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Modeling of the action potential

Background Information

Neurons are the fundamental units of the nervous system and perform complex computations that underlie the way our minds work. They communicate with each other through electrical events called action potential and chemical signals called neurotransmitters. Typically generated in the axon, action potentials are brief electrical impulses that travel the length of the axon and cause the release of neurotransmitters into the synapse. These chemicals then travel across the synapse and can excite or inhibit target neurons. A single neuron can be thought of as a logical machine that is constantly integrating its inputs and firing action potentials based on its calculations.

Neural computation is a rapidly growing field that seeks to mathematically model the nervous system. The primary goal of modeling is to develop engineering level descriptions of brain circuits and how they relate to cognition. Several models exist today, that make use of high-level statistics, complex data sets, and artificial intelligence algorithms (*Direct.mit.edu*). These models have wide ranges of applications such as studying/ predicting neurodegenerative disorders such as Alzheimer's disease, simulating cognition to understand how memories work, to even making virtual machines that are inspired by the human brain.

There are several notable works from the past that have served as foundational pillars for the advancements in neural computation today. One of them is the Hodgkin-Huxley model of action potentials. The Hodgkin-Huxley model, or conductance-based model, is a mathematical model that describes how action potentials in neurons are initiated and propagated (Hodgkin & Huxley, 1952). It is the result of the experiments carried out by Alan Hodgkin and Andrew Huxley in 1952 to explain ionic mechanisms that underlie the initiation and propagation of action potentials in the squid giant axon and is still a widely used model to represent action potential spikes today.

Model Development

The model used for the report is based on the Hodgkin-Huxley neural circuit model, and so factors in the nonlinear interaction between the cell's membrane potential (voltage) and the opening and closing of Sodium and Potassium ion channels. The overall differential equation for the model is as follows:

$$I_m(t) + C\,\frac{dV(t)}{dt} = I_e(t),$$

Where I_m is the total membrane current, C is the membrane capacitance V(t) is the membrane potential, and I_e is the input current based on the equivalent circuit model.

This relation is further broken down stochastically to model the time and voltage dependence. This is done using gating variables, which represent the fraction of channels activated/ deactivated. The activation of the sodium and the potassium conductance is represented by the gating variables m and n respectively.
For potassium conductance, 4 potassium channels are assumed to be independent of each other, leading to the following expression for the probability of potassium channels being open (P_k):
$P_K = n^4$
Unlike the potassium channels, the 4 sodium channels are not independent of each other. So, the probability of the sodium channels being open is modelled as follows:
$P_{Na} = m^3h$
Here, h is another gating variable called the inactivation gating variable. For sodium channels, the mechanism of activation and inactivation are assumed to be independent of each other. Physiologically, the h variable represents a loop of amino acids on the inside of the sodium ion channel that responds to depolarization by falling in and blocking the ion channel pore. So, the assumption of activation and inactivation being independent is actually not a 100% accurate but was used as a reasonable simplification of the system.

To code for this in MATLAB, a simple algorithm was used to follow the Hodgkin Huxley model for finding the membrane voltage as a function of time for a current clamp experiment. The algorithm used consisted of a loop that was built upon the following steps: First, a depolarizing external current of magnitude of 10 μA/cm^2 was applied for 20 milliseconds, for an initial voltage V_0 at time step t_0 . Second, the rate constants, **α** and **β** , of the gating variables m, n and h were found for that voltage using the following six expressions:

1) $\alpha_h(V) = 0.07 \times exp(-0.05 \times (V + 70))$
2) $\beta_h(V) = \dfrac{1}{1 + exp\,(-0.1 \times (V + 40))}$

3) $\alpha_m(V) = \dfrac{0.1(V + 45)}{1 - exp\,(-0.1 \times (V + 45))}$

4) $\beta_m(V) = 4 \times exp(-0.0556 \times (V + 70))$

5) $\alpha_n(V) = \dfrac{0.01(V + 60)}{1 - exp\,(-0.1 \times (V + 60))}$

6) $\beta_n(V) = 0.125 \times exp(-0.0125 \times (V + 70))$

Third, using the 6 rate constants, the steady state values and time constants of the gating variables were computed for an initial voltage V_0 at time step t_0.
The time constants for m, n and h were found using the following expression:

