EC60007: COMPUTATIONAL NEUROSCIENCE
PROJECT-2

NAME : PRANAV NYATI
ROLL: 20CS30037

Ques(1):

(a) The unit set: milliseconds, microamps/cm 2 , millivolts, microfarads/cm 2 and millisiemens/cm 2 is consisent and this can be easily shown using the concepts of units and dimensionss.

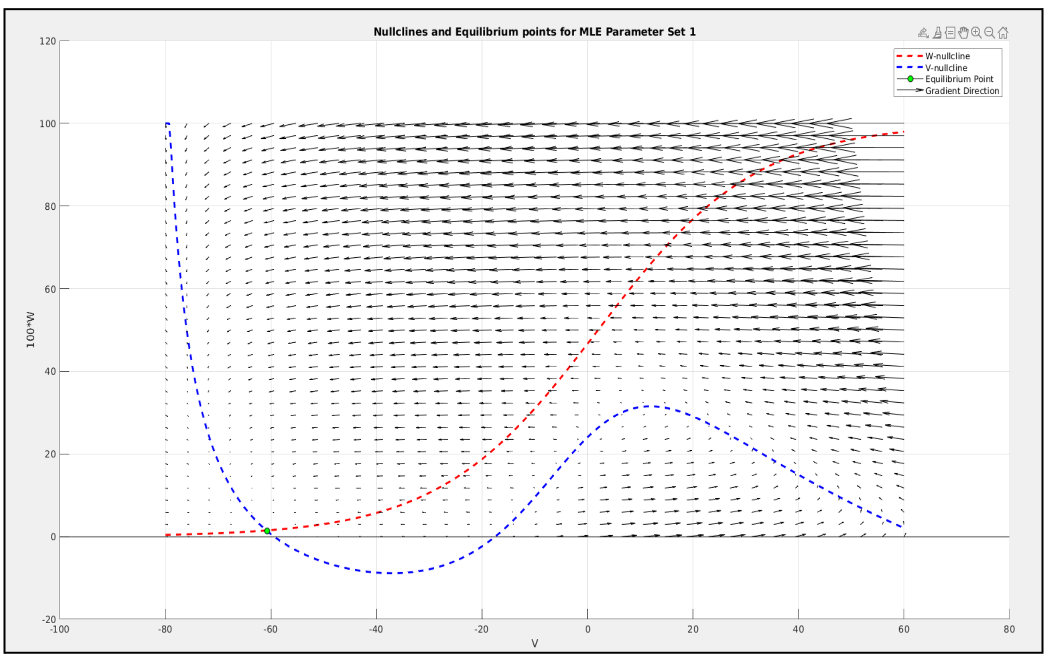
(b) A consistent set of units given the unit of conductance as microsiemens/cm 2:

Voltage: milliVolts;   time: milliseconds;
Area: cm2; Current Density : nanoAmp/ cm2;
Capacitance per unit area: nanoFarad/ cm2;

(c) No, the solution is not unique, and we can change the units of any one quantity (say Voltage) and correspondingly units for other quanties would change.

Ques(2):

Figure(1)
Phase Plane plot of nullclines and equilibrium point for MLE param set 1



Method 1: Finding equations of nullclines and evaluating the V and w null-clines functions for a range of V values using the linspace function. Then, if the difference between the value of w and V nullcline expressions at a particular (V, w) point is very close to 0 (< 0.002 is considered), then it is an equilibrium point.

Resultant equilibrium point using M1:
Equilibrium point for parameter set 1 for the case of I_ext = 0 for MLE:
W_eq = 0.014, V_eq = -60.702

Method2: Using the fsolve functionality of the sym package in MATLAB to find the solution to a system of equations nearest to a given start point. The method uses a numerical optimization method to iteratively compute the simulation solution to the system of equations.(Exact code is given in the .m file)

```
F = @(x) [(1/C)*(I_ext + (-g_Ca*( (0.5*( 1 +
tanh((x(1)-V1)/(V2))))*(x(1)-V_Ca)) + (-g_K*(x(2)*(x(1)-V_K) )) + (-g_L*(x(1)
- V_L)));  phi*(0.5*(1 + tanh((x(1)-V3)/(V4)) ) -
x(2))/(1/cosh((x(1)-V3)/(2*V4)))];
starting_pt = [-60; 0.01];
[x,~] = fsolve(F,starting_pt);
disp("Equilibrium point for MLE with first set of variables, i external = 0")
Eq_pt_method2 = x;
disp(Eq_pt_method2);
```

Resultant equilibrium point using M2:
Equilibrium point for MLE with first set of variables, i external = 0
-60.8554
0.0149

Ques(3):

Stability Analysis for MLE set 1 Equilibrium point: **W_eq = 0.014, V_eq = -60.702**

Jacobian matrix for the first set of MLE parameters (for I_ext = 0):

-0.1004	-9.2578
0.0000	-0.0320

The eigenvalues for the Jacobian matrix are:
-0.0959
-0.0366
The given equilibrium point is a Stable Equilibrium.

Ques(4):

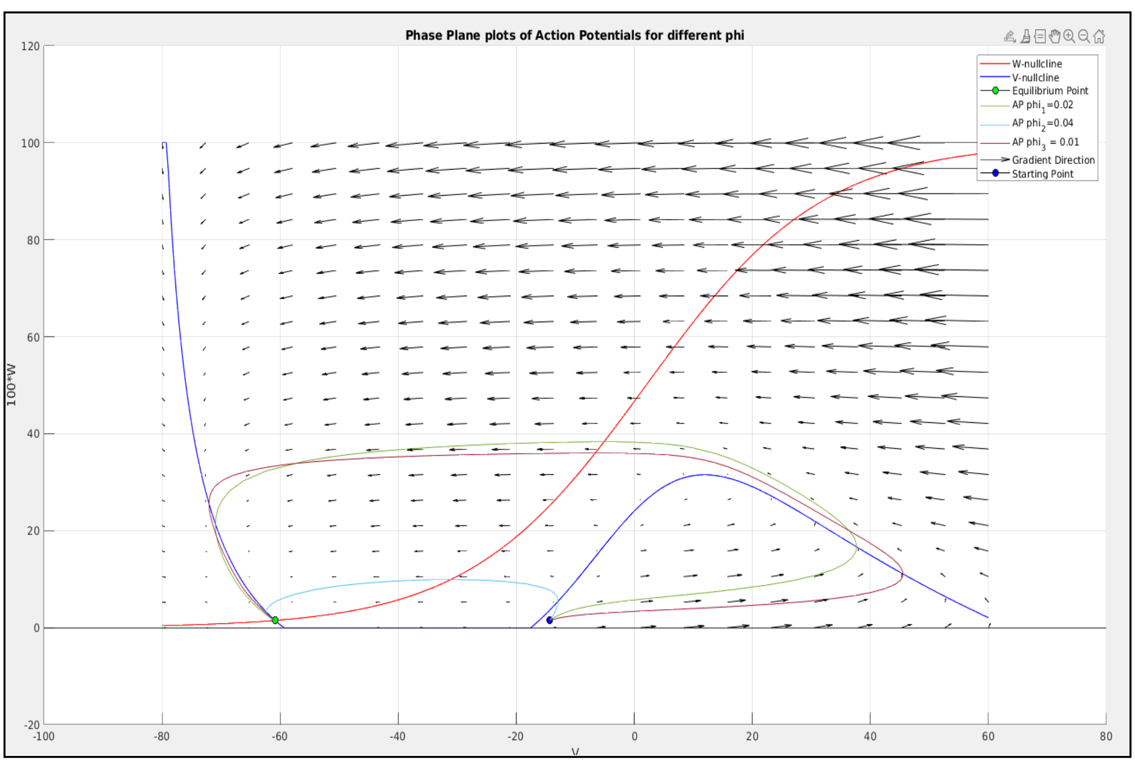
(a)
The default tolerance values (AbsTol=10 -6 and RelTol=10 -3) are reasonable as in MLE we are dealing mostly with values that are precise upto 4 places of decimal (or single values as MATLAB likes to call them) and hence the Absolute tolerance of 10^-6 is much more than sufficient to estimate the solutions to the differential equations and run the simulations.

