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Analysis the Effects of leakage conductance on the Action potential of Excitable cell using GUI

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ABSTRACT

The Hodgkin-Huxley (HH) model of a neuron was developed mathematically in 1952 and had its importance in modern neurobiology. Numerous variants of this presented model have already been established. Still, neuroscientists have so far utilized the HH model of the axonal membrane, which works by taking the help of circuit analog. With the involvement of several biological phenomena of the membrane in addition to the conductance, this model can easily reproduce electrophysiological measurements with almost a high degree of accuracy.

The dynamics of the HH model is related to different neurological and pathological diseases such as Parkinson's, epilepsy, Addison, Alzheimer's disease, pathological heart rhythms, etc. Dynamics of HH parameters relate to an electrochemical imbalance in the body, which mainly responsible for the generation of an action potential. The action potential is simulated in graphical user interface using MATLAB

1. Introduction

Electrophysiological problems can be accurately studied using HH model [1] of neuron. This model consists of four differential equations which are based on voltage clamp data. The main parameters associated with these channels are: external current (excitation *I*), ionic batteries (V_{Na} and V_k), maximal

sodium conductance ($\overline{g_{Na}}$), maximal potassium conductance ($\overline{g_k}$) and leakage conductance ($\overline{g_l}$). Depending upon the various parameters, HH model shows a variety of qualitatively different behaviors. One of the most important properties of this model is its stability. A stable model is one that reaches a rest state at last. In this paper, using the concept of stability theory, original HH model is used to investigate the importance of leakage conductance ($\overline{g_l}$) and keeping others parameters at desired values. Stability of the model can be studied by using bifurcation point obtained by taking $\overline{g_l}$ as variable. Simulation results have been compared with relevant diseases caused by leakage conductance anomaly [2], [8].

2. Computational Method

The model scheme used in this work is the Hodgkin-Huxley formalism where the change in the membrane potential, V with respect to time is given by contributions from active and passive membrane currents and applied stimulus.

$$\frac{dv}{dt}=\frac{1}{C_M}[I-\overline{g_K}n^4(V-V_K)-\overline{g_{Na}}m^3h(V-V_{Na})-\overline{g_l}(V-V_l)]$$

……. Equation 1

$$\frac{dm}{dt}=\alpha_m(V)(1-m)-\beta_m(V)m$$

$$\frac{dh}{dt}=\alpha_h(V)(1-h)-\beta_h(V)h$$

$$\frac{dn}{dt}=\alpha_n(V)(1-n)-\beta_n(V)n$$

Where,

$$\alpha_n(V)=0.01(V-10)/(1-\exp[-(\frac{V-10}{10})])$$

$$\beta_n=0.125\exp(-V/80)$$

$$\alpha_m=0.1(V-25)/(1-\exp[-(\frac{V-25}{10})])$$

$$\beta_m=4\exp(-V/18)$$

$$\alpha_h=0.07\exp(-V/20)$$

$$\beta_h=1/1+\exp[-(\frac{V-30}{10})]$$

Here, V is the transmembrane potential. $0 \leq m \leq 1$ and $0 \leq h \leq 1$ are the gating variables indicating activation and inactivation of sodium ion current, respectively. $0 \leq n \leq 1$ is the gating variable showing activation of potassium ion current. $\overline{g_{Na}}$, $\overline{g_k}$, and $\overline{g_l}$ represent the maximal conductance of corresponding currents. C = 1.0 F/cm^2 is membrane capacitance. I_{ext} is the current injected into the neuron. Here we have considered I_{ext} = 0 and $\overline{g_{Na}}$ = 120 mS/cm^2, $\overline{g_k}$ = 36 mS/cm^2 and $\overline{g_l}$ = 0.3mS/cm^2, which are the ideal experimental data.

3. Computation for Stability and Bifurcation

Let us suppose that (V^*, m^*, n^*, h^*) is the equilibrium points of the HH model. Therefore it will make the right side of equations 1 equal to zero. Thus we get the following equations :

$$I-\overline{g_K}n^{*4}(V^*-V_K)-\overline{g_{Na}}m^{*3}h^*(V^*-V_{Na})-\overline{g_l}(V^*-V_l)=0$$

$$\alpha_m(V^*)(1-m^*)-\beta_m(V^*)m^*=0$$
$$\alpha_h(V^*)(1-h^*)-\beta_h(V^*)h^*=0$$
$$\alpha_n(V^*)(1-n^*)-\beta_n(V^*)n^*=0$$

Since the equation 1 is a complex nonlinear system, it may have many equilibrium points. Therefore, firstly it is required to use nonlinear system theory to linearize the system for stability test. Now linearization of equation 1 around the equilibrium can be obtained as [5]:

$$\frac{dv}{dt}=A_{11}V+A_{12}m+A_{13}h+A_{14}n$$
$$\frac{dm}{dt}=A_{21}V+A_{22}m$$
$$\frac{dh}{dt}=A_{31}V+A_{33}h$$
$$\frac{dn}{dt}=A_{41}V+A_{44}n$$

