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PERIODIC FIRINGS IN NEURONS WITH EXTERNAL SINUSOIDAL APPLIED CURRENT

AVINITA GAUTAM[1] AND ANUPAM PRIYADARSHI[2,*]

[1]DST-CIMS, Institute of Science, Banaras Hindu University, Varanasi-221005, India

[2]Department of Mathematics, Banaras Hindu University, Varanasi-221005, India

Abstract: The distinct qualitative behavior exhibited by neuron at externally applied current stimuli is well known in the Hodgkin-Huxley model (HH model). The resting state and periodic firings in neuron correspond to solutions of the HH model having stable fixed points and unstable fixed point (periodic solutions through Hopf bifurcation points). The one-parameter bifurcation with respect to externally applied current stimuli suggests a periodic window between two stable fixed point solutions in the HH model. The externally applied sinusoidal current stimuli generate periodic firings at very low current and a large periodic region is observed. The generations of limit cycles and possible chaotic behavior in the HH model is explored through numerical simulations extensively.

Keywords: neuron; external current; bifurcation; resting state; periodic firing.

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[*]Corresponding author

E-mail address: anupam240@gmail.com

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1. INTRODUCTION

The network of neurons in the brain is very complex and study about its dynamics is also very complicated. A human brain consists of approximately 10^{11} neurons [1]. The neuron is like a signal converter since it receives stimulus via *dendrites* at the *synapse* and transmits through the *axon* to other neurons [2]. This process continues as the firing of the *action potential*. A sufficient input is required for firing of action potential because below that threshold values no firing of the action potential is possible [3]. This period of no action potential is called the *refractory period* [2,4].

The cell membrane has a lipid structure which is completely stable from inside and outside. These are ion channels inside the cell which allow the specific type of ions to pass through it. When ions pass across the cell membrane, it creates a potential difference between inside and outside of the cell membrane. Therefore the cell membrane can behave as a capacitor. The behavior of neurons depends on voltage-dependent ionic channels [5]. Hence Hodgkin and Huxley proposed a model by an equivalent circuit.

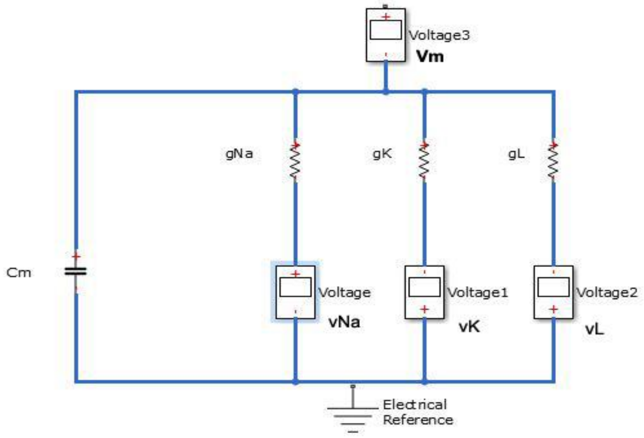


FIGURE 1. An electrical equivalent circuit for cell membrane

According to Ohm’s law, the current through a conductor between two points is directly proportional to the voltage across the two points. Using the voltage-clamped method Hodgkin-Huxley made the cell membrane isopotential, where the same potential is measured across the cell membrane. For the different ion channels (Na, K and leakage ions), the transverse current is given as follows

$$I_i = g_i(V_m - G_i) \qquad where\ i = Na, K\ and\ L \tag{1}$$

Kirchhoff's current law states that the sum of all currents in a closed system equals to zero.

$$\sum_j I_J = 0 \qquad for\ j \in \mathbb{N} \tag{2}$$

The ionic current for sodium, potassium, and leakage ions are considered at maximum corresponding conductance which is given as

$I_{Na} = -g_{Na}m^3h(V - V_{Na})$, $I_K = -g_K n^4 (V - V_K)$, and $I_L = -g_L(V - V_L)$

Hodgkin-Huxley model of a cell membrane is important to model for the study of nonlinear dynamics. It is highly nonlinear ODEs [6, 7, 8, 9, 10] and given by system four differential equations (system 3) and six voltage-dependent coefficients (system 4) as follows:

$$\begin{aligned}
\frac{dV}{dt} &= [-g_{Na}m^3h((V+65) - V_{Na}) - g_K n^4((V+65) - V_K) \\
&\quad - g_L((V+65) - V_L) + I]/C \\
\frac{dx}{dt} &= \alpha_x(V)(1-x) - \beta_x(V)x \\
&where\, x = m, n, h
\end{aligned} \tag{3}$$

$$\begin{aligned}
\alpha_m &= 0.1(25 - (V+65))/(\exp((25-(V+65))/10) - 1) \\
\beta_m &= 4\exp(-(V+65)/18) \\
\alpha_h &= 0.07\exp(-(V+65)/20) \\
\beta_h &= 1/(1+\exp(30-(V+65))/10)) \\
\alpha_n &= 0.01(10-(V+65))/(\exp(10-(V+65))/10) - 1) \\
\beta_n &= 0.125\exp(-(V+65)/80)
\end{aligned} \tag{4}$$