(b) If we changed the unit of voltage to kV, the absolute tolerance would be affected as we'd require a precision of a greater order for the Voltage values in MLE. For example the equilibrium point for parameter set 1 in MLE: -60.8553 mV value would then be represented as -0.0000608553 kV and thus atleast 6 more decimal places (ratio of kV/mV) 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.

The values can be set in the equation as:
Options = odeset('RelTol',1e-3,'AbsTol',1e-12, 'refine',5, 'MaxStep',1);

Ques(5):

Figure(2)
Plot showing variation of Action Potentials with different values of phi

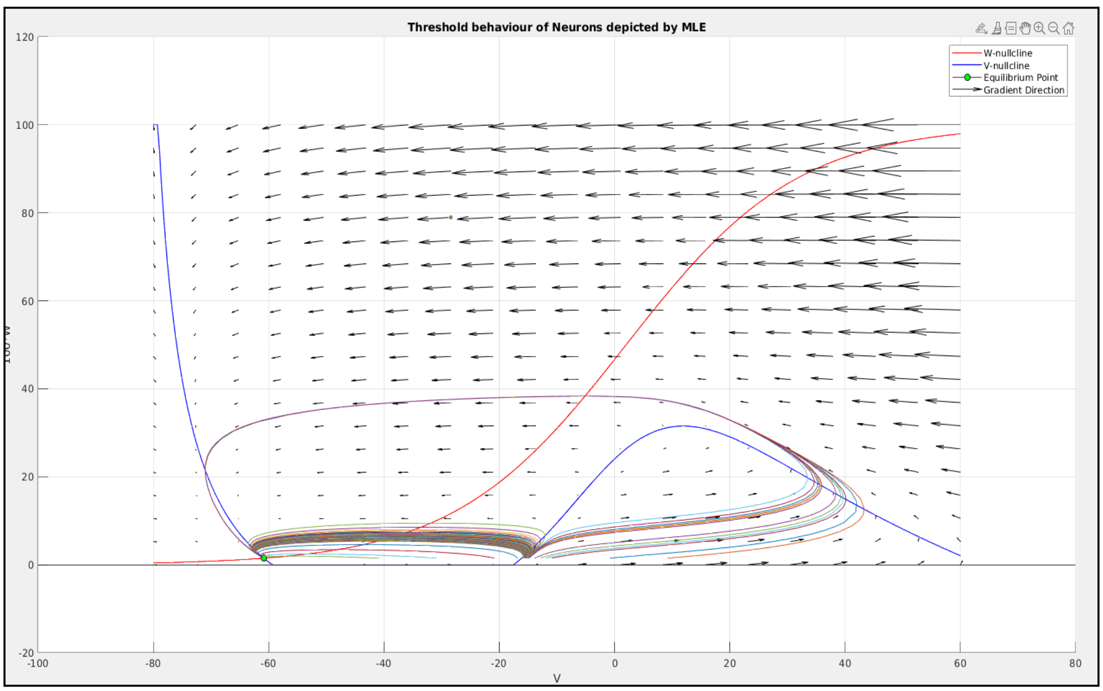


Starting point of all the three (phi = 0.02, 0.04 and 0.01) trajectories is:
V_init = -14.35 mV; 100* w_init = 1.4915

From the plot , it can be inferred that the effect of increasing the value of phi is (1)the onset of an Action Potential increases and (2) The maximum potential reached during an Action Potential decreases.
The reason for this is increasing phi has the effect of decreasing the time constant of w (potassium) activation, hence the rate of potential increase and then subsequent drop also increases.

Ques(6):

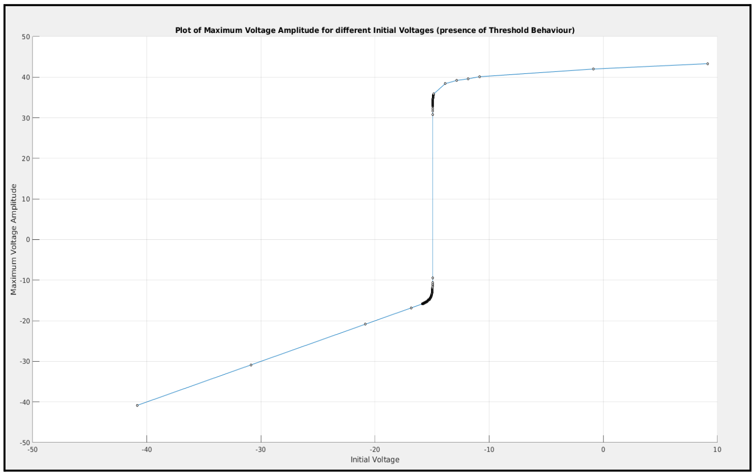
Figure(3)
Phase-plane trajectories for different values of initial depolarization



The above phase plane plot and the Max Voltage vs Initial Voltage plot below depicts a kind of threshold for the current depolarization pulses , below which there is no Action Potential produced and above which there is an Action Potential. However, it is not a true threshold, as it is continuous and steeply rises in the range of initial potentials of **-14mV to -13.9 mV.**
Also, depolarizations of >= 46 uA/cm2 are sufficient to produce an Action Potential, however a true threshold behaviour does not exist.

Figure(4)

Plot of Maximum Voltage Amplitude for different initial Voltages after depolarising pulse

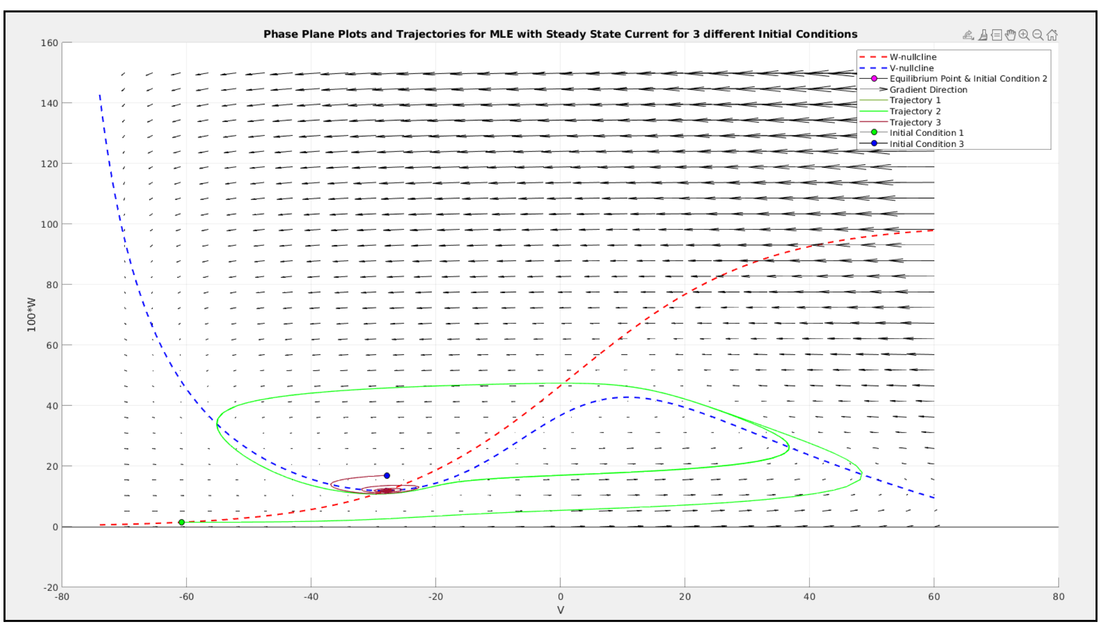


Ques(7) and ques (8):

Equilibrium point for the case of Steady Externel Current Density = 86 uA/cm2 for MLE: W_eq = 0.119, V_eq = -27.990. The system has a stable equilibrium point and a stable limit cycle separated by a UPO.

