Computational Neuroscience, CS F433

Semester II, 2022-2023

Recreation and Analysis of Results Obtained in Hodgkin Huxley Papers of 1952 Using Neuron Simulator

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Acknowledgements

At the outset of this report, we would like to acknowledge and extend our gratitude to all those individuals without whom the completion of this report would not have been possible – primarily, we would like to thank Ms. Basabdatta Bhattacharya, the Instructor-in-Charge of the course Computational Neuroscience [CS F433], for providing us with this opportunity and for enabling us to gain a deeper understanding on the topic of Hodgkin and Huxley's neuron model. We would like to sincerely thank our instructor for her guidance and constant support which helped us greatly during the course of writing this report. Through this project, we were exposed to a considerable amount of new information regarding a topic that was in uncharted waters for us prior, the exploration of which then caused our interests to bloom. We are profoundly grateful for this opportunity.

Abstract

The Hodgkin-Huxley model, which was proposed by Alan Hodgkin and Andrew Huxley in 1952, is a momentous contribution to the field of neuroscience, as it provided the first quantitative explanation of how action potentials are generated in neurons. This report explores the Hodgkin-Huxley model and aims to understand and reproduce the results that were obtained by them.

To achieve this objective, the report is divided into two sections. In the first section, we provide an explanation of the results pertaining to the Hodgkin-Huxley model of the neuron. This includes an overview of the model's mathematical formulation and the key concepts behind it. We also discuss the implications of their research and the impact it has had on our understanding of how neurons function.

In the second section, we use the NEURON software suite to replicate the plots obtained by Hodgkin and Huxley. This involves applying their mathematical formulation to a computational model of a neuron and visualising the resulting data. By doing so, we are able to gain a deeper appreciation for the experimental techniques used by Hodgkin and Huxley, as well as the insights they provided into the workings of the nervous system.

By delving into the underlying mathematics and replicating their results, we are able to gain a more nuanced understanding of how neurons function and the impact of Hodgkin and Huxley's pioneering work.

Introduction

The idea of membrane potential – the voltage difference across a neuron's cell membrane – is the very foundation of the Hodgkin-Huxley model. This potential difference, which is essential for neuronal signalling, is generated due to the uneven distribution of ions inside and outside the cell.

As per the Hodgkin-Huxley model, ions migrate through a neuron's membrane via ion channels. These channels are specialised proteins that only permit specific ions to pass through them. The model includes ion channels of several sorts, such as leak, sodium, and potassium channels. Each of these channels has a different conductance, which reflects how easily ions may pass through it.

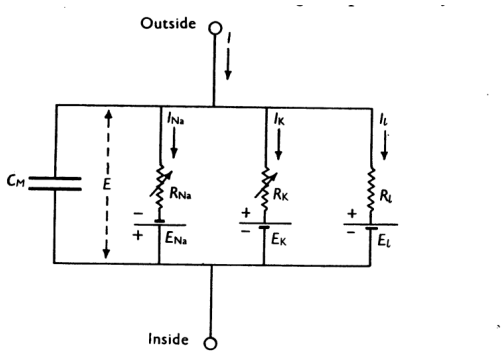
The dynamics of the membrane potential and ion conductances over time are described by the Hodgkin-Huxley model using a set of differential equations. These equations account for both the passage of ions across the membrane and the opening and closing of ion channels.

According to the Hodgkin-Huxley model, ion channels, which are specialised proteins that only allow specific ions to pass through them, allow ions to move through the membrane of a neuron. Ion channels of various types, including sodium, potassium and leak channels, are included in the model. The conductance of each of these channels is different and it indicates how easily ions may move through it. Via the experimental results, Hodgkin and Huxley were able to model the electrical behaviour of the neuron. They were able to explain a trilogy between

neuronal behaviour, mathematical equations which can model these neurons and physical circuits which can behave in a similar manner.

In this report we will use the NEURON simulator to replicate some of the images of these series of papers by using some packages and will also use the mathematical formulations in these papers to plot some curves in order to justify their results using some python libraries.

Electrical counterpart to ion channel currents in neurons:



Here, I_{Na} and I_K represent the current carried by sodium and potassium ions respectively. I_l represents the leak current, which denotes the current carried by other ions like chloride. The currents are through the membrane by two possible methods. One is by charging membrane capacity (C_M) , or by the movement of ions through the resistances(R_{Na}, R_K, R_l), which are in parallel with the capacitance. g_{Na} and g_K are the conductances of sodium and potassium respectively. Hodgkin and Huxley determined that g_{Na} and g_K are functions of time, and E_{Na} , E_K, E_l, g_l, and C_M are constants. Hodgkin and Huxley thus demonstrated how electrical situations can replicate the neuronal behaviours during some current stimulus (I, here).

