Computational Neuroscience (EC60007)
PROJECT II (15th August)
Autumn 2018

***Due*: *14th September* (by EMAIL before start of class at 7:00 pm)**
Presentations: 14th September in class (~10 minutes each group)

The second project has 2 parts. The first part is designed for you to numerically simulate the Moris Lecar Equations (MLE) and perform phase plane analysis and understand the topics (*being*) discussed in class. In the second part the project builds on the MLE to simulate Hodgkin Huxley (HH) equations and then simulations of other HH type models of neurons. All parts are to be answered by each group; for your presentations you will be asked to present only parts of it. So you should prepare your presentations including all answer. There are in all 6 groups (5 or 6 each, as shared with you) and you are supposed to all work together because one person, *randomly chosen*, from your group will present for the group. This is to ensure that all are on the same page and is an important aspect of working together, which is usually required in such interdisciplinary areas. Please respect each other in the process. Do not worry about grades – enjoy doing the projects.

You are required to submit a **precise and cogent write up with figures (one *.pdf* file only)** answering all questions (please make it short – no need for an elaborate, lengthy write up); please be to the point; one person in your group, please email it to Sharba (sharba AT ece dot iitkgp dot ernet dot in cc-ing all group members. In the very beginning write your names and roll numbers (group members) with contributions against each person's name, clearly stating who did what (if certain sections are jointly done say so). Please also submit (email) **one (1) *m-file* so that running it produces all the figures that are there in your write up.**

Project:

1. An essential step in developing a neural model is working out a consistent set of units for the variables. Usually it is desirable to make the numerical values of variables of the order 1; that is, it is possible to specify currents in amps, but then the numbers will be very small, which can cause problems with the numerical algorithms (see question 4 below). In neuron models, it is usually better to specify currents in microAmps or nanoAmps. The same thing goes for potentials (mV), time (ms), and impedances. You are not free to choose any set of units, however, in that the units must be consistent. Thus volts, amps, siemens (1/ohms), farads, and seconds are a consistent set of units. For example, Ohms law requires that current=conductance x voltage, or amps=siemens x volts. If you change volts to mV, you must make corresponding changes in the other units so that Ohm's law is still numerically true.
Choose the following units: milliseconds, microamps/cm^2, millivolts, microfarads/cm^2 and millisiemens/cm^2. Show that this is a consistent set of units.
Suppose that it had been desirable to specify conductance as microsiemens/cm^2. Give a set of units consistent with μS/cm^2 for current. Is your solution unique?

2. Set the parameters for MLE as follows as in Rinzel and Ermentrout Chapter 7 (R&E) also available on the website:
http://www.math.drexel.edu/~medvedev/classes/2008/math723/papers/Chapter_on_Neural_Excitability.pdf
[g_{ca}, g_k, g_l, v_{ca}, v_k, v_l, phi, V_1, V_2, V_3, V_4, V_5, V_6, C] =
[4.4, 8.0, 2, 120, -84, -60, 0.02, -1.2, 18, 2, 30, 2, 30, 20];

Find the equilibrium point for the system with this set of parameters (and with I_{ext}=0). You should come up with two different ways of doing this calculation. Explain your methods. It may be helpful to plot the nullclines. In fact, writing a small program to plot the nullclines, find the equilibrium points, and compute the eigenvalues at the equilibrium points would be useful at this point. In the following, always run the model from its equilibrium point (i.e. set the initial values of V and w to their values at the equilibrium point) unless instructed to do otherwise.
Remember that as you apply a steady-state (D.C.) current I_{ext}, the equilibrium point changes. A useful Matlab plotting subroutine for phase plane analysis is quiver() which can be used to make an arrow plot of the local directions of flow in the phase plane. Be warned, however that Matlab requires that the X and Y values given to this function must have similar magnitudes. If you place V (max value about 100) on one axis and w (max value about 1) on the other axis, it is necessary to multiply W by 100 to get a "good looking" plot (i.e. plot V versus 100*w).
In the following, when you make phase plane plots, it will usually be very helpful to your understanding to plot both trajectories and nullclines on the same plot. The result of this part should be a phase-plane plot with nullclines, equilibrium points, and arrows. The numerical values of V and w at the equilibrium point should be given.

3. Is the equilibrium point found in Q2 stable (with I_{ext} = 0)? Check this by computing the eigenvalues of the Jacobian of the system at the equilibrium point. Obtain the Jacobian using Matlab. Once you have the Jacobian, evaluate its eigenvalues.

4. Explain why the default numerical tolerance values built into matlab (*AbsTol*=10^{-6} and *RelTol*=10^{-3}) are reasonable for the MLE. Suppose you set the units for the voltage variable in the MLE to kV (kilovolts). This would be a stupid thing to do, but if you did it, how would you have to change the values of *AbsTol* and *RelTol*? Understanding this issue is essential for accurate use of the ODE solvers.

