HAND IN (2): THE BACKBONE OF THE BACKBONE OF YOURSELF

DUE: May 29th 2018 in groups of four people

The main idea of this hand-in is to read a little bit about the properties of ion channels and produce a small computational model. More specifically, we want you to understand neurons a little better. As you know from Biophysics I (and the last topics of Biophysics II), the backbone of neuron behavior is the membrane potential (and the related action potentials). The hand-in consists on reading about ion channels and to implement a set of equations (the Hodgkin-Huxley model) in matlab to mimic the behavior of the action potential. The details about the delivery and the content of the hand-in are at the end of this file .

Preliminary reading

R1) The most important ion channels (proteins that control ions going through the membrane) are the sodium, potassium and calcium channels. There are many different proteins with slightly different names that act as ion channels. They also have different structures. But the most common potassium (and sodium) ion channel has a well known set of subunits. Please, make a search of the different potassium (and sodium) channels that exists in neurons. Do also a search checking if calcium channels are more important in neurons or in cardiomyocytes.

R2) Read now the notes for hand-in 2 in TOPIC 7. Consider a collectivity of sodium channels, each composed by two subunits of type m and one subunit of type h. The possible states of each channel and the transition probabilities can be obtained from the state of the i subunits of type m and j of type h. You can call m and h the probabilities that the subunits of the type m and h are open and relate it with the model that you must code below.

R3) Read now a little bit about long-term potentiation in synapses and how they can be related with your memories

The Hodgkin-Huxley model

The main equation to code (do not use RK4, Euler is easier and faster,or ode matlab functions) is the evolution of the membrane potential according to a simple HH model that incorporates sodium and potassium channels plus a third current which encompasses "all the rest". The model reads:

$$\frac{dV}{dt} = I(t) - g_1 m^3 h(V - V_1) - g_2 n^4 (V - V_2) - g_3(V - V_3) \tag{1}$$

where V is voltage expressed in millivolts and time t is in ms, while g_1, g_2, g_3 and V_1, V_2, V_3 are constants. $I(t)$ is a function you set at zero first, while n, m and h are dynamic variables obeying

$$\frac{dn}{dt} = \alpha_n(u)(1 - n) - \beta_n(u)n \tag{2}$$

$$\frac{dm}{dt} = \alpha_m(u)(1 - m) - \beta_m(u)m \tag{3}$$

$$\frac{dh}{dt} = \alpha_h(u)(1 - h) - \beta_h(u)h \tag{4}$$

where $u = V + 65$ and

$$\alpha_n(u) = \frac{0.01(10 - u)}{e^{1-0.1u} - 1} \tag{5}$$

$$\beta_n(u) = 0.125e^{-u/80} \tag{6}$$

$$\alpha_m(u) = \frac{0.1(24 - u)}{e^{2.4-0.1u} - 1} \tag{7}$$

$$\beta_m(u) = 4e^{-u/17} \tag{8}$$

$$\alpha_h(u) = 0.07e^{-u/20} \tag{9}$$

$$\beta_h(u) = \frac{1}{1 + e^{3-0.1u}} \tag{10}$$

Use the following parameters to test your code: $g_1 = 120, g_2 = 34, g_3 = 0.33$ ms^{-1} ,$V_1 = 51, V_2 = -75, V_3 = -55$ mV

Work with the model

a) Check that, after a transient, the system reaches a fixed point: a state of the system where ($V = V_f, m = m_f, n = n_f, h = h_f$) and none of them change with time.

b) Get in a single graph the evolution of voltage and, in other colors, the dynamics for the different gates (n, h and m). Multiply the value of the gates by a factor in the graph, if needed, for clarity.