TABLE 1. Notations of Variables and parameters

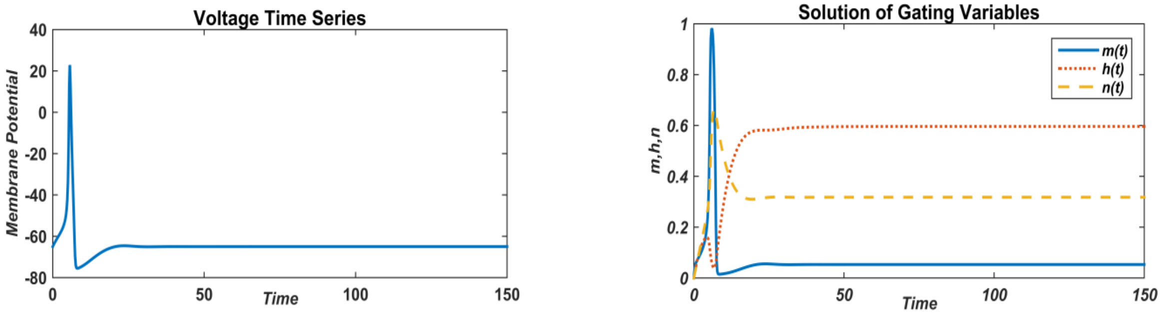
Variable & Parameters	Representations	Units
Membrane potential	V	mV
Potential for sodium (Na)	V_{Na}	mV
Potential for potassium (K)	V_K	mV
Potential for leakage current	V_L	mV
Membrane capacitance	C	$\mu F / cm^2$
External Applied Current	I	$\mu A / cm^2$
Sodium activation	m	-
Potassium activation	n	-
Sodium inactivation	h	-
Rate constants	α_n, α_m and α_h	-
Rate constants	$\beta_{n,}\ \beta_m$ and β_h	-
Maximum conductance for Sodium ions	g_{Na}	mS / cm^2
Maximum conductance for Potassium ions	g_K	mS / cm^2
Maximum conductance for Leakage ions	g_L	mS / cm^2

The system (3) and (4) are so complex that they are mathematically intractable. Hence, extensive numerical simulations are carried out by MATLAB, Mathematica and XPPAUT.

2. PRELIMINARIES

If the neuron is at rest then there is no transmission of information within or in between neurons. In the following subsections we describe the voltage time series and the effects of external stimuli when it is constant and when it is periodic specifically sinusoidal:

No Stimulus to neuron

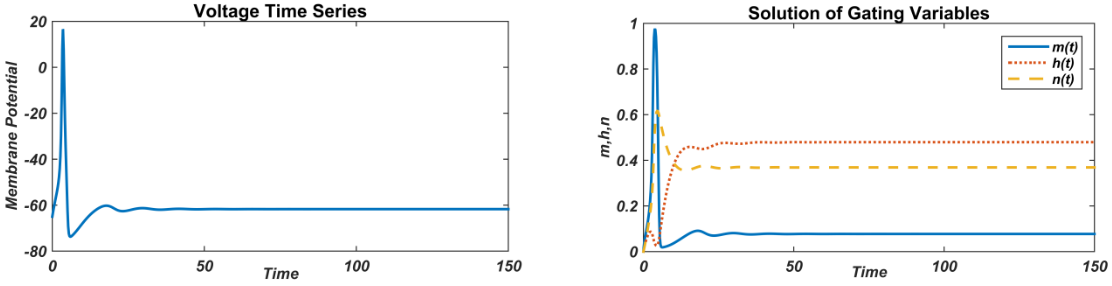


(a) (b)

FIGURE 2. Responses of membrane potential (left) and gated variable (right) without an external current (I=0 μA/cm^2)

The equilibrium state is followed by a single spike when there is no external stimulus given to neurons (Fig. 2). Since the system is very complex so at all initial conditions, it always gives a single spike. In this manuscript we are analyzing the effect of external current, so firstly constant external current is applied to the system (3) and behavior has been observed.

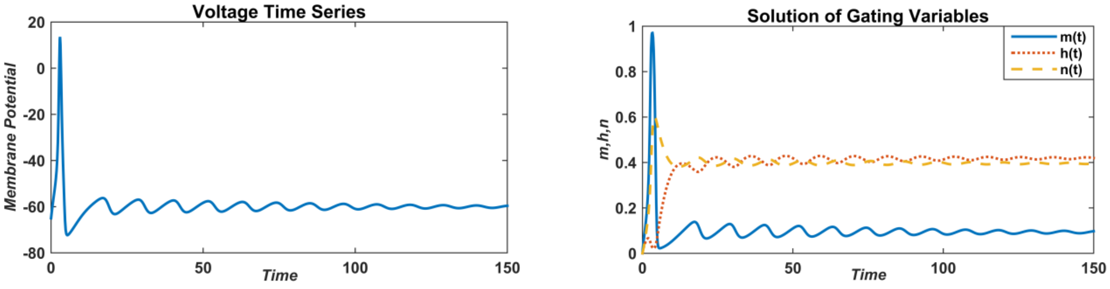
Constant Stimulus



(a) (b)

FIGURE 3: Responses of membrane potential (left) and gated variable (right) with a constant external current value, $I=5\ \mu A/cm^2$

As the external current is increased to some positive value (say 5 $\mu A/cm^2$) then it has been observed that new disturbance in voltage is arising with very low amplitude. But immediately it goes back to the equilibrium state (Fig. 3).

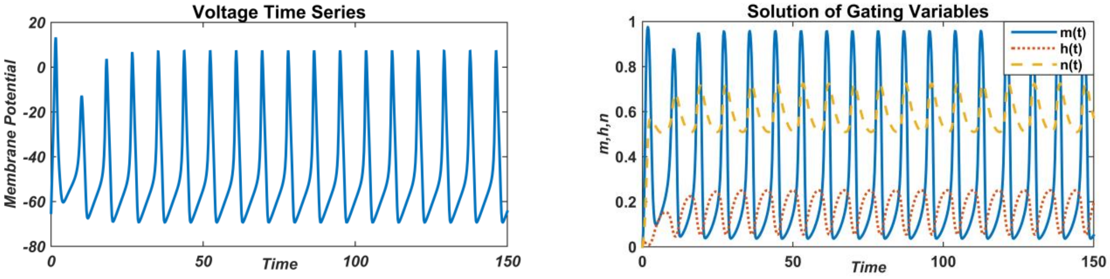


(a) (b)

FIGURE 4: Responses of membrane potential (left) and gated variable (right) with a constant external current value, I=8.8 $\mu A/cm^2$

When the external current is increased to value I=8.8 $\mu A/cm^2$, then it has been found that smooth oscillations occur but it disappears after 150 milliseconds (Fig. 4).