To demonstrate similar results we will be explaining the plots of current and voltage clamp methods and their variations that we obtained by using the NEURON simulator.

Ionic Conductance and Membrane Potential

It was noted that sodium conductance increased much more rapidly than that of other ions in response to change in membrane potential. This was attributed to charged molecules being present on both sides of the membrane, and derived that sodium conductance is directly proportional to the number of these molecules. Thus changes in ionic permeability depends on a component of the membrane which has a large charge or is a dipole. Ultimately, there was no evidence of any change in current associated with sodium permeability, apart from that of sodium ions themself.

In the subsequent section, we will try to reflect upon some of these findings by replicating some sodium and potassium conductance plots using some of the mathematical formulations of the Hodgkin-Huxley model.

Literature review

Hodgkin and Huxley published a series of four papers in 1952, three of which form a large chunk of the literature that was studied over the course of writing this report.

We start with an introduction to the notion of ionic conductance by Hodgkin and Huxley in this paper. The 1952 (a) edition of paper describes a quantitative description of membrane current and its significance in nerve conduction and excitation. They underline the vital part it plays in determining membrane potential, and establish the behaviour of sodium and potassium ions by conducting studies on the squid giant axon. They also suggest a mathematical framework to describe the variations in ionic conductance during the formation and propagation of action potentials.

The 1952 (b) edition of paper gives us a detailed analysis of each element that contributes to membrane conductivity in the giant axon of the squid species *Loligo*. They specifically look at how ions like sodium, potassium, and others affect how the membrane conducts overall. They present empirical data and equations that offer insight into the behaviour of ionic currents and the intricate mechanisms driving membrane conductance. They do this by combining experimental observations and mathematical modelling.

The 1952 (d) paper provides explanations for the currents that pass through the squid giant axon's membrane as sodium and potassium ions. To understand how sodium and potassium currents behave differently depending on the voltage, Hodgkin and Huxley give extensive experimental results and mathematical models.

They provide important insights into the mechanisms behind the electrical characteristics of the membrane by discussing the relative contributions of these ions to the generation and propagation of action potentials.

These papers laid the groundwork for the modelling of equations that we use to obtain the time course of the membrane potential and the ionic currents during an action potential, as predicted by the Hodgkin-Huxley model. The graphs we tried to simulate complement the experimental results and explanations described in the paper.

Methodology

The Hodgkin Huxley papers framed a mathematical model suitable for their experimental results, and tried to explain their model for action potentials and ion channels in quantitative terms.

We also try to simulate a neuron under varying membrane potentials and currents to get the shape of an action potential by plotting some variations. This is followed by fitting equations to the various parameters describing the mechanisms in Hodgkin Huxley models, and plotting the current and potential values based on these equations.

First, we construct a model neuron using the Python NEURON library and record its behaviour with changing membrane potentials (under a current clamp) and membrane currents (under a voltage clamp). We then vary different attributes which are available in NEURON for “iclamp and vclamp” functions like dur, amp ,delay and so on to analyse the respective effects on the behaviours of the dependent variables.

For the next part, we started by defining similar mathematical notation for an electrical system representation of a neuron, focusing on the Potassium (K) and Sodium (Na) voltage-gated ion channels. After setting up the differential equations from the papers, we solve them to compute graphs for parameters describing the ion channel mechanisms and currents under varying conditions of membrane potentials. For this we have used the python library - “odeint” for solving differential equations.

Results And Discussions

In this section, we analyse the plots we obtained from NEURON simulations and other python packages.

We have recreated 14 images from the Hodgkin - Huxley series of papers and now we will analyse these images.

In a voltage clamp, the membrane potential of a cell is held at a constant voltage while the current flowing across the membrane is measured. The resulting graph shows the relationship between the membrane current and the membrane voltage.

In a current clamp, a constant current is applied to a cell and the resulting changes in membrane potential are measured. The resulting graph shows the relationship between the membrane potential and the injected current, and is typically represented as a single trace. The trace provides information about the excitability and responsiveness of the cell membrane.