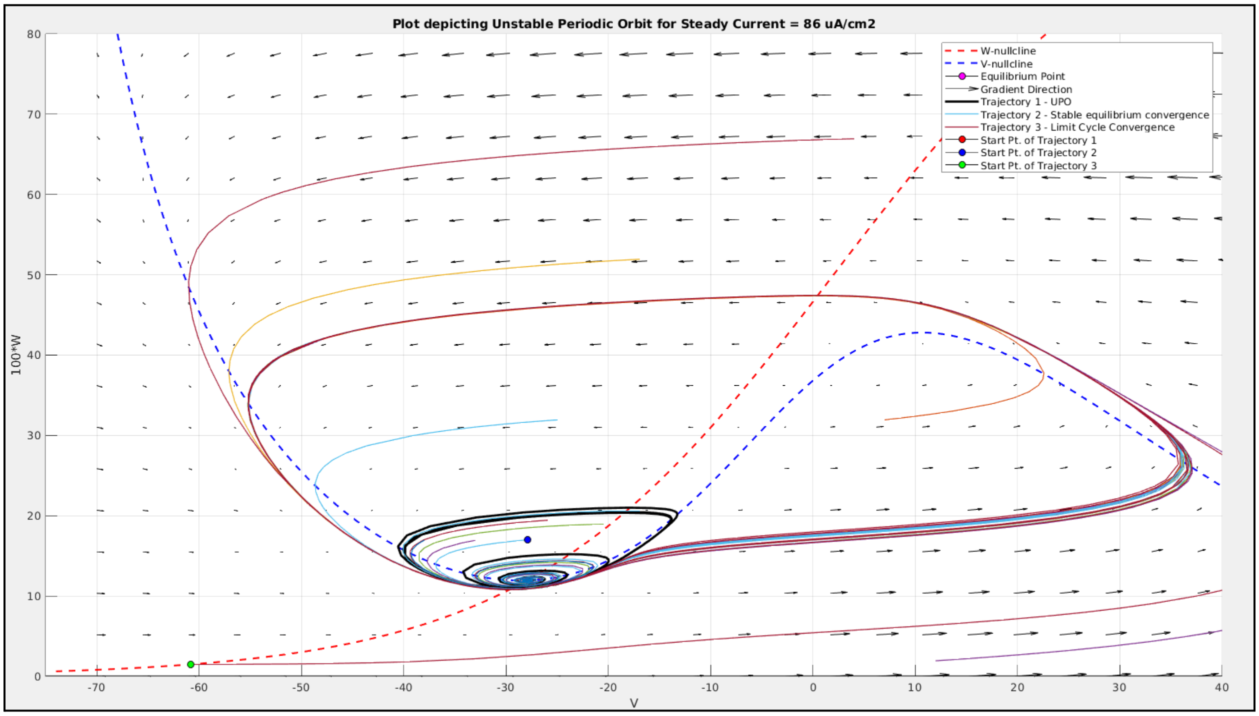
Figure(5)

Phase Plabe Plot for MLE with Steady State Current for three different initial conditions



The first case when the initial condition is set as the equilibrium point of MLE for I_ext = 0 uA gives us the action potentials. This method can be used in patch clamp recording to generate action potentials.
The second case when the initial condition is set to Equilibrium point for I_ext = 86uA/cm2 can help us to judge the stability of the system at a given point.

Figure(6)
Plot depicting the Stable Equilibrium Point, Limit Cycle and UPO



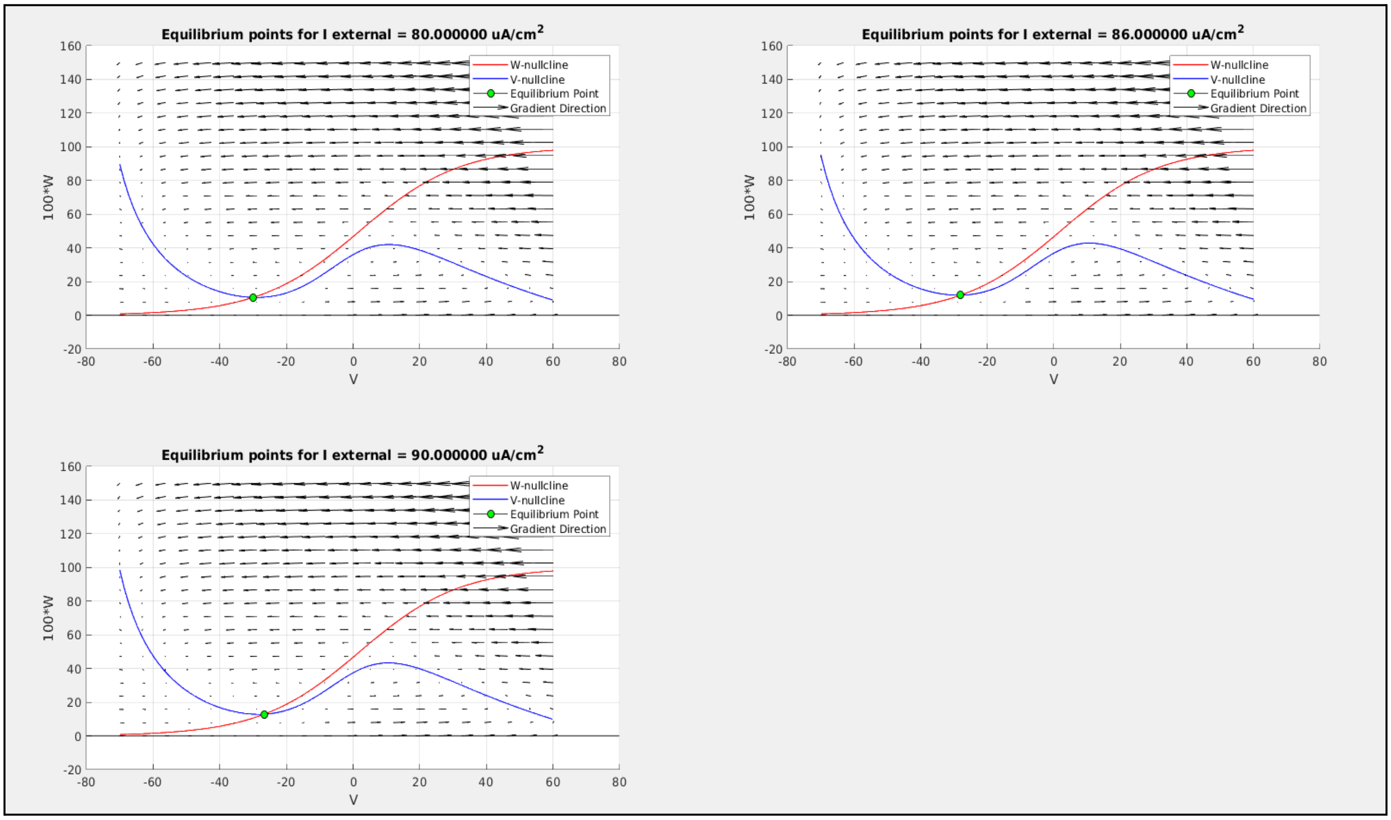
The contour that divides the phase plane into those initial conditions that converge to the equilibrium point and those that converge to the limit cycle is called an **Unstable Periodic Orbit**.
The trajectories starting from initial points that lie outside the UPO converge to the stable limit cycle while the trajectories starting from initial points inside the UPO converge to the stable equilibrium point as can be seen from the above plot.
Thus, the UPO acts as a true threshold as the trajectories starting just slightly outside converge to the LImit Cycle and thus generate the oscillating Action Potentials, where those starting just slightly inside the UPO converge to the stable equilibrium and don't lead to an Action Potential, but rather a subthreshold oscillatory waveform that slowly decays.