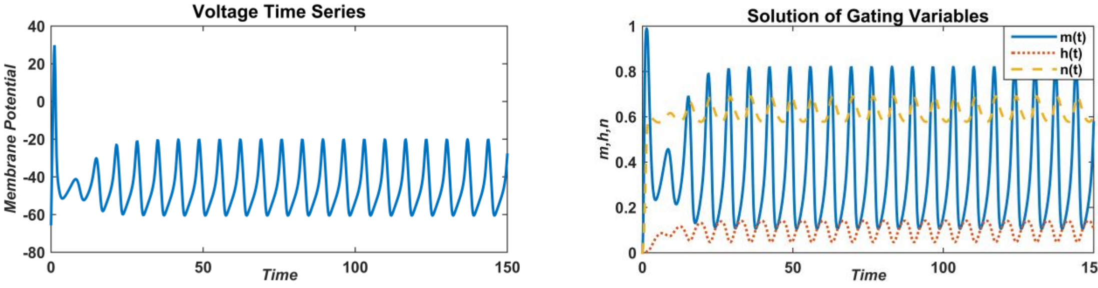
For the external current values, I=50 $\mu A/cm^2$, continuous oscillation with high spike has been observed for membrane potential and gating variables (Fig. 5). For sodium activation gated variable (m), spikes are very high as compared to potassium activation gated variable (n) and sodium inactivation gated variable (h).



(a) (b)

FIGURE 5: Responses of membrane potential (left) and gated variable (right) with a constant external current value, I=50 $\mu A/cm^2$

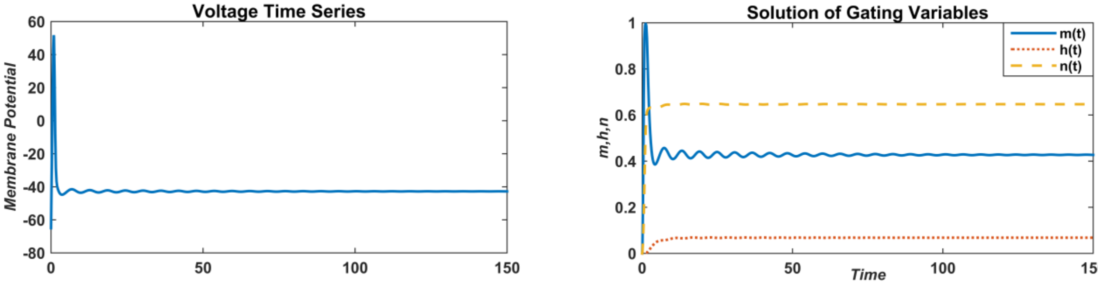
But as the external current is increased up to $I=100\ \mu A/cm^2$, the amplitude of spikes decreased as compared to initial spike but the oscillations go on and not disappear in the case of membrane potential (Fig.6). But for the gated variables, the amplitude of spike decreases very little as compared to membrane potential (Fig. 6).



(a) (b)

FIGURE 6: Responses of membrane potential (left) and gated variable (right) with a constant external current value, $I=100\ \mu A/cm^2$

However, when the external current is increased to the value $I=160\ \mu A/cm^2$ then it has been observed that after a single spike again oscillations disappear within *100* millisecond time period for both membrane potential and gated variables (Fig. 7).



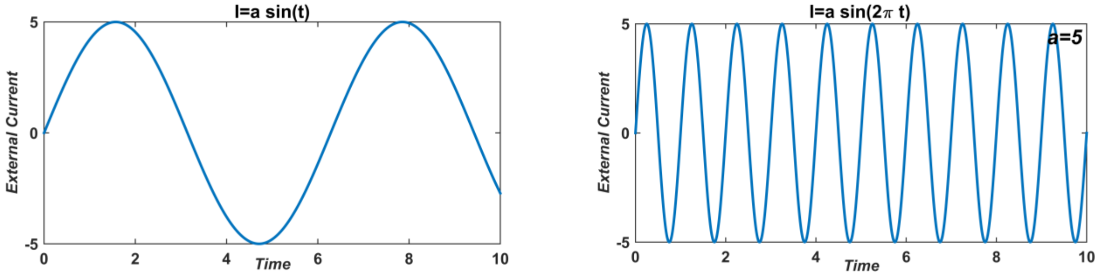
(a) (b)

FIGURE 7: Responses of membrane potential (left) and gated variable (right) with a constant external current value, $I=160\ \mu A/cm^2$

Therefore, it has been observed that for constant external current neurons behave in two ways such as stable and oscillatory in the case of constant stimulation. Now for better understanding, we have explored the behavior of neurons for varying external current that is when the external current becomes a function of time.

Sinusoidal Stimulus

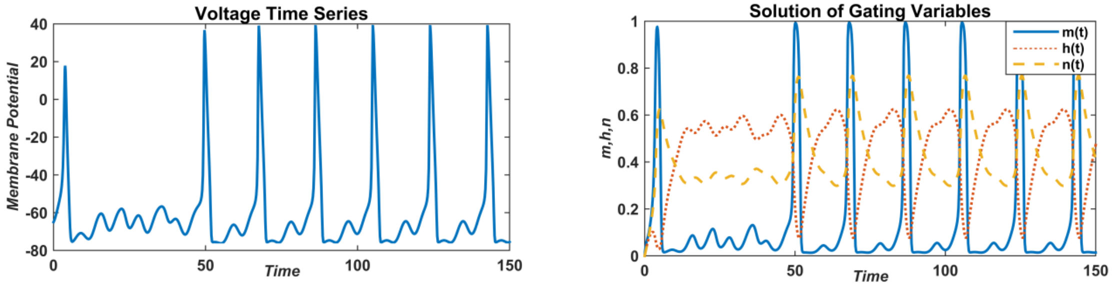
Now, an external current is being varied by a sine function with period 2π that is $I = a\sin t$ and $I = a\sin 2\pi t$ with period 1 (Fig. 8).