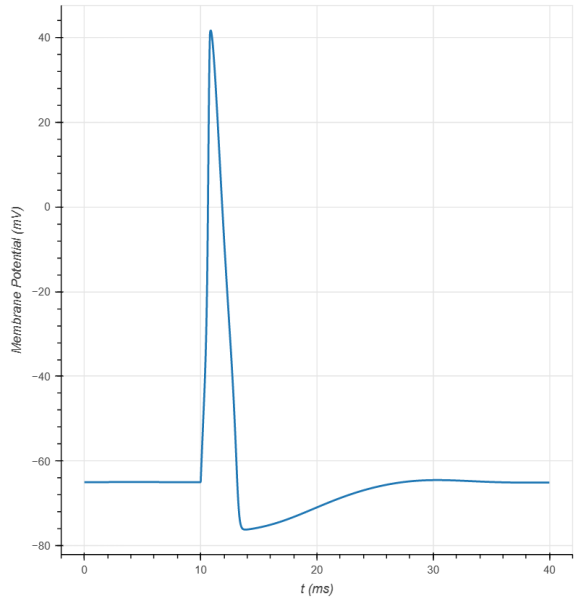


Fig 1 : Membrane potential (mV) vs time (msec)

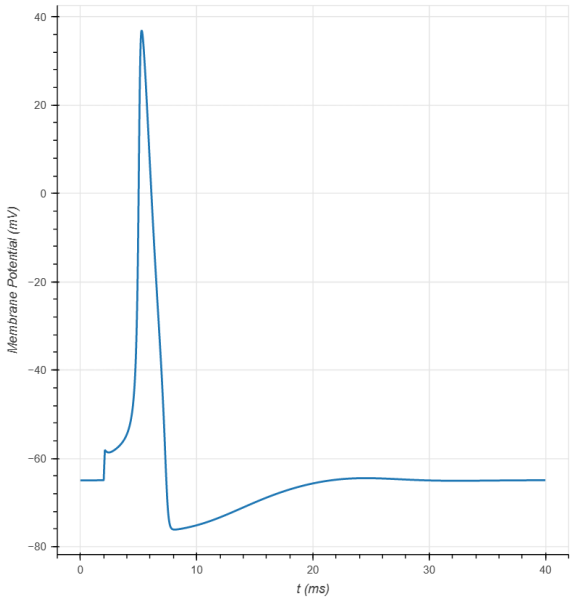


Fig 2 : Membrane potential (mV) vs time (msec)

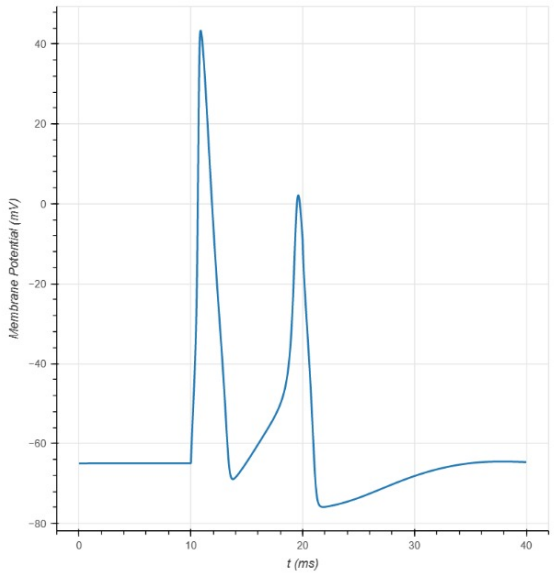


Fig 3 : Membrane potential (mV) vs time (msec)

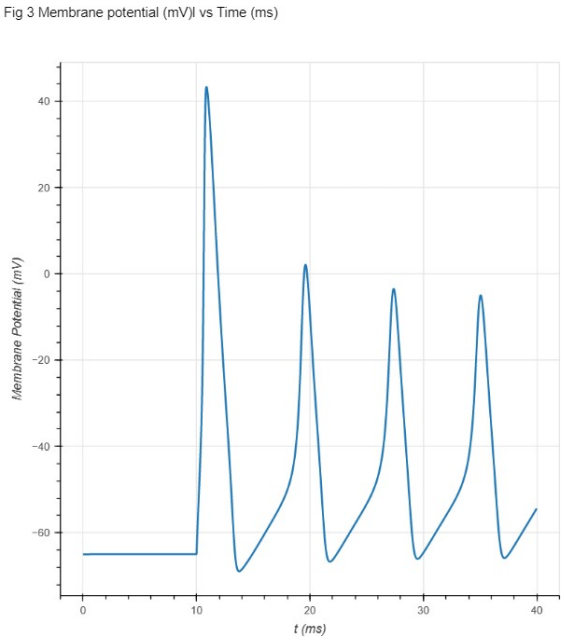


Fig 4 : Membrane potential (mV) vs time (msec)

