Assignment 1
Theoretical Neuroscience [Gatsby]

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1. **Subthreshold neurons**

   As we saw in class, the membrane potential, V, of a totally passive neuron (with external input) obeys the equation

$$\tau \frac{dV}{dt} = -(V - \mathcal{E}_L) + V_{in}(t) \tag{1}$$

   where $V_{in}(t)$ is the external input. Show that this has the solution

$$V(t) = \mathcal{E}_L + \big(V(t_0) - \mathcal{E}_L\big) + \int_{t_0}^{t} \frac{dt'}{\tau} \, e^{(t'-t)/\tau} V_{in}(t') \,. \tag{2}$$

   Show that under the change of variables $t' = t - s$, this becomes

$$V(t) = \mathcal{E}_L + \big(V(t_0) - \mathcal{E}_L\big)e^{-(t-t_0)/\tau} + \int_{0}^{t-t_0} \frac{ds}{\tau} \, e^{-s/\tau} V_{in}(t-s) \,. \tag{3}$$

   This has an especially nice form in the limit $t_0 \to \infty$,

$$V(t) = \mathcal{E}_L + \int_{0}^{\infty} \frac{ds}{\tau} \, e^{-s/\tau} V_{in}(t-s) \,. \tag{4}$$

2. **The Hodgkin-Huxley neuron**

Numerically integrate the Hodgkin-Huxley equations with matlab (or your favorite package). If you're using matlab, it's a good idea to use the Matlab `ode45` function, or if you're using Python, scipy.solve_ivp. The equations are:

$$
\begin{aligned}
C\frac{dV}{dt} &= -\overline{g}_{Na}m^3h(V-E_{Na}) - \overline{g}_K n^4(V-E_K) - \overline{g}_L(V-E_L) + I_{stim} \\
\frac{dx}{dt} &= \alpha_x(1-x) - \beta_x x \qquad \text{where } x \text{ is } m, n \text{ or } h \\
\alpha_n(V) &= 0.01(V+55)/\left[1-\exp(-(V+55)/10)\right] \\
\beta_n(V) &= 0.125\exp(-(V+65)/80) \\
\alpha_m(V) &= 0.1(V+40)/\left[1-\exp(-(V+40)/10)\right] \\
\beta_m(V) &= 4\exp(-(V+65)/18) \\
\alpha_h(V) &= 0.07\exp(-(V+65)/20) \\
\beta_h(V) &= 1/\left[\exp(-(V+35)/10)+1\right]
\end{aligned}
$$

Let $C = 10\,\mathrm{nF/mm^2}, \overline{g}_L = .003\,\mathrm{mS/mm^2}, \overline{g}_K = 0.36\,\mathrm{mS/mm^2}, \overline{g}_{Na} = 1.2\,\mathrm{mS/mm^2}, E_K = -77\,\mathrm{mV}, E_L = -54.387$ mV, and $E_{Na} = 50$ mV. Use an integration time step of 0.1 ms.

Remember to keep your units consistent. F/S = Farad/Siemens = 1 second.

(a) Run the simulations with $I_{stim} = 200$ nA/mm^2. Plot the membrane potential (V) and gating variables (m, h, and n) versus time.

(b) Write down expressions for the equilibrium values of the gating variables (m_∞, h_∞, and n_∞), and plot them versus voltage.

(c) Plot the firing rate versus I_{stim}, up to a firing rate of 50 Hz. The firing rate should jump suddenly from zero to a non-zero value. This is called a type II behavior. Type I behavior is when the firing rate begins at zero and increases continuously without any jumps.

(d) What happens to the plot of firing rate versus I_{stim} as you decrease $\overline{g}_K$?

(e) Spikes are initiated at the axon hillock, where the axon meets the soma. This is because $\overline{g}_{Na}$ is very high there. What happens to the plot of firing rate versus I_{stim} as you increase $\overline{g}_{Na}$?

3. **The linear integrate and fire neuron**

An approximate treatment of spiking neurons is to think of them as passively integrating input and, when the voltage crosses threshold, emitting a spike. This leads to the linear integrate and fire neuron (sometimes called the leaky integrate and fire neuron, and often abbreviated LIF), which obeys the equation

$$C\frac{dV}{dt} = -g_L(V-\mathcal{E}_L) + I_0\,.$$

This is just the "linear integrate" part. To incorporate spikes, when the voltage gets to threshold (V_t), the neuron emits a spike and the voltage is reset to rest (V_r).

(a) Compute the firing rate of the neuron as a function of I_0. This firing rate will be parameterized by three numbers: $\mathcal{E}_L$, V_t, and V_r.
Hint #1: The firing rate is the inverse of the time it takes to go from V_r to V_t.
Hint # 2: Changing variables, and defining new quantities, almost always makes life easier. For example, you might let $v = V - \mathcal{E}_L$ and define $V_0 \equiv I_0/g_L$ and $\tau \equiv C/g_L$.

(b) Let $I(t) = g_L V_0 \sin(\omega t)$, $V_r = \mathcal{E}_L$, $V_t = \mathcal{E}_L + \Delta V$, and define $C/g_L \equiv \tau$. Start with $V_0 = 0$ and integrate for a long enough time that the neuron equilibrates. Then increase V_0 *very* slowly compared to the time constant, τ. Show that the neuron will start spiking repetitively when $V_0 > (1 + \tau^2\omega^2)^{1/2}\Delta V$.

