) &= 0.32(54 + V)/(1 - exp(-(V + 54)/4)) \\ b_m(V) &= 0.28(V + 27)/(exp((V + 27)/5) - 1) \\ \alpha_h(V) &= 0.128exp(-(50 + V)/18) \\ b_h(V) &= 4/(1 + exp(-(V + 27)/5)) \\ \alpha_n(V) &= 0.032(52 + V)/(1 - exp(-(V + 52)/5)) \\ b_n(V) &= 0.5exp(-(57 + V)/40) \end{aligned}$$

In this paper, all simulations were performed using a personal laptop, with 10.0 GB RAM and 2.4 GHz Intel i5 processor. Moreover, solutions of differential equations were obtained by using the *ode45* function (implements fourth order Runge-Kutta numerical integration algorithms) in MATLAB software (R2012b) on a 64-bit mac os x operation systems.

2.2. **Phase Response and Phase Transition Curves.** Assume that HH neuron oscillates under constant applied current and has a period of T_0. Small weak perturbation is given at time dt after from action potential. This could change period of oscillation and suppose the perturbed neuron oscillates with a period T_p. Time of perturbation, dt, corresponds to phase of oscillation. The PRC is defined as [13],

$$PRC(\phi_{dt}) = \frac{T_0 - T_p}{T_0} \tag{2.3}$$

Phase transition curve (PTC) also gives an idea about how weak perturbation change period of neuron oscillation. PTC is plotted as new phases versus old phases [13]. PTC is given by,

$$PTC(\phi_{dt}) = (PRC(\phi_{dt}) + \phi_{dt}) \quad mod\ T_0$$

PRC and PTC are similar approaches but PRC is suitable when the phase shifts are small, PTC is suitable when the phase shifts are large [13]. The direct computation of PRC by using Eq. 2.3 is quite simple however it is inaccurate [22], since duration and strength of perturbation could change. Because of this reason, the standard and famous adjoint method [11, 21] was used for PRC calculation

2.3. **Excitability of HH Model and Types of PRCs.** Excitability of HH model was derived as follow, HH model simulated under various constant applied current starting from zero, and these simulations reveal firing frequencies. Consequently, the firing frequencies versus corresponding applied currents were plotted.

