Problem Set 1:
The Hodgkin-Huxley Model

Week 4, SoSe 2022 — Benoit Scholtes
Computational Neuroscience — & Stefan Rotter

The Hodgkin-Huxley equations model the interaction between the membrane potential and the voltage-gated channels of the squid axon. It is by using an *active* model of the membrane, in that the electrical properties of the membrane *change* with membrane potential, that the model is able to produce the characteristic spike waveform and other, less obvious neuronal phenomena. We will look at **NEST Dekstop** simulations of the HH-model to understand what is happening microscopically during spiking, refraction, excitation, and inhibition. For reference, the Hodkin-Huxley equations are:

$$\begin{aligned} C\dot{U} &= -\bar{g}_{Na}\, m^3 h\,(U - E_{Na}) - \bar{g}_K\, n^4\,(U - E_K) - \bar{g}_L\,(U - E_L) + I \\ \tau_m \dot{m} &= m_\infty(U) - m \\ \tau_h \dot{h} &= h_\infty(U) - h \\ \tau_n \dot{n} &= n_\infty(U) - n. \end{aligned} \tag{1}$$

Please use the default parameter values in Nest Desktop to simplify marking.

Problem 1: Spiking threshold — 4 points

Determine (to the nearest picoampere) the height of impulse (spike) input to a HH-neuron at rest required to bring the neuron to fire. Which additional parameters of the input contribute to its impact? Plot the evolution of the membrane potential $U(t)$ and the gating variables $m(t), n(t), h(t)$ caused by below and above threshold impulse input. Use these plots to explain how the all-or-none behaviour arises from the channel and membrane potential dynamics in response to the input.

Solution.

Figure 1 below shows gating variables and membrane potential responses in failed and successful spike excursions. The impulse heigh required for a neuron at rest is approximately 1264 pA.

By looking more closely at the channel activation responses in time to input just above and below the threshold, in Figure 2, we see that an action potential is caused only if the positive feedback loop of $m(t) \uparrow \rightarrow U(t) \uparrow \rightarrow m(t) \uparrow$ is able to push the membrane potential $U(t)$ above the threshold at approximately $U_{thr} = -55\text{mV}$ (for a neuron starting at rest). Once this occurs, then the positive feedback loop will dominate the membrane dynamics further and cause a spike to occur. This is because the increasing loop causes the inflow current (caused by activation of sodium channels given by $m(t)$) to overcome the outflow current (caused by the linear leak and the activation of potassium channels given by $n(t)$) and the inactivation of the sodium channels (given by $h(t)$) reducing the inflow current.

