Technical University of Munich

Neuroprosthetics Exercise 4 Report

Student Name: Abdelrahman Elsissy
Student Number: 03780605

1. ION CHANNELS

Action potentials are generated due to the movement of specific ions in and out of the cell membrane. To be more precise, as sodium ions move into the cell membrane and potassium moves out of the cell, membrane potential reaches the voltage threshold and then spikes an action potential. The sodium ion channels have three activation subunits (m) and one inactivation subunit (h). The inactivation subunit allows the membrane potential to go back to resting potential. The potassium channel has four activation subunits. Each ion channel has its parameters that can describe its opening and closing rates α_x and β_x,$x \in \{m, n, h\}$. The steady-state value (x_∞) is the opening probability of each gate when the difference between the number of opening gates and the number of closed gates over time ($\frac{dx}{dt}$) is 0. **Equation 1** below illustrates $\frac{dx}{dt}$ with respect to the time constant τ_x, steady-state value (x_∞), and gating variable x.

$$\frac{dx}{dt} = \mathrm{a}(1 - x_i) - \beta x_i = (a_x + b_x)\left(\frac{a_x}{a_x + b_x} - x\right) = \frac{1}{\tau_x}(x_\infty - x) \tag{1}$$

Equations 2, 3, and 4 show the opening and closing rates of each gate α_x and β_x with respect to membrane voltage (V). Additionally, **equation 5** showcases the steady-state value (x_∞) with respect to the opening and closing rates of each gate α_x and β_x. In contrast, **equation 6** illustrates the time constant τ_x, with respect to temperature coefficient k and the opening and closing rates of each gate α_x and β_x. Finally, **equation 7** showcases the temperature coefficient with respect to initial and final temperatures. All these equations are essential to iterate our results after performing the plots required in the exercise with the voltage and temperature values given in the handout.

$$a_m = \frac{2.5 - 0.1V}{e^{(2.5-0.1V)} - 1}, \beta_m = 4e^{-V/18} \tag{2}$$

$$a_n = \frac{0.1 - 0.01V}{e^{(1-0.1V)} - 1}, \beta_n = 0.125e^{-V/80} \tag{3}$$

$$a_h = 0.07e^{-V/20}, \beta_h = \frac{1}{e^{(3-0.1V)} + 1} \tag{4}$$

$$x_\infty = \frac{a_x}{a_x + b_x} \tag{5}$$

$$\tau_x = \frac{1}{k.(a_x + b_x)} \tag{6}$$

$$k = Q_{10}{}^{(T-T_0)/10}, Q \approx 3 \tag{7}$$

If we substitue **equations 5 and 6** in **equation 1** we can finally obtain **equation 8** below.

$$\frac{dx}{dt} = k.(a_x(1 - x) - b_x) = \ k.(a_x + b_x)(\frac{a_x}{a_x + b_x} - x) \tag{8}$$

Figure 1(Top) illustrates the voltage(mV) and time constant(ms) characteristics and **figure 1(Bottom)** showcases the membrane voltage(mV) and opening probability characteristics of each subunit at 6 degrees Celsius. In addition, **figure 2(Top)** illustrates the voltage(mV) and time constant(ms) characteristics and **figure 2(Bottom)** showcases the membrane voltage(mV) and opening probability characteristics of each subunit at 28 degrees Celsius. As we can see from the plots and as expected from the equations, the opening probability of each gate is not affected by the change in temperature from 3,6 to 28 degrees Celsius. However, the time constant decreases drastically with approximately a factor of 0.1 when the temperatures increases from 6.3 to 28 degrees Celsius, the temperature coefficient (k) increases with roughly a factor of 10.