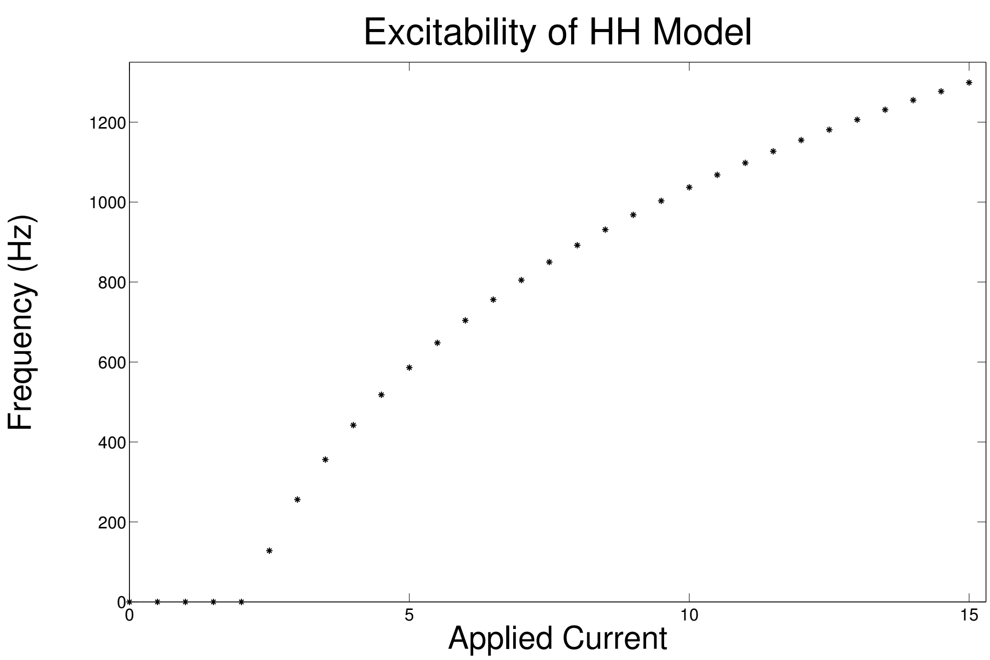

FIGURE 1. The Excitability of HH Model

The HH model neuron cannot fire until a certain applied current Figure 1. After then, firing frequency of model starts to increase. Firing frequency of HH model is not continuous, i.e. frequency does not start from zero and increase continuously. HH model did not fire at 2 μA, applied current but at 2.5 μA, model fired with firing frequency of 128 Hz. This type of graph is known as Class-2 excitability and if firing frequency getting start from zero and increase continuously, this is known as Class-1 excitability. To sum up, the used HH model have Class-2 excitability. Class-1 and Class-2 excitability give clue about the shape of PRCs of neurons. Class-1 excitable neurons have only strict positively PRC, however, the shape of PRC at Class-2 excitable neurons have both positive and negative parts [13].

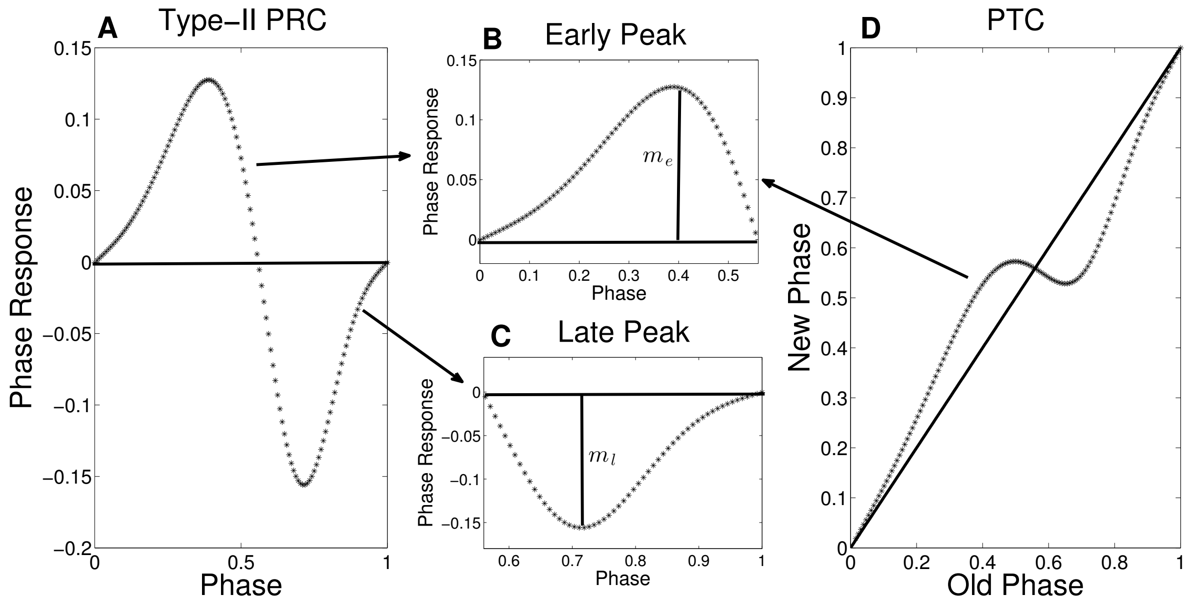

FIGURE 2. A, Tpye-II PRC, B-C, Peak-to-baseline ratio and D, Phase transition curve

2.4. **Peak-to-baseline ratio.** The shape of PRC gives us invaluable information about neurons but a short explanation of a PRC is need to investigate some properties of same or different types of neurons [5, 23, 28]. The peak-to-baseline ratio is given as,

$$r = \frac{|m_l - m_e|}{|m_l + m_e|} \tag{2.4}$$

At the Eq. 2.4, r represents peak-to- baseline-ratio, and m_e, m_l implies local extrema of early and late respectively [5]. Figure 2-A illustrates the shape of type-II PRCs that imply Class-2 excitable neurons. As seen from the Figure 2-A, PRC composes of positive and negative parts and this is known as type-II PRC. This types of PRCs have local peaks not only in negative part but also in positive part and this implies that m_l and m_e have opposite signs. The early peak, m_e, of peak-to-base ratio is shown in Figure 2-B and the late peak, m_l, of the peak-to-base ratio is given in Figure 2-C and corresponding PTC graph is illustrated in the Figure 2-D. To conclude that, in our study, the used HH model has Class-2 excitability.