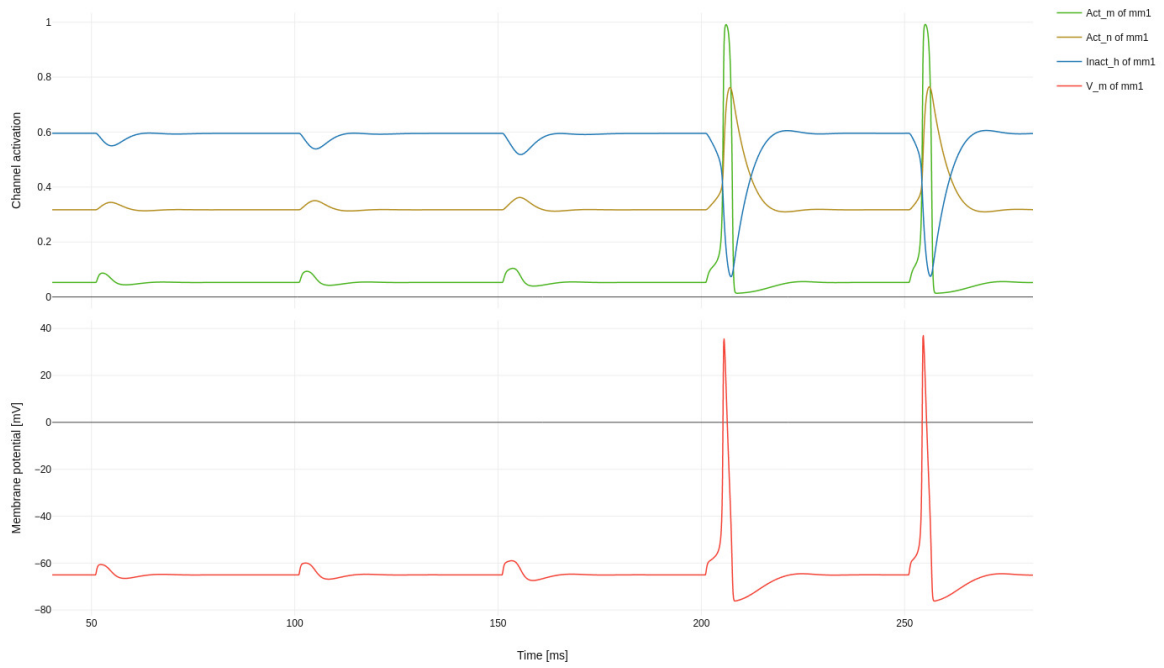

Figure 1: *Plot of the gatin variables and the membrane potential for impulse heights* $I_0 = (1000, 1100, 1200, 1300, 1400)$ *pA at times* $t = (50, 100, 150, 200, 250)$ *ms.*

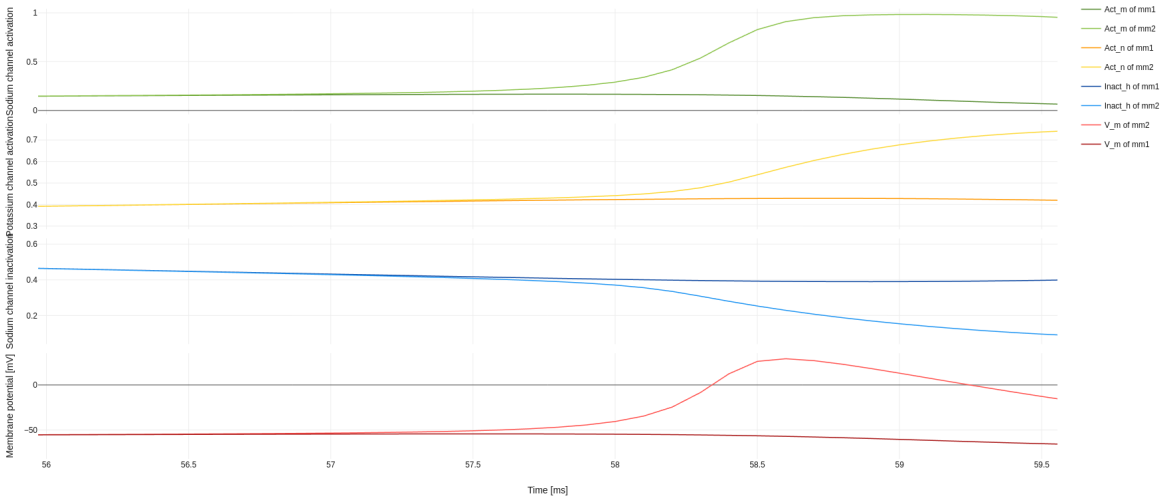

Figure 2: *Plot of the gating variables and membrane potential early time response to impulse heights* $I_0 = (1263.8, 1264)$ *pA at* $t = 50$ *ms, recorded from two different neurons.*

If the input impulse is too small, the positive feedback loop acts too slowly in raising $U(t)$ and I_{Na^+}, such that the outflow current has time to increase and overcome the inflow current before the membrane potential reaches U_{thr}, causing the membrane potential to fall (approximately $t = 57.5$ ms) and decay back to rest.

Note that at $t = 57.5$ ms, both gating variables $h(t)$ and $n(t)$ have evolved nearly identically, due to their slow time constants, while the $m(t)$ and $U(t)$ responses to the

different inputs already start to differ, as a result of their faster time constants. Thus, it is the faster time constant of the sodium activation gating variable results in its more significant impact on the early $U(t)$ dynamics in response to input.