c) Using the fixed point as the initial conditions, consider now $I(t)$ to be a constant external current $I = I_o$ different than zero. If the current I_o is very small nothing remarkable happens. The fixed point just moves a bit. But if you increase I_o there is a moment where V does not reach a fixed point (in mathematical terms it is called a bifurcation in the dynamical system). Find this threshold current I_t (with two or three significant digits) where you see $V(t)$ transform into a periodic function where V generates spikes periodically. Do not confuse this value with the excitatory limit where the neuron is excitable and might generate a short transient (a spike) but still comes back to the same fixed point.

d) A real neuron does not receive a constant current from the neighboring neurons. The pre-synaptic neurons (those neurons whose synapses are connected to the one we are dealing) discharge currents thanks to the neurotransmitters in the form of short pulses. Whenever a pre-synaptic neuron fires at time t_a it sends a current to the neuron i which is connected to. This current can be approximated by $I_s(t) = I_c \exp(-(t - t_a)/10)$ where time is in ms and I_c is the characteristic strength of the synapse. Given that a neuron has a lot of pre-synaptic neurons, it receives a barrage of currents starting at different times $t_a = t_1, t_2, t_3, ..., t_n$ being the input current $I(t) = \sum_{j=1}^{n} I_c \exp(-(t - t_j)/10)$. If the number of pulses (firings) that the neuron receives per unit time is large enough, our neuron would generate spikes. If the number of pulses received per unit time is not large enough our neuron will rarely generate a spike. So write a second code where you force the neuron with a series of j pulses with the form $I_s = 0.5 \exp(-(t - t_j)/10)$ reaching the neuron at a series of random times t_j. In order to fix how many pulses the neuron receives you must use your identity card number. For example, if your DNI is 43784258, run the simulation first with 4 pulses in one second (first number of the DNI) and record if at any time the neuron fired during this second, then do the same for 43 pulses in one second (two first numbers), then 437 pulses in a second, and finally 4378. All in all four runs.

e) Now, using the two first numbers of your DNI (43 pulses per second), repeat the previous analysis for different values of the strength of the pulse I_c. This is, instead of using $I = 0.5 \exp -(t - t_a)/10$, use $I = I_c \exp(-(t - t_a)/10)$ for different values of I_c going from 0.1 V/s up to whatever value you need to observe more than 40 spikes responses per second of your neuron. Run the simulation 100 times (or run the simulation for 100 seconds) for each I_c changing randomly the position of the inputs.

DELIVERY

The delivery consists of three matlab files, and one text (or pdf) file.

The pdf file must contain the following:

- A description of around 250-500 words of what an alpha subunit is and how is it related with a sodium channel and its basic structure. Define briefly the different subunit structures present in the channels of neurons. Also dicuss where calcium channels are more relevant. (1p)

- An explanation of around 250-500 words of what a gated variable is. Among other things, comment how they are used to model currents across the membrane and how they are related with the alpha and beta subunits. (1p)

-Give the fixed points of the HH system (solution of question a), the graph requested in section b) above and the current threshold I_t which leads to periodic pulses (solution of question c)(4p-including codes)

- A graph showing the input current constructed in section d) for the four cases identified with your DNI. Also a graph with the resulting response of the neurons indicating the times where the neuron fired in the different runs (2p)

-A graph indicating the average of the number of spikes per second of your neuron as a function of I_c and its error bar as a solution of section e. (1.5p)

- Finally around 100-200 words about how the previous model can be used to code the two first number of your identity card number (or at least the first one) relating this with what you have read about long term potentiation. (0.5p)

The three matlab codes must contain the following:

The first code must give the solution to questions a,b and c. The second code must lead to the answer of section d. The third one must give the solution of section e.

Upon running the first matlab code, the graph requested in questions b must be directly obtained.

Upon running the second code the four different graphs of input and the four responses must be obtained

Finally, the third code does not have to produce any direct graph, it just must be the one used to solve the last section.

The two first matlab codes must be shortly commented with a brief description at the beginning of the code with the authors name and the general structure of the code. Furthermore, along the code, brief comments must be introduced. The idea is to provide short and clear phrases at key points of the code. Do not produce a full commented code but make it useful to read. Third code does not need to be commented.