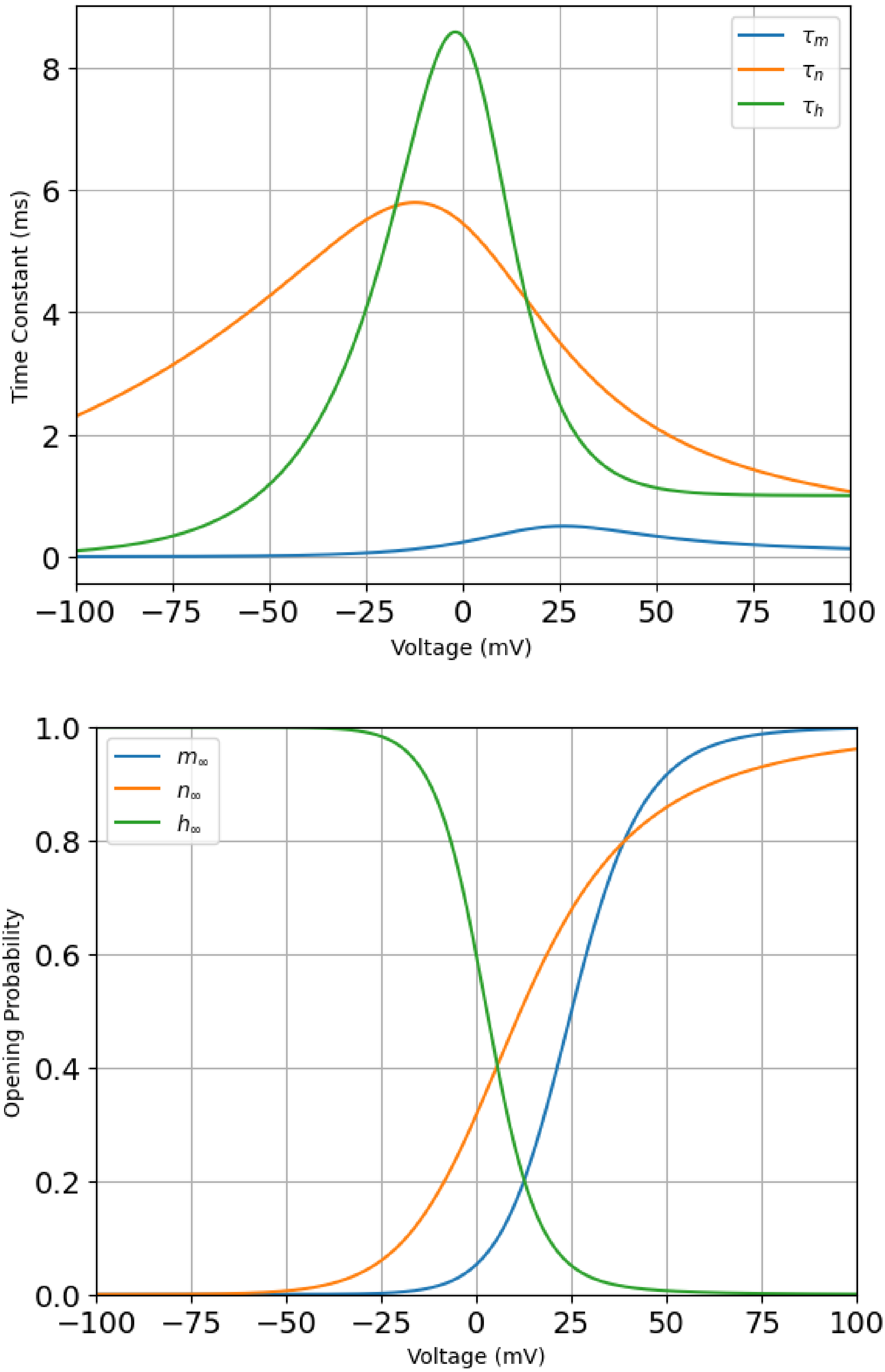


Figure 1. Parameters τ and x∞ for the gating variables m, n and h for 6.3 degrees Celsius. Top: membrane voltage (mV) and parameter τ Characteristics. Bottom: membrane voltage (mV) and gating variable m, n, h characteristics.

