Computational Neuroscience

Project - II

Name – Gopal Gupta **Roll No. – 20CH30008**

Part A - Morris Lecar Equations (MLE) Simulation

Question 1:

Ans:

```
G_Ca = 4.4 ; % mS/cm^2
G_K = 8.0; % mS/cm^2
G_l = 2; % mS/cm^2
V_Ca = 120; % mV
V_K = -84; % mv
V_l = -60; %mV
phi = 0.02; % ms^-1
V_1 = -1.2; %mV
V_2 = 18; %mV
V_3 = 2; %mV
V_4 = 30; %mV
V_5 = 2; %mV
V_6 = 30; %mV
C = 20; % µF/cm^2
I_ext = 0; % µA/cm^2
```

If we choose conductance as ‘mS/cm^2’, voltage as ‘mV’ and use the relation current=conductance x voltage, we will get the unit of current as µA/cm^2 which is consistence same can be done with other set of units.

If we choose conductance as µS/cm^2 then it depends on the unit of voltage we choose, if we choose V or mV, then the unit of current can be µA/cm^2 or nanoampere/cm^2. So, the solution for a unit cannot unique.

Question 2:

Ans: For evaluating the equilibrium point we can do by either plotting the nullcline of the ‘V’ and ‘w’ on the quiver plot and finding the intersection point from the plot which is given in figure-1.
We can use ‘vpasolve’ command in the MATLAB to find the intersection of the derivative of ‘V’ and ‘w’ to zero.

We can also use Ode15s solver to get the equilibrium point by giving some initial point on the phase plane.

The Equilibrium point is given as:

V_res = -60.8554 mV
w_0 = 0.0149

Code for the both method is:

```
[V, w] = meshgrid(-80:1.2:40, 0:0.01:1);
dVdt = (1/C)*(I_ext - G_Ca * (0.5*(1+tanh((V-V_1)/V_2))).*(V-V_Ca) - G_K * w .* (V - V_K) - G_l * (V - V_l));
dwdt = phi * (((0.5 * (1+tanh((V-V_3)/V_4)))-w) .* cosh((V-V_3)/V_4));
```

```
quiver(V, w*100 ,dVdt,dwdt*100,0.9,LineWidth=1);
hold on;
plot(V(1,:),((I_ext - G_Ca * (0.5*(1+tanh((V(1,:)-V_1)/V_2))).*(V(1,:)-V_Ca)- G_l
* (V(1,:) - V_l))./(G_K * (V(1,:) - V_K)))*100,LineWidth=1); % plot of null clines
dV/dt=0


plot(V(1,:),(0.5* (1+tanh((V(1,:)-V_3)/V_4)))*100,LineWidth=1); % plot of null
clines dw/dt=0
set(gca,'FontSize',20);axis([-80 40 0 100]);

% finding the equilibrium point by fsolve
fun = @(V_r) ((I_ext - G_Ca * (0.5*(1+tanh((V_r-V_1)/V_2)))*(V_r-V_Ca)- G_l * (V_r
- V_l))/(G_K * (V_r - V_K))) - (0.5* (1+tanh((V_r-V_3)/V_4)));
V_res = fsolve(fun,-60);
w_0 = (0.5* (1+tanh((V_res-V_3)/V_4)));
plot(V_res,w_0*100,'ro');
legend('','Nullcline of V','nullcline of w');
xlabel('Voltage(mV)');ylabel('w * 100');
title('Phase plane plot with nullclines - V and w * 100');
```

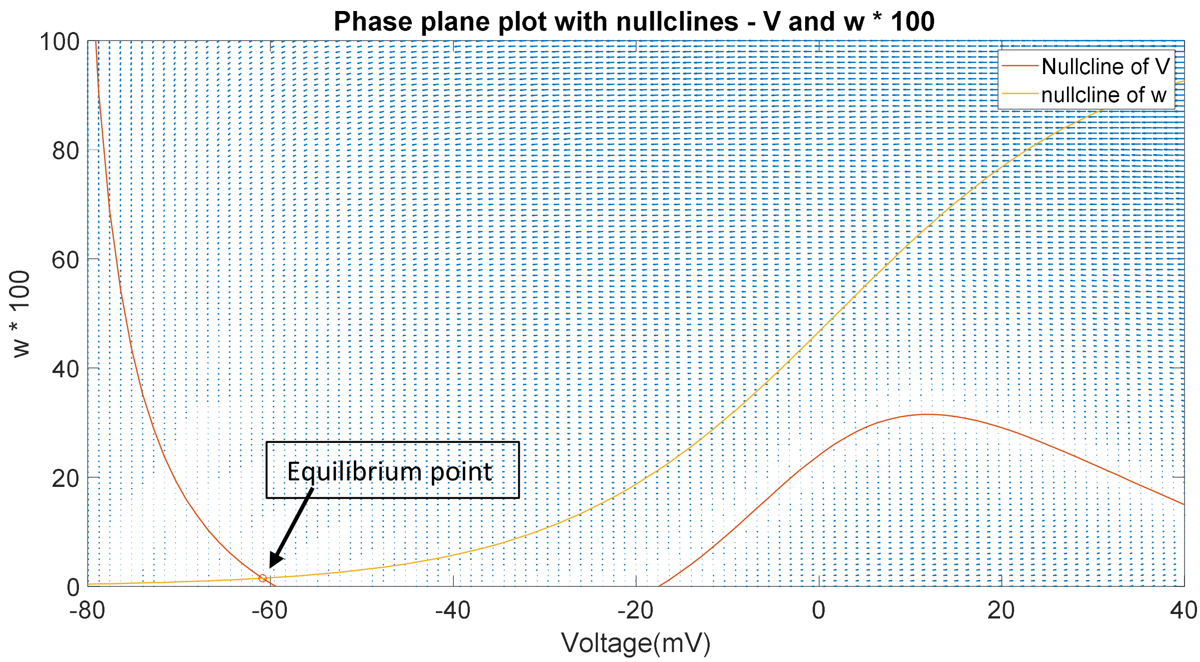

Figure – 1

Question 3:

Ans: The Jacobian of the system at the equilibrium point and the Eigenvalues is given as:

Jacobian Matrix(J) at equilibrium point = $\begin{bmatrix} -0.1004 & -9.2578 \\ 0.0001 & -0.0825 \end{bmatrix}$.

Eigenvalues = (-0.0915 + 0.0258i), (-0.0915 - 0.0258i).

For finding the equilibrium point is stable or not we have to check the determinant and trace of Jacobian matrix.

det(J) = 0.009 and trace(J) = -0.1829.

Thus, the equilibrium point is stable since det(J) > 0 and trace(J) < 0.

Question 4:

Ans: The value of AbsTol = 10^ (-6) is reasonable because we are working with values that are significant up to 4 decimal places and hence AbsTol = 10^ (-6) is more than sufficient to estimate the solution of differential equation. The RelTol = 10^ (-3) (0.1%) is also acceptable because we are generating approximate nullclines. If we change the unit of Voltage in the MLE from mV to kV the equilibrium potential will be 0.0000608554 kV the absolute tolerance will be affected badly as it would require more order of precision and thus 6 more decimal places are required to get the same precision and hence the absolute tolerance would have to be decreased by at least a factor of 10^6. On the other hand, relative tolerance won't be much affected by units.

To change the values of AbsTol and RelTol we can write the code as:

```
Options = odeset ('RelTol',1e-3,'AbsTol',1e-12, 'refine',5, 'MaxStep', 1);
```

Question 5:

Ans: The phase plane plot of the action potential generated for $\emptyset = 0.02$ and $\emptyset = 0.04$ are given in the figure – 2.
We plotted for different value of initial voltage like -24 mV, -12 mV and 0 mV and observed that at -24 mV action potential is not generated and for -12 mV and 0 mV action potential is generated thus showing us that after particular initial voltage or threshold action potential is generated.
If we increase the value of ∅ we see that maximum amplitude of the voltage decreases and the onset of action potential actually becomes faster, which is logical since in a way we are decreasing the time constant of w (K) activation. Hence the drop is faster.