7) $\boldsymbol{\tau}_i(V) = \frac{1}{\alpha_i(V) + \beta_i(V)}$

Here, i = m, n or h. Similarly, the steady state values of m, n and h were found using the following expression:

8) $i_\infty(V) = \frac{\alpha_i(V)}{\alpha_i(V) + \beta_i(V)}$

Fourth, using the steady state values and time constants, the initial m, n and h values were updated using the exponential-Euler method to integrate by one time step:

9) $i(t) = i(t-1) + \frac{di}{dt}\Delta t\,, where\ i = m, n, h$

Fifth, the updated m, n and h were used to find the updated Potassium and Sodium conductance using the following expressions:

10) $G_k = G_k(max) \times n^4$

11) $G_{Na} = G_{Na}(max) \times m^3 \times h$

Sixth, the leak conductance, updated sodium and potassium conductance were used to find the total membrane current, which was then used to find the steady state voltage (V_∞) and the membrane time constant.

Finally, the steady state voltage and membrane time constant were used to find the update value of the membrane potential by solving for the following expression using a similar exponential-Euler method:

12) $V(t) = V(t-1) + \frac{dV}{dt}\Delta t$

Once the updated membrane voltage for the time step was found, this voltage was used as the initial voltage for the next time step so that all of the previous steps could be looped to find yet another updated voltage. This loop was further repeated for the remaining number of time steps allowed during the square current, to obtain an array of voltage values corresponding to the array of time values.

Simulation and results

Using the algorithm described above, a MATLAB script was made to plot the membrane voltage vs time and different scenarios were tried out.
The equilibrium potentials for sodium, potassium and leak channels were set to 55mV, -75mV and -60mV respectively, and the maximum conductances were set to 120,30 and 0 mS/cm^2 respectively. While these parameters would vary depending on the neuron in real life, these particular values were chosen to represent realistic values according to literature (Zhang et al., 2014).

First, a depolarizing external current of magnitude of 10 μA/cm^2 was applied for 10 milliseconds (between 20 and 30 milli seconds), for an initial voltage of -70mV. The following plot was obtained:

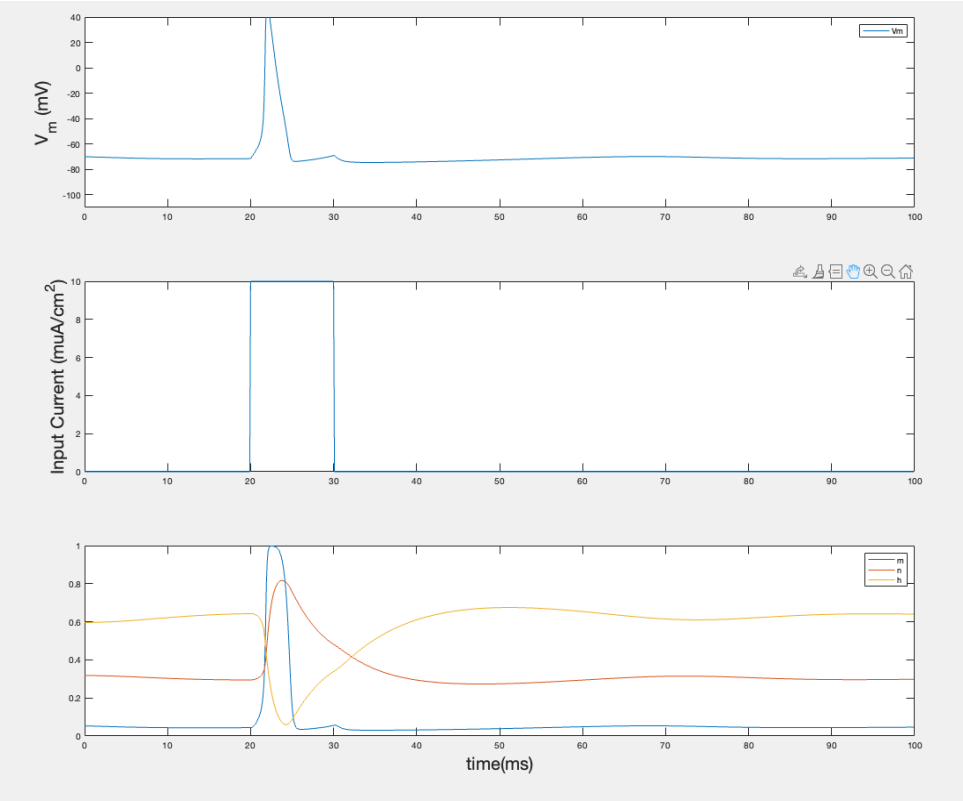

Figure 1 The membrane potential, external current applied, and gating variables as a function of time for the first run of the model where an input current of 10 μA/cm2 was applied for 10 milliseconds.

