NEURON SIMULATION OF ION CHANNELS IN HODGKIN HUXLEY MODEL AND THE INTRODUCTION OF NOISE

By Shreyash S.[1], Elin Saks[2], Jay Sethi[3]

, Daksh Dilip Talreja[4], Rudra Pratap Singh Chouhan[5], Syed Mohd Faran[6]

Birla Institute of Technology & Science Pilani, Goa

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[1] f20190276@goa.bits-pilani.ac.in
[2] i2022001@goa.bits-pilani.ac.in
[3] f20191002@goa.bits-pilani.ac.in
[4] f20190014@goa.bits-pilani.ac.in
[5] f20190064@goa.bits-pilani.ac.in
[6] f20190867@goa.bits-pilani.ac.in

Abstract

In **Chapter 1** of this study, we aimed to reproduce the h_∞, m_∞, and n_∞ graphs described in the classic Hodgkin-Huxley paper using the NEURON software and Python notebook where h_∞, m_∞, and n_∞ are commonly used notations to denote the steady-state activation or inactivation values of specific ion channels in a neuron. Specifically, we investigated how voltage clamping affects the activation and inactivation curves of these ion channels, and sought to compare our results to those reported in the original paper. Our findings indicate that the NEURON simulations are able to reproduce the Hodgkin-Huxley graphs to very high accuracy, and provide further insight into the underlying mechanisms of neuronal excitability. These results have important implications for understanding the behaviour of ion channels and for modelling the behaviour of neural networks.

In **Chapter 2**, we extended the model by adding noise to it as first described by Goldwyn and Shea-Brown [1]. This was done by introducing noise terms in Hodgkin Huxley equations, which makes the simulation more realistic. Noises were introduced in two forms to replicate the real world scenarios and graphs were plotted accordingly for both forms.

Chapter 1

Hodgkin-Huxley Model Simulation

1.1 Introduction

The Hodgkin-Huxley model was created by Alan Hodgkin and Andrew Huxley and it describes the behaviour of action potentials in neurons. It is a mathematical model that simulates the behaviour of ion channels and the flow of ions through them.

The model consists of a system of four differential equations that describe the behaviour of the ionic currents that underlie the action potential in neurons. These equations are solved numerically by iteratively advancing the system.

To simulate the model, initial conditions for the system variables are set (e.g., membrane potential, membrane currents and ion channel gating variables), and then the equations are solved over a time interval of interest. The resulting output provides a prediction of the membrane potential over time, which can be compared to experimental data acquired.

There are several software packages and programming languages that can be used to simulate the Hodgkin-Huxley model, including NEURON, and Brian. These tools provide a variety of features, such as graphical user interfaces, built-in functions for generating input stimuli, and visualisation tools for analysing simulation results. There are also python libraries which helps in creating the intended plots to great precision.

To implement this Hodgkin-Huxley Model, we created cells (Neurons) using python on JUPYTER Notebook, introduced channels to the model, used Voltage and Current clamps etc. The created cells were given a proper morphology in the 3-Dimensional plane, using "The Ball and Stick" model to demonstrate

the morphology of the neuron and how after including the channels it will function like real neurons. This also showed how the positioning of neurons in the space affected the strength of the action potential where neurons in the vicinity of the stimulated neuron had more signal strength than those who were placed far away in the configuration.

1.2 Hodgkin Huxley Formulas

In one of the parts in the paper by Hodgkin and Huxley [2], they analyse how the activation and inactivation occurs for sodium and potassium. The steady-state value of the fraction of gates is denoted by x_∞ where x is n, m or h. That is, the values of potassium activation, sodium activation and sodium inactivation, respectively.

To validate the results obtained with the Hodgkin-Huxley model we created with NEURON, we compared the results from those recordings with the theoretical values according to the formulas in [2]. The value of n_∞ is calculated from the rate of which n particles flow in and out, α_n and β_n respectively. α_n and β_n are calculated by:

$$\alpha_n = \frac{0.01(V + 10)}{\exp \frac{V+10}{10} - 1} \tag{1.1}$$

$$\beta_n = 0.125 \exp \frac{V}{80} \tag{1.2}$$

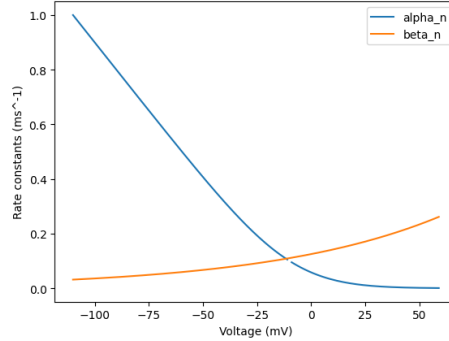Figure 1.1 shows α_n and β_n at different voltage levels.