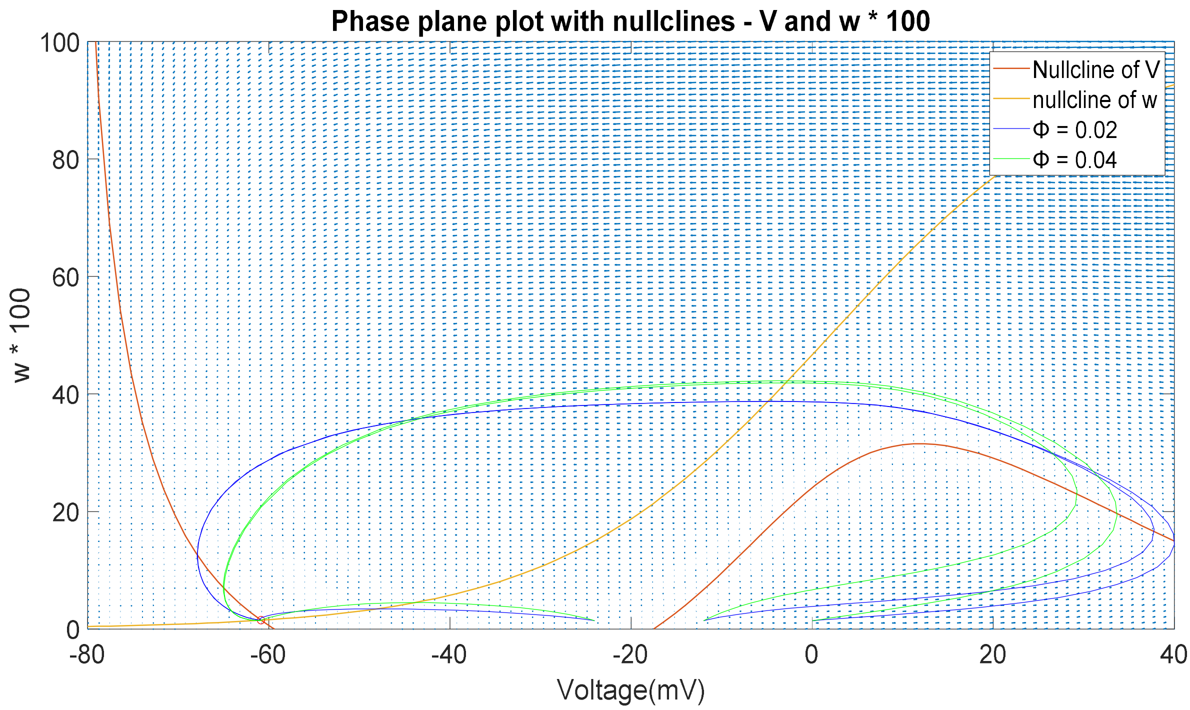

Figure – 2

Thus, we can observe from the figure-3 that when the value of $\emptyset = 0.01$ the maximum amplitude of voltage crosses the 40-mV limit which we set on the plot. These plots are generated keeping the I_ext = 0.

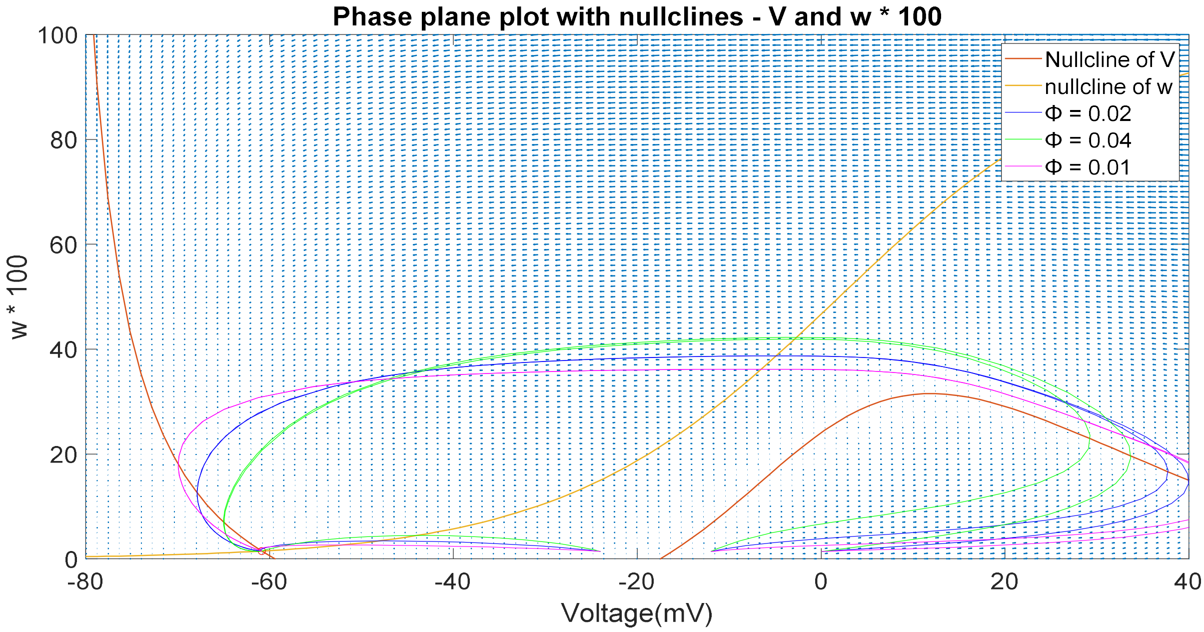

Figure – 3

Question 6:

Ans: By depolarizing current pulses of various amplitudes by setting the voltage initial condition to a succession of values positive to the resting potential while starting w at the equilibrium point, we get the phase plot as shown in the figure – 4.

We can see that after a certain value of depolarizations the action potential are generated.

If we zoom into the phase plane plot which is shown in figure – 5, we can see that below an initial value of voltage of -14.95 mV no action potentials are generated but when the depolarization is above -14.9 mV it is sufficient to produce action potentials.

To see that if the MLE shows threshold behaviour or not, we took initial value of voltage within the range of -14.95 mV to -14.9 mV and plot of the maximum amplitude of the action potential versus initial value of V which is shown in the figure – 6. We can see that in the range of -14.932095 and -14.932062 are random so we can conclude that it does not show us strict or true threshold behaviour.