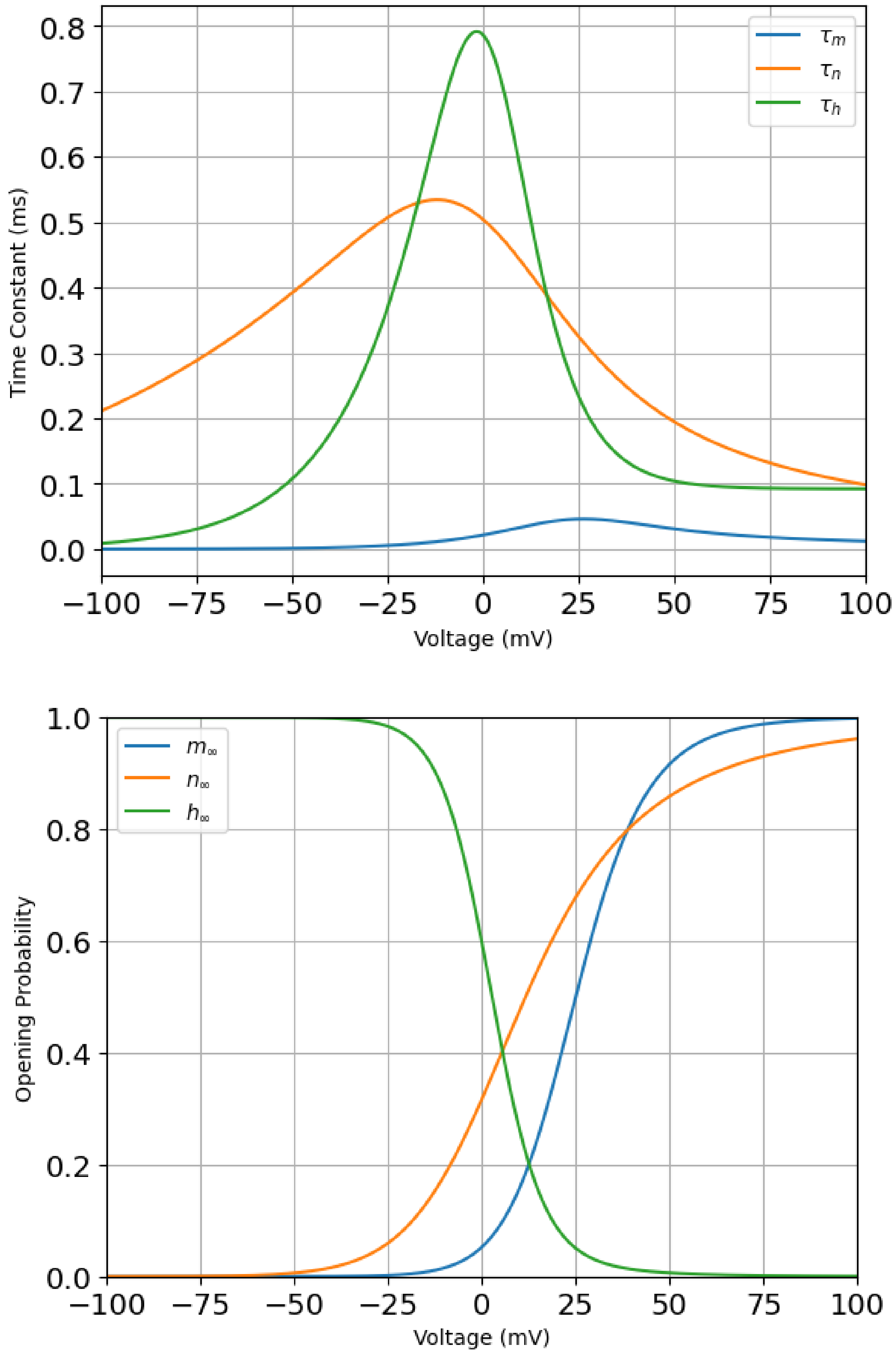


Figure 2. Parameters τ and x∞ for the gating variables m, n and h for 28 degrees Celsius. Top: membrane voltage (mV) and parameter τ Characteristics. Bottom: membrane voltage (mV) and gating variable m, n, h characteristics.

2. Hodgkin and Huxley Neuron Model

The Hodgkin-Huxley neuron model is developed around iterating how neurons generate an action potential. They are based on the equations used in section 1 of this exercise and the appendix. In the second part of the exercise, we will apply the knowledge we obtained in the previous exercise about differential equations and differential equation solvers to the equations we learned about the Hodgkin-Huxley models. We will then combine all this to simulate the Hodgkin-Huxley neuron model.

2.1. Implementation

2.1.1. Hodgkin-Huxley Gating Variables

As instructed in the exercise, we should apply the exponential DEQ solver to be able to implement a function that calculates the gating variables (m_{n+1}, n_{n+1}, h_{n+1}) at a future timestep(t_{n+1}) based on gating variables (m_n, n_n, h_n) at current time(t_n). As we recall from the last exercise, the exponential Euler can be used for equations similar to **Equation 9**. **Equation 6** below shows the formula of the exponential Euler method:

$$\frac{dV}{dt} = A(t)V(t) + B(V,t) \tag{9}$$

$$V_{n+1} = V_n e^{A(t_n).\Delta t} + \frac{B(t_n)}{A(t_n)} e^{A.\Delta t} - 1 \tag{10}$$

Now, we can rearrange **equation 8** to get **equation 11** below. After that, we can compare **equation 11** and equation 9 to obtain the A and B variables below.

$$\frac{dx}{dt} = k.(a_x(1-x) - b_x) = k.a_x - k.(a_x + \beta_x).x \tag{11}$$

$$A = -k.(a_x + \beta_x), B = k.a_x$$

Finally, after obtaining the parameters from **equation 11** and applying them in **equation 10,** we get **equation 12,** which helps us calculate the gating variables (m_{n+1}, n_{n+1}, h_{n+1}) at a future timestep(t_{n+1}) based on gating variables (m_n, n_n, h_n) at the current time(t_n).

$$x_{n+1} = x_n.e^{-k.(a_x+\beta_x).\Delta t} + \frac{k.a_x}{-k.(a_x+\beta_x)}.(e^{-k.(a_x+\beta_x)} - 1) \tag{12}$$

2.1.2. Hodgkin-Huxley membrane potential

As stated in the exercise, we should apply the forward (explicit) Euler to calculate the membrane potential (V_{n+1}) at a future timestep(t_{n+1}) based on the membrane potential (V_n) at the current time (t_n). As we have learned from the previous exercise, explicit Euler takes the slope at a point, multiplies it by the change in time, and adds this value to the value of the initial point, so that we can compute the next point. **Equation 13** below illustrates the explicit Euler method.

$$V_{n+1} = V_n + f(V_n, t_n)\Delta t \tag{13}$$

The slope of the membrane voltage can be obtained from the equation in the appendix, as illustrated in **equation 14.**

$$\frac{dV}{dt} = \frac{1}{C_m}.(I_{stim} - I_{ions}) \tag{14}$$

Equation 15 below shows the 3×1 matrix for the I_{ions} elements in the appendix, where $\hat{g}$ is the channel conductivity when all are open and is a constant given in the appendix. Additionally, the V_{ions} are provided as constants in the appendix.

$$\begin{gathered} I_{Na} = \hat{g}_{Na}.m^3.h.(V - V_{Na}) \\ I_K = \hat{g}_K.n^4.(V - V_k) \\ I_L = \hat{g}_L.(V - V_L) \end{gathered} \tag{15}$$

We can combine the term obtained in **equation 14** in **equation 13** to obtain **equation 16,** which helps us calculate the membrane potential (Vn+1) at a future timestep(tn+1) based on the membrane potential (Vn) at the current time (tn).

$$V_{n+1} = V_n + \Delta t \frac{1}{C_m}.(I_{stim} - I_{ions}) \tag{16}$$

The last step of this part of the exercise is to define the equations of α_x and β_x and the three elements of i_{ions}. We should also initialize a variable for V_0=0, α_0= $\alpha_x(V_0)$, β_0= $\beta_x(V_0)$, and finally obtain the initial gating variables ($x_0 = \frac{a_0}{a_0+b_0}$). Then, we should apply the functions we defined based on a single future time step and define all of the matrices we need for every future time step by iteration using a for loop.

