Neuroprothetics Exercise 4

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1 Hodgkin & Huxley Neuron Model

The Hodgkin & Huxley Model is a mathematical model, developed by Alan Hodgkin and Andrew Huxley in 1952, which describes how action potentials (APs) in neurons are initiated and propagated after receiving electrical stimulation. The sodium and potassium channels are the most important ion channels for AP generation, which are opened and closed by gating variables. The gating variables of sodium ion channels consist of three subunits labeled $'m'$ and an inactivation subunit labeled $'h'$, while the gating variables of potassium ion channels consist of four subunits labeled $'n'$. Each of these subunits is voltage-dependent and has individual time constants and steady-state values.
There are two important concepts that need to be distinguished: The gating variables m, n, and h describe the opening probability of sodium (Na^+) and potassium (K^+) ion channels, with values ranging from 0 (closed) to 1 (fully open). Whereas $\alpha_m, \alpha_n, \alpha_h$ represent the rate at which the gating variables transition from a closed to an open state, $\beta_m, \beta_n, \beta_h$ represent the rate at which the gating variables transition from an open to a closed state.

1.1 Ion channels

The proportion of open channels ($x \in m, n, handx \in [0, 1]$) can be given by the following differential equation 1. This equation describes how the gating variable x changes over time. The change in x is due to two processes: the opening of closed channels (increased by $\alpha(1 - x)$ and the closing of open channels (decreased by $\beta(x)$.

$$\frac{dx}{dt} = \alpha_x(1 - x) - \beta_x x \tag{1}$$

x_∞ is the steady state value of the gating variable when the membrane potential is held constant. It can be found by setting $\frac{dx}{dt}$ to zero, leading to

$$x_\infty = \frac{\alpha_x}{\alpha_x + \beta_x} \tag{2}$$

τ_x is the time constant for the variable to reach that steady state and it is the inverse of the sum of the rates, so

$$\tau_x = \frac{1}{\alpha_x + \beta_x} \tag{3}$$

So equation 1 can be further simplified to a first-order linear differential equation showing the movement towards the equilibrium proportion of open channels x_∞ with a time constant τ_x:

$$\frac{dx}{dt} = \alpha(1-x) - \beta x = (\alpha+\beta)(\frac{\alpha}{\alpha+\beta} - x) = \frac{1}{\tau_x}(x_\infty - x) \tag{4}$$

The rate equations for the gating variables are defined as follows:

$$\alpha_m = \frac{2.5 - 0.1V}{e^{(2.5-0.1V)} - 1} \tag{5}$$

$$\alpha_n = \frac{0.1 - 0.01V}{e^{(1-0.1V)} - 1} \tag{6}$$

$$\alpha_h = 0.07e^{-\frac{V}{20}} \tag{7}$$

$$\beta_m = 4e^{-\frac{V}{18}} \tag{8}$$

$$\beta_n = 0.125e^{-\frac{V}{80}} \tag{9}$$

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

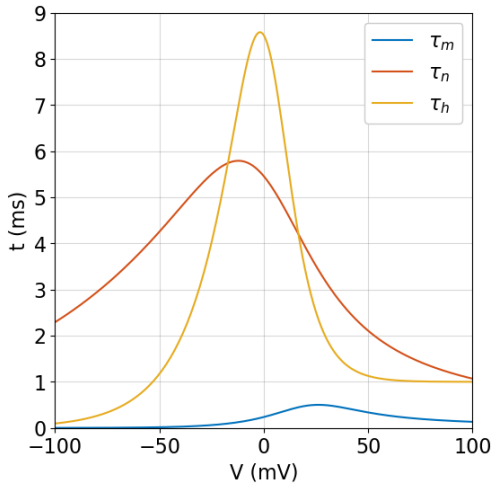
Equation 11 delineates the temperature correction factor k in the Hodgkin-Huxley model. This factor modifies the rate constants of the gating variables in accordance with changes in temperature. Utilizing this factor enables precise modeling of ion channel dynamics under temperature conditions that vary from those of the original experiments.

$$k = 3^{0.1(T-6.3)} \tag{11}$$

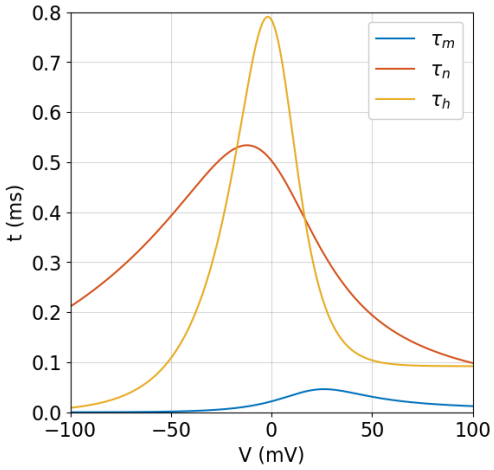
According to the above equations can get Figure 1, which depicted τ_x and x_∞ against the voltage $V \in [-100\,\text{mV}, 100\,\text{mV}]$ at $6.3°C$ and $28°C$. It can be observed from Figure 1, that

(1) As the temperature increases, τ_x decreases, which means the ion channel responds faster to changes in membrane potential.

