Effect of External Sinusoidal Voltage on AP Firing Pattern of a Modified HH-Neuron with TRP-Like Channels

Parastou Sadatmousavi
Department of Bioengineering
University of California, San Diego
psadatmo@ucsd.edu

Abstract

The transient receptor potential (TRP) channels are group of ion channels on mammal neurons plasma membrane that have an important role in some inflammatory and nociceptive processes. This study investigates the impact of magnetic electrical field-induced external sinusoidal voltage application on the pattern of action potential (AP) firing of a modified Hodgkin-Huxley neuron. The impact of frequency and amplitude variation of the external sinusoidal voltage is investigated with different TRP-like channel activity.

1 Introduction

TRP channels are non-selective ligand-gated cation channels permeable to sodium, calcium, and magnesium. These channels are activated and regulated by wide variety of stimuli such as:

1. Exogenous vanilloid compounds like capsaicin and resiniferatoxin
2. Endogenous chemical compounds like protons, bradykinin, and leukotrienes produced in inflamed tissues.
3. Noxious heat [2]

TRP-like channels are involved in transmission and modulation of pain as well as integration of diverse painful stimuli[1]. Although the precise mechanism of TRP receptor activation in anti-nociceptive action is mostly unknown, studies show that TRP-like channels are activated by heat greater that 43^0C, low pH, anadamide, and capsaicin. These type of sensory nerves release pro-inflammatory/pro-nociceptive sensory neuropeptides such as substance P and calcitonin gene-related peptide into the innervated area [1]-[3]. Although the available data on the effect of static magnetic field (SMF) on nociceptive process is contradictory, previous studied show that the capsaicin-sensitive neurons are involved in SMF-induced anti-nociceptive action[3].

This study investigates the effect of external sinusoidal voltage from a static magnetic field resource with varying frequency and amplitude on the pattern of action potential firing of a neuron. The modified Hodgkin-Huxley squid neuron simulation with additional TRP channel is used to model the neuron in this study.

2 Method

The modified Hodgkin-Huxley (HH) model is mathematically used to simulate a sensory neuron in this study. The first modifications are addition of TRP-like channels on neuron membrane, so the TRP-like current is expressed in this sensory neuron. The second modification is exposure of the neuron to the external sinusoidal voltage. Figure 1 illustrates the circuit model of this specific modified HH-model neuron.

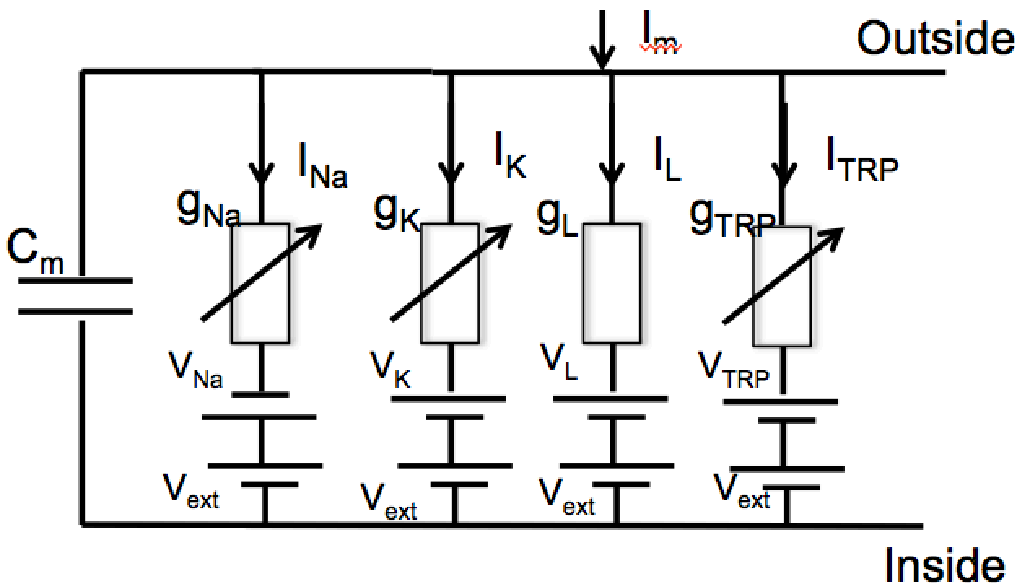

Figure 1 Circuit model of a modified HH model neuron including TRP current and exposed to external sinusoidal voltage (V_{ext}) [1]