Second, two pulses of 3 μA/cm^2 were applied 5ms apart at 10ms and 20ms respectively. The following plot was generated:

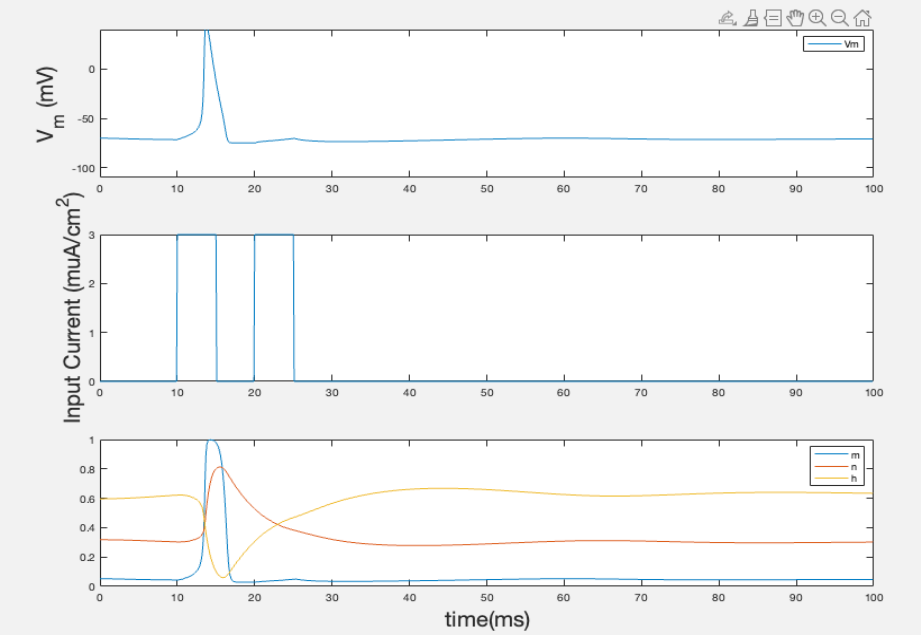

Figure 2a The membrane potential, external current applied, and gating variables as a function of time for the second run of the model. Two input currents of 3 μA/cm2 were applied for 5 milliseconds each, 5 milliseconds apart.

Similarly, the same two currents were then applied with 10ms intervals instead of 5ms and the following results were seen:

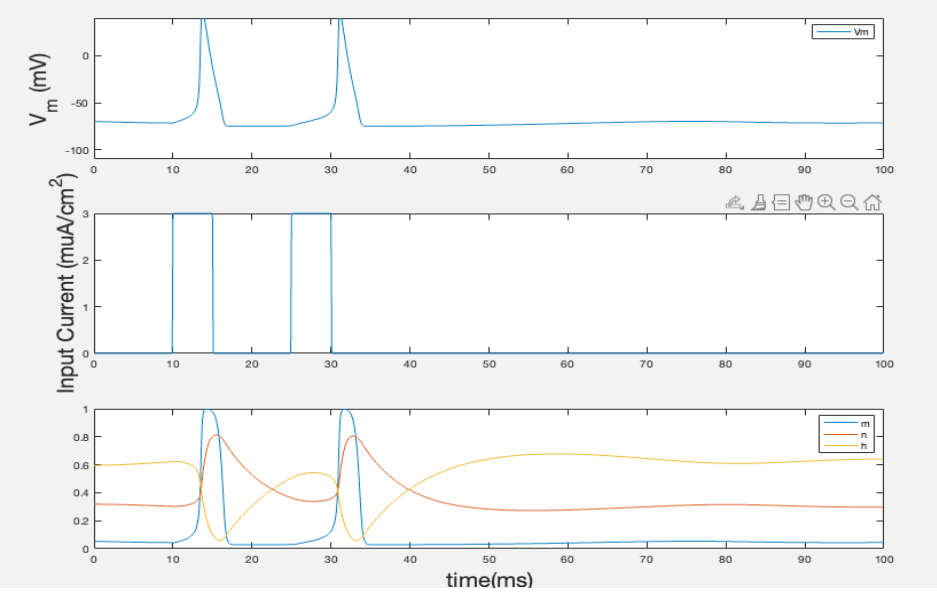

Figure 2b The membrane potential, external current applied, and gating variables as a function of time for the second run of the model. Two input currents of 3 μA/cm2 were applied for 5 milliseconds each, 10 milliseconds apart.

Third, a single pulse of 10 μA/cm^2 was applied for a longer time of 70 milli seconds between 10ms and 80ms.

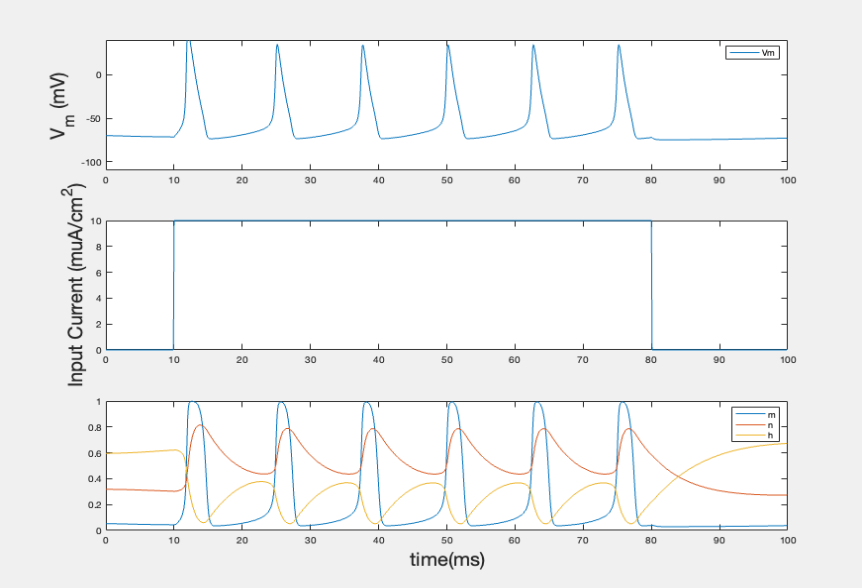

Figure 3 The membrane potential, external current applied, and gating variables as a function of time for the third run of the model. An input current of 10 μA/cm2 was applied for 70 milliseconds.

Lastly, for the same 70ms time range, a current of lower magnitude (3 μA/cm^2 instead of 10 μA/cm^2) was injected to get the following results:

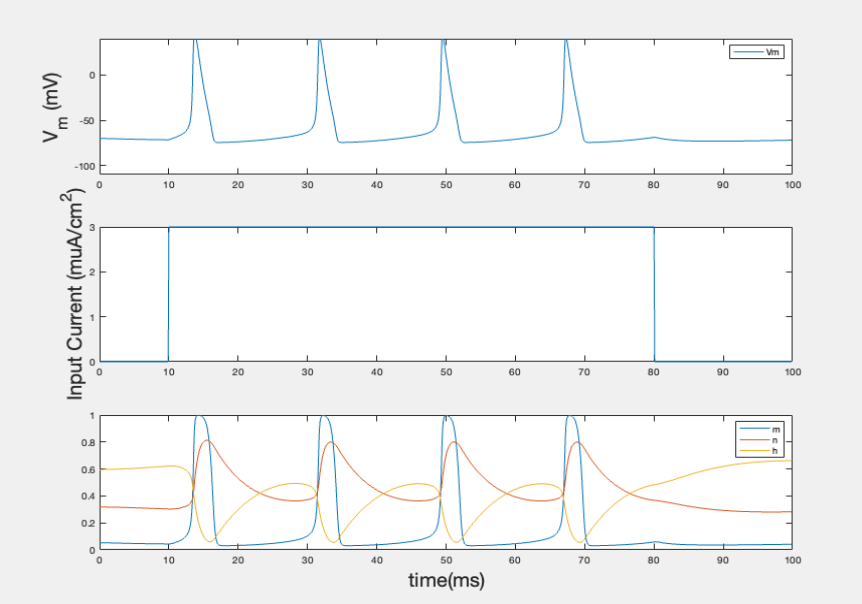

Figure 4 The membrane potential, external current applied ,and gating variables as a function of time for the fourth run of the model where an input current of 3 μA/cm2 was applied for 10 milliseconds.