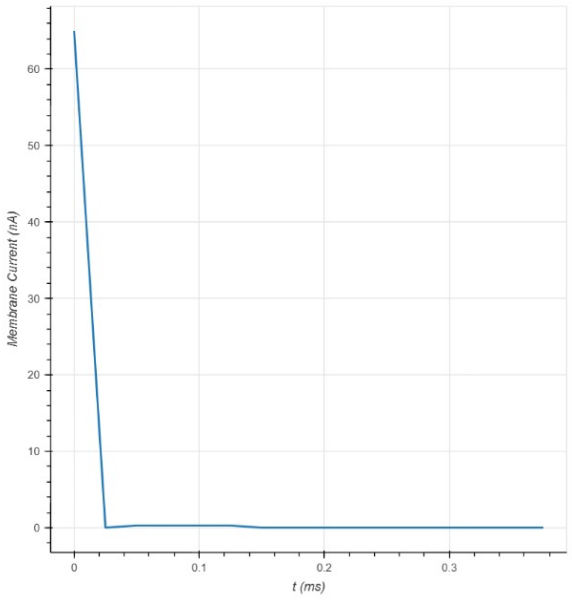


Fig 5 : Membrane current (nA) vs time (msec)

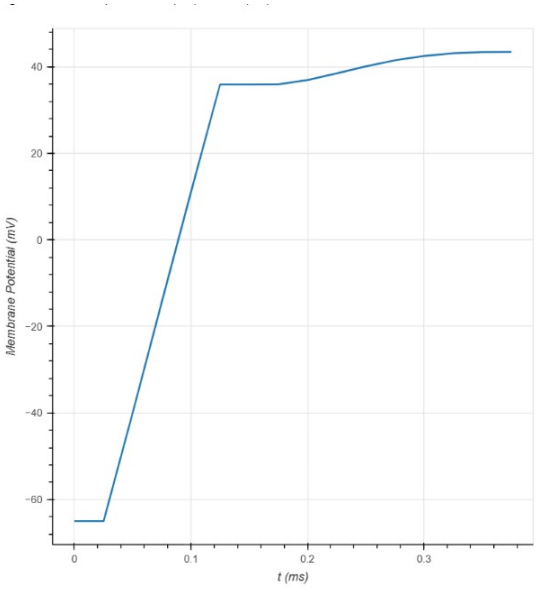
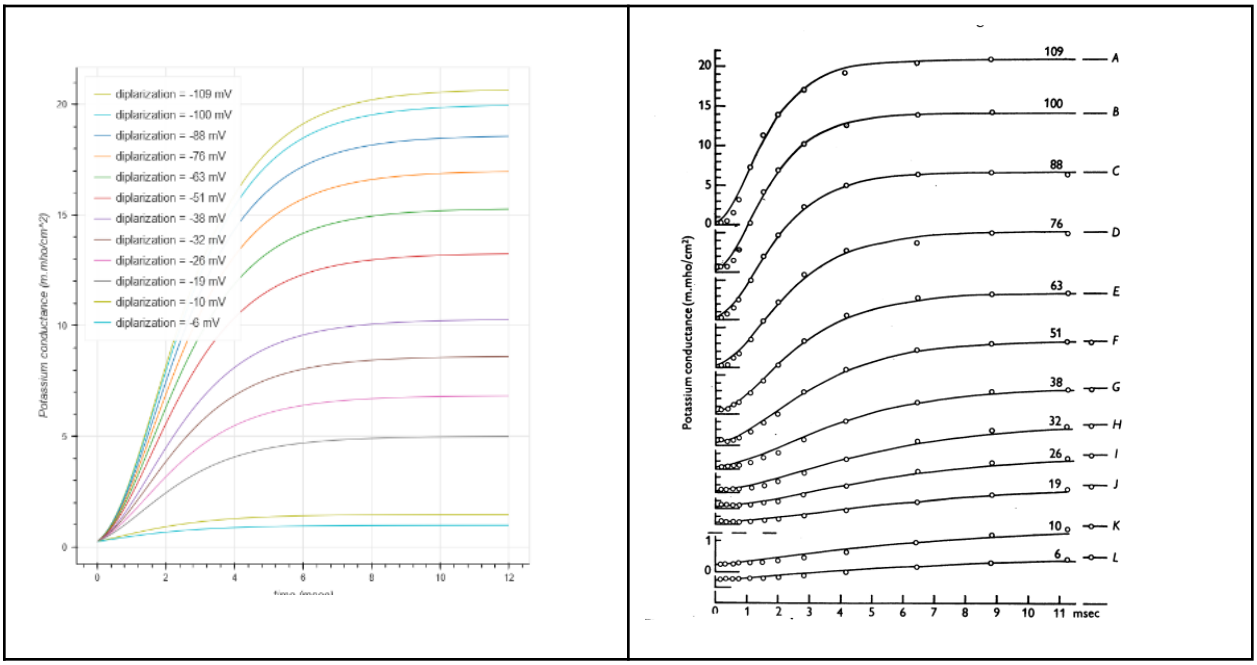


Fig 6 : Membrane potential (mV) vs time (msec)

One interesting point to note is that increasing the duration of current stimulus in Fig 1 - 4, resulted in increased number of spikes as is expected from the theoretical analysis of the Hodgkin Huxley model.