The reversal potential of the TRP channel is assumed to be zero, since these channels are non-selective cation channels. The differential equations for the modified HH-model are as follows:

$$C_m \frac{dV}{dt} \quad \left(I_{Na} + I_K + I_L + I_{trp}\right) + I_{inj} \tag{1}$$

$$\begin{aligned} &+ g_{Na} m^3 h (V + V_{ext} \quad E_{Na}) \\ &+ g_K n^4 (V + V_{ext} \quad E_K) \\ &+ g_L (V + V_{ext} \quad E_L) \\ &+ g_{trp} (V + V_{ext} \quad E_{trp}) | + I_{inj} \end{aligned}$$

$$\frac{dm}{dt} \quad \alpha_m(V)(1 \quad m) \quad \beta_m(V) m \tag{2}$$

$$\frac{dn}{dt} \quad \alpha_n(V)(1 \quad n) \quad \beta_n(V) n \tag{3}$$

$$\frac{dh}{dt} \quad \alpha_h(V)(1 \quad h) \quad \beta_h(V) h \tag{4}$$

Where C_m is the membrane capacitance, V is the membrane potential, and t is time. The values g_{Na}, g_K, and g_{TRP} are the maximal conductance of inward Na^+ current (I_{Na}), outward K^+ current (I_K), and TRP-like current (I_{TRP}), respectively, and g_L leak current conductance. The reversal potential of sodium, potassium, leak, and TRP-like channel current are noted by E_{Na}, E_K, E_L and E_{TRP} respectively. I_{inj} is the current injected into the cell, which in this study is assumed to be zero. Finally, V_{ext} is the sinusoidal voltage with V_A amplitude and f frequency.

$$V_{ext} \quad V_A \sin(2\pi f t) \tag{5}$$

The dimensionless gating variables are presented by m, h, and n. The gating variable dynamics modeled as the solution of the first order ordinary differential equation [1]. The rate constraints in the simulation are defined as:

For I_{Na}:

$$\alpha_m \quad \frac{0.1(V + 40)}{1 + e^{V \; 40}} \tag{6}$$

$$\beta_m = 4e^{-\frac{V+65}{18}} \quad (7)$$

$$\alpha_h = 0.07e^{-0.05(V+65)} \quad (8)$$

$$\beta_h = \frac{1}{1+e^{-0.1(V+35)}} \quad (9)$$

For I_K:

$$\alpha_n = \frac{0.01(V+55)}{1-e^{-0.1(V+55)}} \quad (10)$$

$$\beta_n = 0.125e^{-0.0125(V+65)} \quad (11)$$

Table 1 includes all parameters' default values in the modified HH-model used in this study.

Table 1 Default parameter values used for the modified HH-model

Symbol	Description	Value
C_m	Membrane capacitance	$1 \mu F/cm^2$
g_{Na}	Na^+ current conductance	$120\ mS/cm^2$
g_K	K^+ current conductance	$36\ mS/cm^2$
g_L	Leak current conductance	$0.3\ mS/cm^2$
g_{TRP}	TRP-like current conductance	$0.03\ mS/cm^2$
E_{Na}	Na^+ reversal potential	50 mV
E_K	K^+ reversal potential	-80 mV
E_L	Reversal potential for leak current	-49 mV
E_{TRP}	Reversal potential for TRP-like current	0 mV

The simulations of this study are done with Python's Integrated Development Environment (IDLE) version 2.7.2.

3 Results

The first part of the study determines the effect of TRP-like channel conductance on the pattern of AP firing. The initial values for the variables V, m, h and n are *71 mV, 0.038, 0.69, and 0.159 respectively to solve the ordinary differential equation. Also, the amplitude and frequency of the external voltage is 8 mV and 0.3 Hz. The plots in figure 2 illustrate the pattern of AP firing with two different TRP conductance levels 0.03 mS/cm^2 and 0.06 mS/cm^2. These plots suggest that when external sinusoidal voltage is decreased to its minimum value, it lets the membrane potential to resulting bursting pattern with a 30:1 phase locking when g_{TRP} is 0.03 mS/cm^2 and 48:1 phase locking pattern when g_{TRP} is increased to 0.06 mS/cm^2. In addition, the higher TRP-like channel conductance.