2.2. EXPERIMENTS

We now need to run the model "HH_NeuronModel_Run" for 100 ms and with (Δt = 0.01 ms), with the following settings. We have two input currents (I_{stim}) to apply for each temperature as follows:

- At 6.3 degrees Celsius: I_{stim} is defined as a stair of five 5 ms long rectangular current pulses with a gap of 10ms and the amplitudes 2 µA, 3 µA, 4 µA, 6 µA, 8 µA.
- At 28 degrees Celsius: I_{stim} is defined as a stair of five 5 ms long rectangular current pulses with a gap of 10ms and the amplitudes 2 µA, 4 µA, 8 µA, 16 µA, 32 µA.

With the two different input currents at different temperatures, we could obtain the membrane voltage with varying currents of simulation using the functions we defined in section 2.2. **Figure 3** showcases the two different input currents for the two different temperatures, while **figure 4** illustrates the membrane voltage at the two different temperatures with two different input currents. Additionally, **figure 5** shows the gating variables at the two different temperatures with two different input currents. Also, **Figure 6** showcases the currents i_{na} and i_k voltage at two different temperatures with two different input currents. Finally, **figure 7** shows a closeup of the gating variables at 28 degrees Celsius, and for the input current visible in **figure 3(bottom).**

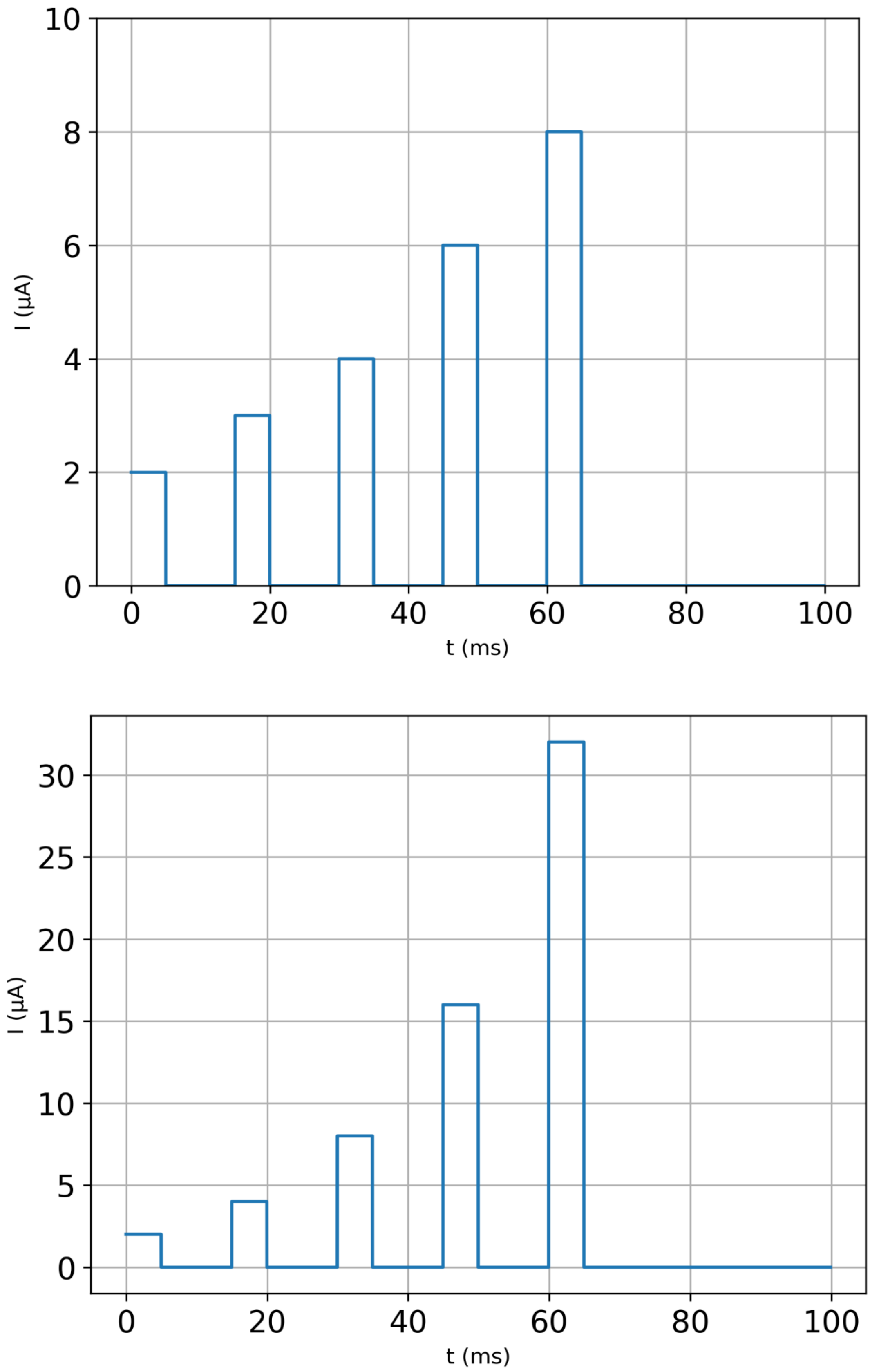


Figure 3. Input currents for the different temperatures. Top: Input currents at T =6.3 degrees Celsius. Bottom: Input currents at T =28 degrees Celsius.