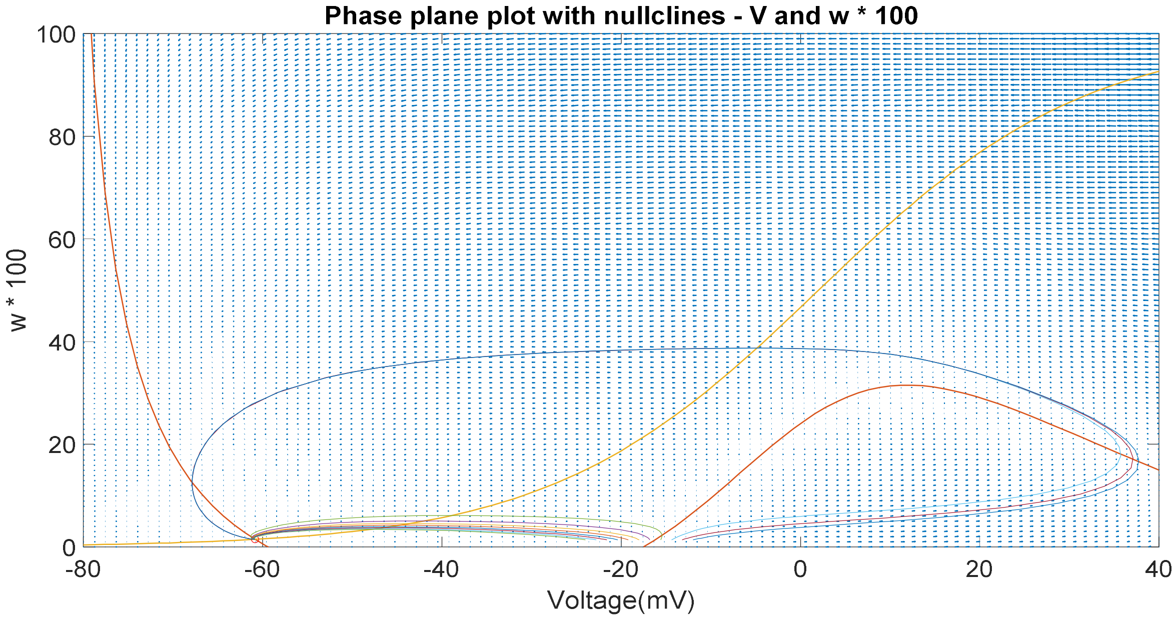

Figure - 4

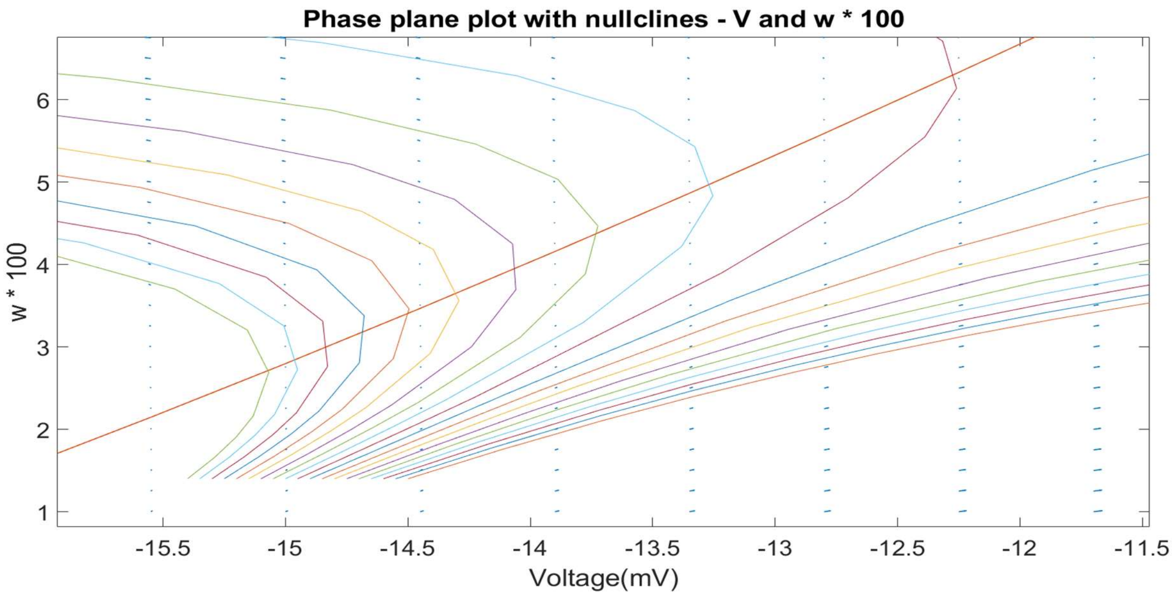

Figure - 5

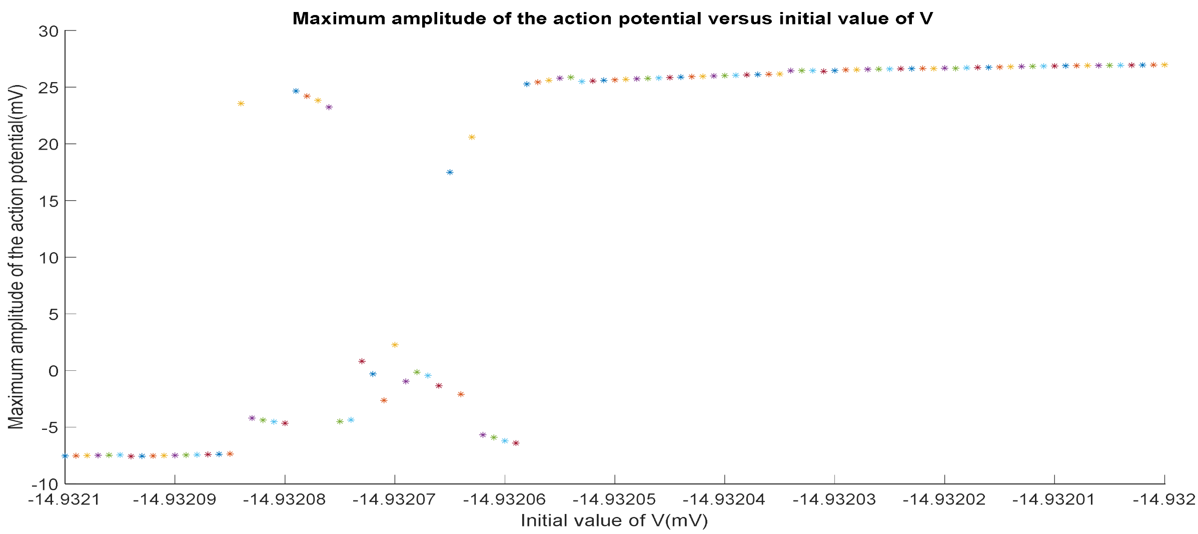

Figure - 6

Question 7:

Ans: The Jacobian of the system at the equilibrium point and the Eigenvalues is given as:

Jacobian Matrix(J) at equilibrium point = $\begin{bmatrix} 0.0090 & -22.4190 \\ 0.0002 & -0.0308 \end{bmatrix}$.

Eigenvalues = (-0.0109 + 0.0667i), (-0.0109 - 0.0667i).

For finding the equilibrium point is stable or not we have to check the determinant and trace of Jacobian matrix.

det(J) = 0.0046 and trace(J) = -0.0218.

Thus, the equilibrium point is stable since det(J) > 0 and trace(J) < 0.

The trajectories are once again calculated by solving the differential equation for different initial conditions.

As we can observe in the figure – 7, when we increase the current form zero to 86 μA/cm^2 we see that the equilibrium point shift upward and if we start from the equilibrium point when I_ext = 0 (the blue line trajectory) we see action potential is generated and it turns out to force the trajectory into a limit cycle. If we start from the equilibrium point of I_ext = 86 μA/cm^2 it is solution of the differential equation so starts and end there in no time. If we start with initial values close to the equilibrium point as (-27.9, 0.17) we see the trajectory with color magenta, the curve spiral into the equilibrium point.

The first method can be used in patch clamp recording to generate action potentials. The third case can help us to judge the stability of the system at a given point.

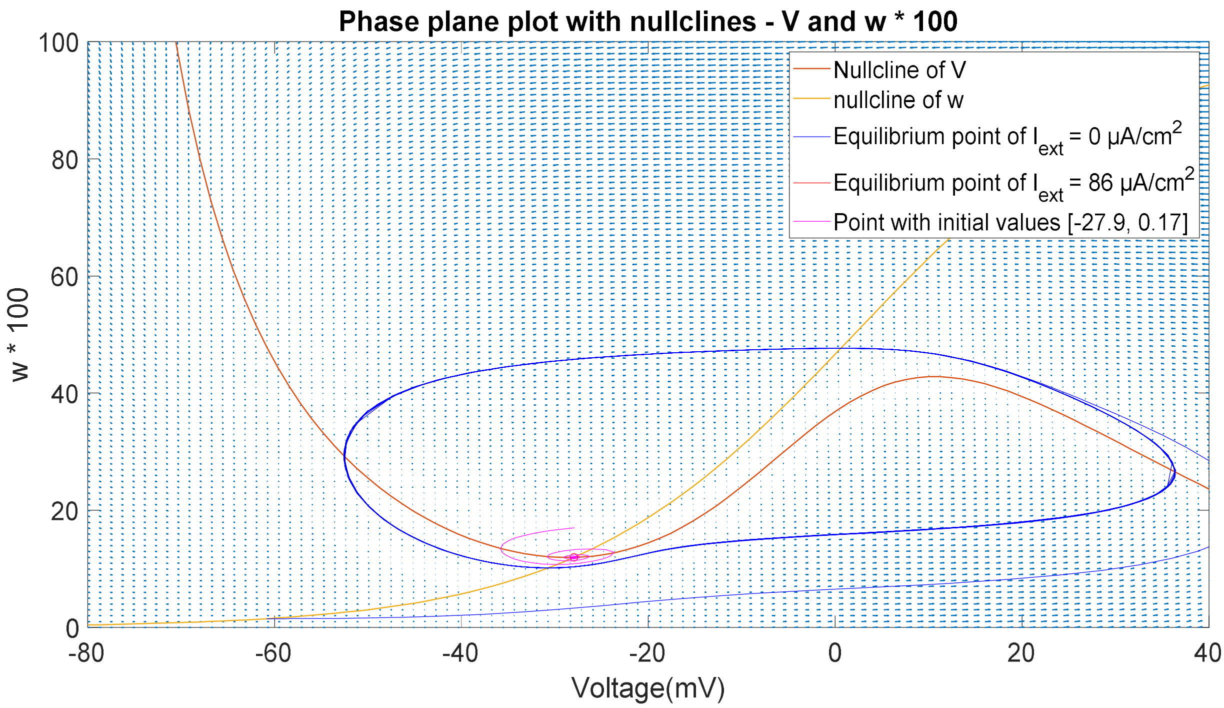

Figure - 7

Question 8:

Ans: We can find the contour that divides the phase plane into those initial conditions that converge to the equilibrium point and those that converge to the limit cycle by running the differential equation in negative time by starting from the initial values close to the equilibrium point as (-27.9, 0.17) and the unstable periodic orbit trajectory is shown as black color in the figure – 8. When we run back the model backward in time the nullclines and equilibrium point is unaffected but the stable and unstable solutions are affected. Any point inside the blue limit cycle or the black limit cycle turns out to force the trajectory into a black limit cycle. The the nature of equilibrim point chnages, it becomes unstable in nature. While any point outside the blue limit cycle it diverges outside.

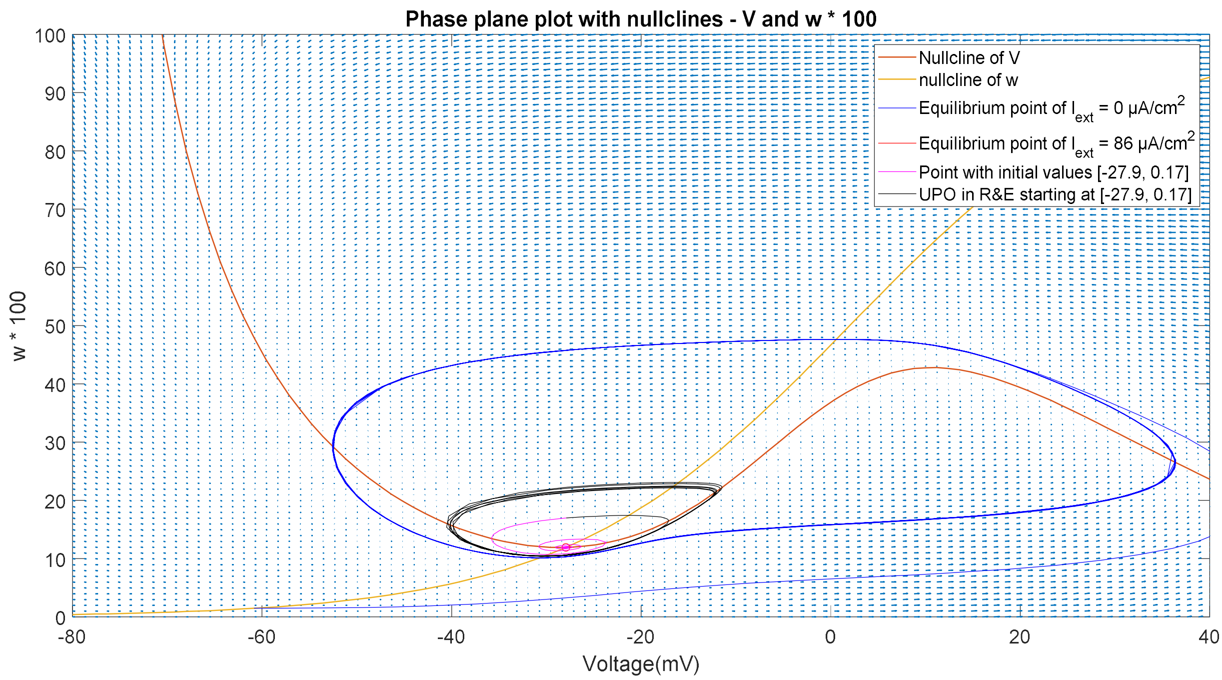

Figure - 8

The threshold behaviour is shown in the figure – 9 where we can see that any point inside the black limit cycle converges to the equilibrium point and any point outside this black limit cycle turns out to force the trajectory into a blue limit cycle.