Figure 1.1: α_n and β_n

The resulting values are used to obtain n_∞ in the following manner:

$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n} \tag{1.3}$$

Sodium has both activation and inactivation particles. The rate at which the activation particles, m, flow is obtained by the following equations. The inward

flow is, once again, denoted by α and the outward flow by β:

$$\alpha_m = \frac{0.1(V + 25)}{\exp \frac{V+25}{10} - 1} \tag{1.4}$$

$$\beta_m = 4 \exp \frac{V}{18} \tag{1.5}$$

When α_m and β_m is plotted together we get figure 1.2.
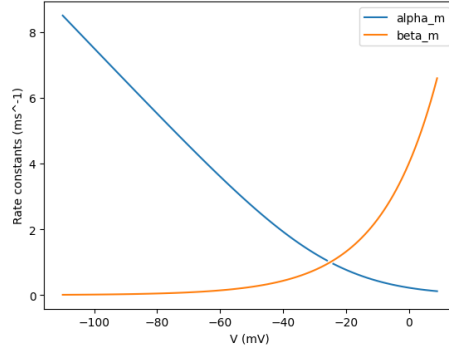
Figure 1.2: α_m and β_m

m_∞ is calculated by the same formula as n_∞:

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m} \tag{1.6}$$

Lastly, we have the sodium inactivation, h, α and β are given by equations 1.7 and 1.8.

$$\alpha_h = 0.07 \exp \frac{V}{20} \tag{1.7}$$

$$\beta_h = \frac{1}{\exp \frac{V+30}{10} + 1} \tag{1.8}$$

Figure 1.3 shows α_h and β_h at different voltage levels.

h_∞ is calculated through the same formula as before:

$$h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h} \tag{1.9}$$

When we later refer to the theoretical values of n_∞, m_∞ and h_∞, these formulas above are the ones those values are given by.
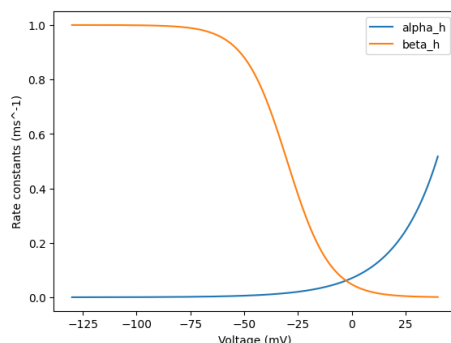
Figure 1.3: α_h and β_h

1.3 Results

1.3.1 Gating Behaviour of NEURONS on Constant Voltages

The graphs plotted h_∞, m_∞, n_∞ refer to the steady-state activation or inactivation probabilities of different ion channels in a neuron. These values are dependent on the membrane potential of the neuron. When voltage clamping is applied, the value of n_∞, m_∞ and h_∞ can be measured at different static voltage levels (i.e. the membrane potential is fixed which results in a steady state value for the activation and inactivation variables). Figure 1.4a shows the value of n_∞ at different membrane potentials maintained by voltage clamping, figure 1.4b shows the membrane potentials for m_∞ and figure 1.4c shows membrane potential for h_∞.

These graphs show that the theoretical value and the recorded values (using NEURON software) are very similar.

1.4 Discussion

As the membrane potential of a neuron changes, the activation and inactivation probabilities of different ion channels also change. This can lead to changes in the firing properties of the neuron.

In general, when the membrane potential becomes more positive (depolarises), the activation probability of voltage-gated sodium channels increases, leading to an increase in the probability of action potential firing. Conversely, when the membrane potential becomes more negative (hyper-polarises), the activation probability of voltage-gated potassium channels increases, leading to a decrease in the probability of action potential firing.
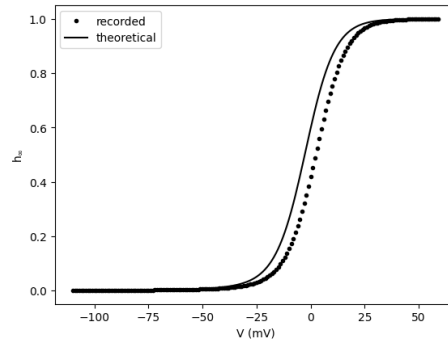
The values of h_∞, m_∞, n_∞ can also change with changes in the membrane

4
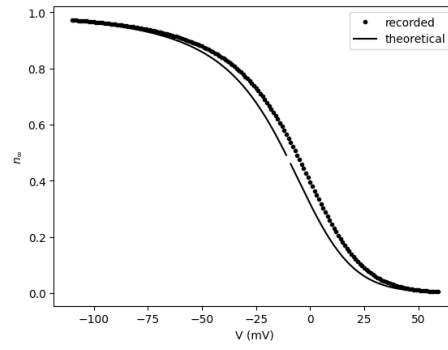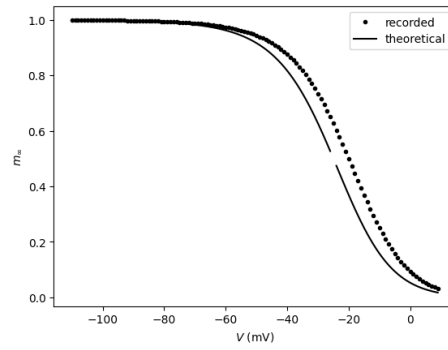
(a) The value of n_∞.