(a) (b)

FIGURE 8: Graph of external current with respect to time $I = a\sin t$ (left) and $I = a\sin 2\pi t$ (right)

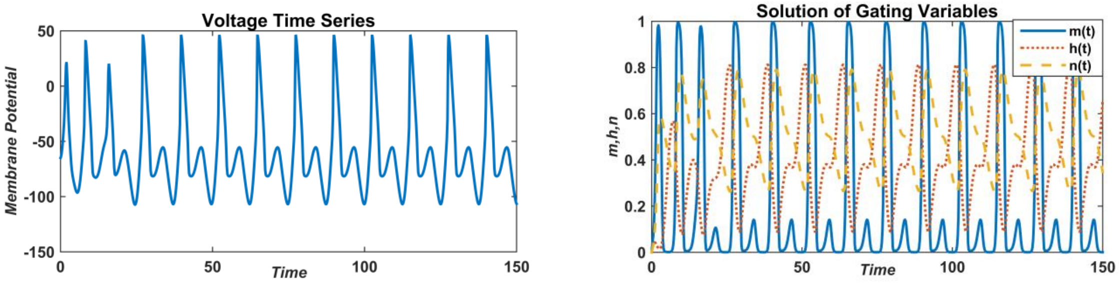
With varying external current, we have analyzed the behavior of the *HH model* and found that it shows chaotic behavior for membrane potential with high spikes (Fig. 9(a)). In case of gating variables, the behavior is also chaotic but spikes of sodium activation *(m)* are high as compared to sodium inactivation *(h)* and potassium activation *(n)* for lower amplitude $a=5$ (Fig. 9(b)).



(a) (b)

FIGURE 9: Responses of membrane potential (left) and gated variable (right) with a sinusoidal external current, $I=5 \sin(t)\ \mu A/cm^2$

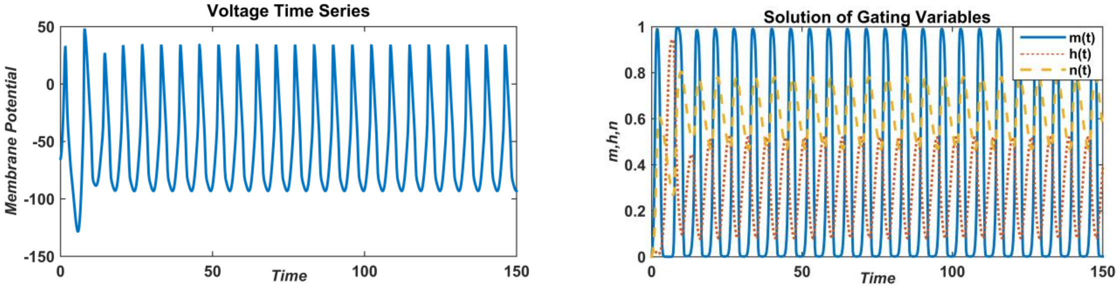
As we increase the value from 5 to 50, we have found a change in the behavior of the system. It shows double periodic in both the case of membrane potential and gating variables (Fig. 10).



(a) (b)

FIGURE 10: Responses of membrane potential (left) and gated variable (right) with a sinusoidal external current, I=50 *sin (t) μA/cm*^{2}

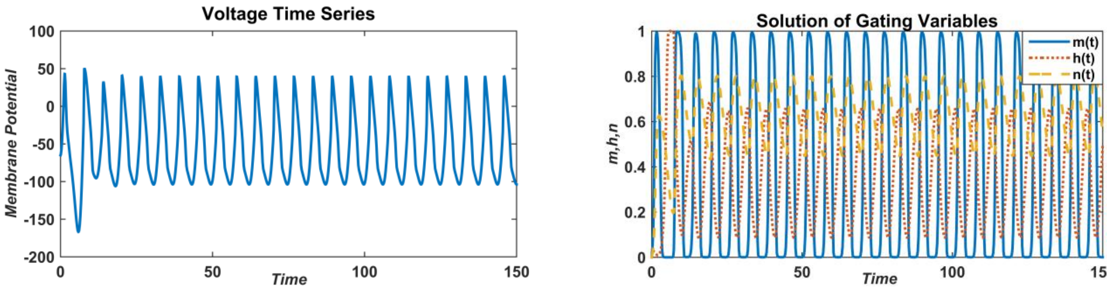
For higher values of a system shows continuous oscillations with high spikes in both the cases of membrane potential and gating variables with high spikes (Fig. 11).



(a) (b)

FIGURE 11: Responses of membrane potential (left) and gated variable (right) with a sinusoidal external current, I=100 *sin (t) μA/cm*^{2}

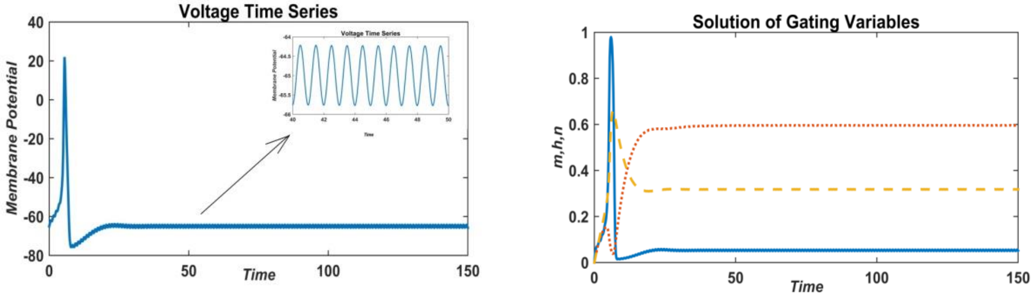
But for the value, *a=150* spikes of membrane potential are low as compared to figure 11, although it shows continuous oscillations for both membrane potential and gating variables (Fig. 12).



(a) (b)

FIGURE 12: Responses of membrane potential (left) and gated variable (right) with a sinusoidal external current, I=150 *sin (t)* $\mu A/cm^2$

Now we are changing the frequency of sinusoidal current as $I = a\sin(2\pi t)$. In this case, we have found a continuous periodic solution for both membrane potential and gating variables for lower and higher values of *a* (Fig. 13). We can clearly observe from zoom picture of the behavior of membrane potential (Fig. 13(a)) and gating variables (Fig. 14) that the solutions are periodic.