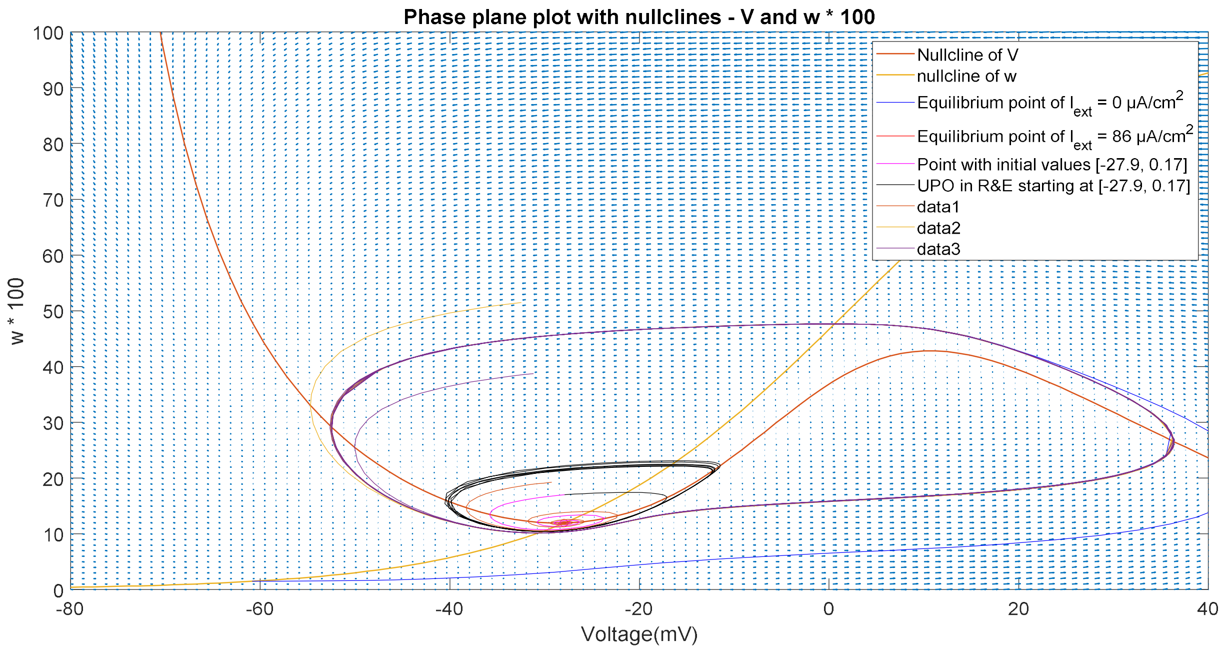

Figure – 9

Question 9:

Ans: If we analyse the equilibrium points for I_ext = 80, 86 and 90 μA/cm^2 we find the equilibrium points and eigenvalues as:

```
------------------------- I_ext = 80 ------------------------------
The equilibrium point is located at (-29.966175,0.106113)
The eigen values are -0.010925+0.066729i, -0.010925-0.066729i
------------------------- I_ext = 86 ------------------------------
The equilibrium point is located at (-27.952413,0.119536)
The eigen values are -0.010925+0.066729i, -0.010925-0.066729i
------------------------- I_ext = 90 ------------------------------
The equilibrium point is located at (-26.596867,0.129379)
The eigen values are -0.010925+0.066729i, -0.010925-0.066729i
```

From the eigen values of the equilibrium points we see that they are stable spiral.

For I_ext = 80 μA/cm^2 we see that the if we start with any initial value of voltage, it would converge to the stable equilibrium point. There is no limit cycle. But for I_ext = 90 μA/cm^2 we see a limit cycle and the UPO cycle enlarge in this case as compared to I_ext = 86 μA/cm^2.

If we look in the plot of Rate of firing action potential versus Applied current as shown in the figure – 10, we will see that after a current of 92 μA/cm^2 rate of firing action potential increase rapidly reach to constant firing rate for a time span of 0 to 1000 ms.

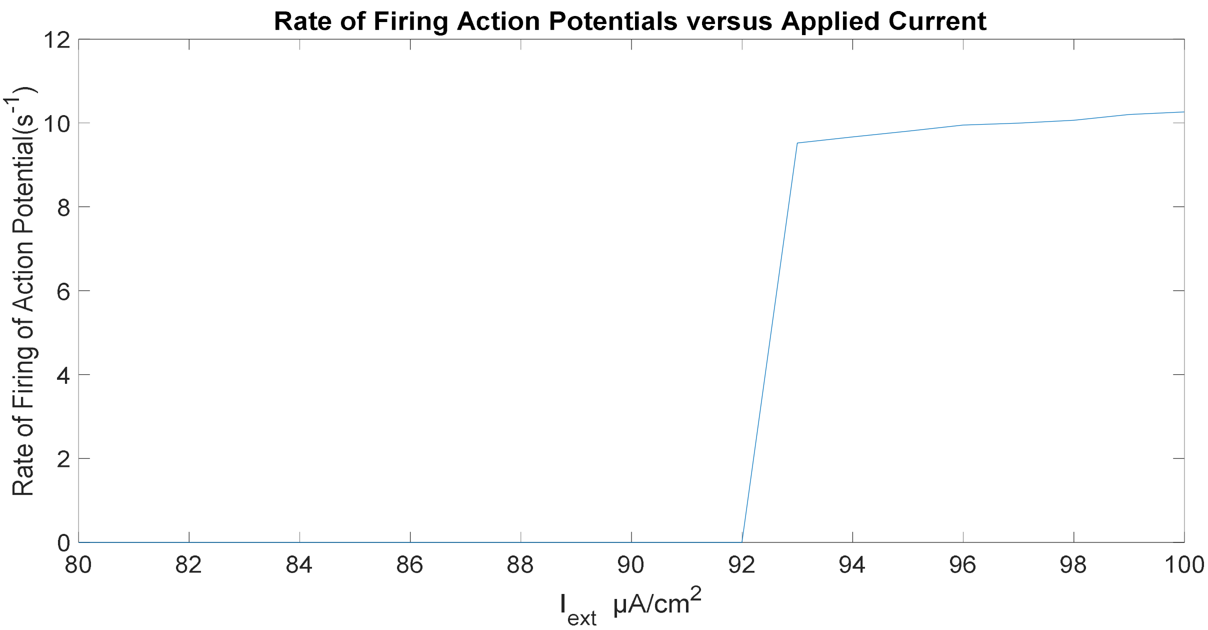

Figure - 10

Question 10:

Ans: If we solve the nullclines we will get three equilibrium points as:
Equilibrium point : 1. (-41.845162, 0.002047) is stable equilibrium point.
The corresponding eigen values are -0.068880+0.000000i, -0.733420+0.000000i.
Equilibrium point : 2. (-19.563243, 0.025883) is saddle point.
The corresponding eigen values are 0.137173+0.000000i, -0.164847+0.000000i.
Equilibrium point : 3. (3.871510, 0.282051) is unstable equilibrium point.
The corresponding eigen values are 0.091076+0.182604i, 0.091076-0.182604i.

We plot the phase plane plot, nullclines, equilibrium points and the manifolds which can be seen from the figure – 11. We can see the unstable manifolds in black color and stable manifolds as magenta color.

