ES226r Problem set 1 - Due Tuesday March 2

(1) Numerical Simulations of the Full Hodgkin Huxley Model
Using Matlab or python, simulate action potentials from the Hodgkin Huxley model. Note this model is essentially a 4th order differential equation (4 coupled 1st order differential equations – 3 nonlinear & 1 linear), so you can use one of Matlab's differential equation solvers (ode45, ode23, etc) to simulate the HH model. To use ode23, for example, you will need to write a matlab function (m-file) that takes time (t), and a state vector = [v, m, h, n] as input returns as output the time derivative of the state vector (4 elements: dv/dt, dm/dt, dh/dt, dn/dt). For initial conditions, use the resting potential for E (-61.2mv), and the asymptotic values of m, h, & n at v=-61.2mV. Note that for the nominal parameter values given in the accompanying handout, if we suppress the units then the equations work out to give time in milliseconds, potential in millivolts, and current in microamps/cm^2. Note also that the form the of the activation and inactivation kinetics in the Hodgkin Huxley model is the same for the m, h, & n particles – the only difference is their dependence on voltage (v) derived from the different dependences of a(v) and b(v) on voltage.

(a) Plot m_∞, h_∞, and n_∞ as a function of voltage (over the range of v_K to v_{Na}). Label the plot and indicate the resting potential.

(b) Stimulate the model with a constant current of 1 to 10 microamps/cm^2 and plot the membrane potential for 30 msec. You can use a command like:

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for k=1:10, i_const=k; [T,Y] = ode45('hh_fun',[0:.001:30],y0); subplot(5,2,k); plot(T,Y(:,1)); end
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(c) Stimulate with a current pulse of 1 msec duration and magnitude of 10 microamps/cm^2, and then plot membrane potential, and the sodium and potassium conductances as function of time.

(d) Stimulate with a current pulse of 1 msec duration and a magnitude varying from 0 to 10 uA/cm^2. Plot the relationship between stimulating current pulse magnitude and peak membrane voltage.

(e) Stimulate with an initial 10uA current pulse of 1 msec duration and then with a second pulse with magnitude varying from 1 to 20 ([1:20]) microamps/cm^2, and then plot the relationship between current pulse magnitude and peak membrane voltage for the 2nd pulse when it comes 1-30 ms after the first pulse (1ms intervals [1:30]).

(f) Plot the relationship between firing rate and stimulating current (for constant (non-pulsed) stimulating currents). To do so you'll need to determine a reasonable range of current densities to use.

For each part above write a terse (1-3 sentence) description & explanation of the behavior observed.

(2) Simplified versions of the Hodgkin Huxley Model
(a-b) Compare the 2-D Hodgkin-Huxley simplification we covered in class [the nv-only model with {n+h=c (with c=0.8), $m=m_{inf}(v)$}] with the full 4-D HH model.
Compare **(a)** the time course of the action potentials, v(t) produced by each and **(b)** the 2-D phase-plane curves for the simplified vs the full model. [you can simply reuse the simulation from 1c above]

(c) Construct a phase-plane vector field plot of this 2-D Hodgkin-Huxley simplification [You can use the matlab function "quiver" for this], decorate this plot with the dv/dt=0 and the dn/dt=0 nullclines, and sketch a couple possible phase plane trajectories atop the plot.

(d-f) Propose a second 2-D HH simplification and repeat the analysis in part a-c above.

For each part above write a terse (1-3 sentence) description & explanation of the behavior observed.

Hodgkin-Huxley Action Potential Model

This formula is used to calculate the membrane potential assuming some initial state. The calculation is based on Sodium ion flow, Potassium ion flow and leakage ion flow (which lumps all the less significant & non-voltage-dependent (NVD) currents – mainly the NVD K+ & Cl-). If there is a mother of computational neuroscience this is it. It resulted in an Noble Prize for the authors, and more than half a century later it is still probably the single important quantitative model in neuroscience (Hodgkin, A. L. and Huxley, A. F. (1952) "A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve" Journal of Physiology 117: 500-544)

The Main formula

$$C\frac{dV}{dt} = I_{tot} = I_{Na} + I_K + I_L + I_{ext} = -g_{Na}(V - V_{Na}) - g_K(V - V_K) - g_r(V - V_r) + I_{injected}$$

The Variable Definitions

The parameter names in bold are fixed variables.