(a) (b)

FIGURE 13: (a) Response of membrane potential with a sinusoidal external current, I=5 *sin* $(2\pi t)$ $\mu A/cm^2$ and (b) Responses of gating variables with a sinusoidal external current, I=5 *sin* $(2\pi t)$ $\mu A/cm^2$.

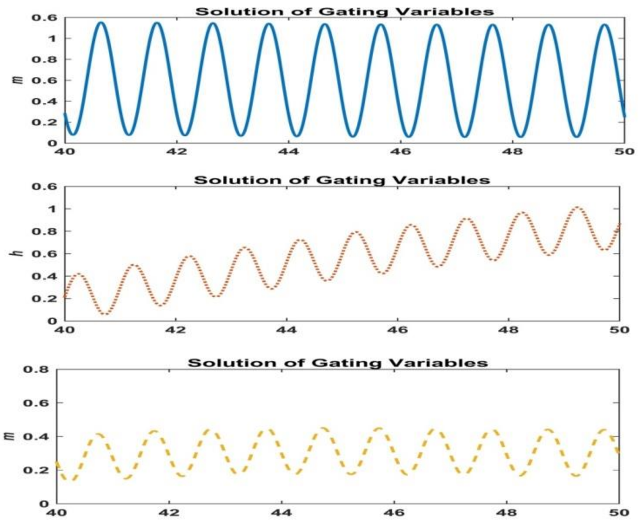
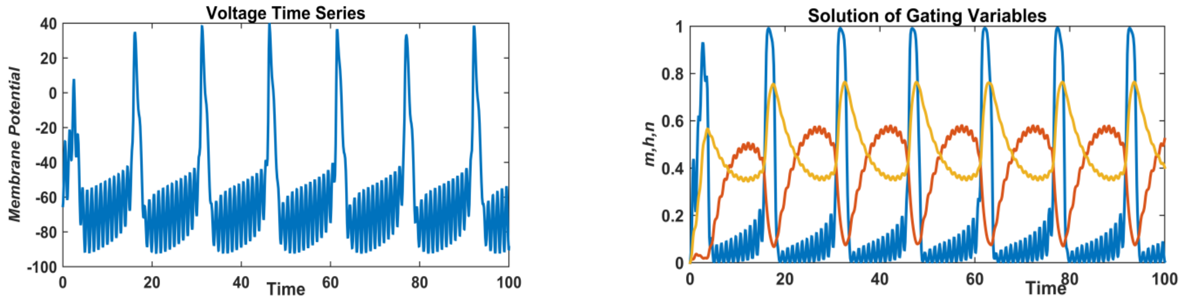


FIGURE 14: Magnified picture of figure 13 (responses of gating variables with a sinusoidal external current, $I=5\sin(2\pi t)\ \mu A/cm^2$)

Different behavior has been observed for higher values of a. This shows that system (3) exhibits continuous periodic solutions for the applied external current given by $I = a\sin(2\pi t)$.



(a) (b)

FIGURE 15: (a) Response of membrane potential with a sinusoidal external current, $I=120\sin(2\pi t)\ \mu A/cm^2$and (b) Responses of gating variables with a sinusoidal external current, $I=120\sin(2\pi t)\ \mu A/cm^2$.

3. MAIN RESULTS

It has been observed in the above section with the help of time series analysis that model behaves differently for different values of externally applied current. Bifurcation will occur at equilibrium points of the system when the externally applied current is injected into the neurons [10]. Since the system is very complex so we will study the model analytically for external current $I=0$. Stability of models can be analyzed easily with the help of equilibrium points. Let $E=(v_1,m_{1,}h_1,n_1)$ be the equilibrium point of the model (1) which obtained by equating right-hand sides of the system (1) equal to zero.

Now we have Jacobian matrix after linearization of the system (1) as [11]:

$$J=\begin{bmatrix} f_{11} & f_{12} & f_{13} & f_{14} \\ f_{21} & f_{22} & f_{23} & f_{24} \\ f_{31} & f_{32} & f_{33} & f_{34} \\ f_{41} & f_{42} & f_{43} & f_{44} \end{bmatrix} \tag{5}$$

Where,

$$f_{11}=-\frac{g_{Na}m^3h+g_Kn^4+g_L}{C}$$

$$f_{12}=-\frac{3g_{Na}m^2h(V-V_{Na})}{C}$$

$$f_{13}=-\frac{g_{Na}m^3(V-V_{Na})}{C}$$

$$f_{14}=-\frac{4g_Kn^3(V-V_K)}{C}$$

$$\begin{aligned} f_{21}=&(2\,\mathrm{m}\exp(-\mathrm{v}/18-65/18))/9+(\mathrm{m}-1)/(10(\exp(-\mathrm{v}-40)/10-1))+\\ &(\exp(-\mathrm{v}-40)(\mathrm{v}/10+4)(\mathrm{m}-1))/(10(\exp(-\mathrm{v}-40)/10-1)^2)\end{aligned} \tag{6}$$

$$f_{22}=(\mathrm{v}/10+4)/(\exp(-\mathrm{v}-40)/10-1)-4\exp(-\mathrm{v}/18-65/18)$$

$$f_{23}=0\ ,\ f_{24}=0$$

$$f_{31}=(7\exp(-\mathrm{v}/20-13/4)(\mathrm{h}-1))/2000-(\mathrm{h}\exp(-\mathrm{v}-35))/(10(\exp(-\mathrm{v}-35)/10+1)\text{^}2)$$

$$f_{32} = 0$$

$$f_{33} = -\,(7\exp(-\,v/20 - 13/4))/100 - 1/(\exp(-\,v - 35)/10 + 1)$$

$$f_{34} = 0$$

$$f_{41} = (3n\exp(-\,v/80 - 13/16))/2000 + (n - 1)/(100(\exp(-\,v - 55)/10 - 1)) + \\ (\exp(-\,v - 55)\,(v/100 + 11/20)(n - 1))/(10(\exp(-\,v - 55)/10 - 1)^2)$$

$$f_{42} = 0,\quad f_{43} = 0$$

$$f_{44} = (v/100 + 11/20)/(\exp(-\,v - 55)/10 - 1) - (3\exp(-\,v/80 - 13/16))/25$$