(b) The value of m_∞.

(c) The value of h_∞.

Figure 1.4: The values while clamping at different voltage levels.

potential, which can affect the excitability and firing properties of the neuron. For example, as the membrane potential becomes more positive, the activation probability of voltage-gated calcium channels may increase, leading to an increase in neurotransmitter release and synaptic plasticity.

On plotting the recordings from NEURON, the graphs were mirror images of the graphs in [2] with the pivot being the resting potential. Thus, an assumption was made that membrane potentials were recorded from outside the cell in [2] and from inside the cell in NEURON.

Chapter 2

Adding Noise to the HH Model

2.1 Theory

Conductance-based equations are a commonly used mathematical framework to study electrically active cells in computational biology. These equations, which Hodgkin and Huxley originally proposed, describe how ionic currents affect a cell's voltage and how the voltage, in turn, affects the currents. This feedback loop creates the rapid and dynamic behaviour of the action potential.

In order to better capture the behaviour of action potentials and currents in cells, researchers introduced channel noise into the equations. Channel noise has been extensively studied in different neural systems such as the electrical stimulation of the auditory nerve by cochlear implants, the entorhinal cortex, cerebellar granule cells, and hippocampal CA1 pyramidal neurons. Modelling studies have demonstrated that channel noise can significantly impact information processing, spike time reliability, stochastic resonance, firing irregularity, sub-threshold dynamics, as well as the initiation and propagation of action potentials in detailed models of neuronal morphology.

Various methods can be used to introduce channel noise in conductance-based models. One direct approach is to model each of N channels as a discrete-time Markov chain, where the channels of a particular type transition independently and randomly among different configuration states with voltage-dependent transition probabilities. This method is considered a gold standard for channel noise modelling and provides a continuous-time Markov chain that can recover deterministic equations like the classic HH equations when $N \to \infty$. However, for finite values of N, the Markov process can be simulated using Gillespie-type algorithms.

In order to incorporate the effects of channel noise in models, simpler approaches involve introducing noise terms in established models. Two approaches discussed in this paper are Current Noise and Conductance Noise. These techniques enable efficient simulation of channel noise and its impact on the model's behaviour.

2.1.1 Current Noise

One straightforward way to introduce noise in the Hodgkin-Huxley (HH) equations is to include a current term $\xi_V(t)$ that varies randomly over time. This current term represents the stochastic fluctuations in the ion channels that are not accounted for in the deterministic HH equations. By adding $\xi_V(t)$ to the HH equations, the resulting model can simulate the impact of channel noise on the behaviour of the neuron.

$$C\frac{dV}{dt} = -\bar{g}_{Na}m^3h(V - E_{Na}) - \bar{g}_K n^4(V - E_K) - \bar{g}_L(V - E_L) + I + \xi_V(t) \quad (2.1)$$

2.1.2 Conductance Noise

An alternative method for incorporating noise in the HH equations is to add fluctuations directly to the fractions of open channels, as these fractions determine the ionic currents. According to our understanding of the HH equations, which has been made rigorous in several studies, the mean fractions of open and channels can be expressed as m^3h and n^4. Hence, a direct approach to introduce channel noise to the HH equations involves adding zero-mean stochastic processes to the deterministic values of m^3h and n^4.

$$C\frac{dV}{dt} = -\bar{g}_{Na}(m^3h + \xi_{Na}(t))(V - E_{Na}) - \bar{g}_K(n^4 + \xi_K(t))(V - E_K) - \bar{g}_L(V - E_L) + I$$
$$(2.2)$$

So, time-varying random equations $\xi_{Na}(t)$ and $\xi_K(t)$ are added to m^3h and n^4 respectively to simulate this.

2.2 Results

2.2.1 Current Noise

From 2.1.1, for simulating noise, a current clamp was applied at each millisecond with a randomly varying amplitude. This caused some fluctuations in the recorded voltage of the neuron as seen in 2.2

2.2.2 Conductance Noise

From 2.1.2, for simulating noise, sodium conductance was changed at every time step to match as in equation 2.2. $\xi_{Na}(t)$ and $\xi_K(t)$ were from a normal distribution with 0 mean and 0.001 variance.