To find the UPO, we need to simulate the system by reversing time. There is no effect of running the system backward in time on the null-clines, however the above stable equilibrium point becomes an unstable one, and thus a solution which was stable earlier becomes an unstable solution , and vice versa.

Ques(9):

Figure(7)

Plot depicting the equilibrium points for I ext = 80, 86, and 90 µA/cm 2 for param set 1



Output of the Stability Analysis for the equilibrium points for I_ext = 80, 86 and 90 uA/cm2 (generated by the .m file) =>

 # I_ext = 80

Equilibrium point for parameter set 1 for the case of I_ext = 80.000000 uA/cm2 for MLE:

W_eq = 0.106, V_eq = -29.925

Jacobian matrix for the first set of MLE parameters (for I_ext = 80.000000 uA/cm2):
-0.0122 -21.6301
0.0001   -0.0229
The eigenvalues for the Jacobian matrix are:
-0.0175 - 0.0558i
-0.0175 + 0.0558i

The given equilibrium point is a Stable Spiral.

 # I_ext = 86
Equilibrium point for parameter set 1 for the case of I_ext = 86.000000 uA/cm2 for MLE:
W_eq = 0.119, V_eq = -27.970

Jacobian matrix for the first set of MLE parameters (for I_ext = 86.000000 uA/cm2):
0.0087 -22.4120
0.0002   -0.0225

The eigenvalues for the Jacobian matrix are:
-0.0069 - 0.0574i
-0.0069 + 0.0574i

The given equilibrium point is a Stable Spiral.

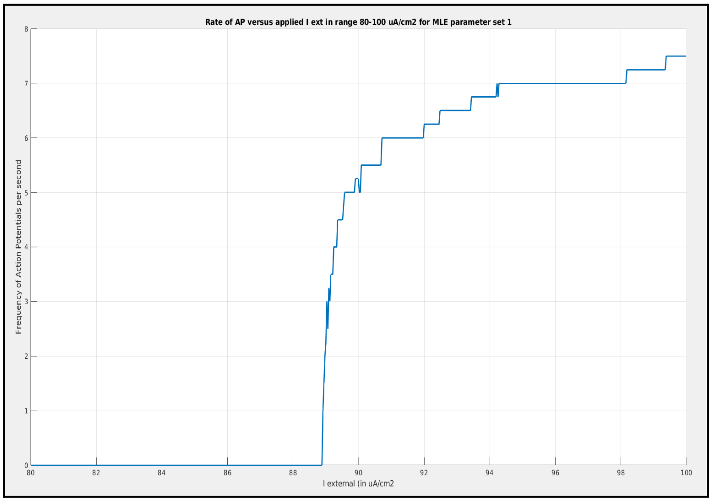
 # I_ext = 90
Equilibrium point for parameter set 1 for the case of I_ext = 90.000000 uA/cm2 for MLE:
W_eq = 0.129, V_eq = -26.667

Jacobian matrix for the first set of MLE parameters (for I_ext = 90.000000 uA/cm2):
0.0248 -22.9333
0.0002   -0.0223

The eigenvalues for the Jacobian matrix are:
0.0012 - 0.0572i
0.0012 + 0.0572i

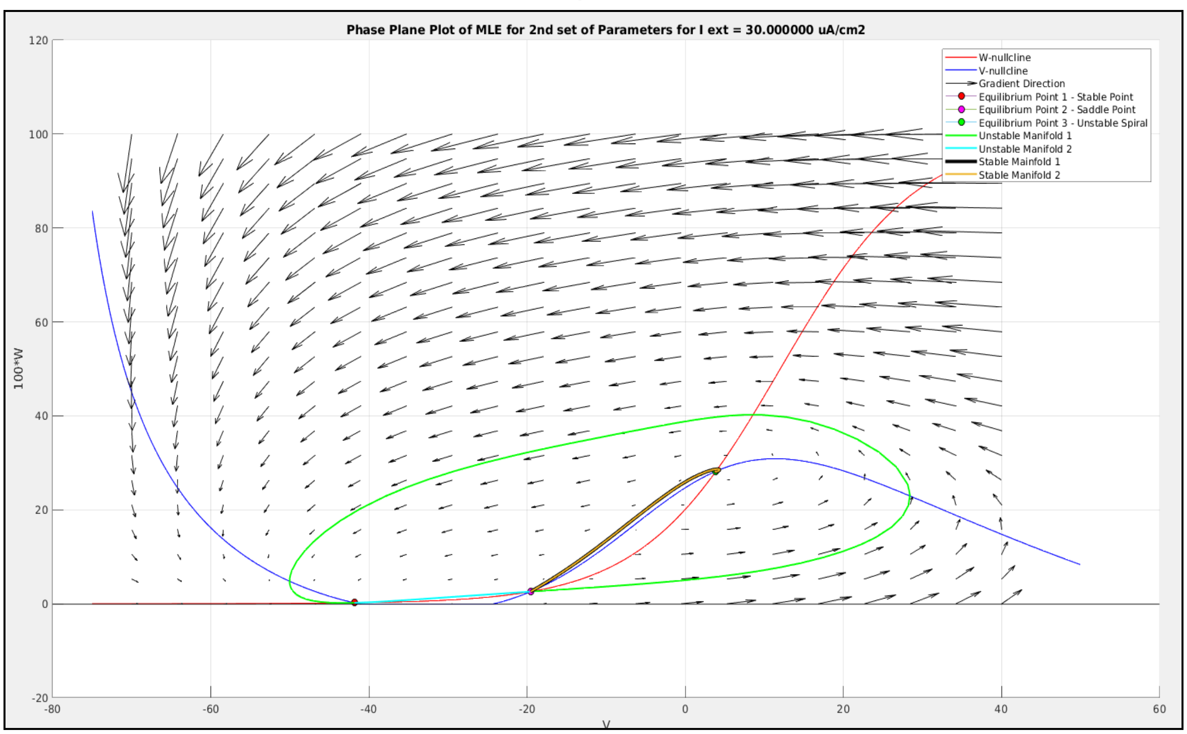
The given equilibrium point is a Unstable Spiral.