And the characteristic equation of matrix J with is given as:

$$\lambda^4 + a_1\lambda + a_2\lambda + a_3\lambda + a_4 = 0 \tag{7}$$

where,

$$a_1 = -(f_{11} + f_{22} + f_{33} + f_{44})$$

$$a_2 = f_{11}(f_{22} + f_{33} + f_{44}) + f_{22}(f_{33} + f_{44}) + f_{33}f_{44} - f_{12}f_{21} - f_{13}f_{31} - f_{14}f_{41} \tag{8}$$

$$a_3 = f_{12}f_{21}(f_{33} + f_{44}) + f_{13}f_{31}(f_{22} + f_{44}) + f_{14}f_{41}(f_{22} + f_{33}) \\ - f_{11}f_{22}(f_{33} + f_{44}) - (f_{11} + f_{22})f_{33}f_{44}$$

$$a_4 = f_{11}f_{22}f_{33}f_{44} - f_{12}f_{21}f_{33}f_{44} - f_{13}f_{22}f_{31}f_{44} - f_{14}f_{22}f_{33}f_{41}$$

According to Rourth-Hurwitz Criterion, roots of equation (7) have negative real roots, if

$$a_1 > 0,\ a_1 a_2 > c,\ a_4 > 0 \text{ and } a_1 a_2 a_3 > a_3^2 + a_1^2 a_4 .$$

Otherwise, roots have non-negative real parts.

By putting all the values fixed we may have *E= (-54.4, 8.6800e-11, 1, 3.7836-04)*

$$A = \begin{bmatrix} -0.3789 & 0.0000 & 0.0000 & -610.8728 \\ 0.0000 & -2.2198 & 0 & 0 \\ -0.0000 & 0 & -0.0412 & 0 \\ 0.0121 & 0 & 0 & -0.1115 \end{bmatrix} \tag{9}$$

The characteristic polynomial of matrix A is given by

$$\lambda^4 + 2.7514\lambda^3 + 8.6341\lambda^2 + 16.8527\lambda + 0.6799 = 0 \tag{10}$$

$$where, \quad a_1 = 2.7514, a_2 = 8.6341, a_3 = 16.8527, a_4 = 0.6799$$

According to Routh- Hurwitz Criterion, since

$$\begin{aligned} & a_1 = 2.7514 > 0 \\ & a_1 a_2 = 23.7557 > c \ (= 16.8527) \\ & a_4 = 0.6799 > 0 \\ & a_1 a_2 a_3 = 400.3483 > c^2 + a^2 d \ (= 289.1602) \end{aligned} \tag{11}$$

Therefore, roots of polynomial equation (10) have negative real parts. Also from matrix A, we have eigenvalues with negative real parts:

$$\begin{aligned} & \lambda_1 = \text{-0.2452 + 2.7155i}, \ \lambda_2 = \text{-0.2452 - 2.7155i} \\ & \lambda_3 = \text{-2.2198 + 0.0000i}, \ \lambda_4 = \text{-0.0412 + 0.0000i} \end{aligned}$$

Bifurcation Analysis

We have observed the behavior of the *HH model* on the dependence of externally applied current. The action potential is produced by neurons when the external current is applied continuously. The behavior of the *HH model* can be observed in two ways for the lower value of current and for higher values of current. So here the region in figure 16 is divided into three parts (Region 1, Region 2 and Region 3) to make a clear understanding. Regions for the current values less than I_1 (I=7.9 *μA/cm*^{2}), $I_1 < I < I_2$ and for greater than I_2 (I=154.5 *μA/cm*^{2}) are represented by Region 1, Region 2 and Region 3 respectively. For *I>9.7 μA/cm*^{2} system shows an equilibrium point and a stable limit cycle in region 2, which disappears at I_2 (I=154.5 *μA/cm*^{2}) after a Hopf bifurcation HB2. Region 3 shows stable equilibrium point higher values of currents. At HB1 sub-critical Hopf bifurcation emanates unstable limit cycle whereas at HB1 super-critical Hopf bifurcation emanates stable limit cycles (Fig. 17). It can be observed clearly from region 1, that multistability occurs around HB1. Saddle-node bifurcation occurs at DC1 and DC2 and also it generates a pair of the stable and unstable limit cycle at DC3 (Fig. 17). As the external applied current increases, the amplitude of stable limit cycles decrease and abort at I_2.

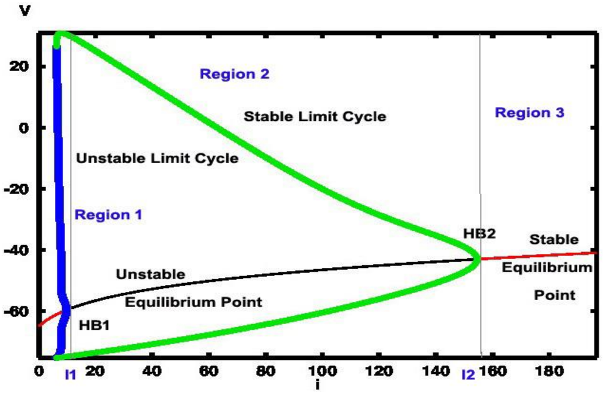
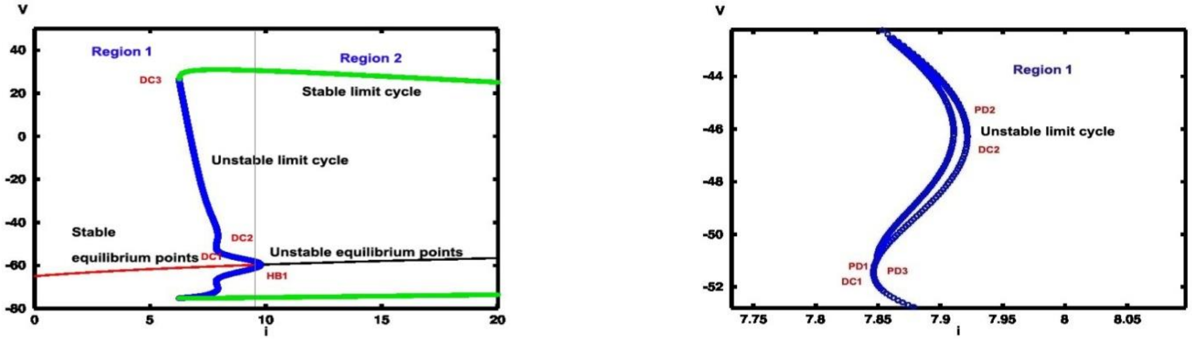