The change in sodium conductance did not introduce a noise in current but if
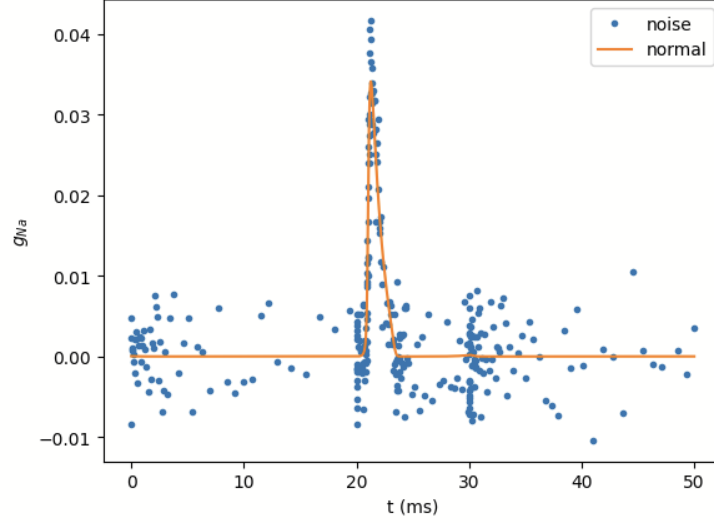it would have, it would have looked as in Fig 2.3

Figure 2.1: Sodium conductance after adding noise

2.3 Discussion

While the method of adding a fluctuating current term $\xi_V(t)$ to the equation is
simple, it may not fully capture the stochastic behaviour of ion channels that
give rise to channel noise. It is possible that the noise term is also dependent
on V, or other variables. Additionally, a major limitation of this method is the
lack of a standardised approach for quantifying the intensity of the noise, which
can make it difficult to compare results across studies.

In paper [1], noise is added to the conductance which translates to current noise
since the latter is dependent on the former according to equation 2.1. We added
the conductance noise to our model as seen in figure 2.2 but, because no available
libraries support time-dependent constants, the values of the current were not
updated according to the formula at each time step. To simulate how it would
have looked like, we made figure 2.3. It shows potassium and sodium current
that both are dependent on time and voltage, and that has a random noise
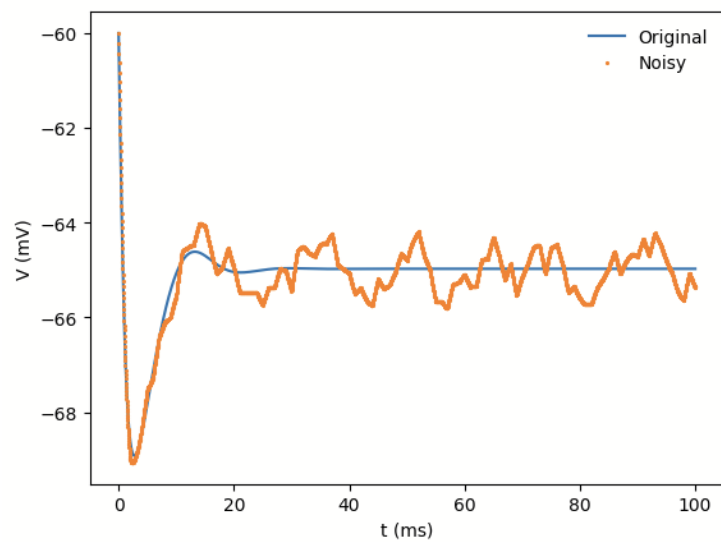constant. The difference is that the noise was not added during the recording
but afterwards.
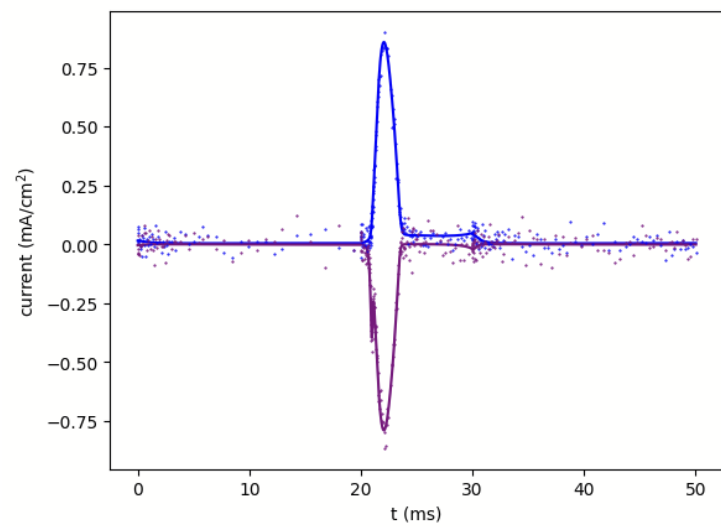
9

Figure 2.2: Voltage after adding current noise

Figure 2.3: Noise in current after adding conductance noise

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