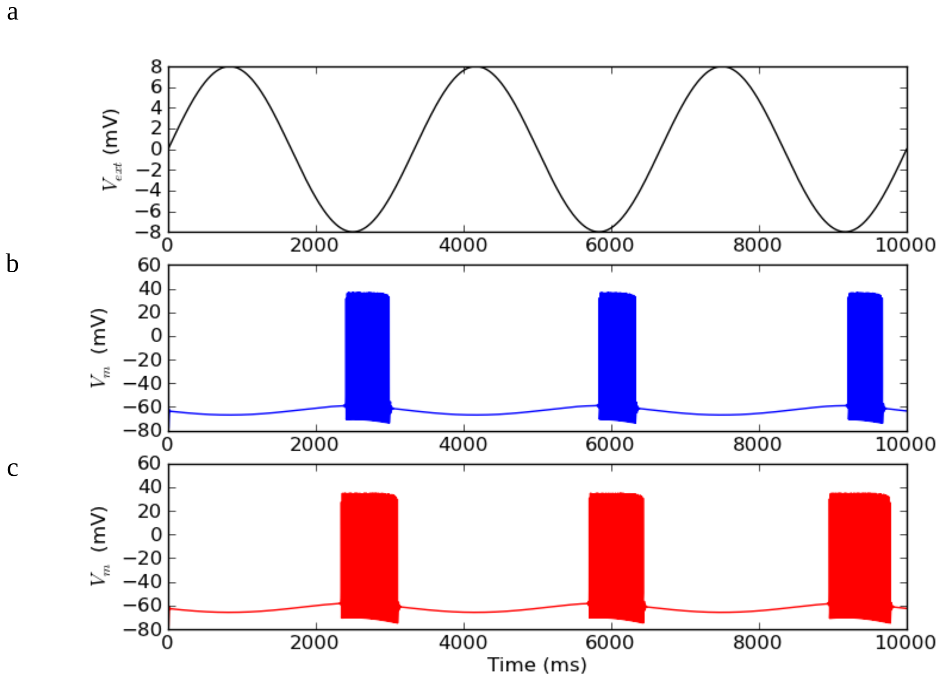

Figure 2 (a) External Sinusoidal Voltage (V_{ext}) over 10000 mS (b) Membrane potential when g_{TRP} = 0.03 mS/cm^2 (c) Membrane potential when g_{TRP} = 0.06 mS/cm^2

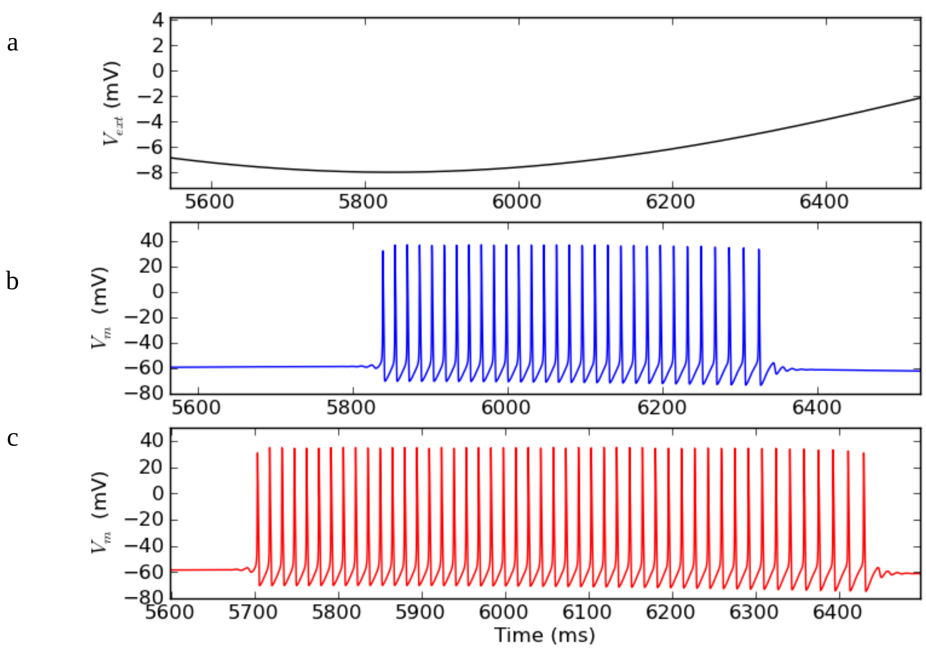

Figure 3 (a) External Sinusoidal Voltage (V_{ext}) (b) Membrane potential with entrainment pattern of 30:1 when g_{TRP} = 0.03 mS/cm^2 (c) Membrane potential when g_{TRP} = 0.06 mS/cm^2 with entrainment pattern of 48:1. There are 30 and 48 Aps generated for one cycle stimulation in (b) and (c) respectively.

