Neurodynamics - Fall 2017

BENG 260 / BGGN 260 / PHYS 279

Homework 2: Due October 20

Computational Lab

1. *Two State Markov Model* [30 points].

   Assume we have a simple two state Markov model where n denotes the fraction of gates open, and $1-n$ denotes the fraction of gates closed. The opening rate is $\alpha_n(V_m) = \alpha_0 e^{\lambda V_m}$ and the closing rate is $\beta_n(V_m) = \beta_0 e^{-\mu V_m}$. Let $\alpha_0 = \frac{0.7}{s}$, $\beta_0 = \frac{0.9}{s}$, $\lambda = \mu = \frac{0.01}{mV}$. The Markov diagram is as follows:

   $$\mathbf{1-n} \quad \underset{\beta_n(V_m)}{\overset{\alpha_n(V_m)}{\rightleftharpoons}} \quad \mathbf{n}$$

   The rate equation for the mean field for this Markov process is

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

   We apply an input voltage $V_m(t) = 30 * H(t - t_{input})$ where $H(t)$ is the Heaviside step function and $t_{input} = 8\,s$. Assume all gates begin in the closed state.

   (a) Solve for $n(t)$ analytically.

   (b) Plot the time constant, τ_n from -100:100. *Hint:* V_m is a step function, so τ_n should also be a step function.

   (c) Solve for $n(t)$ computationally using an ode solver.

   (d) Simulate this Markov process stochastically to find the fraction of gates open, $n(t)$, for different number of channels $N = 1,\ 400,\ 1000$. Compare your three solutions by plotting $n(t)$ for t from 0 to 16 s.

2. *Simulating Hodgkin-Huxley neurons* [30 points].

   We will simulate the Hodgkin-Huxley (HH) model of action potential generation in the squid giant axon. You will program these equations so you can use them on the homework. The template code provides a coded example of the Morris-Lecar equations which you can use for reference.

   The equations describing the HH dynamics are replicated here for convenience:

$$\frac{dV}{dt} = \frac{1}{C}\left(-I_{Na} - I_K - I_L + I_{ext}\right) \tag{1}$$

$$I_{Na} = g_{Na}\, m^3 h\, (V - E_{Na}) \tag{2}$$

$$I_K = g_K\, n^4\, (V - E_K) \tag{3}$$

$$I_L = g_L\, (V - E_L) \tag{4}$$

with parameters:

$$\begin{aligned}
C &= 1\,\mu F/cm^2 \\
E_{Na} &= 115\,mV; \qquad g_{Na} = 120\,mS/cm^2 \\
E_K &= -12\,mV; \qquad g_K = 36\,mS/cm^2 \\
E_L &= 10.613\,mV; \qquad g_L = 0.3\,mS/cm^2
\end{aligned} \tag{5}$$

where the dynamics of gating variables:

$$\frac{dm}{dt} = \alpha_m(V)\,(1-m) - \beta_m(V)\,m \tag{6}$$

$$\frac{dh}{dt} = \alpha_h(V)\,(1-h) - \beta_h(V)\,h \tag{7}$$

$$\frac{dn}{dt} = \alpha_n(V)\,(1-n) - \beta_n(V)\,n \tag{8}$$

is determined by rate functions:

$$\alpha_m(V) = (25-V)/(10*(\exp((25-V)/10)-1)) \tag{9}$$

$$\beta_m(V) = 4\ \exp(-V/18) \tag{10}$$

$$\alpha_h(V) = 0.07\ \exp(-V/20) \tag{11}$$

$$\beta_h(V) = 1/(\exp((30-V)/10)+1) \tag{12}$$

$$\alpha_n(V) = (10-V)/(100*(\exp((10-V)/10)-1)) \tag{13}$$

$$\beta_n(V) = 0.125\ \exp(-V/80) \tag{14}$$

A. Plot the rates α_m, β_m, α_h, β_h, α_n, and β_n as functions of membrane voltage V, for range -20 to +120 mV.

B. Starting with just I_L, the leak current, leaving out I_{Na} and I_K:

$$\frac{dV}{dt} = \frac{1}{C}\,(-I_L + I_{ext}) \tag{15}$$

$$I_L = g_L\,(V - E_L) \tag{16}$$

$$C = 1\,\mu F/cm^2; \qquad E_L = 10.613\,mV; \qquad g_L = 0.3\,mS/cm^2 \tag{17}$$

We have an RC circuit representing a passive membrane. Plot V as a function of time t. Try different values for the injected current I_{ext}, starting with a value $I_{ext} = 10\ \mu A/cm^2$.

C. Now add I_{Na}, I_K, and their gating variables n, m, and h to observe spiking. Plot the membrane voltage V and the gating variables n, m, and h as a function of time t, for different values of injected current I_{ext} as in (B).