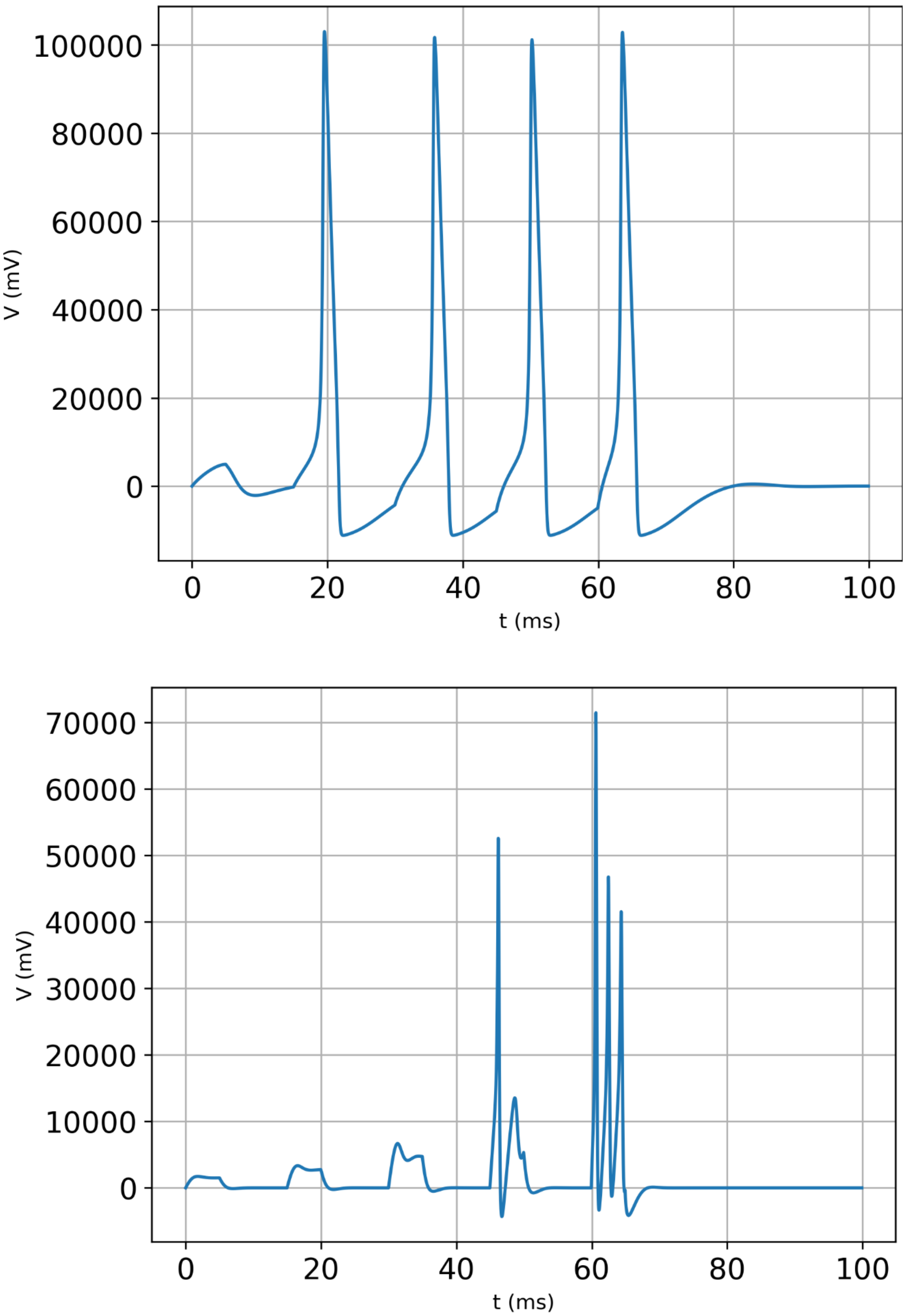
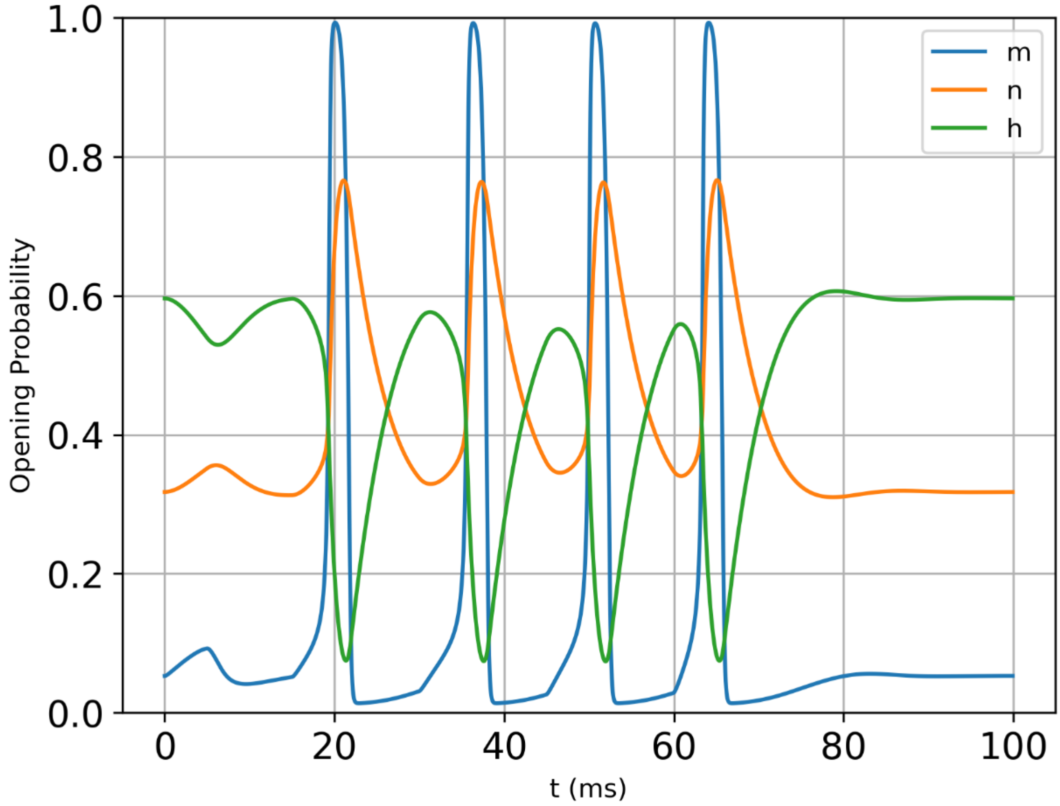