3. RESULTS

Although the HH model had type-II PRC, the shape of PRC curves was changed by applied currents. In this article, we focused on duration of minimum phase differences of two neurons with the same applied current connected to each other via gap junction. Three different applied currents were chosen, 4.6, 10 and 20 μA as a reference current. The shape of PRCs of these reference currents is given in Figure 3. PRC of the HH model under 4.6 μA is composed of only a negative and a positive part but two negatives and one big positive and one tiny positive parts exist at 10 μA and three negatives, two positive parts existed at the 20 μA.

To calculate the peak-to-baseline ratio, r, of the reference currents, m_l and m_e are needed to be found. The values of local extrema were used when there were more than one positive and negative parts and these local extremes were the first negative peaks m_e and the first positive peaks m_l for all PRCs of reference currents. The values of m_e, m_l and r are given in Table 1. As it can be seen from Table 1, the peak-to-baseline ratio is minimum when Iapp=4.6 μA, and maximum when Iapp=10 μA.

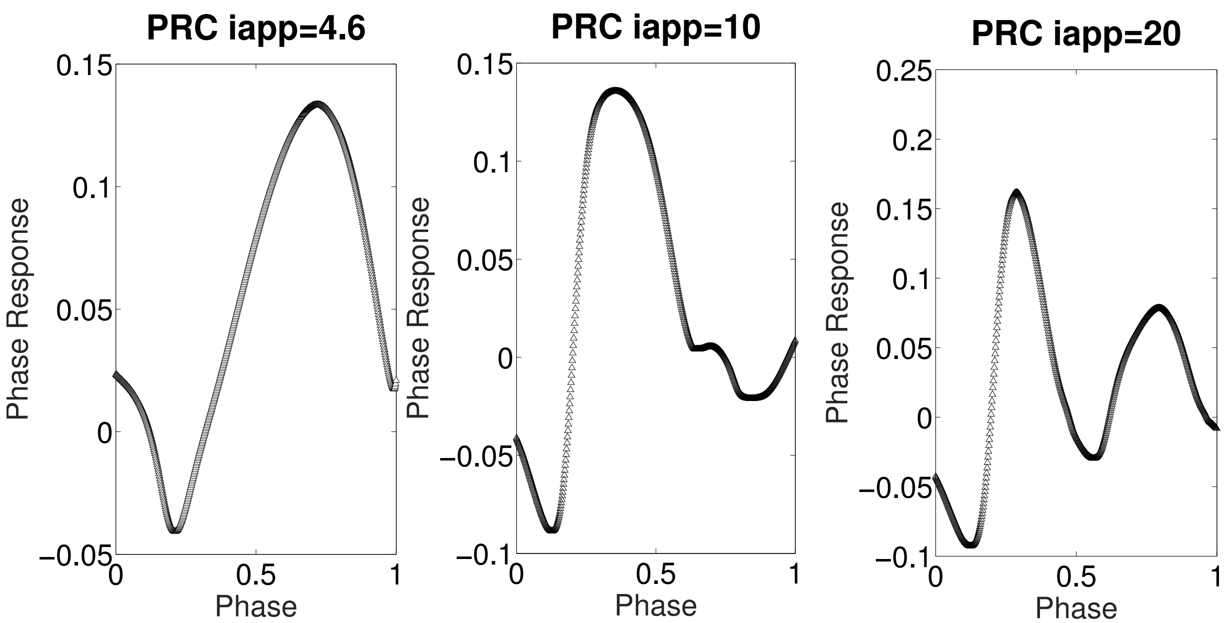

FIGURE 3. PRCs of three different applied current

TABLE 1. The values of m_e, m_l and r of reference currents

Iapp	m_e	m_l	**r**
4.6	-0.040	0.133	1.877
10	-0.089	0.136	4.762
20	-0.092	0.162	3.693