4. **Warmup nullclines.** Consider a model that is bound to come up again, in one form or another,

$$\tau_x \frac{dx}{dt} = -x + \tanh\big(\beta(x-y)\big)$$
$$\tau_y \frac{dy}{dt} = -y + \alpha x.$$

For all questions, assume $\alpha > 0$ and $\beta > 1$.

(a) Draw the nullclines for an α and β of your choice.

(b) What are the conditions on α and β for there to be three fixed points?

(c) Assume α and β are such that there are three fixed points. Determine the stability of each of them. Draw trajectories starting near $x = y = 0$.

(d) Assume α and β are such that there is one fixed point. Determine its stability. Draw trajectories starting near $x = y = 0$.

5. **And more nullclines.** Assume that the x and y nullclines are given by

$$y = a_x x \quad x\text{-nullcline} \tag{7a}$$
$$y = a_y x \quad y\text{-nullcline}\,. \tag{7b}$$

The nullclines cross at $x = y = 0$, so that's a fixed point (the only one). Its stability depends on the dynamics. Define

$$s_x \equiv \left.\frac{dx}{dt}\right|_{x>0} \tag{8a}$$
$$s_y \equiv \left.\frac{dy}{dt}\right|_{y>0}\,. \tag{8b}$$

There are four main possibilities:

$$(s_x, s_y) = (\text{positive, positive}), (\text{positive, negative}), (\text{negative, positive}), (\text{negative, negative}). \tag{9}$$

For each of these, determine, if possible, the sign of the trace and determinant of the linear dynamics, and thus the number of positive and negative eigenvalues, for:

$$1.\ \ a_x > 0 \ \text{ and } \ a_y < 0 \tag{10a}$$
$$2.\ \ a_x < a_y < 0 \tag{10b}$$
$$3.\ \ a_y < a_x < 0\,. \tag{10c}$$

Note the "if possible" part – that's because in some cases the trace and/or determinant can have either sign.

There are 12 possible cases, which seems like a lot, but you'll quickly see patterns.

6. **Hodgkin-Huxley nullclines.** Consider a simplified Hodgkin-Huxley type model,

$$
\begin{aligned}
\tau \frac{dV}{dt} &= -(V - \mathcal{E}_L) - h m(V) V \\
\tau_h \frac{dh}{dt} &= h_\infty(V) - h \\
m(V) &= \frac{1}{1 + \exp(-(V - V_t)/\epsilon_m)} \\
h_\infty(V) &= \frac{1}{1 + \exp(+(V - V_h)/\epsilon_h)}
\end{aligned}
$$

with parameters

$$
\begin{aligned}
\mathcal{E}_L &= -65 \text{ mV} \\
V_t &= -50 \text{ mV} \\
\epsilon_h &= 10 \text{ mV} \\
\epsilon_m &\ll 1 \text{ mV}\,.
\end{aligned}
$$

The remaining parameter, V_h, will be specified as needed (it will take on a range of values).

(a) Sketch the nullclines in V-h space for $V_h = -60, -50$ and -40 mV. Put voltage on the x-axis and h on the y-axis. For each equilibrium, tell us whether it is stable or unstable, or hard to tell without a detailed stability analysis.

(b) Find the condition on V_h that guarantees more than one equilibrium.

(c) For a value of V_h (which you choose) such that there is more than one equilibrium, sketch the trajectories starting at V slightly greater than V_t and $h = 1$.

7. **Green functions**

Consider the equation

$$\tau \frac{\partial G(x,t)}{\partial t} = \lambda^2 \frac{\partial^2 G(x,t)}{\partial x^2} - G(x,t) + \delta(x)\delta(t)\,.$$

Assume $G(x,t)$ satisfies this equation. Now consider a second equation,

$$\tau \frac{\partial U(x,t)}{\partial t} = \lambda^2 \frac{\partial^2 U(x,t)}{\partial x^2} - U(x,t) + i_e(x,t) r_m\,.$$

Show that

$$U(x,t) = \int dx' dt' \, G(x - x', t - t') i_e(x', t') r_m\,.$$

$G(x,t)$ is known as the Green function, and it's occasionally very useful. As in the next problem.

8. **Dendrites.**

As you'll recall from lecture notes (see also http://www.gatsby.ucl.ac.uk/ pel/tn/notes/biocables.pdf), the passive cable equation is

$$\tau \frac{\partial u(x,t)}{\partial t} = \lambda^2 \frac{\partial^2 u(x,t)}{\partial x^2} - u(x,t) + i_e(x,t) r_m$$

where $u(x,t)$ is the membrane potential relative to rest, $i_e(x,t)$ is the injected current density, and r_m is the specific membrane resistance (it's proportional to actual resistance times area).

Let's assume that $i_e(x,t)$ is produced by a fast synapse – like AMPA. Because of the "fast" part, we'll approximate the current density by

$$i_e(x,t) = \alpha e^{-x^2/2d^2} \delta(t)$$

where $\delta(t)$ is the Dirac delta function. Your job is to estimate α. Assume that the amplitude of the PSP (post-synaptic potential) in the dendrite – at the site of injection – is V_{psp}. You can get the Green function from the biocables writeup.