The eigenmatrix of equation this equation can be written as

$$A=\begin{pmatrix}A_{11} & A_{12} & A_{13} & A_{14}\\ A_{21} & A_{22} & 0 & 0\\ A_{31} & 0 & A_{33} & 0\\ A_{41} & 0 & 0 & A_{44}\end{pmatrix}$$

Where

$$A_{11}=-\frac{\overline{g_{Na}}m^{*3}h^*+\overline{g_k}n^{*4}+\overline{g_l}}{C_M}$$

$$A_{12}=-\frac{3\overline{g_{Na}}m^{*2}h^*(V^*-V_{Na})}{C_M}$$

$$A_{13}=-\frac{\overline{g_{Na}}m^{*3}(V^*-V_{Na})}{C_M}$$

$$A_{14}=-\frac{4\overline{g_k}n^{*3}(V^*-V_k)}{C_M}$$

Stability theorem can now be applied on the characteristic equation. For example, if Routh-Hurwitz stability is applied then according to this criterion, the real parts of all roots will be minus if $a_1>0$, $a_1b_1>c_1$, $d_1>0$, $a_1b_1c_1>c_1^2+a_1^2d_1$. Otherwise, all the real parts will be positive. The main results in this work consist of identifying bifurcation points for $\overline{g}_l$. To find the variation of V^* with respect to $\overline{g}_l$, $\overline{g}_l$ is varied from 0 to 20 mS/cm^2 and

for each value of $\bar{g}_l$, the corresponding value of V^* can be obtained from equation through computer simulation. The relationship between $\bar{g}_l$ and the equilibrium point V^* is shown in Fig.1. From this, it can be observed that V* rises exponentially and shows unstable behavior when $\bar{g}_l \in [0, 2]$. The normal value of $\bar{g}_l$ is 0.3 mS/cm^2. Thus, it can be concluded that the bifurcation point will lie in the range $\bar{g}_l \in [0, 2]$.

Therefore to find the bifurcation point, simulation has been performed for the range $\bar{g}_l \in [0, 2]$. and using the method of bisection as explained in the previous chapter, one bifurcation point $\bar{g}_l^b$ is obtained at 0.299.

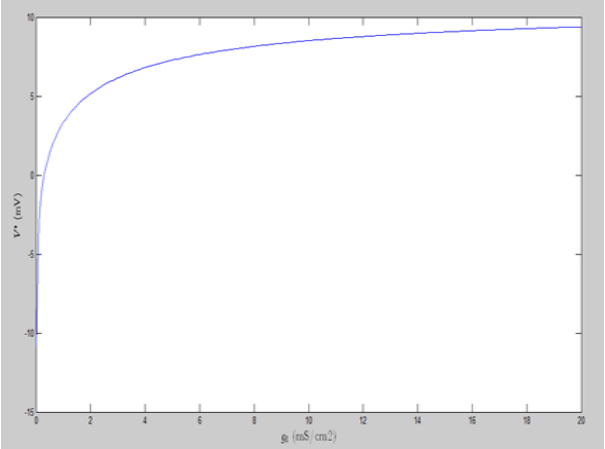


Fig. 1: *Relationship between* $\bar{g}_l$ *and V**

The simulation results are shown in figure 2 and figure 3. Figure 2 shows the response of V and m, h, and n at different $\overline{g_l} < 0.299$. It is observed that, when $\overline{g_l} < 0.299$, the system is unstable. All potential-time (V-t) curves within this range show that the action potential V becomes periodic. Also the Figures displaying the trajectory of gating variables m, h, and n with time show that the electrophysiological activity of cell does not reach an equilibrium state at last within this range.

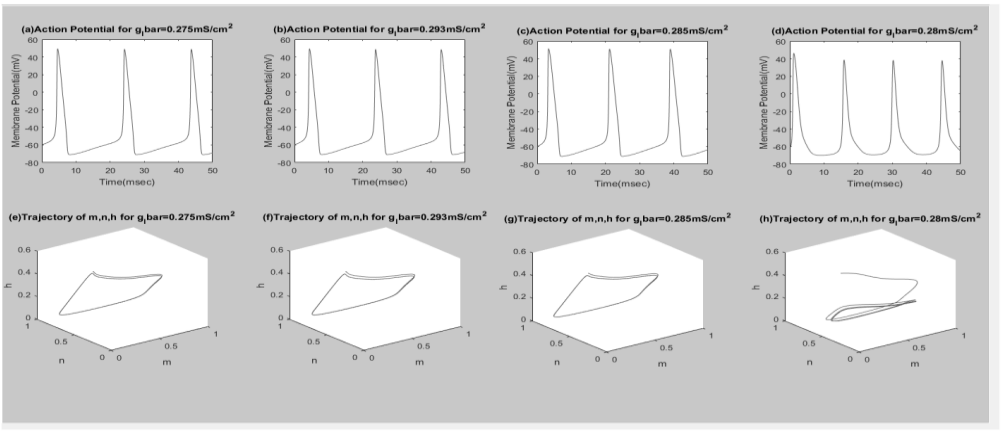


Fig. 2: *Response of action potential and trajectory of m, n, h for* $\overline{g_l} < 0.299$ *mS/cm2*

Figure 3 shows the response of V and m, h, and n to different $\overline{g_l} > 0.299$. It demonstrates that the system is stable when $\overline{g_l} > 0.299406$. It is observed from all V-t graphs that when $\overline{g_l} > 0.299$, the potential reaches a steady state at last. It means that the action potential becomes stable.