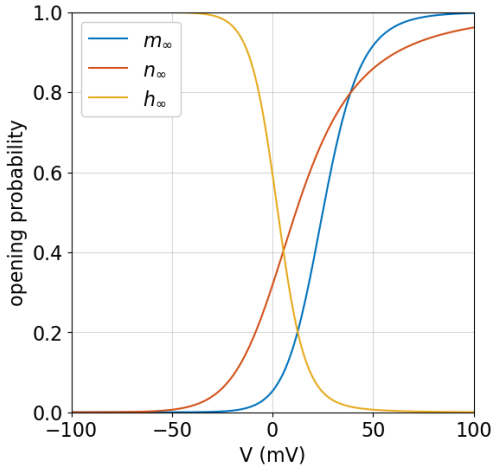
(2) When the membrane potential rises and exceeds the threshold voltage, the values of m and n increase, while the value of h decreases. Specifically, the value of m increases sharply, indicating that sodium ion channels are more likely to enter the activation state, allowing more sodium ions to rapidly enter the cell. The value of n also increases, but the rate of increase is relatively slower. This indicates that potassium ion channels gradually open, allowing potassium ions to flow out of the cell at a relatively slower rate. Simultaneously, the value of h decreases, inhibiting the sustained opening of sodium ion channels, thereby limiting the influx of sodium ions.



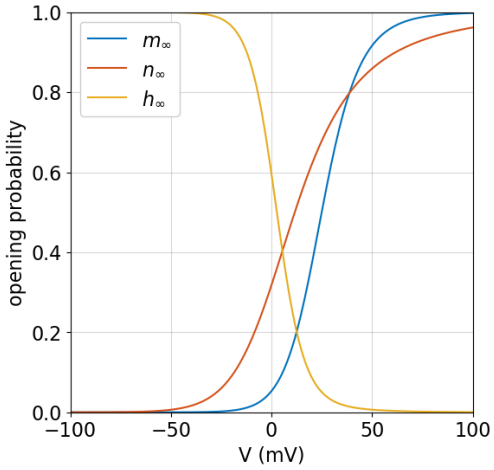
(a) τ_x for 6.3°C



(b) τ_x for 28°C



(c) x_∞ for 6.3°C



(d) x_∞ for 28°C

Figure 1: Parameters τ and x_∞ for the gating variables m, n and h for 6.3°C and 28°C

1.2 Implementation

The Hodgkin & Huxley Neuron Model (*HH_NeuronModel_Run*) can be implemented through the decomposition into three functions:
(1) *hh_gating*: This function utilizes the values of gating variables (m_n, n_n, h_n) and the membrane potential (V_n) at the current timestep (t_n) to calculate the values of the gating variables $(m_{n+1}, n_{n+1}, h_{n+1})$ for a single future timestep (t_{n+1}).
Note that in this exercise, we set the initial value for the potential V0 to be equal to V_{rest}, and the initial value for the gating variables $m[0]$, $n[0]$, and $h[0]$ to be equal to their steady state values at the resting potential, denoted as m_∞, n_∞, and h_∞.

$$\frac{dm}{dt} = [\alpha_m(1-m) - \beta_m m]k \tag{12}$$

$$\frac{dn}{dt} = [\alpha_n(1-n) - \beta_n n]k \tag{13}$$

$$\frac{dh}{dt} = [\alpha_h(1-h) - \beta_h h]k \tag{14}$$

(2) *hh_model*: then we can use the values of m,n,h from function(1) to calculate the ionic currents (INa, n, IK, n) for a current timestep (tn). Hier $\overline{g}_{Na} = 120mS$, $\overline{g}_K = 36mS$, $\overline{g}_L = 0.3mS$, $V_{Na} = 115mV$, V_K = -12mV, $V_L = 10.6mV$.