The observations how that in low frequency of Vext, as g_{TRP} changes, the shape of each single AP is the same and they spike to about 40 mV. This result suggest that as low frequency of external sinusoidal voltage applied, the neuron with varying TRP conductance can reach activation threshold of AP. However, the pattern of entrainment varies with the activity of TRP-like channels.

Figure 4 illustrates the interspike interval (ISI) pattern with number of intervals (n). In the other words, these plots are histogram of ISIs, dividing the 10,000 mS to 200 time intervals. This plot indicates that by varying g_{TRP}, the spikes are occurring around the same time but the spiking duration time is longer when TRP-like channels have higher activity level.

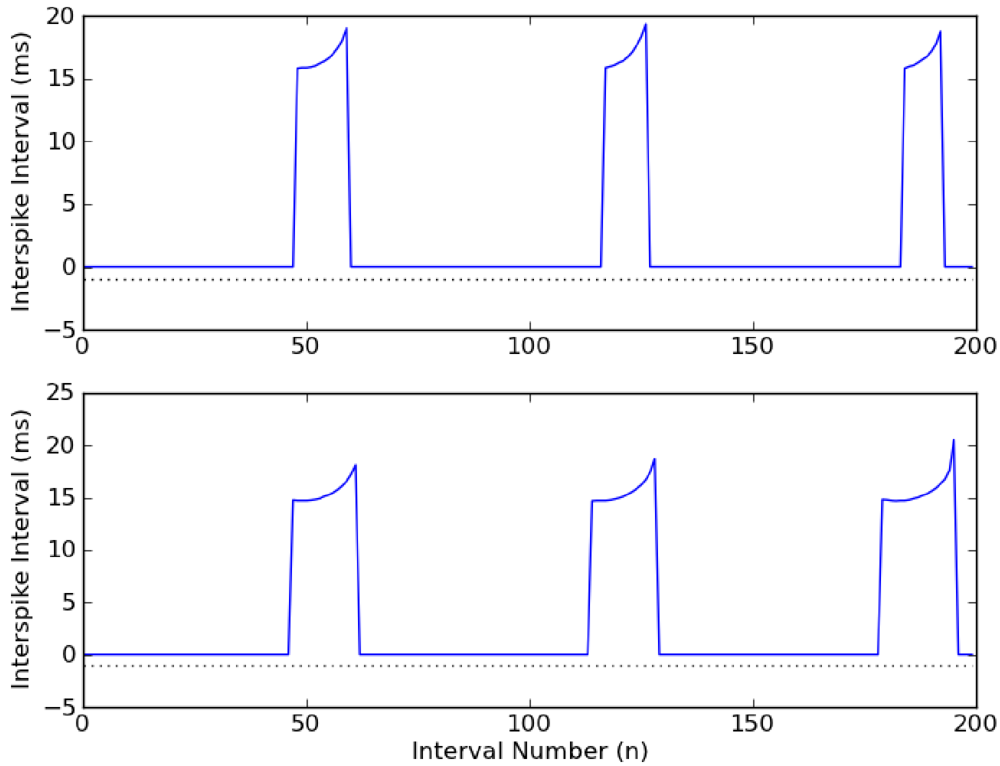

Figure 4 Interspike interval (SI) versus interval number (a) g_{TRP} = 0.03 mS/cm^2 (b) g_{TRP} = 0.06 mS/cm^2. The pattern of ISI map is similar in a and b.

