Exercise in FYS4715: A simple model of neuronal calcium dynamics - November 19, 2019

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In the experiments you did with Kristian Lensjø, you probably saw images of neurons flashing (in green) when responding to certain visual stimuli. The interpretation of these experiments is that: (1) a flash indicated elevations in the intracellular Ca^{2+} concentration ($[Ca^{2+}]$) , (2) the $[Ca^{2+}]$ elevation indicated that the neuron fired an action potential, and (3) the action potential indicated that the neuron received a sufficiently strong external input to drive it above firing its threshold. In this exercise, we will make a simple model that captures the relationship between the input, the action potential and the $[Ca^{2+}]$ dynamics in a neuron. We will use the good old Hodgkin-Huxley (HH) model for action potential generation as a starting point, and you have been an implementation of this in the python file 'Exercise.py'. Your task is to expand this model to also include a Ca^{2+} channel and intracellular $[Ca^{2+}]$ dynamics.

The standard Hodgkin-Huxley model:

The standard HH-model is defined by the following set of differential equations:

$$C\frac{dV}{dt} = I - \bar{g}_K n^4 (V - E_{K^+}) - \bar{g}_{Na} m^3 h (V - E_{Na^+}) - g_L (V - E_L) \quad (1)$$

$$\frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)} \quad (2)$$

$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)} \quad (3)$$

$$\frac{dh}{dt} = \frac{h_\infty(V) - h}{\tau_h(V)} \quad (4)$$

It is convenient to rewrite the last three equations in the form:

$$\frac{dx}{dt} = \alpha_x(V)(1 - x) - \beta_x(V)x \qquad \text{where } x \in \{n, m, h\}. \quad (5)$$

The coefficients $\alpha_x(V)$ and $\beta_x(V)$ represent the (voltage-dependent) activation and inactivation rates, respectively, for the gate x. With these coefficients, the steady-state activation variables $x_\infty(V)$ and the time constants $\tau_x(V)$ in the Hodgkin-Huxley equations are given by

$$x_\infty(V) = \frac{\alpha_x(V)}{\alpha_x(V)+\beta_x(V)} \qquad \text{and} \qquad \tau_x(V) = \frac{1}{\alpha_x(V)+\beta_x(V)}. \tag{6}$$

The code below uses a simple forward Euler method to run the Hodgkin-Huxley model (Eqns. 1-4) when responding to a rectangular input-current pulse:

$$I(t) = \begin{cases} I_{\text{max}} & t_{\text{stim,on}} \le t \le t_{\text{stim,off}} \\ 0 & \text{else} \end{cases} \tag{7}$$

and with the initial conditions:

$$\begin{aligned} V(0) &= V_{\text{rest}} && (8)\\ n(0) &= n_\infty(V_{\text{rest}}) && (9)\\ m(0) &= m_\infty(V_{\text{rest}}) && (10)\\ h(0) &= h_\infty(V_{\text{rest}})\ . && (11) \end{aligned}$$

Here, V_{rest} denotes the resting potential of the neuron, i.e. the stationary membrane potential in the absence of any input I. The default parameters are given in Table 1. Note that these parameters are already implemented in the function 'set_parameters()'. You may run the code to check that it works as it should plot the input current $I(t)$ and the resulting membrane potential $V(t)$, and produce a response with two action potentials.

Problem 1: Speed up the Hodgkin-Huxley model

Problem 1i: The HH-model was based on recordings from a squid giant axon in cold temperature. The activation/inactivation rates (α_x and β_x) under those circumstanses were quite slow compared to what they are in neurons that live inside a nice and warm brain. The first task is therefore to make the HH-model more *in-vivo* brain-like by speeding up all rates by a factor 2. That is, multiply all reaction rates by 2 and run a new simulation. Compare the response to that in the original HH-model.

Problem 1ii: Just to get some insight in what the HH-model does, adjust the stimulus (strength and duration) to find the $f-I$ curve (firing rate as function of input current) of the modified HH-neuron. Note that for some 'subthreshold' currents, the HH-model responds

by firing spikes for a while before becoming silent. Let this "unsustained" firing correspond to a zero firing rate. What is the threshold current for sustained firing for the speeded-up version of the HH-model?

P.s. Don't spend too much time on this. You could write an algoritm for counting spikes here, but it is sufficient to instead just run a short series of manual trials, count spikes, and plot a few data points to get the essential picture.

Problem 2: Add a Ca^{2+} channel to the (speeded-up) model:

The HH-model has only two active ion channels, i.e., the Na^+ and K^+ channels responsible for generating action potentials. Most neurons have several additional ion channels. For example, many neurons have so called high-voltage-activated Ca^{2+} channels. As their name indicate, these open at high voltages, such as during an action potential, and and while they are open, Ca^{2+} rushes into the cell. It is the resulting increase in $[Ca^{2+}]$ that is recorded in Ca^{2+} imaging experiments.