Figure 4 indicates the situation of a cell to cell coupling of the HH model neurons with Iapp=4.6 μA via gap junction of strength $g_{juction}$=0.1 μS. Figure 4-A shows the voltage-time graph of cell one and Figure 4-B shows the voltage-time graph of cell two with the same applied current, Iapp=4.6, and different initial conditions. Figure 4-C indicates the voltage-time relation of two identical neurons with different initial condition coupled via gap junction. The black continuous line represents neuron-1 and black discrete line implies neuron-2, see the legends. As can be seen from these figures that behavior of two neurons getting close to each other when the time variable getting around 90 ms. Figure 4-D shows the phase-time relation of coupled neurons. Neuron-1 and neuron-2 have represented as above and at first, the phases of coupled neurons were getting separated and the maximum separation was seen at the time interval between 40-50 ms and next, phases of neurons were getting close to each other at the approximately 90 ms.

Phase differences of the coupled neurons under three reference applied currents are given in Figure 5. Figure 5-A shows coupled neurons with Iapp=4.6 μA and as we mention at Figure 4, the phase differences firstly getting increase and there after getting minimum at the time of 95 ms. Figure 5-B demonstrates the phase difference of the identical neurons with different initial conditions under same 10 μA applied current and these two coupled neurons had minimum phase differences at time 46 ms. Minimum phase difference time under 20 μA applied current was reached at 56 ms shown in Figure 5-C.

4. DISCUSSION

In this study, the excitability of used HH model was derived, type-II PRC was stimulated and the peak-to-baseline ratio was investigated. Although the HH model has type II PRC, the shape of PRCs and local extremes were changed by applied currents. The answer of, which factors were dominated for reaching minimum phases difference; when the two identical neurons with different initial conditions connected to each other via gap junction?, examined by using

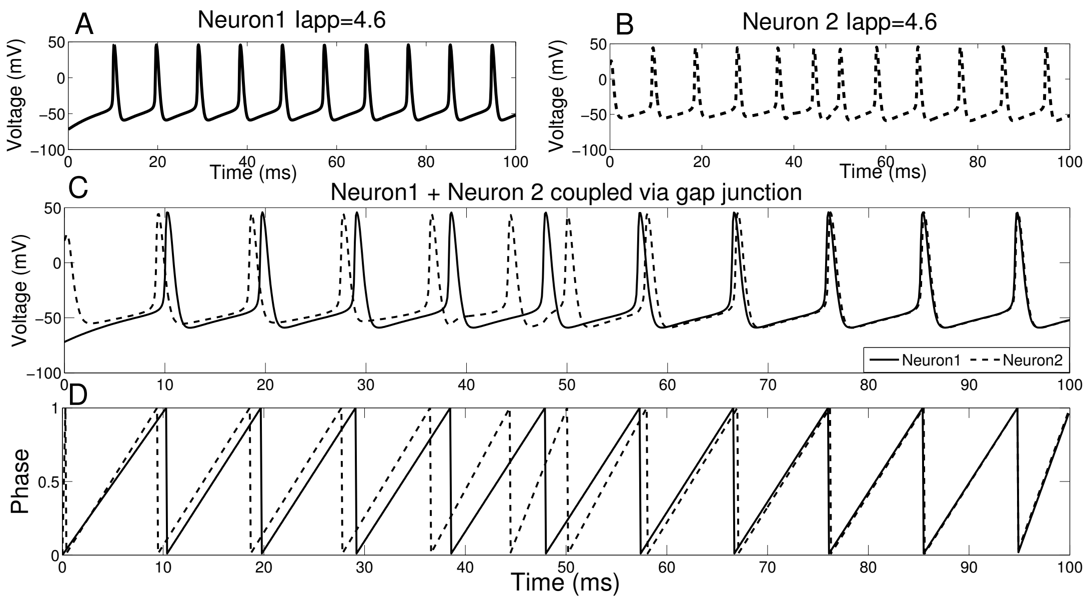

FIGURE 4. The behaviour of two coupled neurons with same 4.6 μA applied current and different initial conditions