Fig 7 Potassium ion conductance g_K vs. time in msec, at different degrees of depolarizations.



y-axis: potassium conductance g_K

x-axis: time in msec

Fig 7 shows the rise of potassium conductance associated with different depolarizations.

This graph shows how the potassium conductance decreases when the voltage to which the neuron membrane is depolarized becomes less negative.
This graph is based on the following equation used to measure the Potassium conductance:

$$g_K = \overline{g_K}\, n^4 \text{ ---------- (1)}$$

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n \text{ ----- (2)}$$

The g_K represents the potassium conductance of the channel, which is a measure of how easily ions can flow through it. $\overline{g_K}$ is a constant with the dimensions of conductance/cm^2. The variable n represents the proportion of these particles that are in the correct position to allow ion flow through the channel.

The rate constants α_n and β_n determine how quickly the channel opens and closes in response to changes in membrane voltage. These rate constants vary with voltage, but not with time. α_n determines the transfer in the opposite direction. If a particle has a negative charge α_n should increase and β_n should decrease when the membrane is depolarized.

The equations specifically describe the behaviour of the potassium ion channel, which allows potassium ions to cross the cell membrane when four similar particles (i.e., potassium ions) occupy a certain region of the membrane.

In resting state i.e at $V = 0$ and $t = 0$ the value of $n = n_0$ is given by the equitation -

$$n_0 = \frac{\alpha_{n0}}{\alpha_{n0} + \beta_{n0}}$$

When the value of voltage V changes, α_n and β_n will take the voltage corresponding to the new voltage. The solution of the differential equation (2) which satisfies the condition that at $t = 0$,

$$n = n_0 \text{ is}$$

$$n = n_\infty - (n_\infty - n_0)\, exp(-t/\tau_n) \text{ ------ (3)}$$

$$\text{Where } n_\infty = \alpha_n/(\alpha_n + \beta_n) \text{ ---------- (4)}$$

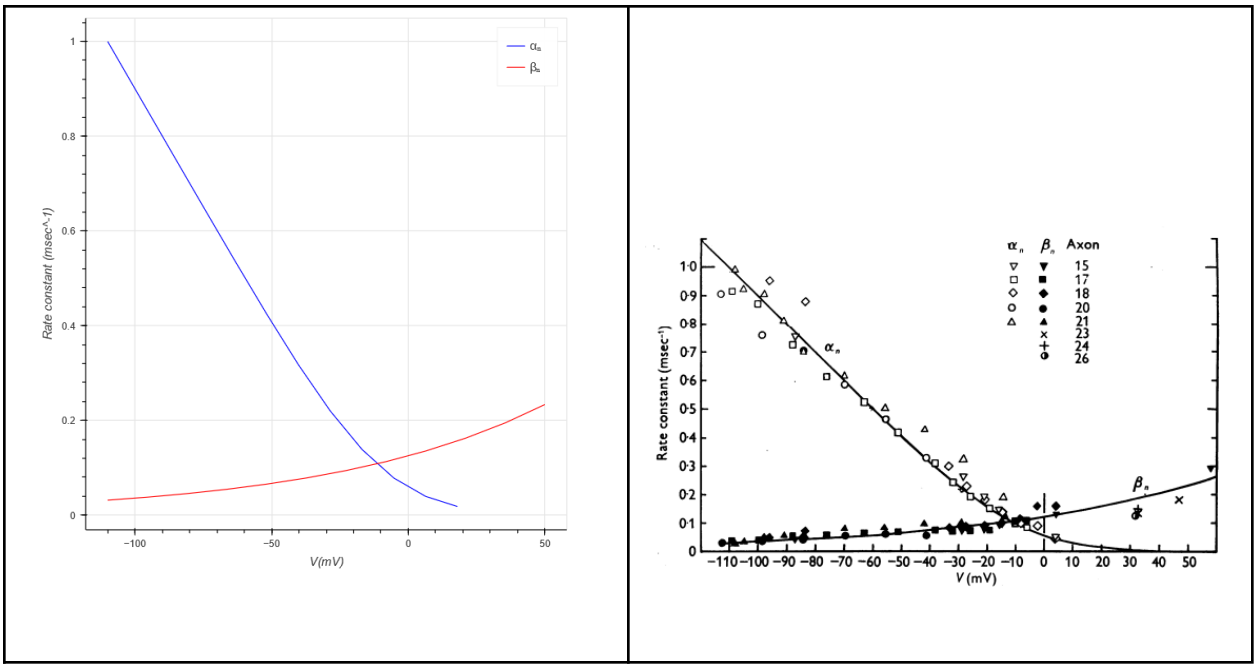
$$\text{And } \tau_n = 1/(\alpha_n + \beta_n) \text{ ----------(5)}$$