Figure(8)
Plot of the rate of firing action potentials versus the applied current



Ques(10):

Figure(9)
Phase Plane depicting the nullclines, equilibrium points and manifolds for MLE param set 2



Equilibrium points and their Stability Analysis (detailed analysis in output of code)**:**

The first equilibrium point is:
-41.8452
0.0020
The given equilibrium point is a **Stable Equilibrium.**

The second equilibrium point is:
-19.5632
0.0259
The given equilibrium point is a **Saddle Point.**
The stable and unstable manifolds associated with the Saddle point have been depicted in the plot above.

The third equilibrium point is:
3.8715
0.2821
The given equilibrium point is a **Unstable Spiral**.

Ques(11):

Change in the Stability of the Equilibrium points for Current Range 30-50 uA/cm2:

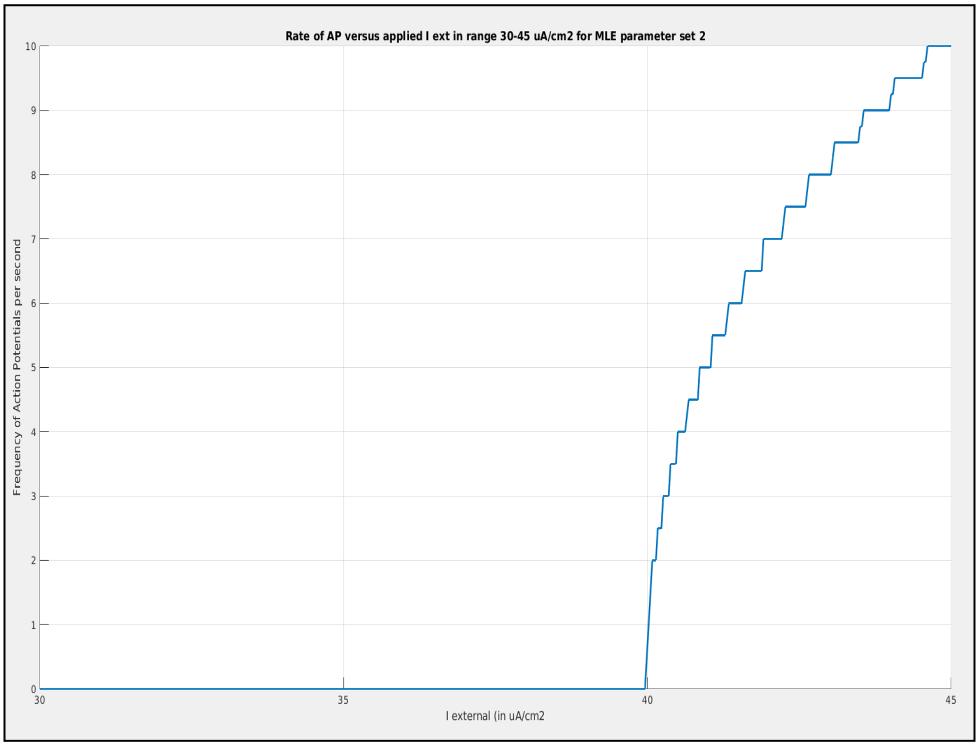
As the current increases, from I_ext = 30 uA/cm2 to I_ext = 39.9 uA.cm2, the three equilibrium points remain as Stable Equilibrium, Saddle Point and Unstable Equilibrium.

For I_ext = 40 uA/cm2, the stability of the 2nd equilibrium point changes to Stable Equilibrium from Saddle point.

After that, the stability of all the 3 equilibrium points changes as current increases above 40 uA/cm2 in a random manner, not following any observable pattern.

The detailed stability analysis for each of the current values in the range 30-50 uA/cm2 is given in the output of the matlab code.

Figure(10)
Plot of rate of firing action potentials versus applied current



From the above plot, we can infer that the rate of firing action potentials increases with the increase in applied external current.

HODGKIN HUXLEY MODEL

Ques(12) and Ques(13):

To find E_L required to make the resting potential = -60 mV :
Equate the dV/dt equation to = 0 at steady state, and replace V with value -60 mV, and n, h, m values with their V_inf values at -60 mV.

Code snippet to determine E_L at V_rest = -60 mV:

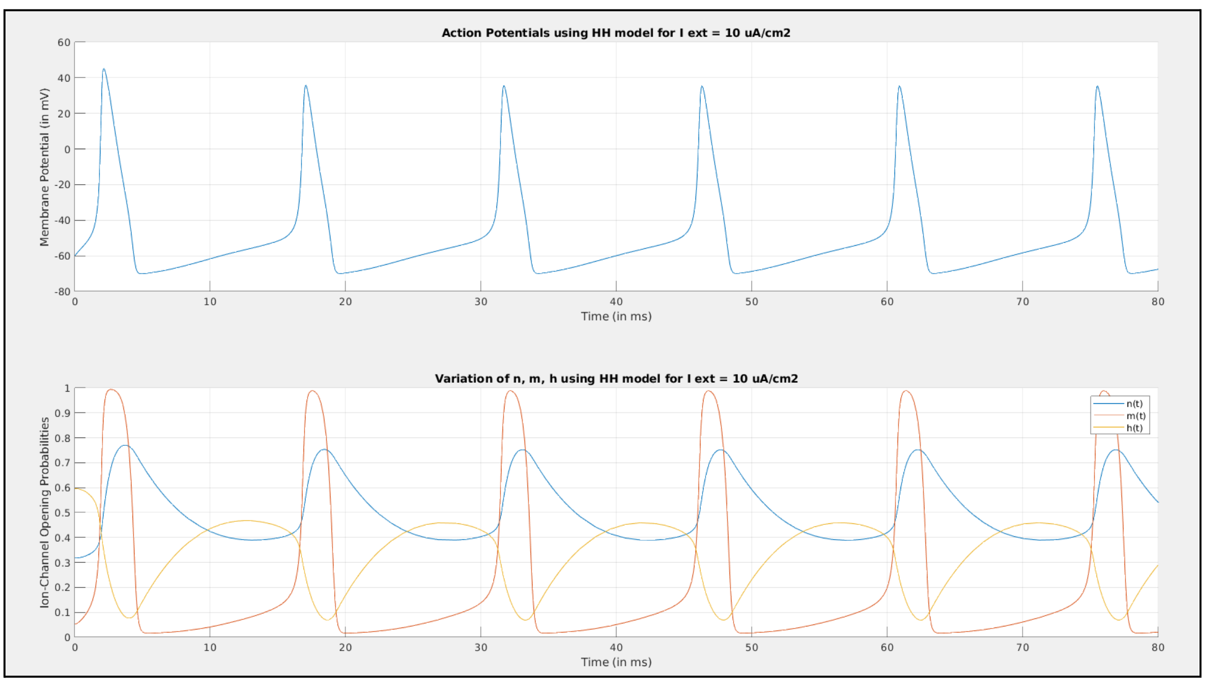
```
syms V_mem
G_K_const = 36; G_Na_const = 120; G_L_const = 0.3;
E_K = -72; E_Na = 55; C = 1;
alpha_n = -0.01*(V_mem + 50)/(exp(-(V_mem + 50)/10) - 1);
beta_n = 0.125*exp(-(V_mem + 60)/80);
alpha_m = -0.1*(V_mem + 35)/(exp(-(V_mem + 35)/10) - 1);
beta_m = 4*(exp(-(V_mem + 60)/18));
alpha_h = 0.07*exp(-(V_mem + 60)/20);
beta_h = 1/(exp(-(V_mem + 30)/10) + 1);
m_inf_V_rest = alpha_m/(alpha_m + beta_m);
n_inf_V_rest = alpha_n/(alpha_n + beta_n);
h_inf_V_rest = alpha_h/(alpha_h + beta_h);
I_ext = 0.0;
E_L = V_mem - ((1/G_L_const)*(I_ext + (-G_K_const*(n_inf_V_rest^4)*(V_mem -
E_K)) + (-G_Na_const*(m_inf_V_rest^3)*(h_inf_V_rest)*(V_mem - E_Na))));
E_L_rest = double(subs(E_L, {sym('V_mem')}, {-60}));
```