5. Generate an action potential using MLE and make a phase plane plot of your action potential with ϕ=0.02 and ϕ=0.04 and explain the difference in the shapes of the two plots, in terms of the effects of the parameter ϕ. You may check your answer by making ϕ even smaller, say 0.01.

6. Simulate 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. Find depolarizations that are sufficient to produce action potentials. Plot phase-plane trajectories for values of initial depolarization that do and do not produce action potentials. Make sure I_{ext}=0 for this part and make sure that the duration of the simulation is large enough to see the whole action potential (300 ms or so). Action potentials are usually thought to have thresholds. Does the MLE with the given set of parameters have a threshold depolarization? If your answer is yes, define what you mean by threshold. Be careful here, you should investigate initial values of V (in a specific interval) very carefully, i.e. to several decimal places; it will be useful to make a plot of the maximum amplitude of the action potential versus initial value of V.

7. Run the model with I_{ext}=86 μA/cm^2 with three sets of initial conditions: 1) Set the initial conditions to the equilibrium point used above, appropriate for I_{ext}=0; 2) Set the initial conditions to the equilibrium point when I_{ext}=86 μA/cm^2; and 3) Set the initial conditions off the equilibrium point for I_{ext}=86 μA/cm^2, say at (-27.9, 0.17). Make sure you set the time span for the simulation to be long enough to see the full response. Plot the three trajectories on a phase plane. Describe the stable states of this system (make sure to characterize the equilibrium point for I_{ext}=86 μA/cm^2).
Explain the difference between trials 1) and 2) above. That is, describe two experiments

in which current is applied to a cell to produce the responses you observed.

8. The system with I_{ext}=86 μA/cm^2 apparently has two stable states. 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. Do this by running the model backwards in time to find an unstable periodic orbit like the UPO in R&E. Make sure you understand what happens to 1) null-clines 2) equilibrium points and 3) stable and unstable solutions when the model is run backwards in time.
Show that the UPO is a true threshold in the sense that an infinitesimal change in V leads from a subthreshold waveform to an action potential.

9. Analyze the equilibrium points for I_{ext}= 80, 86, and 90 μA/cm^2 and explain the observations. Do the results correspond to that predicted by the eigenvalues of the system linearized around the equilibrium point for I_{ext}=86 (do this quantitatively, don't just answer "yes" or "no".)? Make a plot of the rate of firing action potentials versus the applied current over the range 80-100 μA/cm^2. In each case, start the system at its equilibrium point for the applied current.

10. Set your MLE program to the following parameters:
[g_{ca}, g_k, g_l, v_{ca}, v_k, v_l, phi, V_1, V_2,V_3, V_4,V_5, V_6, C]=[4, 8.0, 2, 120, -84, -60, 0.0667, -1.2, 18, 12, 17.4, 12, 17.4, 20]
I_{ext} = 30 starting from time 0 to 2000 ms. Note that the current should be set to a non-zero value throughout your simulation. Determine the equilbrium point(s) of this system (there should be 3) and characterize them as to stability. Show in a phase plane plot, the nullclines, equilibrium points, and manifolds (if there are any).

11. For the system in Q10 show how the equilibrium points and their character change for current range between 30 and 50 μA/cm^2. Pay special attention to the range between 39 and 40. It will be necessary to show what happens to the equilibrium points as the current increases. Make a plot of the rate of firing action potentials versus the applied current over the range 30-45 μA/cm^2. What do you learn?

Hodgkin Huxley Equations

12. Given below are equations for the classical HH model of the squid giant axon from their original paper. The model consists of a membrane capacitance C, a sodium channel G_{Na}, a delayed-rectifier potassium channel G_K, and a leak channel G_L. The equation for membrane potential can be written as given where I_{ext} is externally applied current. The conductances are represented in terms of the HH parameters as provided below and each of the three conductance parameters is governed by a differential equation of the form given (with x, where x = n, m, or h). The functions α_x and β_x have been provided along with the parameters of the model. The rate constants are multiplied by a parameter ϕ, which is an adjustment for the effect of temperature on the rate constants of the model. We assume that ϕ increases with temperature according to the relationship provided. (T is the temperature of the simulation. For the purposes of this project, use T=6.3° so that ϕ=1 (i.e. ignore ϕ).
Write a program to simulate this system of equations. In doing so, 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 which should be handled by you, using a little bit of *your* neurons.

$$C\frac{dV}{dt} = I_{ext} - G_K(V - E_K) - G_{Na}(V - E_{Na}) - G_L(V - E_L)$$

$$G_K = \bar{G}_K n^4(V,t) \qquad G_{Na} = \bar{G}_{Na} m^3(V,t)\, h(V,t) \qquad G_L = \bar{G}_L$$

$$\frac{dx}{dt} = \alpha_x(V)\,(1-x) - \beta_x(V)\,x$$

For the delayed-rectifier potassium channel:

$\bar{G}_K = 36$ mS/cm^2 $\quad E_K$=-72 mV $\quad \alpha_n = \dfrac{-0.01\ \phi\ (V+50)}{\exp[-(V+50)/10] - 1}$ $\quad \beta_n = 0.125\ \phi \exp[-(V+60)/80]$

For the sodium channel:

$\bar{G}_{Na} = 120$ mS/cm^2 $\quad E_{Na}$=55 mV $\quad \alpha_m = \dfrac{-0.1\ \phi\ (V+35)}{\exp[-(V+35)/10] - 1}$ $\quad \beta_m = 4\ \phi \exp[-(V+60)/18]$

$\alpha_h = 0.07\ \phi \exp[-(V+60)/20]$ $\quad \beta_h = \dfrac{\phi}{\exp[-(V+30)/10] + 1}$

For the leakage channel:

$\bar{G}_L = 0.3$ mS/cm^2 $\quad E_L$ = to be determined

Temperature coefficient:

$\phi = Q^{(T-6.3)/10}$ $\quad Q = 3$

Membrane capacitance:

C = 1 μFd/cm^2

BE CAREFUL ABOUT THE UNITS OF THE HH EQUATIONS. NO ATTEMPT HAS BEEN MADE TO PROVIDE A CONSISTENT SET OF UNITS; IF YOU JUST PLUG IN THE NUMBERS, YOU MAY GET RIDICULOUS ANSWERS.

13. Once you have the model running, determine the value of E_L necessary to make the resting potential of the model -60 mV. Fix E_L at this value for the rest of the project. Please use a stiff integration algorithm such as ode15s to avoid instabilities with this model. Make sure you have the numerical error tolerances set properly.
You should be able to produce action potentials with I_{ext}=10 μA/cm^2.

14. Check the stability of the model at rest with I_{ext}=0. Determine the threshold of the model for brief current pulses, approximating them with depolarizations, as discussed in class.

15. Add a steady applied current (like I_{ext} in the MLE model) to your model. Show the behavior of the equilibrium points for steady current injections from 8 μA/cm^2 to 12 μA/cm^2. (Refer to Fig. 7.3 of R&E). When testing for stability, it is not sufficient to simply start the model at some initial condition and then look for a decay into a stable equilibrium point (as a hint, the equilibrium point is stable at 9 μA/cm^2, but the model goes into a limit cycle when started at an initial condition equal to the equilibrium point for zero current, determined above). Thus the equilibrium point will have to be determined at each current by explicitly finding it.

16. One cause of a paralytic muscle disease called myotonia is loss of Na^+ channel inactivation due to a genetic defect. The action potential will be shown to be very

sensitive to small changes in Na^+ channel inactivation. The above situation is modeled by assuming that a fraction f_{ni} of Na^+ channels do not inactivate, so that the sodium current in your HH model is given by:

$$I_{Na} = \bar{g}_{Na}(1 - f_{ni})m^3 h(V - E_{Na}) + \bar{g}_{Na} f_{ni} m^3 (V - E_{Na})$$

The first term is the normal inactivating Na^+ current and the second term is the noninactivating current. Compare the action potentials produced by brief depolarizing curren pulses (modeled by setting the initial condition on membrane potential 7-10 mV depolarized from rest) for values of f_{ni} = 0, 0.1, 0.17, and 0.2. You should observe a change in the action potential shape and a change in the steady-state membrane potential behavior. Describe these changes and give a qualitative explanation for them.

17. It is helpful to use a reduced model with only two state variables to study the effects of noninactivation. As discussed in class, reduce the system to a system with n and V as the only state variables by appropriately setting m and h. Modify your HH model to have this reduced form and generate action potentials with current injections or depolarizations. You should see that the reduced model has the same general behavior as the full model. Note and explain the differences.

18. Construct an (n,V) phase-plane analysis for the reduced model (Q17) including f_{ni} (Q16) and do an analysis over a range of values of f_{ni} (0.02 – 0.4), showing what happens to the equilibrium points and their stability. Explain the behavior observed.

19. A contribution of the HH model was to explain the phenomenon of anode break excitation, wherein the membrane produces an action potential at the end of a hyperpolarizing stimulus pulse (see HH's paper Fig. 22). Show that your model demonstrates anode break excitation (a hyperpolarizing current of -3 μA/cm^2 for 20 ms should suffice). Analyze the parameters of the HH model and explain why anode break excitation occurs.

20. Anode-break can be studied by considering a reduced HH model system with only the V and m state variables as discussed in class. The n and h variables are fixed at some appropriate value, under the assumption that the time constants of m and V are very fast compared to those of n and h, so with m as one state variable, threshold can be studied. Plot phase plane for m and V defined by the usual equations except that n and h are fixed at two values: 1) the values for membrane potential at rest, -60 mV and 2) at the values at the end of the anodal stimulus used to produce the anode break excitation above. Characterize the equilibrium points in the two cases. The phase plane should contain an equilibrium point near the resting potential in one case but not in the other. What happens to the resting equilibrium point in case 2) and what does this have to do with the anode-break action potential?