Problem 2i: Expand the (speeded-up) HH-model to include a simple model of a high-voltage-activated calcium channel with two activation gates (s). We will deal with the calcium dynamics later, but may here start by only modelling the current with the same kind of formalism that was used for the original two HH-channels (and follwing the same logic in the code):

$$I_{Ca} = \bar{g}_{Ca^{2+}} s^2 (V - E_{Ca^{2+}}). \tag{12}$$

Suitable functions for the activation/deactivation rates are:

$$\alpha_s = \frac{1.6}{1 + \exp[-0.072 \cdot (V_m + 8)]} \beta_s = \frac{0.02 \cdot (V_m - 8.3)}{\exp[(V_m - 8.3)/5.6] - 1} \tag{13}$$

For the Ca^{2+} reversal potential you may use $E_{Ca^{2+}} = 120$ mV. For the conductance ($\bar{g}_{Ca^{2+}}$), see point (2ii) below.

Problem 2ii: The high-voltage-activated Ca^{2+} current is typically smaller than the Na^+ and K^+ currents, but it is sometimes big enough to affect the shape of the action potential, normally by prolonging its duration slightly. Try out some different values for the conductance $\bar{g}_{Ca^{2+}}$, and find a value that makes I_{Ca} have a minor but visible (e.g., changes it duration by a few percent) impact on the action potential shape.

Problem 3: Add calcium dynamics to the model:

Problem 3i: Expand the model by adding Ca^{2+} dynamics modelled on the simple form:

$$\frac{d[Ca^{2+}]}{dt} = -k_{Ca} \cdot I_{Ca} + ([Ca^{2+}]_0 - [Ca^{2+}])/\tau_{Ca}. \tag{14}$$

Here, the first term represents Ca^{2+} entering through the Ca^{2+}-channel, and the second term is a simple exponential decay term that represents various processes that work to bring $[Ca^{2+}]$ back to the resting concentration. For the resting (and initial) concentration, you may use $[Ca^{2+}]_0 = 50$ nM $= 5e-5$ mM. For the decay time constant, you may use $\tau_{Ca} =$ 50 ms. Finally, for the constant k_{Ca}, you may use $k_{Ca} = 1e-8$ cm^{2}mM/μA (units matched to give calcium change in mM/ms).

P.s. k_{Ca} converts a transmembrane current density to a concentration change in the intracellular volume, and thus depends on the volume/surface ratio of the cell. However, the majority of the Ca^{2+} ions that cross the membrane are almost instantaneously buffered away by several biochemical reactions, and thus do not "show up" as free intracellular calcium. As k_{Ca} summarizes several processes for which there often is little quantitative data, it is in models normally considered a "free parameter", and is tuned to a value that gives rise to realistic calcium fluctuations. The value suggested above works fine for the current model setup.

Problem 3ii: Give the neuron a brief input pulse that makes it fire a single action potential. Plot the voltage and calcium response, and discuss it in the context of Kristian's Ca^{2+} imaging experiments.

Problem 3iii: (If time) Depending on your choice of g_{Ca}, the calcium elevation during an action potential should be on the order of some tens to some hundreds of nM. If Kristian gave you any quantitative data on the actual calcium signal and magnitude, you may try to tune k_{Ca}, τ_{Ca} and g_{Ca} to reproduce it.

Problem 3iv: (If time) Some neurons have very slow τ_{Ca} and can then use the intracellular $[Ca^{2+}]$-level as an "indicator" of their average firing rate. Explain how this can be possible, and illustrate it with simulations on the model.

Δt	=	0.025 ms
T	=	50 ms
$\alpha_n(V)$	=	$\frac{0.01\ \mathrm{ms^{-1}}(V+55\ \mathrm{mV})}{1-\exp(-[V+55\ \mathrm{mV}]/10\ \mathrm{mV})}$
$\beta_n(V)$	=	$0.125\ \mathrm{ms^{-1}} \exp(-[V+65\mathrm{mV}]/80\mathrm{mV})$
$\alpha_m(V)$	=	$\frac{0.1\ \mathrm{ms^{-1}}(V+40\ \mathrm{mV})}{1-\exp(-[V+40\ \mathrm{mV}]/10\ \mathrm{mV})}$
$\beta_m(V)$	=	$4\ \mathrm{ms^{-1}} \exp(-[V+65\ \mathrm{mV}]/18\ \mathrm{mV})$
$\alpha_h(V)$	=	$0.07\ \mathrm{ms^{-1}} \exp(-[V+65\ \mathrm{mV}]/20\ \mathrm{mV})$
$\beta_h(V)$	=	$\frac{1\ \mathrm{ms^{-1}}}{1+\exp(-[V+35\ \mathrm{mV}]/10\ \mathrm{mV})}$
V_{rest}	=	-65 mV
C	=	1 μF/cm^2
E_{Na^+}	=	50 mV
E_{K^+}	=	-77 mV
E_{L}	=	-54.387 mV
$\bar{g}_{\mathrm{Na}^+}$	=	120 mS/cm^2
$\bar{g}_{\mathrm{K}^+}$	=	36 mS/cm^2
$\bar{g}_{\mathrm{L}}$	=	0.3 mS/cm^2
I_{max}	=	10 μA/cm^2
$t_{\mathrm{stim,on}}$	=	5 ms
$t_{\mathrm{stim,off}}$	=	30 ms

Table 1: Default parameter values and parameter functions.

Figure 1: **Table 1: Parameters**