The value of E_L for V_rest = -60 mV is -49.401079 mV

Generation of Action Potentials using HH model for I_ext = 10uA :

Figure(11):

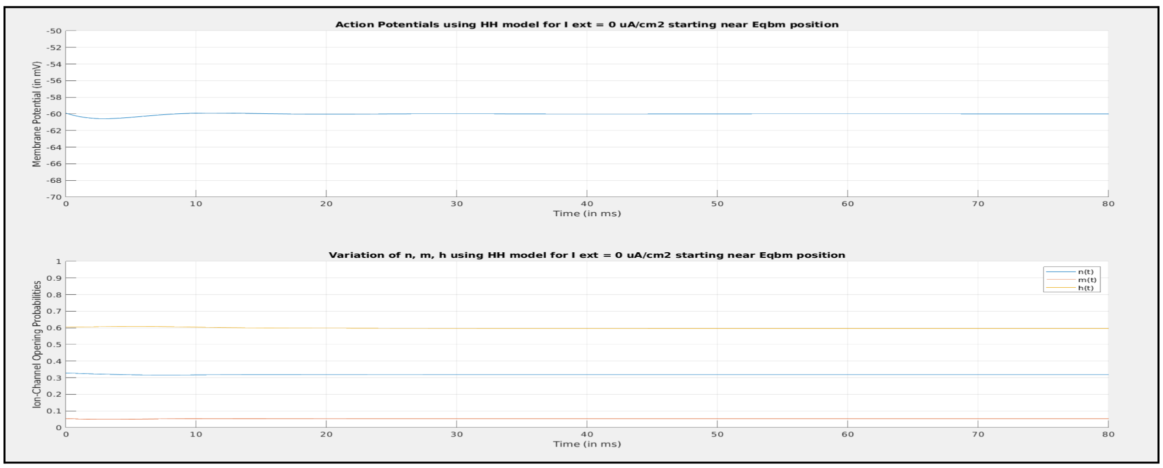
Variation of V, n, h,m as a function of time for HH model for I_ext = 10 uA/cm2



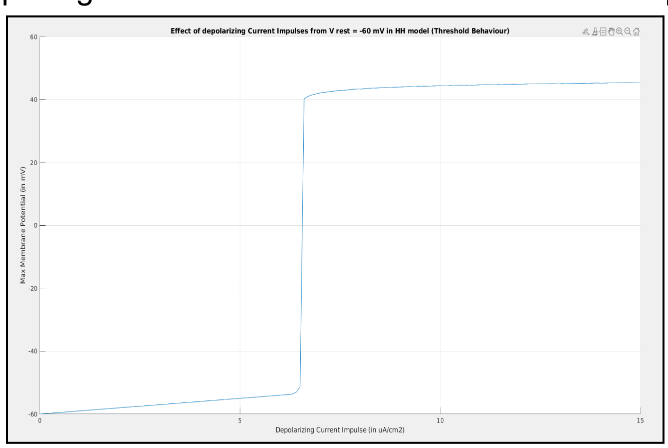
Ques(14):
Equilibrium point:
The Equilibrium condition for HH model for I_ext = 0 uA/cm2 and V_rest = -60 mV is:
V_eq = -60.000000 mV, n_eq = 0.317677, m_eq = 0.052932, h_eq = 0.596121

The plot below depicts the stability of the model at rest with I_ext = 0 uA/cm2. The equilibrium is a stable one as slight deviation from the equilibrium condition does not cause large fluctuations in membrane potential or the rest values of n,m and h.
We cannot check the stability of the equilibrium using phase plane analysis now as the system is 4 - dimensional.

Fig(12)
Plot to check the stability of model at rest for I_ext = 0 uA/cm2



Fig(13)
Plot depicting threshold for the model for brief current pulses



From the plot above, we can find a threshold at around **6.5 uA/cm2.**

Ques(15):

Behavior of the equilibrium points for steady current injections from 8 μA/cm 2 to 12 μA/cm 2:

- **The Equilibrium condition for HH model for steady I_ext = 8 uA/cm2:**
  V_eq = -55.355128 mV, n_eq = 0.390607, m_eq = 0.090048, h_eq = 0.430515

- **The Equilibrium condition for HH model for steady I_ext = 9 uA/cm2:**
  V_eq = -54.952404 mV, n_eq = 0.397027, m_eq = 0.094133, h_eq = 0.416502

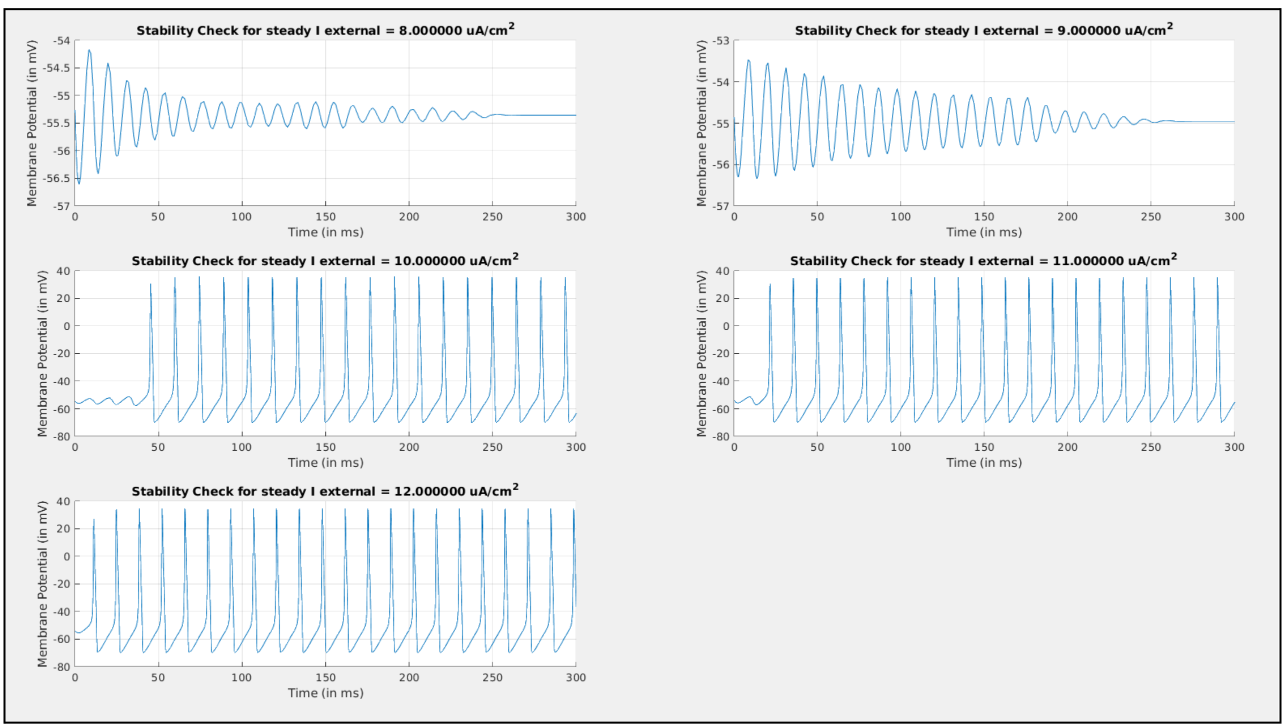
- **The Equilibrium condition for HH model for steady I_ext = 10 uA/cm2:**
  V_eq = -54.572150 mV, n_eq = 0.403092, m_eq = 0.098131, h_eq = 0.403419