Problem 2: Refractory period of the neuron 4 points

Show that an input impulse above the threshold found in Problem 1 is not always guaranteed to induce a spike by focusing on the refractory period of the neuron. Use plots of the gating variables and membrane potential evolutions to explain the cause of neuronal refractoriness. How long (to the nearest millisecond) is the refractory period of the Hodgkin-Huxley neuron? Determine this by finding the shortest time two spikes which are elicited by threshold impulse input can succeed each other.

Solution.

Figure 3 shows that the refractory period of the HH-neuron is approximately 39 ms.

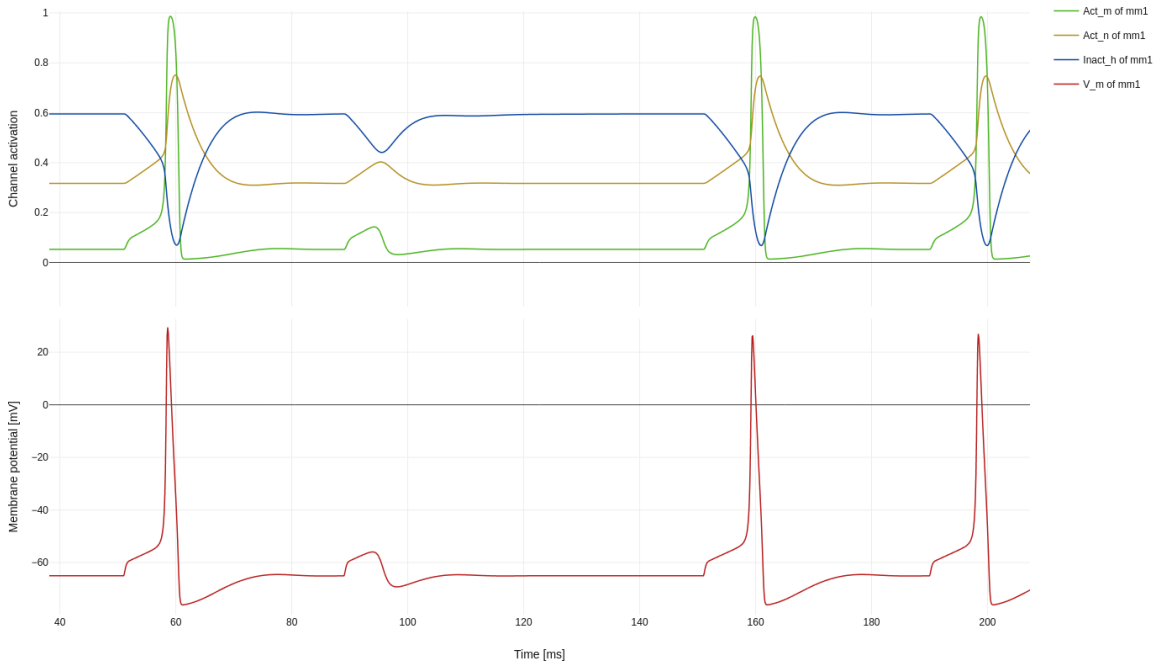

Figure 3: *Plot of the impulse responses of membrane potential and gating variables with impulses of heights* 1264 *pA at times* $t = (50, 88, 150, 189)$ *ms.*

Looking at the plots, especially during the early phase of the refractory period (approximately 10 ms after the spike), we see that there are two main reasons for the failure to elicit a new spike from the same input.

Firstly, the membrane is hyperpolarised (more negative than resting potential), meaning a higher input is required to reach threshold potential U_{thr}.

Secondly, though $m(t)$ has approximately reached its resting state, both $h(t)$ and $n(t)$ are still decaying to their resting state due to the longer time constants τ_h and τ_n.

Consequently, the sodium conductance is not as high, while the potassium conductance is higher, than when the neuron is at rest. This inhibits the inflow of sodium and eases the outflow of potassium, which inhibits the accumulation of positive charge inside the cell required for the action potential (for a similar input). As the refractory period goes on, these effects continue to decay until they reach their resting states.

Thus, we see the gating variables $n(t)$ and $h(t)$ are more important to understanding the refractory period. Note, however, that during the early phase of the refractory period, the gating variable $m(t)$ still hasn't reached equilibrium thus also contributing to the small sodium conductance and the neuron's refractoriness. Also, the hyperpolarised membrane means that transient increases in the potential won't increase $m(t)$ as much as during rest for the same input, thus also inhibiting the positive feedback from taking place to the same extent as when perturbing a neuron at rest.