$$I_{Na} = \overline{g}_{\mathrm{Na}} m^3 h(V - V_{Na}) \tag{15}$$

$$I_K = \overline{g}_K n^4 (V - V_K) \tag{16}$$

$$I_L = \overline{g}_L (V - V_L) \tag{17}$$

(3) *hh_potential*: then we can use the values of I_{Na}, I_K, I_L from function(1) to calculate membrane potential $(Vn+1)$ for a future timestep $(tn+1)$ and then iterate over all future timesteps correspondingly. The general equations of HH model are as follows:

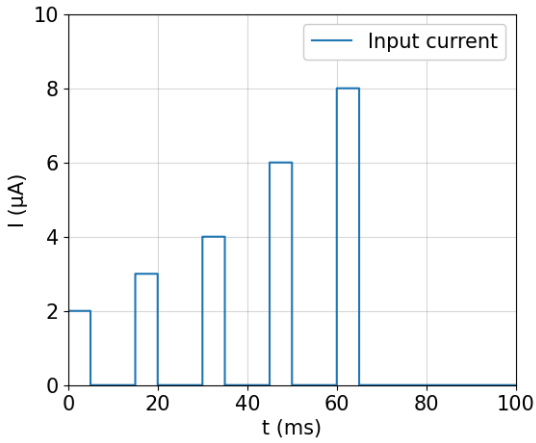
$$\frac{dV}{dt} = \frac{1}{C_m}(-I_{ion} + I_{\mathrm{stimulus}}) \tag{18}$$

$$I_{\mathrm{ion}} = I_{\mathrm{Na}} + I_K + I_L \tag{19}$$

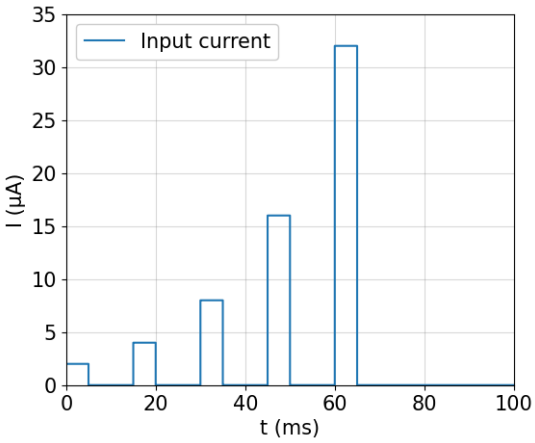
1.3 Experiments

Run the model (*HH_NeuronModel_Run*) for 100 ms ($\Delta t = 0.01ms$), with the following settings:
(1) At 6.3°C induce a stair of five 5 ms long rectangular current pulses with a gap of 10 ms and the amplitudes 2 μA, 3 μA, 4 μA, 6 μA, 8 μA
(2) At 28°C induce a stair of five 5 ms long rectangular current pulses with a gap of 10 ms and the amplitudes 2 μA, 4 μA, 8 μA, 16 μA, 32 μA

Figure 2 displays the input currents in these above two different temperatures.
Figures 3, 4 and 5 are obtained from the functions in 1.2, which respectively represent the membrane potential over time, the gating variables(m, n, h) over time and the ionic currents(I_{Na}, I_K) over time.