Figure 4. Membrane potential for different cases. Top: Membrane potential for 6.3 degrees and the input visible in figure 3(Top). Bottom: Membrane potential for 28 degrees and the input visible in figure 3(Bottom)



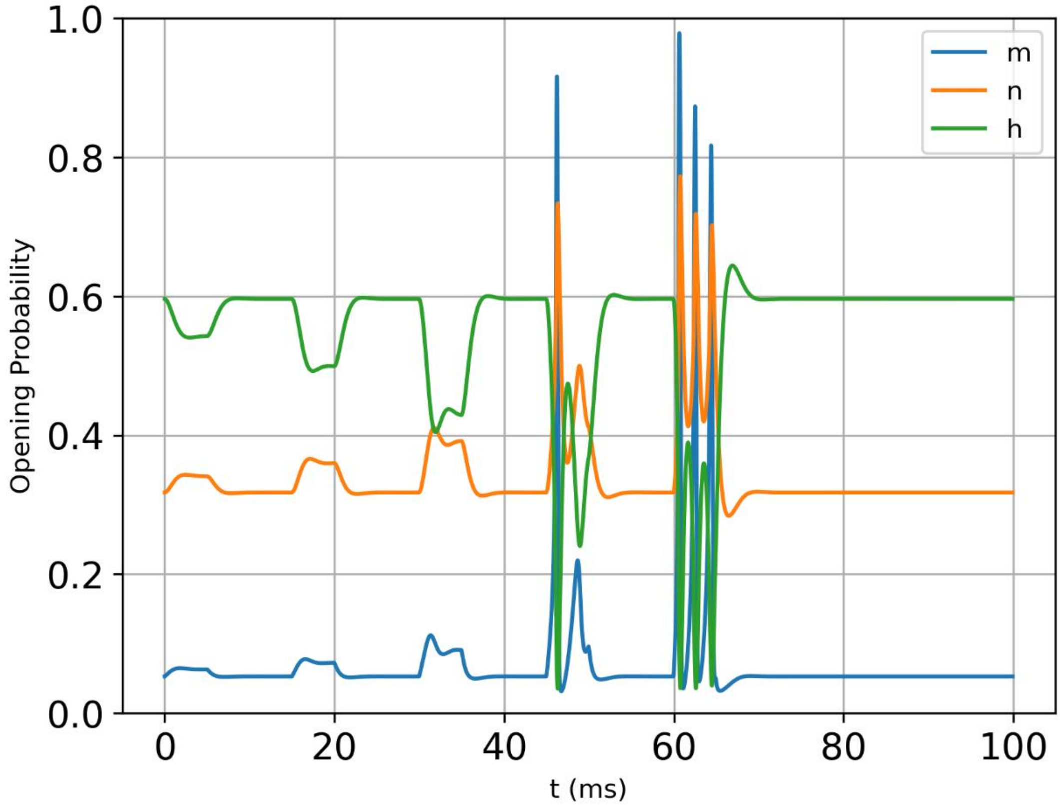


Figure 5. Gating variables m, n, h for different cases. Top: Gating variables m, n, h for 6.3 degrees and the input visible in figure 3(Top). Bottom: Gating variables m, n, h for 28 degrees and the input visible in figure 3(Bottom)