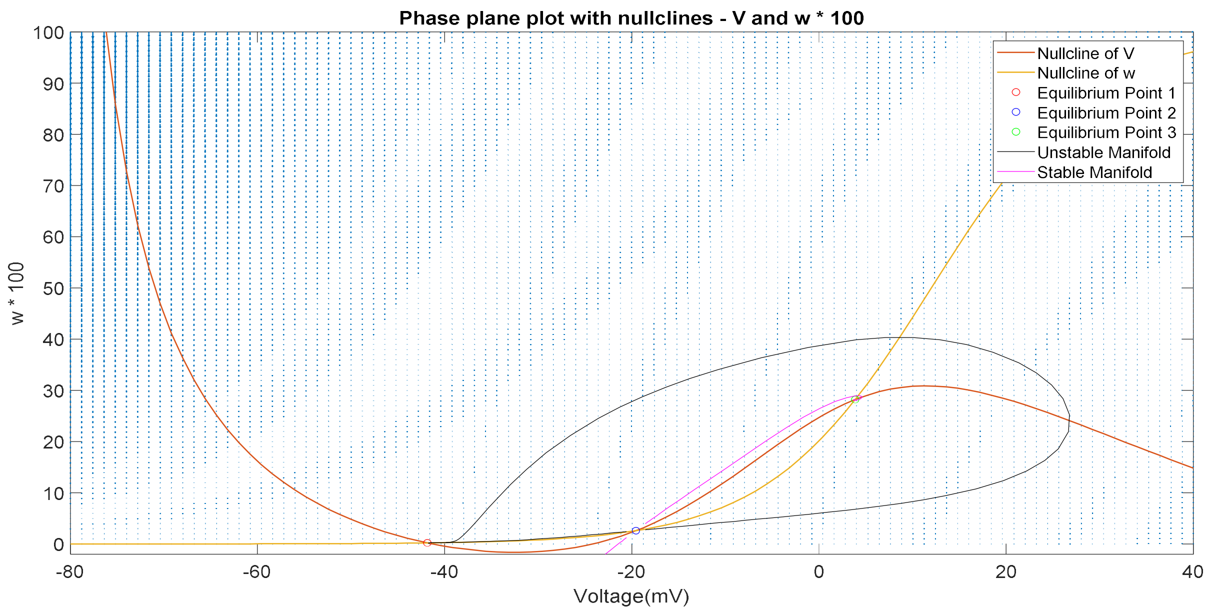

Figure - 11

Question 11:

Ans: As we change the current from 30 to 50 μA/cm^2 the V- nullclines shift upward and at a particular I_ext the number of equilibrium point changes. As we start from 30 to 39 we see that the saddle point and the stable equilibrium point comes closer and at I_ext = 40 μA/cm^2 only one distinct equilibrium point exist which is unstable equilibrium point and it is forced into a limit cycle and start generating action potential. This can be observed in the figure – 12 and figure – 13.

If we look close in the interval between 39 to 40 μA/cm^2, we will find that at I_ext = 39.963153 μA/cm^2 the two equilibrium point almost coincide and after that only one distinct unstable equilibrium point exist.

If we look in the plot of Rate of firing action potential versus Applied current as shown in the figure – 14, we will see that before a current of 39.96 μA/cm^2 rate of firing action potential almost zero and increases rapidly after it and action potential start generating.

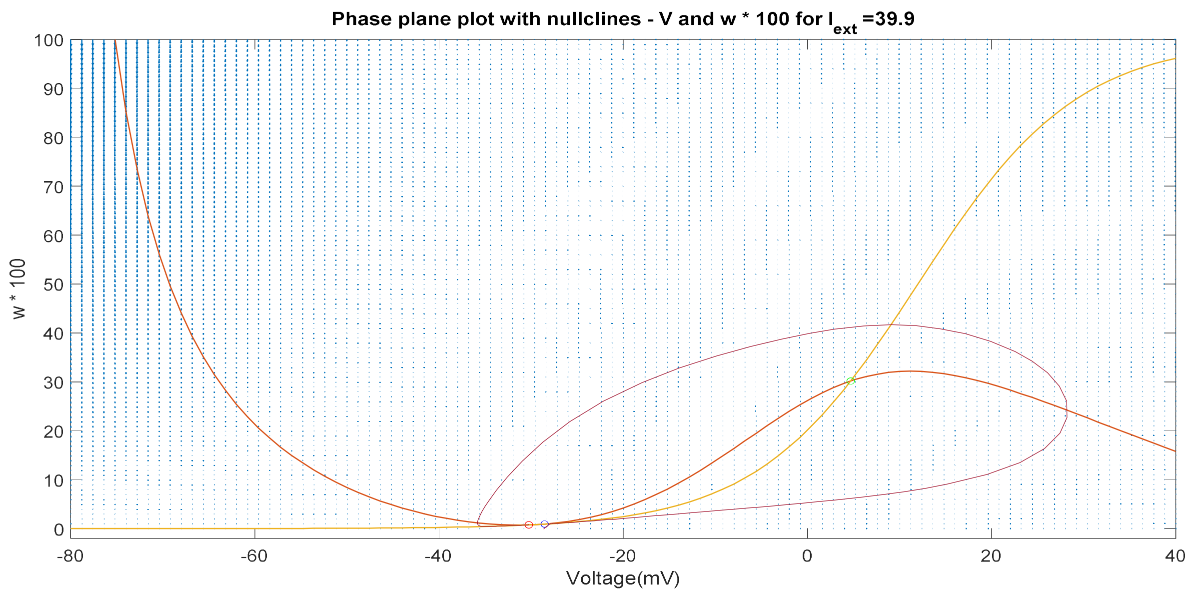

Figure - 12

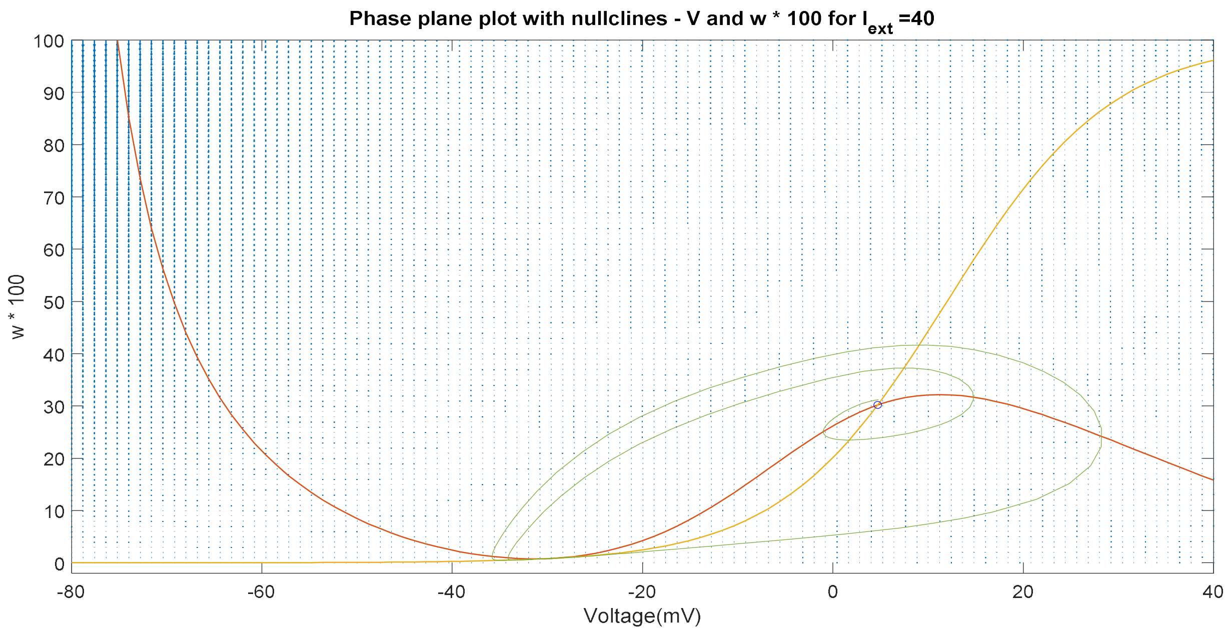

Figure - 13

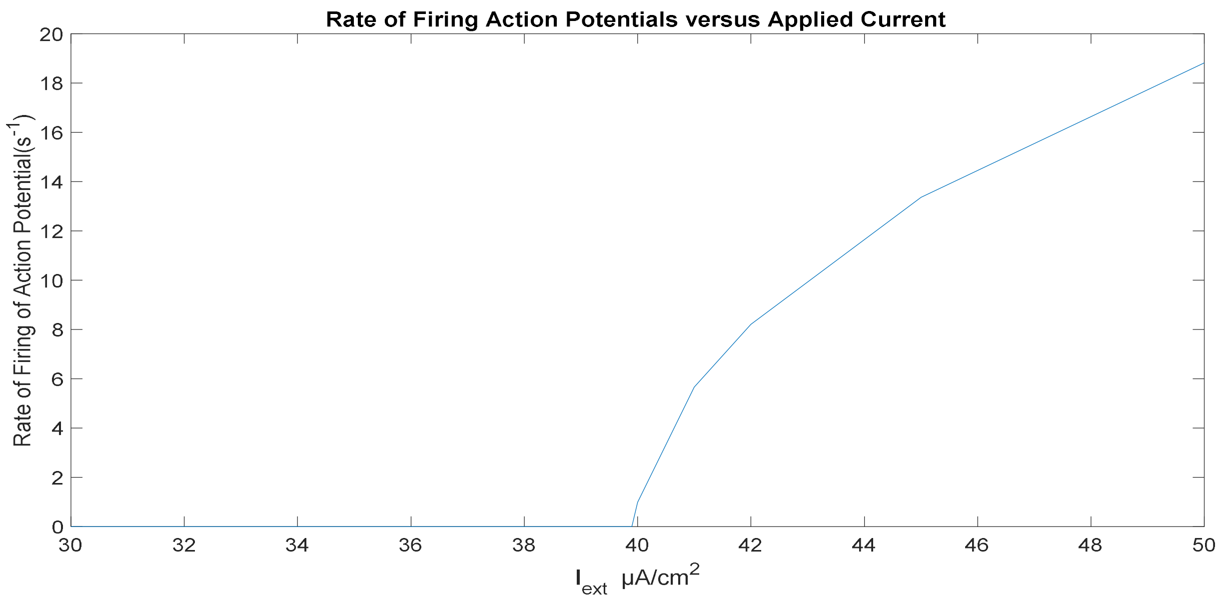

Figure – 14

Part B - Hodgkin Huxley Equations (HH) Simulation

Question 12:

Ans: To take care with the equations for α_n and α_m whose denominator and numerator are both 0 for certain values of V, giving a 0/0 situation we can use correction factor for the voltage such that denominator will never be zero. So, we choose correction factor like 10^ (-10) and change the relative and absolute tolerance to 10^ (-9) so that differential equation does not get any error.