In the other set of simulations, the frequency of Vext was increased to 60Hz and the amplitude to 2.0mV. Figure 5 shows the membrane voltage and current through TRP-like channel in gTRP of 0.015 mS/cm^2 and 0.03 mS/cm^2. It is observed that the entrainment pattern of 4:3 is alternated with 3:2, but when the TRP conductance is increased, the spikes follow a regular pattern.

a b

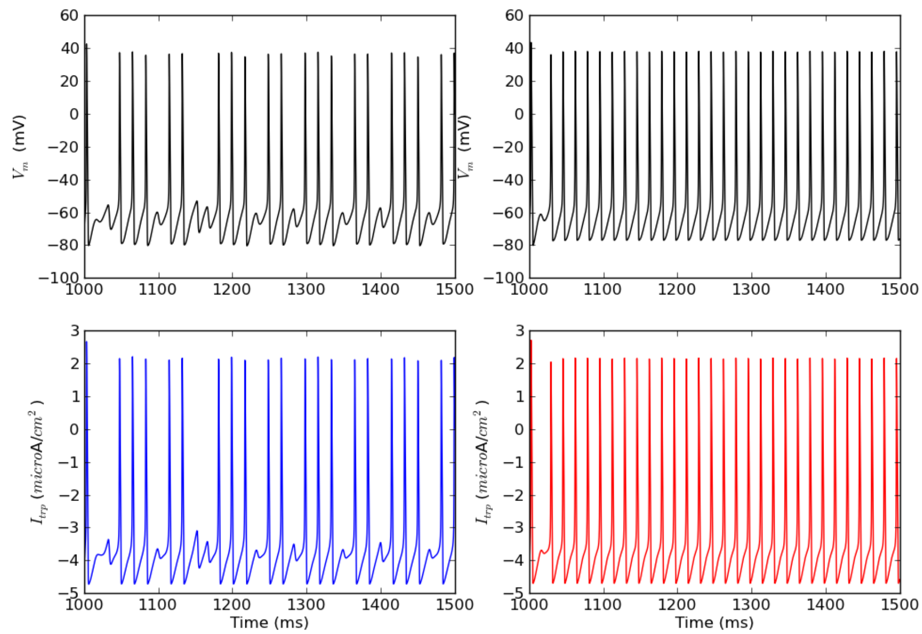

Figure 5 Exposure of modified HH-model neuron to high frequency external sinusoidal voltage when (a) g_{TRP} = 0.015 mS/cm^2 and (b) g_{TRP} = 0.03 mS/cm^2

Finally, to investigate the effect of frequency and amplitude of Vext on the pattern of AP firing, two simulations were done. First varying the frequency of V_{ext} and the second one varying the amplitude of external voltage over time. Figure 6 illustrates the external voltage and membrane voltages when frequency is increasing 10Hz every 1000 mS starting from 10Hz to 100Hz. Figure 7 shows the ISI map for this simulation. These results suggest that as the frequency of Vext increases the spiking pattern of membrane potential occurs with higher frequency. In the other words, interspike interval decreases. Interestingly, this pattern is violated when frequency is increased to 100Hz. Figure 8 illustrates the membrane potential's pattern of AP firing when amplitude of V_{ext} is varying every 3000 mS from 8.0 mV to 32.0 mV. The similar pattern of spiking is observed in two neurons with different TRP activity.