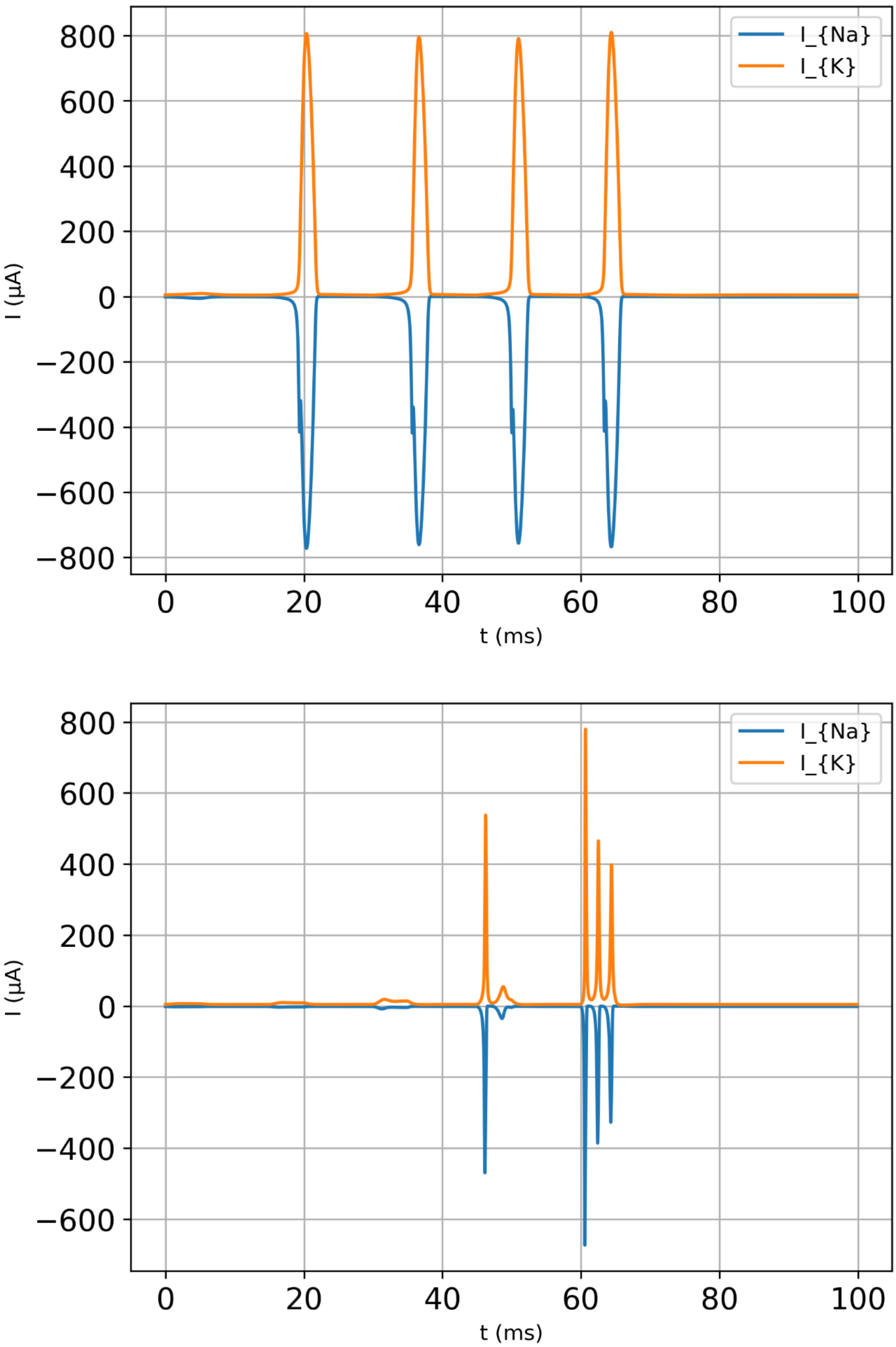


Figure 6. Currents i_{Na} and i_K voltage for different cases. Top: currents i_{Na} and i_K voltage for 6.3 degrees and the input visible in figure 3(Top). Bottom currents i_{Na} and i_K voltage for 28 degrees and the input visible in figure 3(Bottom)