FIGURE 16: Stable (green filled circles) and unstable (blue vacant circles) branches of periodic solution of the *HH model* showing different dynamical behavior

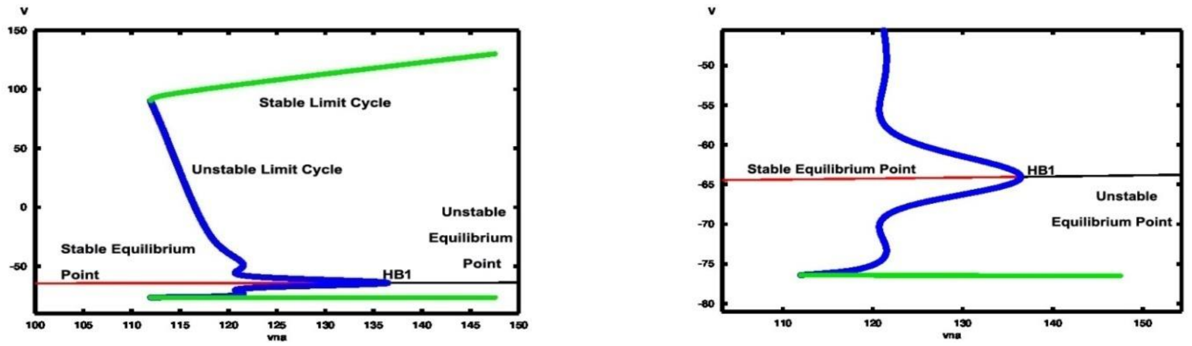
Coexisting of periodic solutions has occurred at $I=9.7\ \mu A/cm^2$ in which one is stable and the other three are unstable periodic solutions in region 1. Period-doubling bifurcations occurred at PD1 and PD2 (Fig. 17(b)). Region 1 shows interesting and complex behaviors of dynamics. Firstly neuron is at resting state but as the external current is applied to it then it fires an action potential. Stable and periodic solutions correspond to the resting and firing state of neurons (Fig. 17).



(a) (b)

FIGURE 17: (a) Magnification of the figure in Fig. 16 and (b) Magnification of (a)

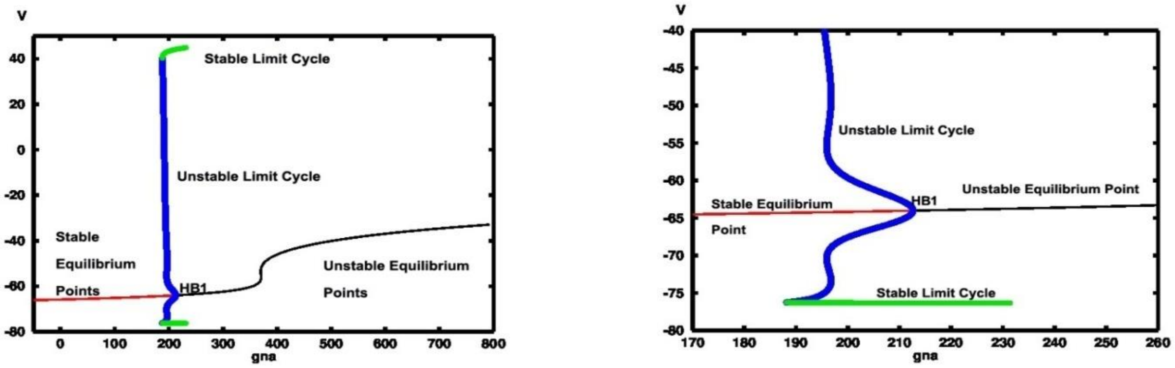
Now we have analyzed the influence of resting potential of *Na* on equilibrium points and bifurcation of the model. It has been observed that membrane potential slowly changes with respect to *Na* potential. The system goes under subcritical-Hopf bifurcation at HB1 ($V_{Na}=136.4$). Figure 18 gives the relation between V and V_{Na} in which for $V_{Na}<136.4$ systems gives a stable solution and for $V_{Na}>136.4$ system gives an unstable solution.



(a) (b)

FIGURE 18: (a) The relation between membrane potential and parameter V_{Na} and (b) Magnification of (a)

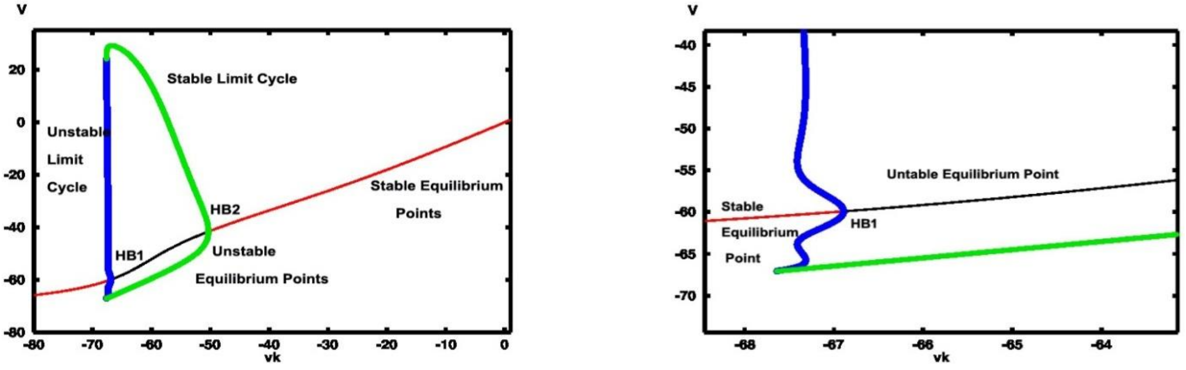
Figure 19 gives the relation between V and g_{Na}, and how g_{Na} influences the dynamics of the system. Figure 19(a) shows that V changes slowly for $g_{Na} \in [0,350]$ and rapidly for $g_{Na} \in [350,800]$. Subcritical-Hopf bifurcation has been observed at HB1. The system shows stable behavior for $g_{Na}<212.6$ and unstable behavior for $g_{Na}>212.6$ [11].