a

b

c

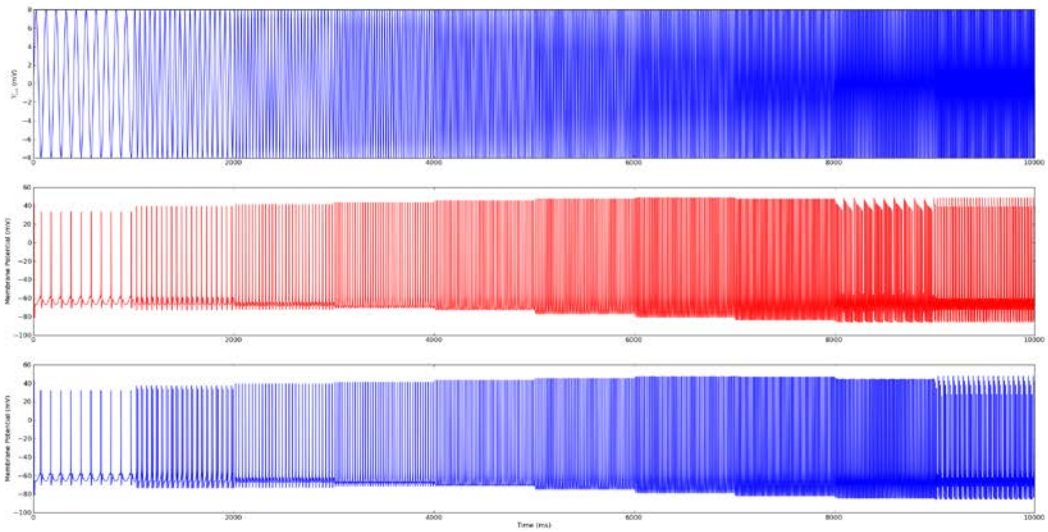

Figure 6 (a) External Sinusoidal Voltage (V_{ext}) with frequency of increasing 10Hz every 1000 mS (10Hz<f<100 Hz) (b) Membrane potential when g_{TRP} = 0.03 mS/cm^2 (c) Membrane potential when g_{TRP} = 0.06 mS/cm^2

a

b

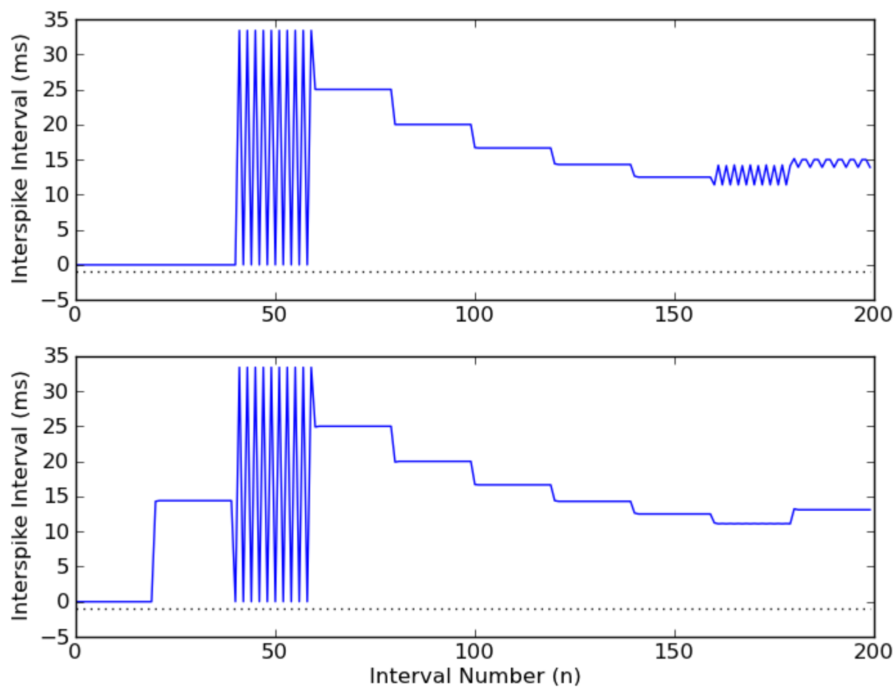

Figure 7 Interspike interval (SI) versus interval number (a) g_{TRP} = 0.03 mS/cm^2 (b) g_{TRP} = 0.06 mS/cm^2. The pattern of ISI map is similar in a and b.