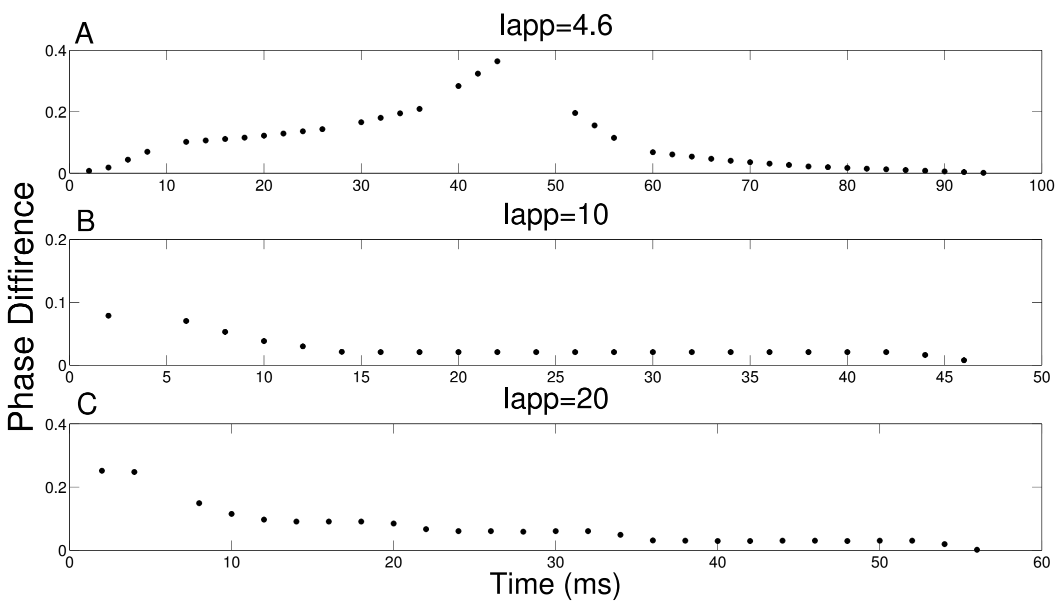

FIGURE 5. Phase difference of two coupled neurons with same applied currents and different initial conditions. A) 4.6 μA, B) 10 μA, C) 20μA

three reference currents; 4.6, 10, 20 μA. The PRC's of the neurons were calculated and peak-to-baseline ratios were obtained from this PRCs.

PRC strongly depends on the unperturbed period of oscillation because recovery of any weak perturbation must be done before the next perturbation [26]. This means that the firing frequency has a close relationship with PRC. The HH model with short firing period must come back to limit cycle attractor before the HH model with long firing period.

Peak-to-baseline ratio modifies in order to show the relation with firing rate [5]. As a result, PRC and peak-to-baseline ratio are important factors for studies related to firing rate.

It is assumed that firing frequency and peak-to-baseline ratio have an inverse relationship to each other, i.e. firing frequency increases decreasing time duration of the minimum phase difference of the same neurons but the results of simulations showed that time interval for minimum phase difference was not linearly depended on applied currents. The required time for minimum phase difference at highest reference current, 20 μA, was bigger than the middle one, 10 μA. On the other hand, the calculated values of the peak-to-baseline ratio, r, gave promising results about time interval of the minimum phase difference. The values of r of the coupled HH neurons with applied current Iapp=4.6, 10 and 20 μA were 1.87, 4.762 and 3.693 and their time interval of minimum phase differences are 95, 46 and 56 ms respectively. The finding of this study clearly showed that the increasing peak-to-baseline ratio, decreases minimum phase difference duration and this also gave extra information about the phase of coupled neurons. Synchronization possibilities and phase locking probabilities in a neural network could be examined with this invaluable tool but this study was limited by three reference currents, one fixed gap junction strength and single conductance based HH neural model. More studies with mentioned limitations are needed to enlighten the relation between peak-to-baseline ratio and phase difference coupled neurons.

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