Question 13:

Ans: If we run the model taking resting potential as -60 mV and evaluate the leaking voltage, we will get it as -49.40108 mV. If we run the model for I_{ext} = 10 μA/cm^2, we will be able to produce action potential as show in the figure – 15.

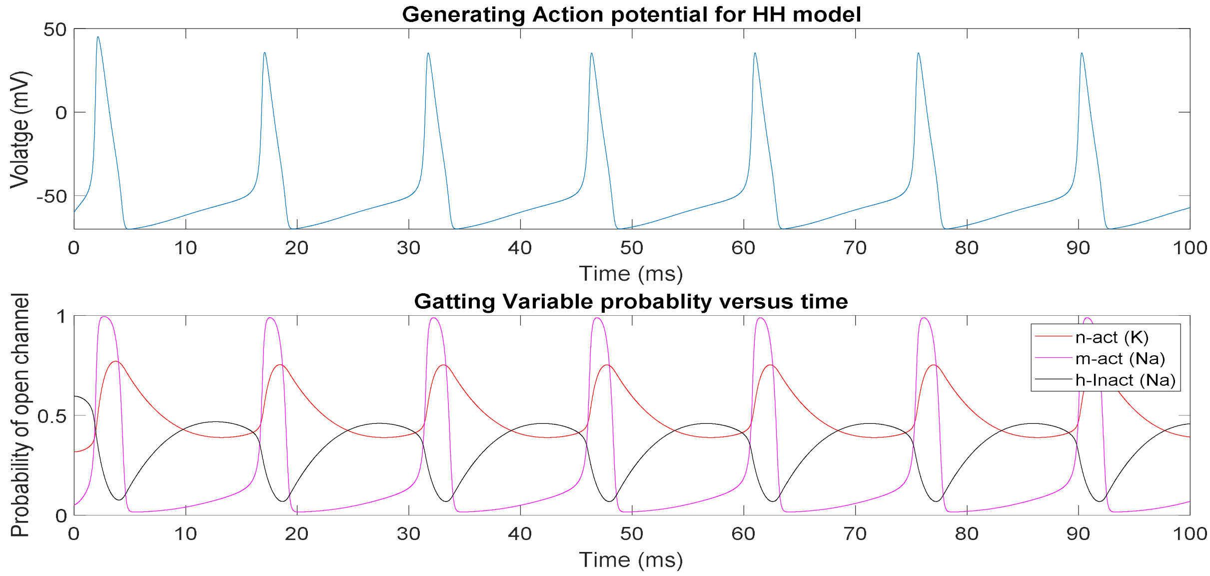

Figure – 15

Question 14:

Ans: If we check the stability of the equilibrium point for I_ext = 0 μA/cm^2 we will get the equilibrium points as:

The Equilibrium points are V_eq = -60.000000 mV, n_eq = 0.317677, m_eq = 0.052932. h_eq = 0.596121

The corresponding EigenValues are:-4.6753 + 0.0000i, -0.2027 + 0.3831i, -0.2027 - 0.3831i, -0.1207 + 0.0000i.

Equilibrium point is stable equilibrium point since Det(J) > 0 and Trace(J) < 0.

If we determine the threshold of the model for brief current pulses we will get the threshold as 6.515152 μA/cm^2. The threshold behaviour can also be seen in the figure – 16.

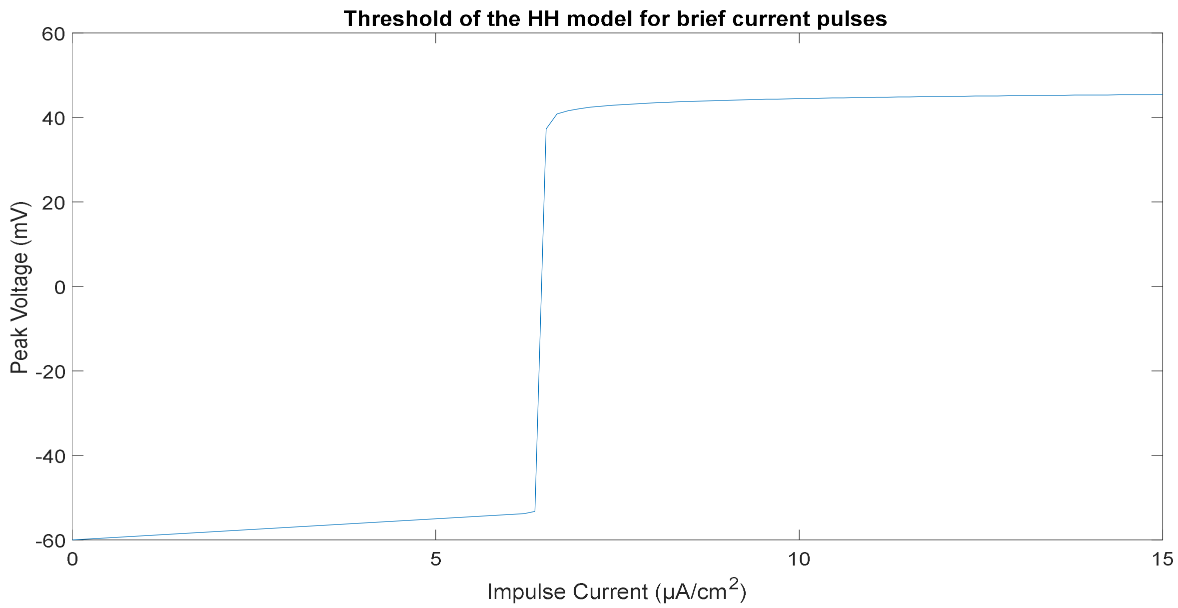

Figure – 16

Question 15:

Ans:

For I_ext = 8 μA/cm^2:
The Equilibrium points are V_eq = -55.355128 mV, n_eq = 0.390607, m_eq = 0.090048. h_eq = 0.430515.
Equilibrium point is stable equilibrium point.
For I_ext = 9 μA/cm^2:
The Equilibrium points are V_eq = -54.952404 mV, n_eq = 0.397027, m_eq = 0.094133. h_eq = 0.416502
Equilibrium point is stable equilibrium point.
For I_ext = 10 μA/cm^2:
The Equilibrium points are V_eq = -54.572150 mV, n_eq = 0.403092, m_eq = 0.098131. h_eq = 0.403419
Cannot say anything about the Equilibrium point (Need to plot in 4 dimensions).
For I_ext = 11 μA/cm^2:
The Equilibrium points are V_eq = -54.211777 mV, n_eq = 0.408841, m_eq = 0.102052. h_eq = 0.391169
Cannot say anything about the Equilibrium point (Need to plot in 4 dimensions).
For I_ext = 12 μA/cm^2:
The Equilibrium points are V_eq = -53.869127 mV, n_eq = 0.414306, m_eq = 0.105899. h_eq = 0.379667
Cannot say anything about the Equilibrium point (Need to plot in 4 dimensions).
Now we run the model at points near these values for respective currents and find the nature of these equilibrium pts.
We can see from figure - 17 that the equilibrium point for 8 μA/cm^2 is stable equilibrium point.
Similarly, from figure – 18 for 9 μA/cm^2 it takes more time to decay but it reaches at equilibrium point so it a stable equilibrium point.
But for 10 μA/cm^2 after some oscillation it is forced into a limit cycle which can be seen from the figure - 19.
After 10 μA/cm^2 like for 11 μA/cm^2 we get the full limit cycle as shown in the figure – 20.