Substituting these in the equation (2) we get the resulting equation as:

$$g_k = \{(g_{K\infty})^{\frac{1}{4}} - [(g_{K\infty})^{\frac{1}{4}} - (g_{K0})^{\frac{1}{4}}]\, exp(-t/\tau_n)\}^4, \text{ -------- (6)}$$

Where $g_{K\infty}$ is the value which the conductance finally attains and g_{K0} is the conductance at $t = 0$.

Fig8 Rate constants α_n and β_n in msec^{-1} vs. membrane potential in mV.



y-axis: The rate constants determining the rise (α_n) or fall (β_n) of potassium conductance at 6°C.

x-axis: The membrane potential minus resting potential in seawater.

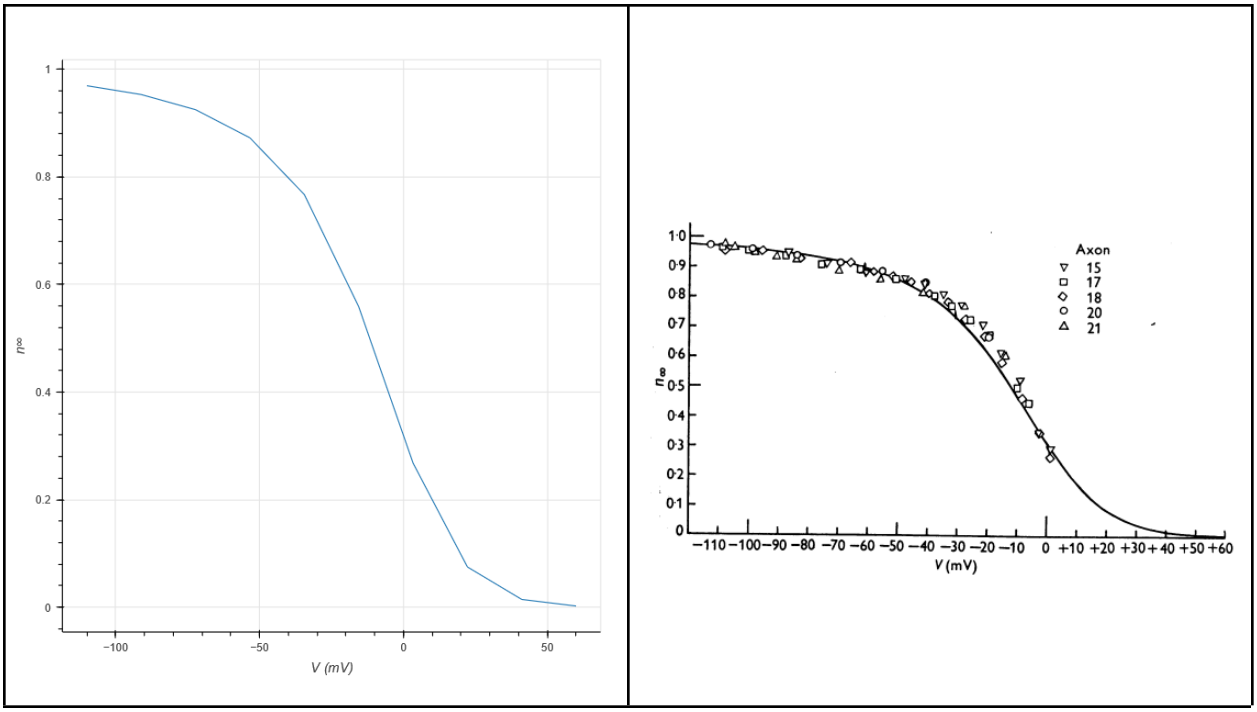
The value of α_n ans β_n are calculated using the equations -

$$\alpha_n = \frac{0.01(V+10)}{[exp\frac{V+10}{10}-1]} \text{ ------ (8)}$$

$$\beta_n = 0.125\, exp(V/80) \text{ -------(9)}$$

It can be inferred from the graph that the value of α_n decreases and β_n increases as the membrane potential becomes more and more positive i.e as the membrane is depolarized, which means the rate of transfer from outside to inside decreases and in turn the transfer from inside to outside increases as the depolarization increases.

Fig 9 n_∞ i.e. Fraction of potassium ions inside the membrane at infinite time vs. membrane potential in mV.



x-axis: The membrane potential minus resting potential in seawater.