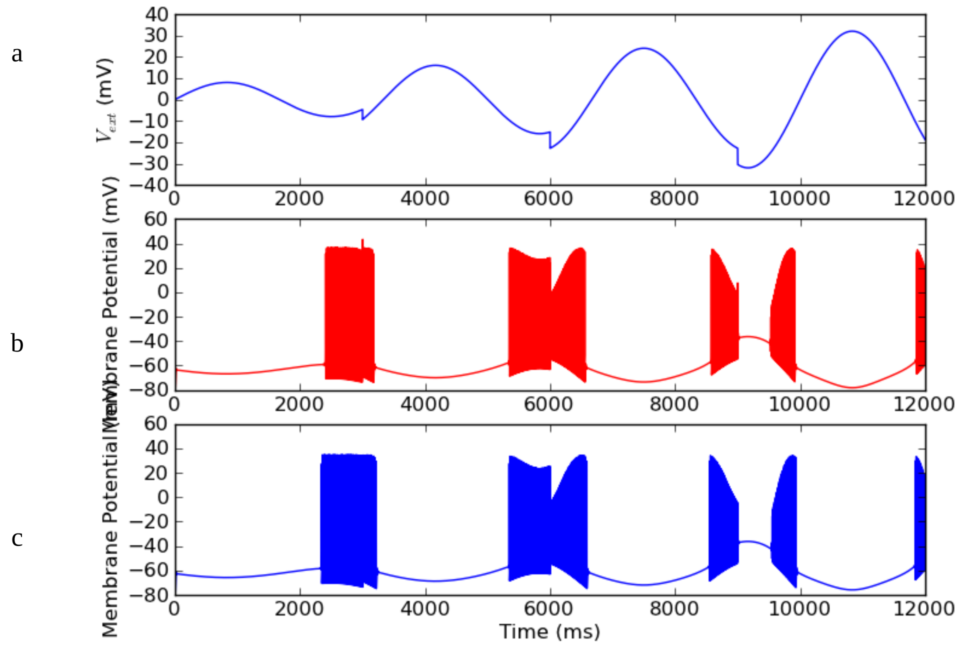

Figure 8 (a) External Sinusoidal Voltage (V_{ext}) with varying amplitude from 8.0 mV to 32.0 mV changing very 3000 mS (b) Membrane potential when g_{TRP} = 0.03 mS/cm^2 (c) Membrane potential when g_{TRP} = 0.06 mS/cm^2

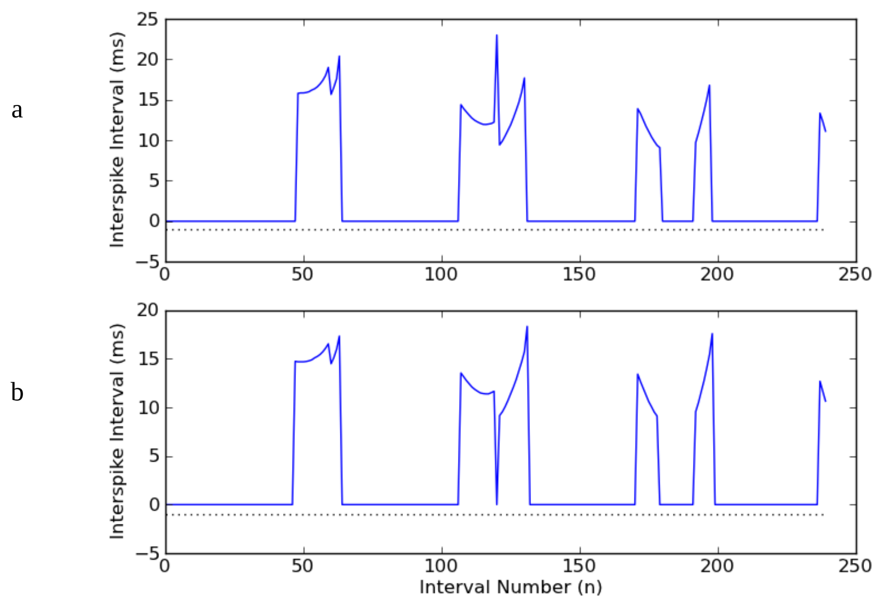

Figure 9 Interspike interval (SI) versus interval number (a) g_{TRP} = 0.03 mS/cm^2 (b) g_{TRP} = 0.06 mS/cm^2. The pattern of ISI map is similar in a and b.

4 Conclusion

As the external low-frequency sinusoidal voltage is applied on a modified HH-model neuron, the membrane potential reaches AP spiking threshold and phase locking pattern emerges even with different activity of TRP-like channels (varying g_{TRP} : conductance level). The activation of TRP-like channel results bursting activity induced by the low frequency sinusoidal voltage. Burst stimulation is more effective than constant-frequency stimulations because of neuropeptide release. As a result, varying range of low frequency sinusoidal voltage would have more significant impact on neural function[1].

When high frequency of external voltage is applied to the cell, membrane potential stays on the AP spiking pattern regularly and Interspike interval is decreased as the frequency increases which proves the tight correspondence of neural behavior to the external sinusoidal voltage. However, when the frequency is increased to 100Hz, the ISI increases. This simulation was also done for longer time and similar pattern observed. As frequency increases greater than 100 Hz, ISI increases. This may occur because the frequency of the input voltage is reaching the natural frequency of the circuit when the differential equations are modeled as homogenous equations with constant coefficients.

5 References

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