Discussion and conclusion

As seen in figure 1, when current is injected, the cell depolarizes, and m(t) is seen to grow. This shows that the sodium current is turning on until the equilibrium potential of sodium is reached. Here the sodium current stops, and n(t) is seen to grow, indicating the potassium current growing and hyperpolarizing the cell. While this happens, h(t) is seen to drop which shuts off the sodium conductance while the potassium conductance brings the cell back to its resting potential.

In figure 2a, two pulses of currents were injected with 5ms intervals, but a second spike was not seen, while on increasing the interval to 10ms in figure 2b a second spike was seen. This shows the refractory period of a cell, where h(t) has not recovered enough in the case of figure 2a for the second current to warrant a spike.

With increasing magnitude of current pulses, the shape of the membrane potential spike is seen to be the same, however there is seen to be a higher number of spikes in the same time range, as seen from figures 3 and 4.

The assumptions made for the model was that the channels for the gating variables are independent of each other. While this is a reasonable assumption for simplification, in reality this might not be true. For example, for sodium channels, the mechanism of activation and inactivation are assumed to be independent of each other. Physiologically, the h variable represents a loop of amino acids on the inside of the sodium ion channel that responds to depolarization by falling in and blocking the ion channel pore (Eaholtz et al., 1999). So, the assumption of activation and inactivation being independent is actually not true. However, this was not known during the 1950s when the HH mathematical models were made. This goes to show that as we understand more about the physiology behind systems, existing assumptions used in modeling should be continually revised so that more accurate models can be formed.

In conclusion, the Hodgkin-Huxley model was able to replicate action potentials for injected currents in a neuron equivalent circuit model. While this is not 100% representative of the membrane potential in actual neurons, the trends in voltage spikes depicted can be used to get a decent understanding of how sodium and potassium ion channels play a role in the formation of action potentials, and the voltage and time dependence of their conductance.

Finally, I would like to end the report by answering some questions asked by my peers during the class presentation. Among the questions asked, most were directed to the other presenters, but I could find two that related to my model. First, Nicholas Saul asked what the need/ relevance of applying this electrical model to the neuron was. To answer this, one of the key challenges in neuroscience is taking large datasets from neurons and making sense of them. Neurons themselves can be of several different types defined by the genes that are expressed

in them and the order of ion channels present. By applying basic models like the Hodgkin Huxley model, researchers can significantly reduce the dimensions of the data and this helps to figure out underlying basic mechanisms behind them.
Second, Trudy asked me about figure 19 of the referenced paper. The figure depicts the refractory period and the role of the gating variables for this behavior. As discussed above, this is due to the inactivation variable h(t) and the time it takes to reset, the effects of which can be seen during the second run of the model in this report.

This concludes my final report, thank you very much for a wonderful semester!

References

- Direct.mit.edu. (n.d.). Retrieved December 11, 2022, from https://direct.mit.edu/neco
- Eaholtz, G., Colvin, A., Leonard, D., Taylor, C., & Catterall, W. A. (1999). Block of brain sodium channels by peptide mimetics of the isoleucine, phenylalanine, and methionine (IFM) motif from the inactivation gate. *Journal of General Physiology*, *113*(2), 279–294. https://doi.org/10.1085/jgp.113.2.279

- Hodgkin, A. L., & Huxley, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *The Journal of Physiology*, *117*(4), 500–544. https://doi.org/10.1113/jphysiol.1952.sp004764

- Zhang, Y., Wang, K., Yuan, Y., Sui, D., & Zhang, H. (2014). Effects of maximal sodium and potassium conductance on the stability of Hodgkin-Huxley model. *Computational and Mathematical Methods in Medicine*, *2014*, 1–9. https://doi.org/10.1155/2014/761907