D. These parameter settings in the HH equations set the resting potential at zero. How would you modify the parameters to set the resting potential at -70 mV? How would you modify the parameters to increase the threshold of injected current I_{ext} for spiking?

Homework Problems

3. *Reduction of HH to two-dimensional dynamics* [40 points].

   The HH equations that you just simulated involve 4 dynamic variables, V, n, m, and h. Now we will try to simplify the dynamics to the smallest possible number of dynamic variables capable of generating spiking dynamics. In this case it will be 2 dynamic variables - systems with fewer than 2 variables can generate limit cycles.

   A. We will first try to collapse h and n into a single dynamical variable, n. For the full HH data that you generated in (2C), show a scatter-plot of h as a function of n. How strong is the relationship? Try a linear regression of h in terms of n:

   $$h = \lambda - \mu n. \tag{18}$$

   B. Next, we will approximate the dynamics of the fast Na activation variable $m(t, V)$ with its instantaneous (equilibrium) value

   $$m_\infty(V) = \alpha_m(V)/(\alpha_m(V) + \beta_m(V)). \tag{19}$$

   For the full HH data that you generated in (2C), show a scatter-plot of $m_\infty(V(t))$ as a function of $m(t)$. How strong is the relationship?

   C. Now rerun the HH simulations of (2C) in reduced form, replacing h with its linear regression from (A), replacing m with $m_\infty(V)$. Compare the reduced HH output with the full HH output of (2C).

   Note: The reduced HH model that you just simulated is similar to the FitzHugh-Nagumo, and Morris-Lecar simplified spiking models in two reduced variables (V and W for FitzHugh-Nagumo, and V_m and w for Morris-Lecar, as in the Week 2 lecture notes.) Two-dimensional models are useful for stability analysis using null-clines as we will see in Week 3.

4. *Hodkin-Huxley Model With Expanded Channel Gating Dynamics* [Bonus Problem: 20 points].

   (a) K^+ Channel Gating Dynamics: Show that $n_4 = n^4$ where n_4 is the only state of the Potassium channel Markov model that corresponds to an active channel, and n^4 denotes the solution of a two state Markov model (using opening and closing rates corresponding to the Potassium channel) raised to the fourth power. The full Potassium channel Markov model is as follows:

   $$\mathbf{n_0} \underset{\beta_n}{\overset{4\alpha_n}{\rightleftharpoons}} \mathbf{n_1} \underset{2\beta_n}{\overset{3\alpha_n}{\rightleftharpoons}} \mathbf{n_2} \underset{3\beta_n}{\overset{2\alpha_n}{\rightleftharpoons}} \mathbf{n_3} \underset{4\beta_n}{\overset{\alpha_n}{\rightleftharpoons}} \mathbf{n_4}$$

   (b) Na^+ Channel Gating Dynamics: Show that $s_{31} = m^3 h$. s_{31} is the only state of the sodium channel Markov model that corresponds to an active channel; m^3 denotes the time course probability of the sodium activation gate being in the open state, raised to the third power; h denotes the time course probability of the sodium inactivation gate being in the open state. The full sodium channel Markov model is as follows:

   $$\begin{array}{ccccccc}
   \mathbf{s_{01}} & \underset{\beta_m}{\overset{3\alpha_m}{\rightleftharpoons}} & \mathbf{s_{11}} & \underset{2\beta_m}{\overset{2\alpha_m}{\rightleftharpoons}} & \mathbf{s_{21}} & \underset{3\beta_m}{\overset{\alpha_m}{\rightleftharpoons}} & \mathbf{s_{31}} \\
   \alpha_h \upharpoonleft\downharpoonright \beta_h & & \alpha_h \upharpoonleft\downharpoonright \beta_h & & \alpha_h \upharpoonleft\downharpoonright \beta_h & & \alpha_h \upharpoonleft\downharpoonright \beta_h \\
   \mathbf{s_{00}} & \underset{\beta_m}{\overset{3\alpha_m}{\rightleftharpoons}} & \mathbf{s_{10}} & \underset{2\beta_m}{\overset{2\alpha_m}{\rightleftharpoons}} & \mathbf{s_{20}} & \underset{3\beta_m}{\overset{\alpha_m}{\rightleftharpoons}} & \mathbf{s_{30}}
   \end{array}$$

(c) Now simulate the entire Hodgkin-Huxley model stochastically and compare with your simulation from Problem 2. Vary your differential equation for V_m by using different combinations of currents. Adjust your external current so that you are slightly below threshold, then increase your current so you are slightly above threshold, and compare.

Submission Guidelines

Solutions without work or explanations where applicable will receive no credit. Submit a single .zip file containing solutions, plots, and Matlab/Python code to both computational lab and homework problems by 3:00pm of due date on TritonEd.

The submission file should follow the naming scheme `LastFirst_A12345678_HW2.zip`.