Problem 3: Current input 4 points

We have seen that a threshold input impulse height cannot be determined as the state of the full system $U(t_0), h(t_0), m(t_0), n(t_0)$ as well as the input I_0 determines whether the system will consequently evolve through a spike excursion. The same holds for time-dependent inputs $I(t)$. Show that this is the case by demonstrating that even a continuous constant input $I(t) = I_0$ will, for standard parameters, elicit only a single spike approximately at the start of the input, after which the system relaxes into a steady state. Find (to the nearest 5 pA) the amplitude range $I_0 \in (I_i, I_f)$ for which this phenomena occurs. By plotting the evolution of the gating variables and membrane potential during the system's evolution, use the ionic channels to explain why no further spikes occur. How does the neuron respond to current amplitudes either side of the range (I_i, I_f)?

Solution.

A direct current input of $I(t) \in (225, 700)$ pA shows the phenomenon. Figure 4 shows an example of this. For currents $I(t) < 225$ pA, no spike is elicited, while for $I(t) > 700$ pA, continuous spiking occurs.

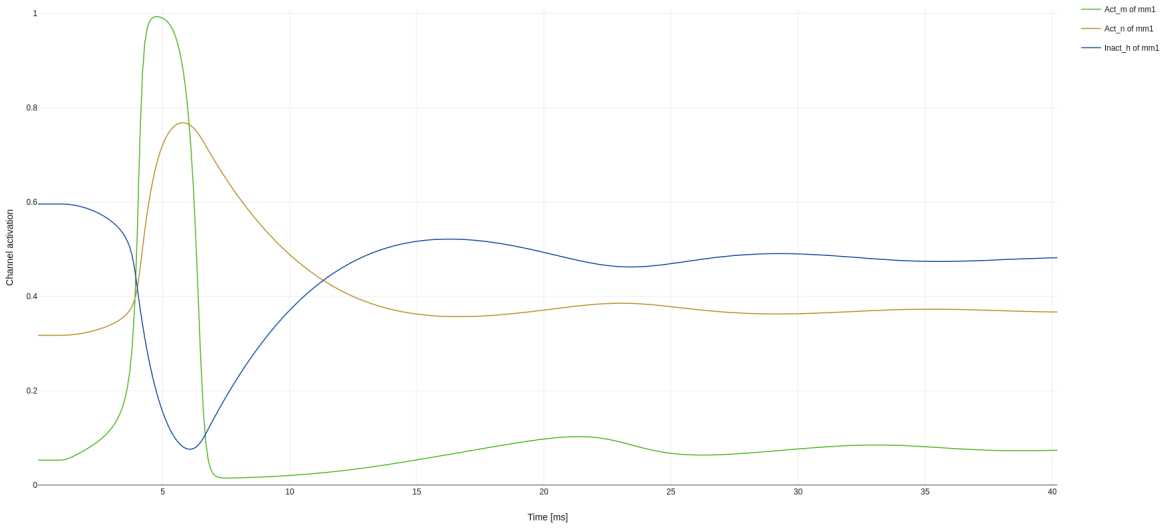

Figure 4: *Plot of the evolution of the gating variables during and after spiking for* $I(t) = 500\ pA$.

The last two problems give hints to what is happening here. Once the input amplitude of the current is large enough, a spike is elicited with similar channel dynamics as seen from Problem 1. That is, the positive feedback effect inducing an inflow of sodium ions overcomes the outflow of potassium ions which activates more slowly. After the spike however, the neuron enters its refractory period exactly as in Problem 2, by which the sodium conductance of the membrane is lower while the potassium conductance is higher.

The constant input however elongates the refractory period. Though the input increases the membrane potential and thus causes $m(t)$ to increase quicker towards its resting state, and even overshoot it briefly, the increased membrane potential also stops $n(t)$ and $h(t)$ from decaying to their resting states. A large enough input ($I(t) > 700$ pA) allows the positive feedback loop to overcome the lower sodium conductance and higher potassium conductance also caused by the input, such that the threshold potential is reached.