- **The Equilibrium condition for HH model for steady I_ext = 11 uA/cm2:**
  V_eq = -54.211777 mV, n_eq = 0.408841, m_eq = 0.102052, h_eq = 0.391169

- **The Equilibrium condition for HH model for steady I_ext = 12 uA/cm2:**
  V_eq = -53.869127 mV, n_eq = 0.414306, m_eq = 0.105899, h_eq = 0.379667

Fig(14)

Plot showing the stability status of the equilibriums for different current injections



Ques(16): **V-n reduced HH model**

For the V-n reduced system,

- h is roughly approximated as 1-n as h and n have similar dynamics, just that n increases with potential increase, while h decreases with increasing potential.
- The time constant for m is very small compared to that of n and h, so the value of m is approximated as m = m_inf_V , where V continuously changes with time.

Similarities and differences from the complete HH model:

- Similarity: The Action Potentials are generated similar to the complete 4-variable HH model, and the variations of n, h and m with time also have high resemblance to the full HH model. The threshold behaviour for current pulses to produce action potentials can also be observed, as given in Fig(16)

- Difference: The shape of the action potentials have changed, and the rise of the action potential is almost instantaneous, as we are considering m to converge to m_inf(V) instantaneously. The shape of the drop has also changed and is now dependent on the dynamics of h.

  Equilibrium points for the V-n reduced system:

- **The Equilibrium condition for steady I_ext = 8 uA/cm2:**
  V_eq = -16.357465 mV, n_eq = 0.827897

- **The Equilibrium condition for steady I_ext = 9.000000 uA/cm2:**
  V_eq = -16.337512 mV, n_eq = 0.828007

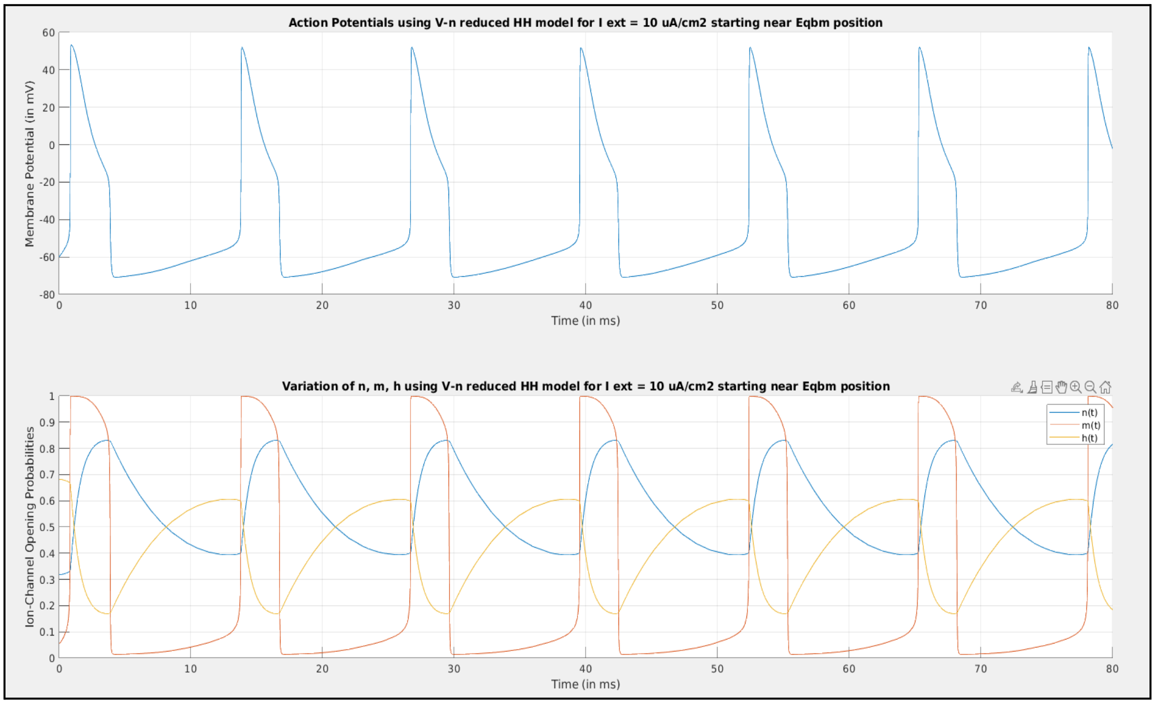
- **The Equilibrium condition for steady I_ext = 10.000000 uA/cm2:**
  V_eq = -16.317587 mV, n_eq = 0.828116

- **The Equilibrium condition for steady I_ext = 11.000000 uA/cm2:**
  V_eq = -16.297689 mV, n_eq = 0.828226

- **The Equilibrium condition for steady I_ext = 12.000000 uA/cm2:**
  V_eq = -16.277817 mV, n_eq = 0.828335

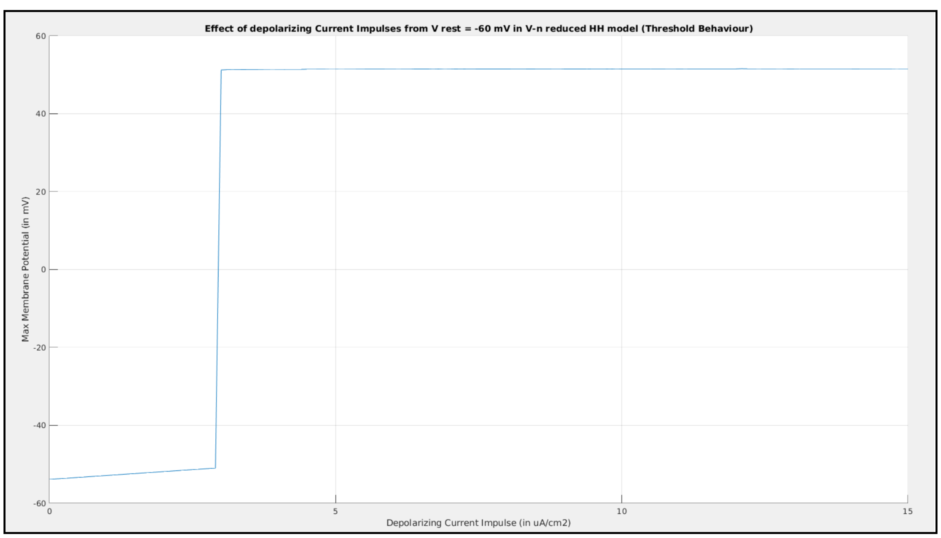
Fig(15)

Plot depicting the Action Potentials for V-n reduced HH model for I_ext = 10 uA/cm2