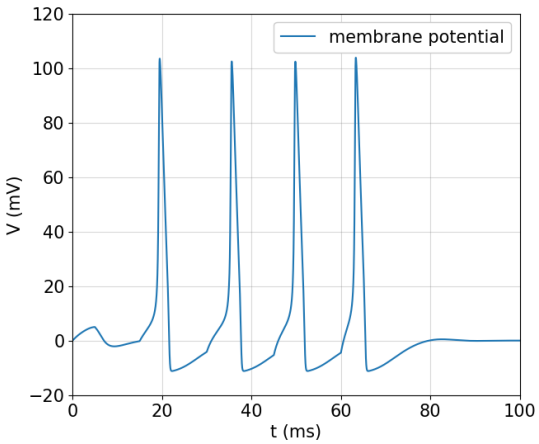


(a) Input currents for the simulation at 6.3°C

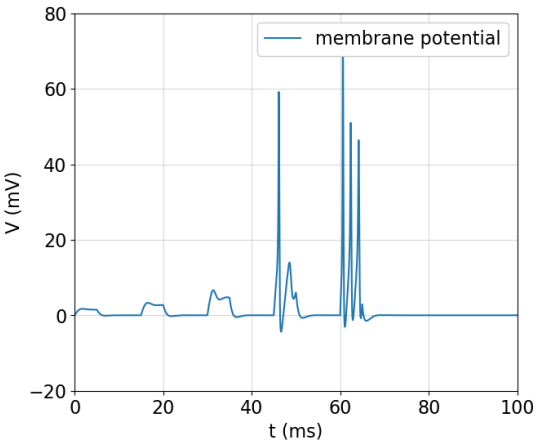


(b) Input currents for the simulation at 28°C

Figure 2: Input currents for different temperatures

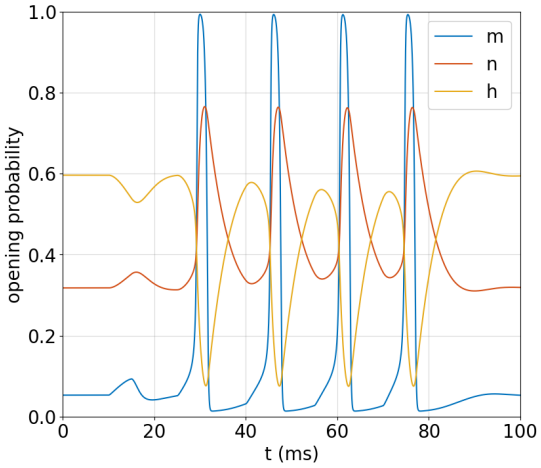


(a) Membrane potential for 6.3°C and the input visible in figure 2a

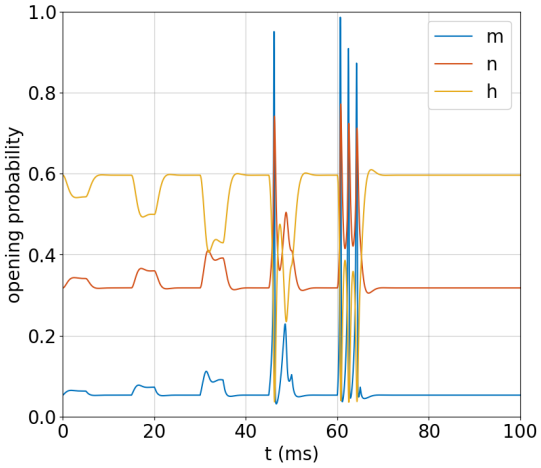


(b) Membrane potential for 28°C and the input visible in figure 2b

Figure 3: Membrane potential for the different cases

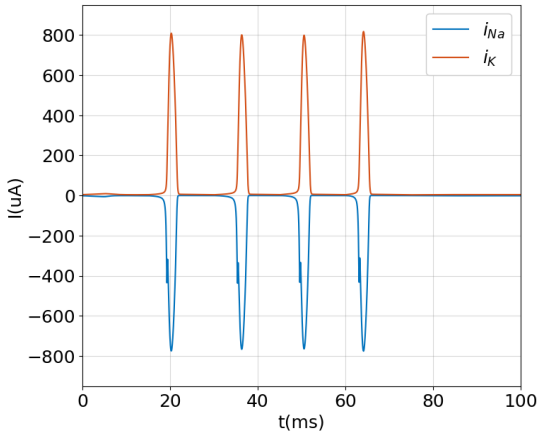


(a) Gating Variables m, n, h at 6.3°C and the input visible in figure 2a

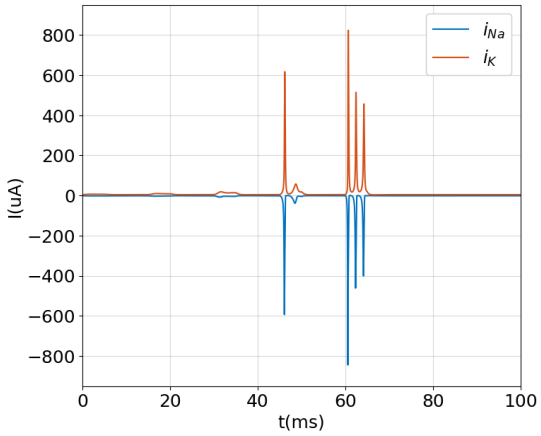


(b) Gating Variables m, n, h at 28°C and the input visible in figure 2b

Figure 4: Gating Variables m, n, h for the different cases



(a) Currents i_{Na} and i_K for 6.3°C and the input visible in figure 2a



(b) Currents i_{Na} and i_K for 28°C and the input visible in figure 2b

Figure 5: Currents i_{Na} and i_K for the different cases

1.4 Analysis of the Results

(1) For the membrane potential, the differences between the results at 6.3°C and 28°C based on the Fig.3 can be explained in terms of the following aspects:

- frequency of APs: At the higher temperature (28°C), the neuron fires action potentials more frequently in response to the input current. This is evident from the increased number of spikes within the same time frame as compared to the plot at 6.3°C.