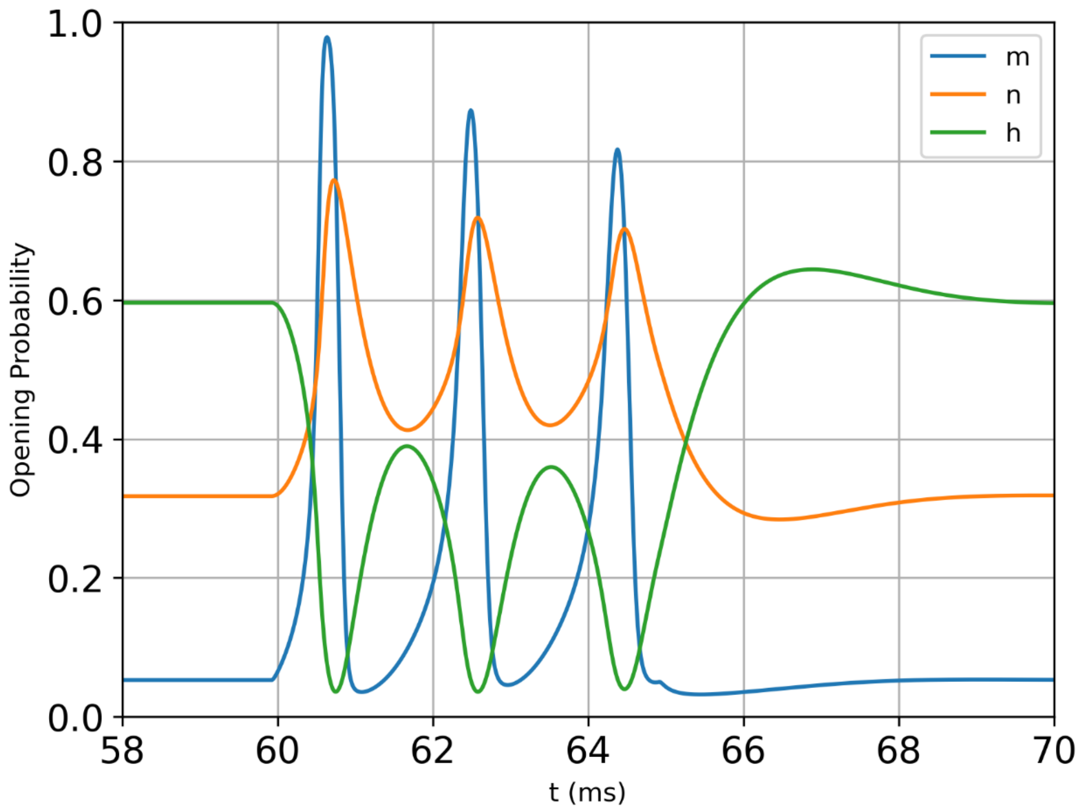


Figure 7. Closeup on the gating variables at 28 degrees Celsius and for the input visible in figure 3(bottom).

2.3. Analysis of the results

2.3.1. For the membrane potential, which are the differences between the results at 6.3 ∘C and 28 ∘C?

Firstly, we can see in **figure 4** that at 6.3 degrees Celsius, we have higher action potential values. If we look at equation 8, we can see a directly proportional relationship between the temperature coefficient k and the rate of change of gating variables over time. When the temperature is equal to 6.3 degrees Celsius, k is approximately 1, which means there will be no change in the rate of change of gating variables over time at 6.3 degrees Celsius. If we then look further at **equations 14, 15, and 16,** we can see that the membrane potential is dependent on i_{ions} and that i_{ions} are dependent on gating variables. On the other hand, when the temperature is 28 degrees Celsius, the temperature coefficient is approximately 10. That is why the gating variables have higher values, which also results in higher values for i_{ions}. That is why we obtain higher action potentials at 6.3 degrees Celsius than 28 degrees Celsius.

The second difference is that the action potential at 6.3 degrees Celsius has stable values, while the action potential at 28 degrees Celsius has unstable values.

Lastly, we can see that the membrane potential always hyperpolarizes to almost the same value at 6.3 degrees Celsius. On the other hand, the membrane potential does not always depolarize or hyperpolarize to the same values at 28 degrees Celsius. The reason for points two and three could be due to the effect of the time constant. The time constant has a meager value when the temperature coefficient is high. Since the temperature coefficient has a higher value at 28 degrees Celsius, this results in a temperature coefficient with a 10 times more increased value. This results in a relatively low time constant. This means that the opening and closing of the gates would be unstable, and the membrane potential would not always reach the resting potential after hyperpolarization and sometimes would not even reach the relative refractory period, as illustrated in **figure 3(bottom).**

2.3.2. WHEN AN ACTION POTENTIAL OCCURS, WHAT IS THE ROLE OF THE DIFFERENT GATING VARIABLES (M, N, H) IN THE IONIC CURRENTS AND THEREFORE IN THE MEMBRANE POTENTIAL CHANGE?

When the membrane potential increases, the n-gating variables allow potassium ions to flow outside the cell. Additionally, when the membrane potential increases, m-gating variables allow sodium ions to flow inside of the cell, which causes a more significant increase in the membrane potential as sodium ions are relatively more positively charged than potassium ions. After reaching the threshold voltage (approximately 20 mV), the opening probability of the sodium gate becomes somewhat higher than that of potassium channels. This causes an action potential; a drastic increase in membrane potential. When the membrane potential reaches a specific value, the sodium inactivation subunit (h) closes and does not allow sodium ions to flow into the cell anymore. Therefore, the membrane potential will repolarize and hyperpolarize as it takes more time for potassium gates to close and stop potassium ions from flowing out of the cell. The way in which these gating factors interact regulates the opening and closing of ion channels, thereby managing the passage of sodium and potassium ions through the neurons.

2.3.3. WHY DO CONSECUTIVE ACTION POTENTIALS DECREASE IN AMPLITUDE AT 28 ∘ C? (CHECK THE CORRESPONDING GATING VARIABLES)

As we can see from **figures 3(bottom), 5(bottom), and 7** the consecutive m and gating variables decrease in amplitude at 28 degrees Celsius, and the consecutive h gating variables increase. This results in a decrease in the amplitude of consecutive action potentials. As iterated in section 2.3.1, this could result from relatively small time constants.