(a) (b)

FIGURE 19: (a) The relation between membrane potential and parameter g_{Na} and (b) Magnification of (a)

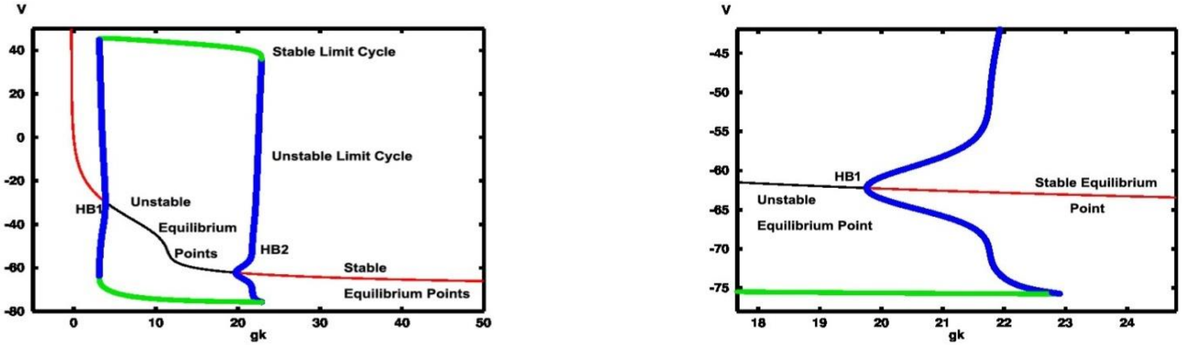
Figure 20 gives the relation between V and V_K, and how V_K influences the dynamics of the system. Figure 20(a) shows that V changes rapidly with respect to $V_{K.}$. There are two Hopf-bifurcation points, HB1 (sub-critical) and HB2 (supercritical). The system shows stable behavior for V_K <-66.89 and V_K >-50.32 whereas unstable behavior for -66.89< V_K <-50.32



(a) (b)

FIGURE 20: (a) The relation between membrane potential and parameter V_K and (b) Magnification of (a)

Figure 21 gives the relation between V and g_K, and how g_K influences the dynamics of the system. Figure 21(a) shows that V decreases rapidly with respect to $V_{K.}$ There are two Hopf-bifurcation points, HB1 and HB2; both are sub-critical Hopf bifurcation points. The system shows stable behavior for g_K <3.844 and g_K > 19.76 whereas unstable behavior for 3.844< g_K <19.76 dynamics of the system [11] is very different in Fig. 21.



(a) (b)

FIGURE 21: (a) The relation between membrane potential and parameter g_K and (b) Magnification of (a)

We have tried to analyze the effect externally applied current on neuron response. Resting-state of the neurons corresponds to the stability of the system. When a small pulse of externally applied current is applied then small perturbation is observed in membrane potential and gating variables, but it goes to resting state again. A larger pulse of externally applied current causes periodic firing or spike. The different behavior of externally applied current shows the dynamics of the neurons. When constant is applied then the system shows stable behavior for lower and higher values of current and periodic behavior for intermediate values. But when externally applied current is of the sinusoidal form then we have observed that continuous firing is observed. Chaotic behavior is observed for lower amplitude and periodic behavior for higher amplitude. We have also observed synchronization in case of sinusoidal impulse.

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Conflict of Interests

The authors declare that there is no conflict of interests.

REFERENCES

[1] M. I. Rabinovich, P. Varona, A. I. Selverston and H. D. I. Abarbanel, Rev. Mod. Phys. 78(2006), 1213–1265.

[2] L. R. Square, F. E. Bloom, N. C. Spitzer, S. Lac, A. Ghosh, and D. Berg, Fundamental of Neuroscience, Third edition, Academic Press, Elsevier (2008).

[3] J. Guckenheimer and A. Oliva, Chaos in the Hodgkin–Huxley model, SIAM J. Appl. Dyn. Syst. 1(2002) 105-114.

[4] I. Tasaki, Demonstration of two stable states of the nerve membrane in potassium-rich media, J. Physiol. (London) 148(1959), 306–331.

[5] B. P. Bean, The action potential in mammalian central neurons, Nat. Rev. Neurosci. 8(2007), 451–465.

[6] W. A. Catterall, Voltage-gated sodium channels at 60: structure, function and pathophysiology, J Physiol. 590 (2012), 2577–2589.

[7] T. Shirahata, Numerical simulation of bistability between regular bursting and chaotic spiking in a mathematical model of snail neurons, Int. J. Theor. Math. Phys. 5(5) (2015), 145-150.

[8] N. I. Krouchev, F. Rattay, M. Sawan, and A. Vinet, From squid to mammals with the HH Model through the Nav channels' half-activation-voltage parameter, PLoS ONE, 10(12) 2015, e0143570.

[9] B. Kashef and R. Bellman, Solution of the partial differential equation of the Hodgkin-Huxley model using differential quadrature, Math. Biosci.19(1974), 1-8.

[10] B. Hassard, Bifurcation of periodic solutions of the Hodgkin-Huxley model for the squid giant axon, J. Theor. Biol. 71(3) (1978), 401–420.

[11] Y. Zhang, K. Wang, Y. Yuan, D. Sui, and H. Zhang, Effects of Maximal Sodium and Potassium Conductance on the Stability of Hodgkin-Huxley Model, Comput. Math. Methods Med. 2014 (2014), Article ID 761907.