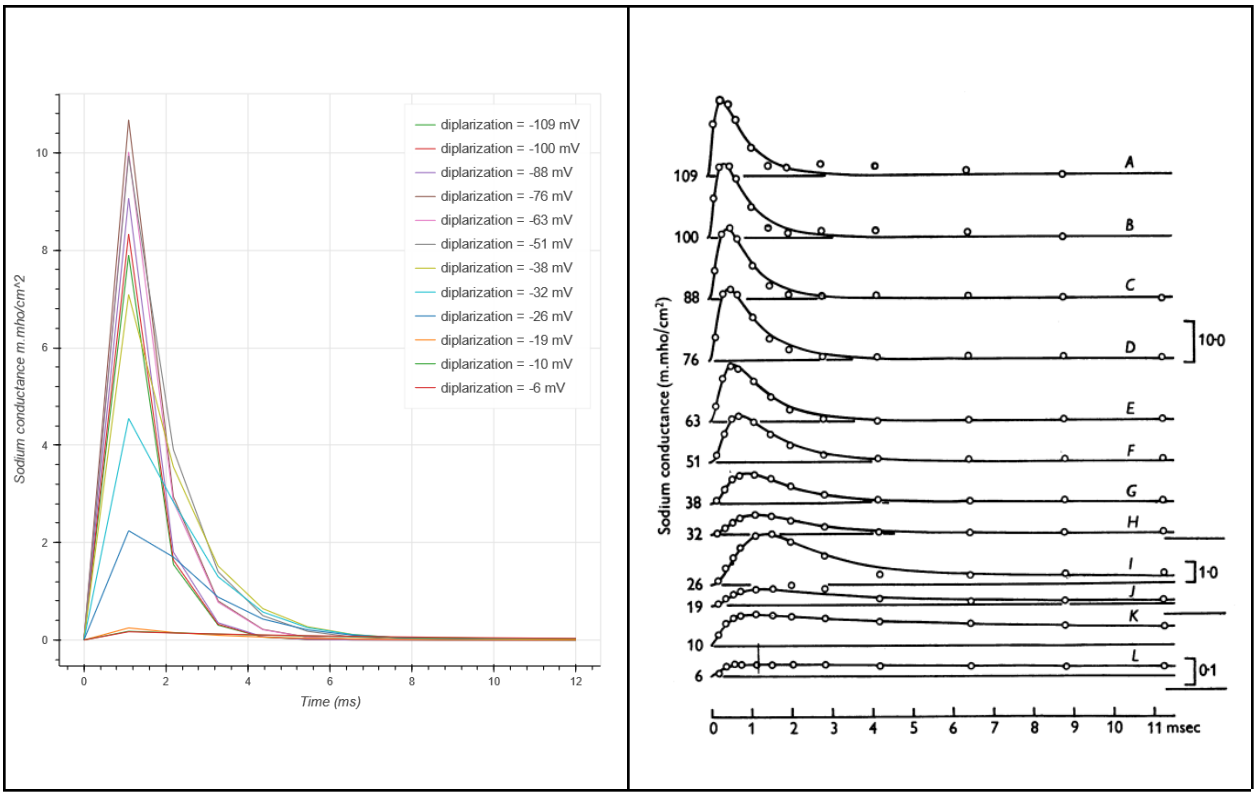
y-axis: n_∞ - represents the proportion of these particles inside the cell membrane at infinite time.

n_∞ is calculated from the steady potassium conductance by the equation (4).

$$n_\infty = \alpha_n/(\alpha_n + \beta_n)$$

It can be inferred from the above graph that the value n_∞ decreases as the depolarization increases. This means the number of particles to allow the flow of potassium ions through the ion channels decreases, thereby decreasing the conductivity of potassium ions.

Fig 10 Sodium ion conductance g_{Na} vs. time in msec, at different degrees of depolarizations.



Y-axis: Sodium conductance g_{Na} and X-axis: Time in msec

HH carried out a comparable analysis of gNa, which was more complicated than for gK since gNa inactivates. They assumed that sodium conductance could be derived from two first-order equations rather than one second-order equation for an easier calculation. Equations used to describe the conductance of Na vs time are -

$$g_{Na} = m^3 h \overline{g_{Na}} \quad \text{-------- (10)}$$

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m \quad \text{-------- (11)}$$

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h m \quad \text{--------- (12)}$$

$\overline{g_{Na}}$ is constant and α_m and β_m are functions of V but don't depend upon t.

m represents the proportion of activating molecules on the inside and m the proportion of activating molecules on the inside and $1 - m$ the proportion outside.

h is the proportion of inactivating molecules on the outside and $1 - h$ the proportion on the inside.