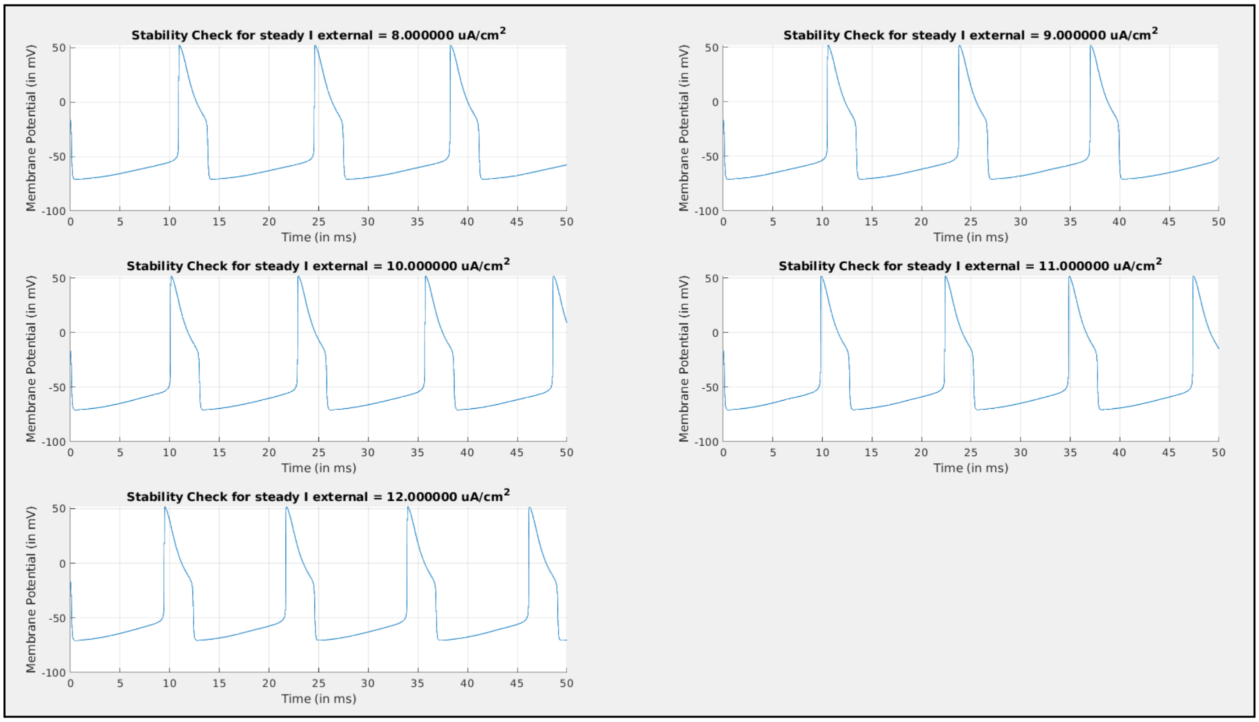
Fig(16)

Plot depicting effect of varying depolarizing current from V-rest condition



Fig(17)

Plot showing the stability status of the equilibriums for different current injections for V-n reduced system



From the above plot, we can infer that system converges to limit cycle for all values of I_ext in range 8-12 uA/cm2 for the V-n reduced HH model.

Ques(17): Anode Break Excitation

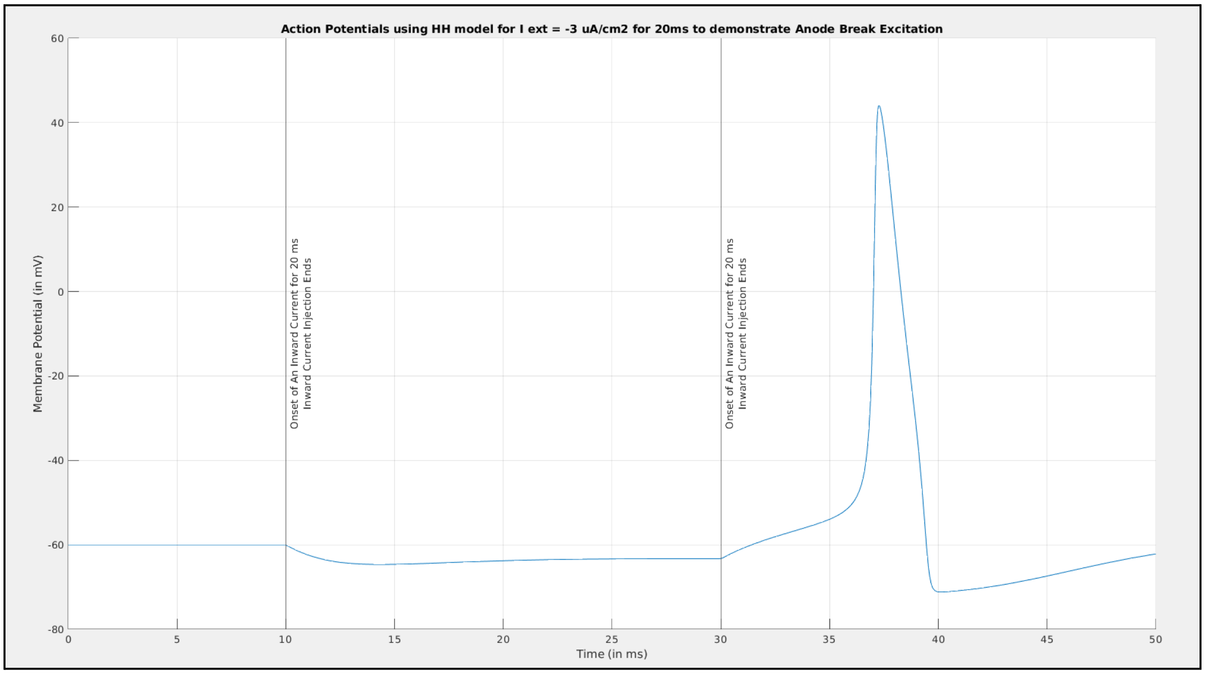
The phenomenon of anode break excitation is a phenomenon in which a neuron fires an action potential after a short duration hyperpolarising current (inward current) is stopped.

The reason for the phenomenon is that as a hyperpolarising current is applied across the membrane, the membrane potential starts decreasing below the resting potential. This also causes a drop in the voltage threshold required to produce the Action Potential as the threshold is directly proportional to the membrane potential.

Now, when the hyperpolarising current is suddenly terminated, the membrane potential across cell quickly rises, but the threshold for producing an action potential is still at the lower value, so the rising potential spontaneously crosses the threshold and produces an Action Potential.

Fig(18)

Plot depicting Anode Break Excitation after a short hyperpolarising current



Ques(18): V-m reduced system:

Equilibrium points in the two cases and their stability analysis

CASE 1 :

Equilibrium point 1 : V_eq = -60.000000 mV m_eq = 0.052932
The given equilibrium point is a Stable Equilibrium.

Equilibrium point 2 : V_eq = -57.382318 mV m_eq = 0.071715
The given equilibrium point is a Saddle Point.

Equilibrium point 3 : V_eq = 53.918714 mV m_eq = 0.999198
The given equilibrium point is a Stable Equilibrium.

CASE 2 :

Equilibrium point 1 for V-m reduced HH model (Case 2) :

V_eq = -63.309740 mV   m_eq = 0.035580
The given equilibrium point is a Stable Equilibrium.

Equilibrium point 2 for V-m reduced HH model (Case 2) :
V_eq = -57.653009 mV   m_eq = 0.069531
The given equilibrium point is a Saddle Point.

Equilibrium point 3 for V-m reduced HH model (Case 2) :
V_eq = 54.316422 mV   m_eq = 0.999219
The given equilibrium point is a Stable Equilibrium.

Fig(19)

Phase plane plot showing nullclines and equilibrium points for
V-m reduced HH model for the two cases