It is seen from simulation results that when leakage conductance is in the range less than the bifurcation value, the HH model will have periodic solution i.e. cell will have continuous action potential after stimulation. These phenomena look like responses of some dysfunctional pathological cell's action potentials. Some of the simulated results within the range (0.299 – 0.255) are compared with the action potentials of cells caused by some diseases or dysfunctional cells and results are presented in Table 1.

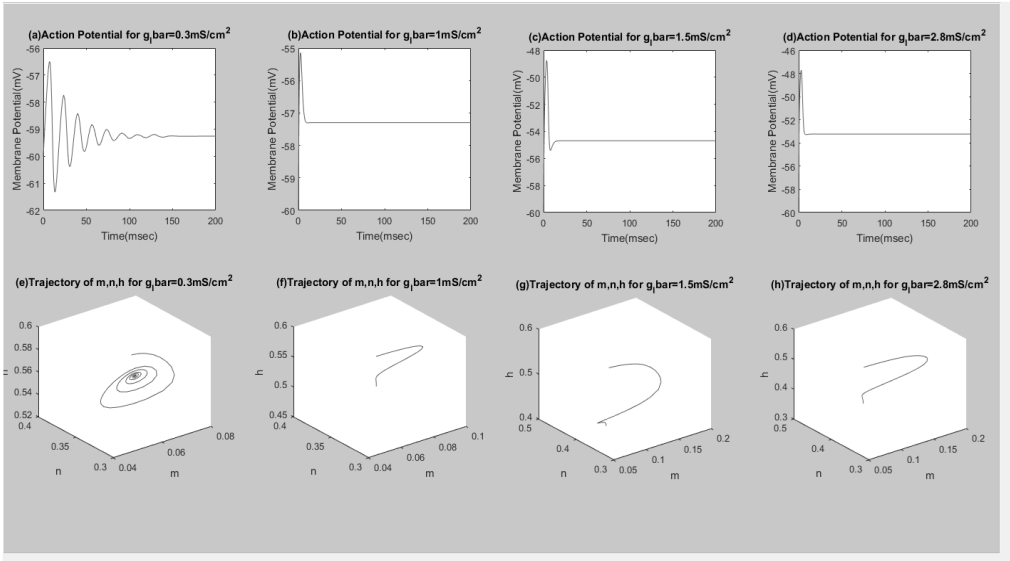
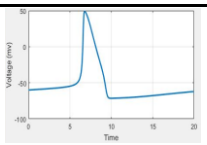
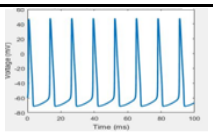


Fig. 3: *Response of action potential and trajectory of m, n, h for 3.3>* $\overline{g_l}$ *> 0.299 mS/cm2*

Table 1: *Comparison of simulated results with action potentials of dysfunctional /diseased cells*

Parameter	**Range of value** mS/cm^2	**Name of disease**	**Simulated action potential from HH**
$\overline{g_l}$	(0.299 – 0.276)	Muscular tonus [10]	
	(0.275-0.257)	Demyelination [11]	

4. Discussion

In this study, the effects of $\bar{g}_l$ on the stability and bifurcation of original HH model have been analyzed and critical value is obtained. When the value of maximal leakage conductance was varied from 0 to 2 (mS/cm^2), a single bifurcation point at $\bar{g}_l^{b}$ = 0.299 mS/cm^2 was obtained. It is observed from Fig. 2 that when $\bar{g}_l$ = 0.299 < $\bar{g}_l^{b}$, the system is unstable and at this range the trajectory of m, n, h become a closed loop indicating that below the bifurcation point both the action potential curves and the trajectory of the gating variables show instability. From Fig 3, it is observed that when 3.3> $\overline{g_l}$ > 0.299, the system is stable and action potential reaches a stable state at last.

It is observed that, in some ranges of maximum leakage conductance as shown in Fig 2 the action potentials look like pathological cell's action potentials caused by muscular tonus and demyelination [10], [11]. However, these action potentials during unstable conditions have not shown the characteristics of seizure like behavior. It does not mean that conductance do not have role in seizure dynamics, but fixed ion concentration of leakage ions (through fixing the values of V_l) and variable conductance parameters are not sufficient for tracking of seizure like behavior. From this analysis, therefore, it may be concluded that the original HH model with fixed intra- and extra ion concentration and variable conductance parameter may be used for characterization of certain pathological disorders of excitable cells but cannot be directly used to characterize some neurological disorders such as seizure like events.

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