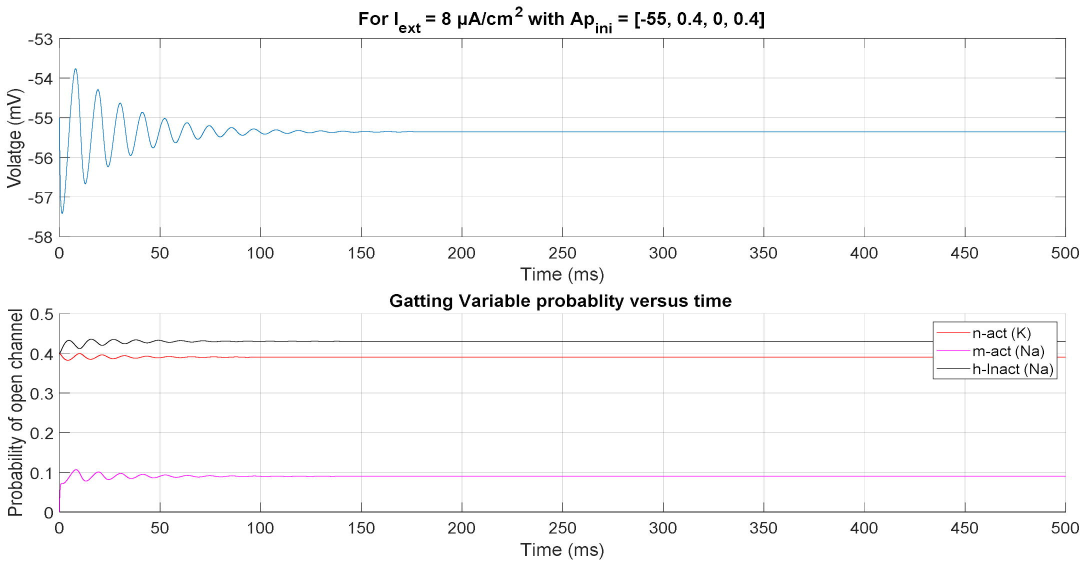

Figure – 17

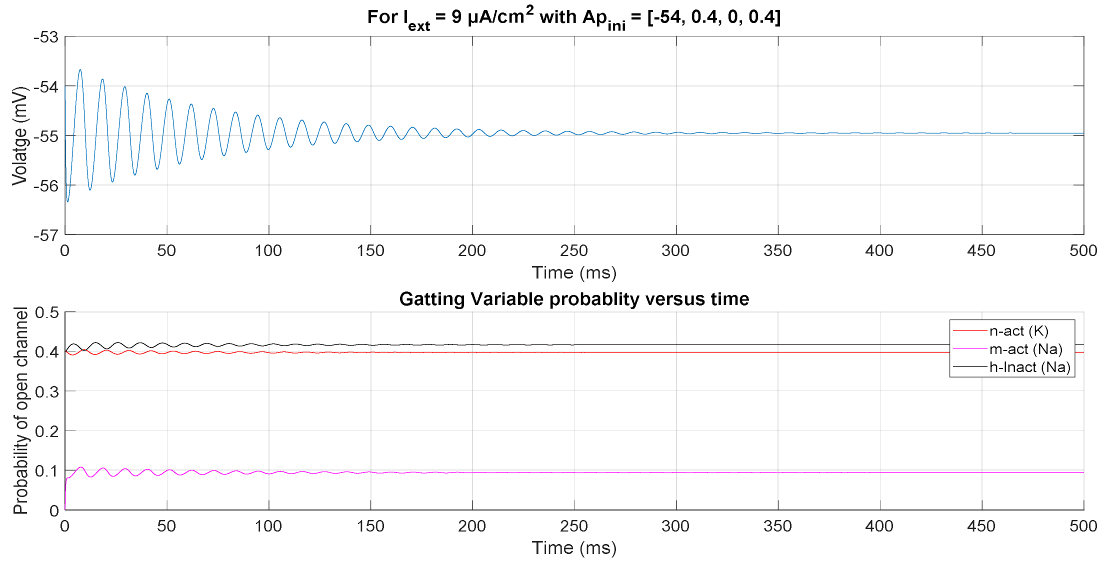

Figure – 18

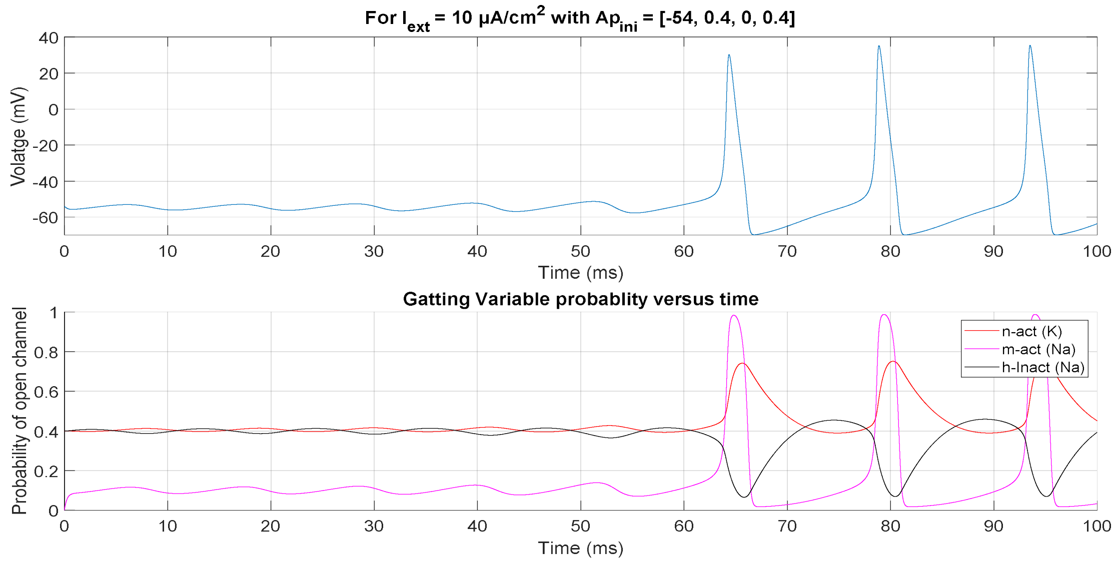

Figure – 19

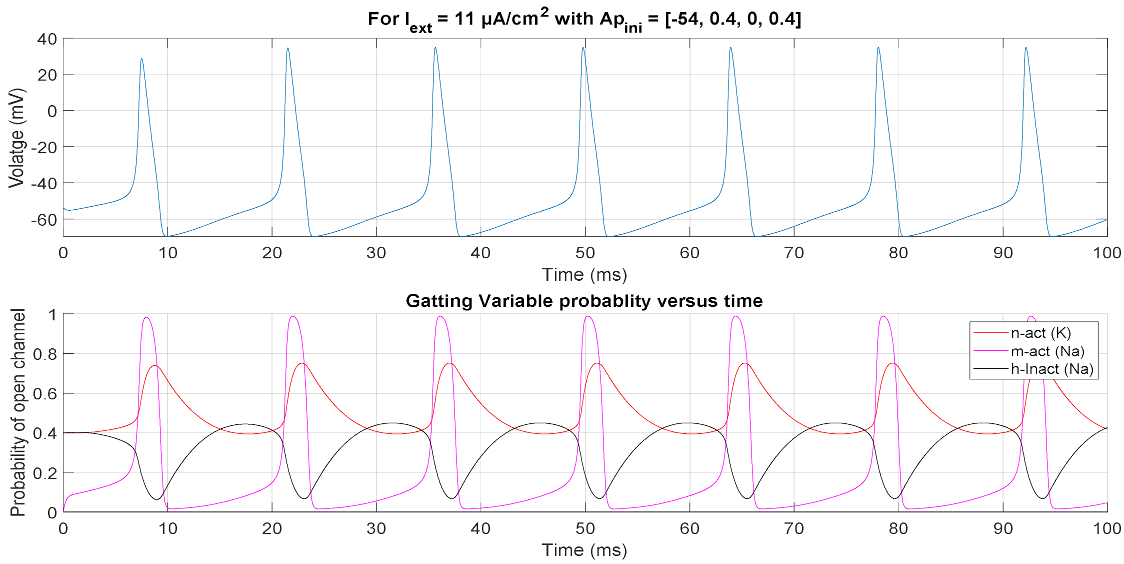

Figure – 20

Question 16:

Ans: Assumption made for the V – n reduced system:

- h and n gate have same behaviour but act opposite in nature so we can assume that h = 1 – n.
- Since m gate variable is instantaneous in nature and the decay time of m is very small as compared to h and n, so we can assume m as constant = m_inf.

By using this assumption, we reduced the model and run it for I_ext = 10 μA/cm^2 we get the action potential generated as show in the figure – 21.

From the figure – 21, we can observe that the action potential is generated same way as for the 4 variable HH model. But the shape of the shape of the action potential is changed as compared to the figure – 15 (4 variable HH model). Since we have assumed m = m_inf, the rising time of action potential is almost zero and the shape of refractory peroid is changed because we assume that the h = 1 – n.

If we check this model for brief current impuse we will get a plot as shown in the figure – 22.