- C: Membrane capacitance (about 1 microFarad/cm^2)
- I : the total ionic current across the membrane (in microAmps/cm^2)
- m : the probability that 1 of the 3 required activation particles has contributed to the activation of the Na gate (m^3 : the probability that all 3 activation particles have produced an open channel)
- h : the probability that the 1 inactivation particle has *not* caused the Na gate to *close*
- **G_Na** : Maximum possible Sodium Conductance (about 120 mOhms^-1/cm2)
- **E** : total membrane potential (about -61.2 mV)
- **E_Na** : Na membrane potential (about 55 mV)
- n : the probability that 1 of 4 activation particles has influenced the state of the K gate.
- **G_K** : Maximum possible Potassium Conductance (about 36 mOhms^-1/cm2)
- **E_K** : K membrane potential (about -72 mV)
- **G_L** : Maximum possible Leakage Conductance (about .3 mOhms^-1/cm2)
- **E_L** : Leakage membrane potential (about -50 mV)

Parameters and Values

Parameter	Value
G_Na 120	mOhms^-1/cm2
G_K 36	mOhms^-1/cm2
G_L .3	mOhms^-1/cm2
E	-61.2 mV
E_Na	55 mV
E_K	-72 mV
E_L	-50 mV

The Activation Particle probability(m) for Sodium

$$\frac{dm}{dt} = a_m(1 - m) - b_m m = \frac{m_{inf} - m}{T_m}$$

$$T_m = \frac{1}{a_m + b_m} \qquad m_{inf} = \frac{a_m}{a_m + b_m}$$

Empirical Formula for the workings of the Sodium gate activation (m)

$$a_m(E) = \frac{-.1\,(40 + E)}{\exp\left(\frac{-(40 + E)}{10}\right) - 1}$$

$$b_m(E) = 4\exp\left(\frac{-(65 + E)}{18}\right)$$

Variable Definitions

- m : the probability that 1 of the 3 required activation particles has contributed to the activation of the Na gate (m^3 : the probability that all 3 activation particles have produced an open channel)
- t : time in msec
- a_m : rate constant for particle not activating a gate
- b_m : rate constant for particle activating a gate
- m_inf : the steady state value of m (m-infinity)
- T_m : the time constant of m
- E : total membrane voltage
- a_m : rate constant for particle not activating a gate
- b_m : rate constant for particle activating a gate

The Inactivation Particle probability(h) for Sodium

$$\frac{dh}{dt} = a_h(1 - h) - b_h h = \frac{h_{inf} - h}{T_h}$$

$$T_h = \frac{1}{a_h + b_h} \qquad h_{inf} = \frac{a_h}{a_h + b_h}$$

Empirical Formula for the workings of the Sodium gate inactivation (h)

$$a_h(E) = .07\exp\left(\frac{-(E+65)}{20}\right)$$

$$b_h(E) = \left(\frac{1}{\exp\left(\frac{-(35 + E)}{10}\right) + 1}\right)$$

The Variable Definitions

- h : the probability that the 1 inactivation particle has *not* caused the Na gate to *close*
- t : time in msec
- a_h : rate constant for particle inactivating a gate
- b_h : rate constant for particle not inactivating a gate
- h_inf : the steady state value of h (h-infinity)
- T_h : the time constant of h
- E : total membrane voltage
- a_h : rate constant for particle inactivating a gate
- b_h : rate constant for particle not inactivating a gate

The Activation Particle probability(n) for Potassium

$$\frac{dn}{dt} = a_n (1 - n) - b_n n = \frac{n_{inf} - n}{T_n}$$

$$T_n = \frac{1}{a_n + b_n} \qquad n_{inf} = \frac{a_n}{a_n + b_n}$$

Empirical Formula for the workings of the Potassium gate activation (n)

$$a_n(E) = \frac{-.01\ (55 + E)}{\exp\left(\frac{-(55 + E)}{10}\right) - 1}$$

$$b_n(E) = .125 \exp\left(\frac{-(E+65)}{80}\right)$$

The Variable Definitions

- n : the probability that 1 of 4 activation particles has influenced the state of the K gate.
- t : time in msec
- a_n : rate constant for particle not activating a gate
- b_n : rate constant for particle activating a gate
- n_inf : the steady state value of n (n-infinity
- T_n : the time constant of n