- response time to stimulus: at 28°C, the neuron's response time to the stimulus is quicker, resulting in action potentials that rise more steeply and reach their peak faster than at 6.3°C.

- amplitude of APs: The amplitude of action potentials at 28°C appears to decrease with consecutive stimulations, which is not observed at 6.3°C.

(2) When an action potential occurs, the role of the different gating variables m, n and h in the ionic currents and therefore in the membrane potential change:

- m: Depolarization is initialed by a stimulus, which makes the menbrane potential more positive, causing the voltage-gated sodium ion channels to start to open. As threshold is reached, many sodium channels open, sodium ions diffuse across the membrane causing depolarization. At the same time voltaged-gated potassium ion channels also also begin to open but more slowly. Therefore depolarization occurs, because more sodium ions diffuse into the cell than potassium ions diffuse out of it, which increase the membrane potential.

- h: It represents the inactivation of sodium channels. After the initial opening, the h variable decreases, which starts to limit the influx of Na+ ions, contributing to the peak and subsequent falling phase of the action potential.

- n: As the membrane potential approaches maximum depolarization, the inactivation gates of the voltage-gated sodium ion channels begin to close and the diffusion of sodium ions decreases. But the potassium ion channels remain open, allowing potassium ions to continue diffusing out of the cell. This heightened permeability to potassium slightly outlasts the duration needed to return the membrane potential to its resting state. Consequently, an increased outflow of potassium ions hyperpolarizes the membrane, making the interior more negative than the resting potential. Once the voltage-gated potassium ion channels close, the sodium-potassium pump actively restores the resting membrane potential.

(3) Figure 6 illustrates that at 28°C, consecutive action potentials have a reduced amplitude.

- The reason behind this is the quicker kinetics of ion channels at higher temperatures, leading to more rapid opening and closing of these channels. In such a scenario, there is inadequate time for ion concentrations to reset between action potentials. Specifically, the gating variable h, which inactivates sodium channels, fails to revert to its resting state before the onset of the next action potential. This limits the availability of sodium channels for subsequent action potentials, resulting in a lower influx of Na+ ions and thus a decreased amplitude. Additionally, the gating variable n, governing potassium channel activation, doesn't completely deactivate in time. This causes an accumulation of K+ ions outside the neuron, elevating the threshold for future action potentials and contributing to the reduction in amplitude.

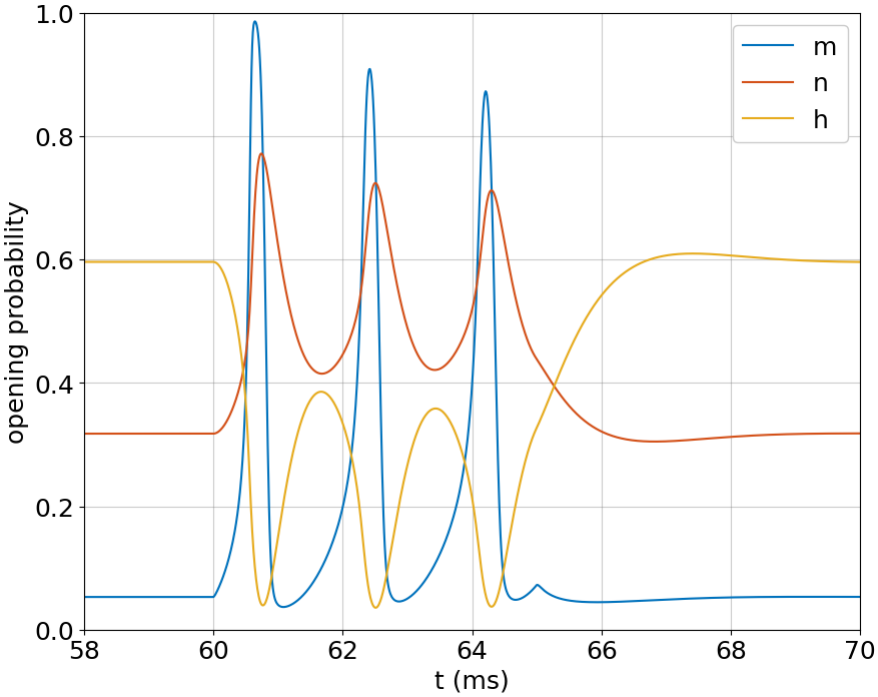


Figure 6: Closeup on gating variables m, n, h at 28°C and for the input visible in figure 2b