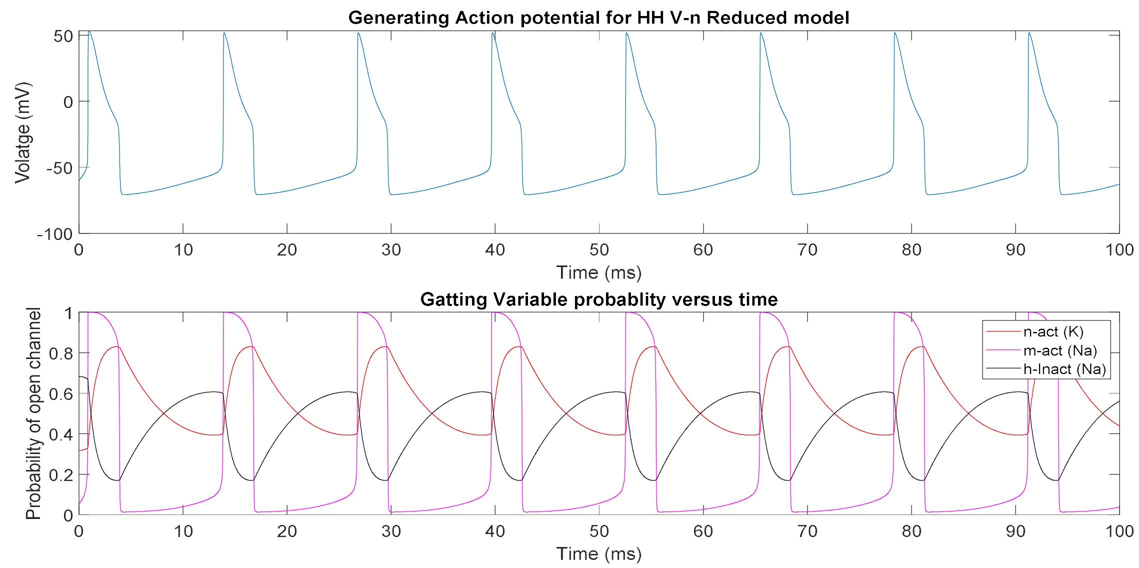

Figure – 21

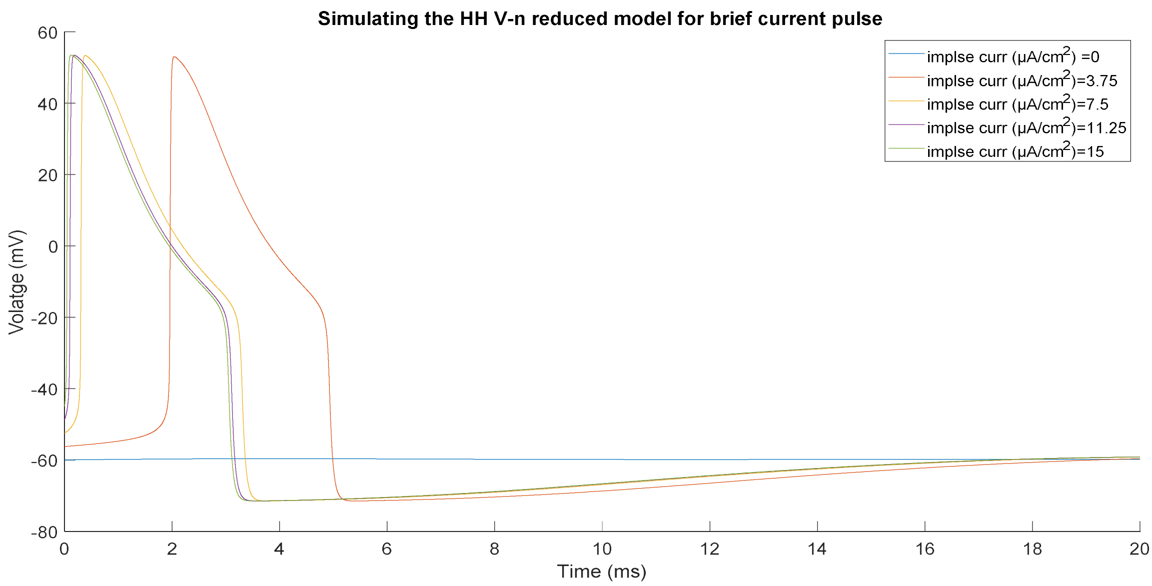

Figure – 22

Question 17:

Ans: As we can observe in the figure – 23 for 20 ms I_ext = -3 μA/cm^2 then it is set to zero. After 20 ms we can see that membrane potential is bring back to resting potential instantaneously. Thus we see a action potential is generated. This is called anode break excitation.

This occurs because when we hyperpolarize the membrane potential the number of available Na channel increases than at resting potential. So when we rapidly bring back the membrane potential to resting potential, the number of open channel is larger than are normally open at rest and that cause more Na channel to open causing an upstroke of action potential. The normal threshold is usually lowered when hyperpolarized the membrane potential thus causing anode break excitation.

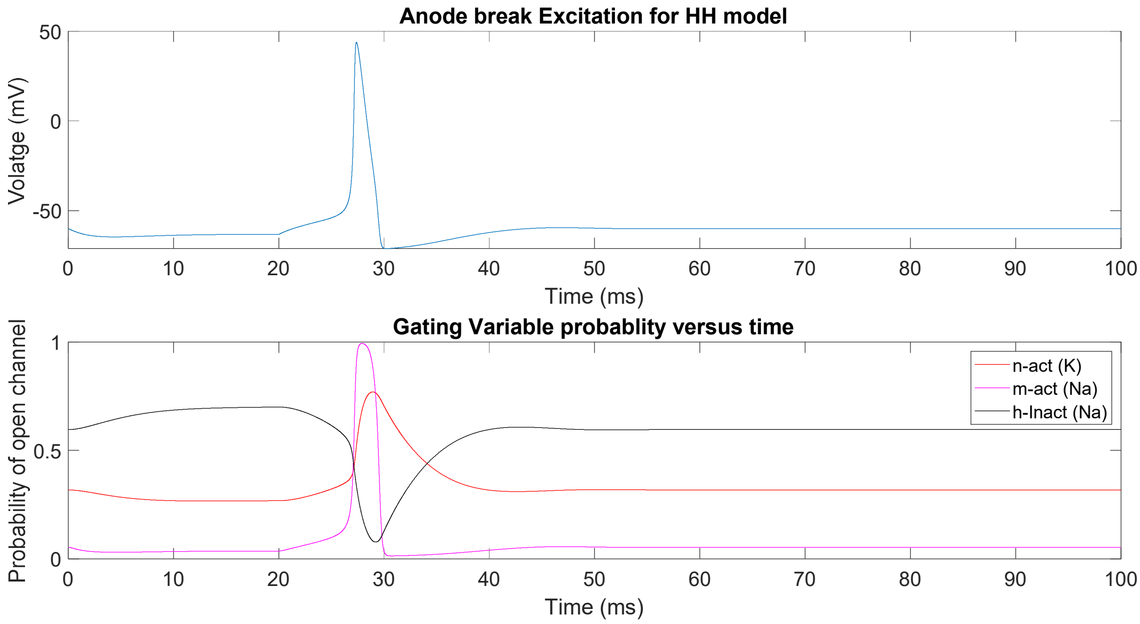

Figure – 23

Question 18:

Ans: If we reduced the HH model to V-m system by fixing the n and h at two values:

Case 1: The values for membrane potential at rest, -60 mV.

Case 2: The values at the end of the anodal stimulus used to produce the anode break excitation in the previous question.

If we plot the phase plane plot of the above cases, we will get the phase plane as shown in the figure – 24.

If we look for the case 1, V – nullcline (blue colour) intersect the m – nullcline (orange colour) near the resting potential. It can also be seen by red circle.

If we hyperpolarize the membrane potential with I_ext = -3 μA/cm^2 and bring it back to I_ext = 0 μA/cm^2 we observe that the V – nullcline (yellow color) is shifted and it intersect the m – nullcline (orange color) at a point (by blue circle) having higher membrane potential thus generating action potential.

Due to change in the n and h values in the case 2 we observe in the figure – 24 that it is shifted.

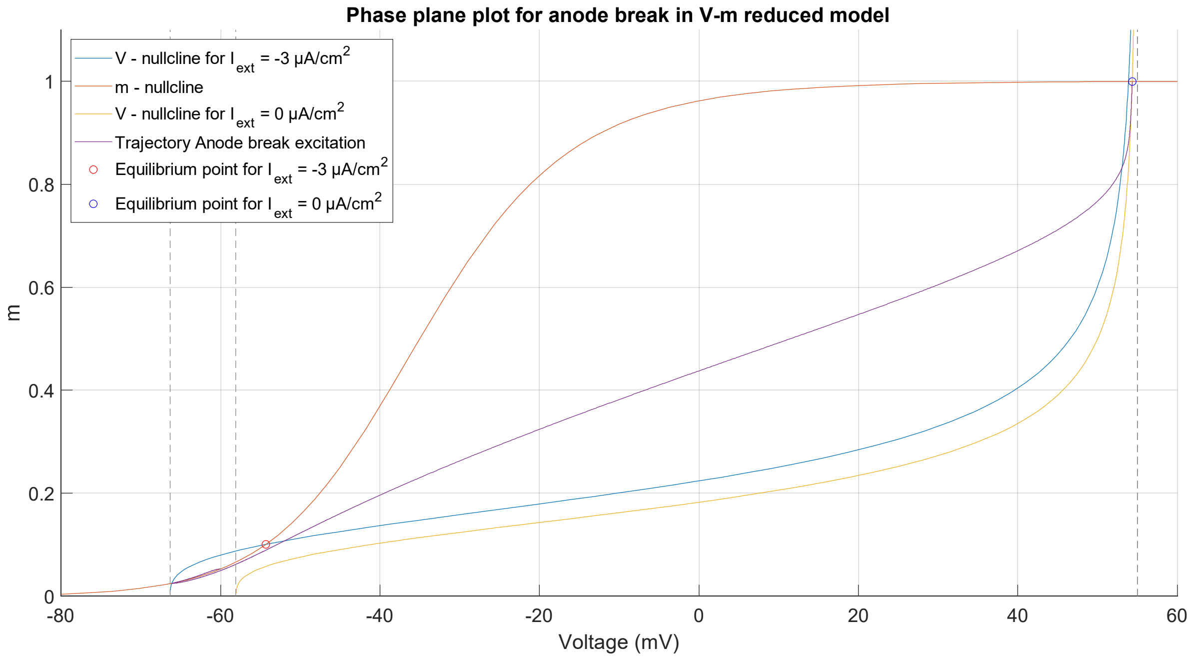

Figure – 24