α_m or β_h and α_h or β_m is the transfer rate constants in inward and inward and outward directions respectively.

The solutions of equations 11 and 12 which satisfy the boundary conditions $m = m_0$ and $h = h_0$ at $t = 0$ are -

$$m = m_\infty - (m_\infty - m_0)exp(-t/\tau_m) \text{ -------- (13)}$$

$$h = h_\infty - (h_\infty - h_0)exp(-t/\tau_h) \text{ -------- (14)}$$

$$m_\infty = \alpha_m/(\alpha_m+\beta_m) \; and \; \tau_m = 1/(\alpha_m + \beta_m)$$

$$m_\infty = \alpha_m/(\alpha_m+\beta_m) \; and \; \tau_m = 1/(\alpha_m + \beta_m)$$

m_0 can be neglected since in resting state the sodium conductance is very small compared with the value attained during a large depolarization. Also h_∞ can be neglected because inactivation is very nearly complete if V < -30 mV.

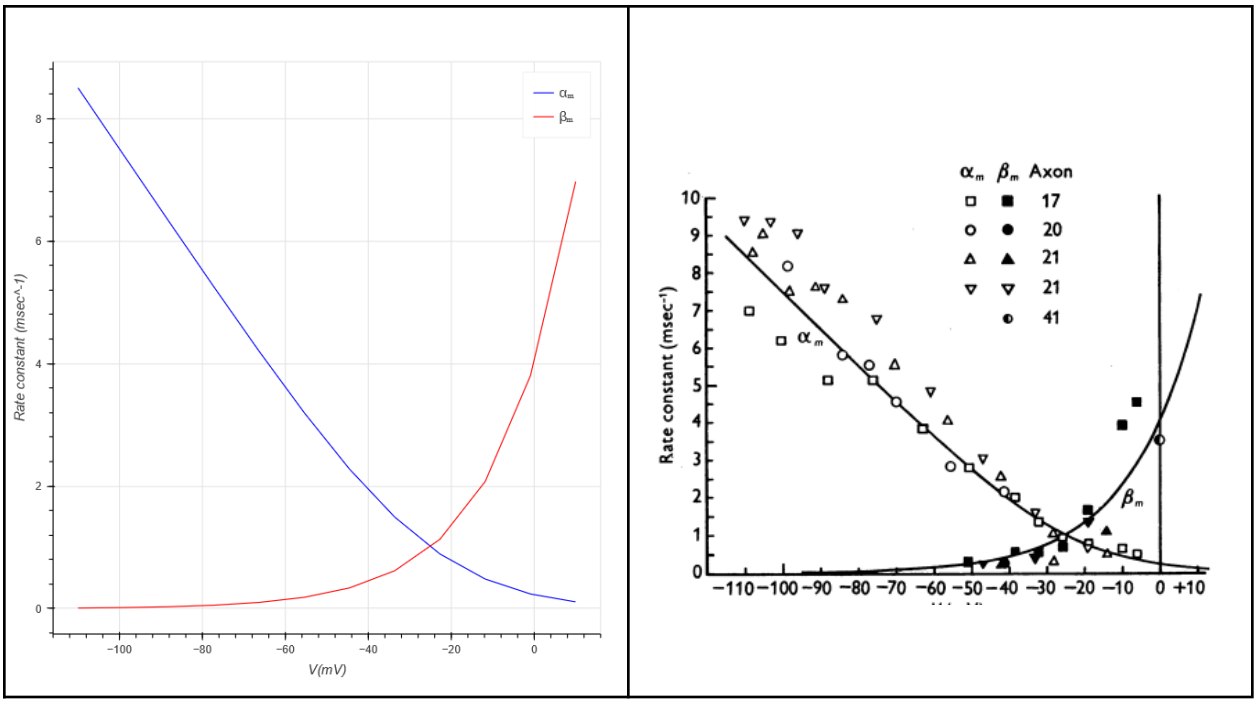
Substituting these solutions in equation 10, the expression for the sodium conductance becomes -

$$g_{Na} = g'_{Na}[1 - exp(-t/\tau_m)]^3 exp(-t/\tau_h) \text{ --------- (15)}$$

This is the resulting equation used to plot the above graph.

From the graph, we can infer that the value of g_{Na} first increases and reaches a maximum value at nearly 1 ms on and then decreases rapidly. The maximum value that g_{Na} reaches increases as the negative value of depolarization increases.

Fig 11 Rate constants α_m and β_m in msec^{-1} vs. membrane potential in mV.



Y-axis: The rate constants determining the rise (α_n) or fall (β_n) of potassium conductance at 6°C.
X-axis: The membrane potential minus resting potential in seawater.

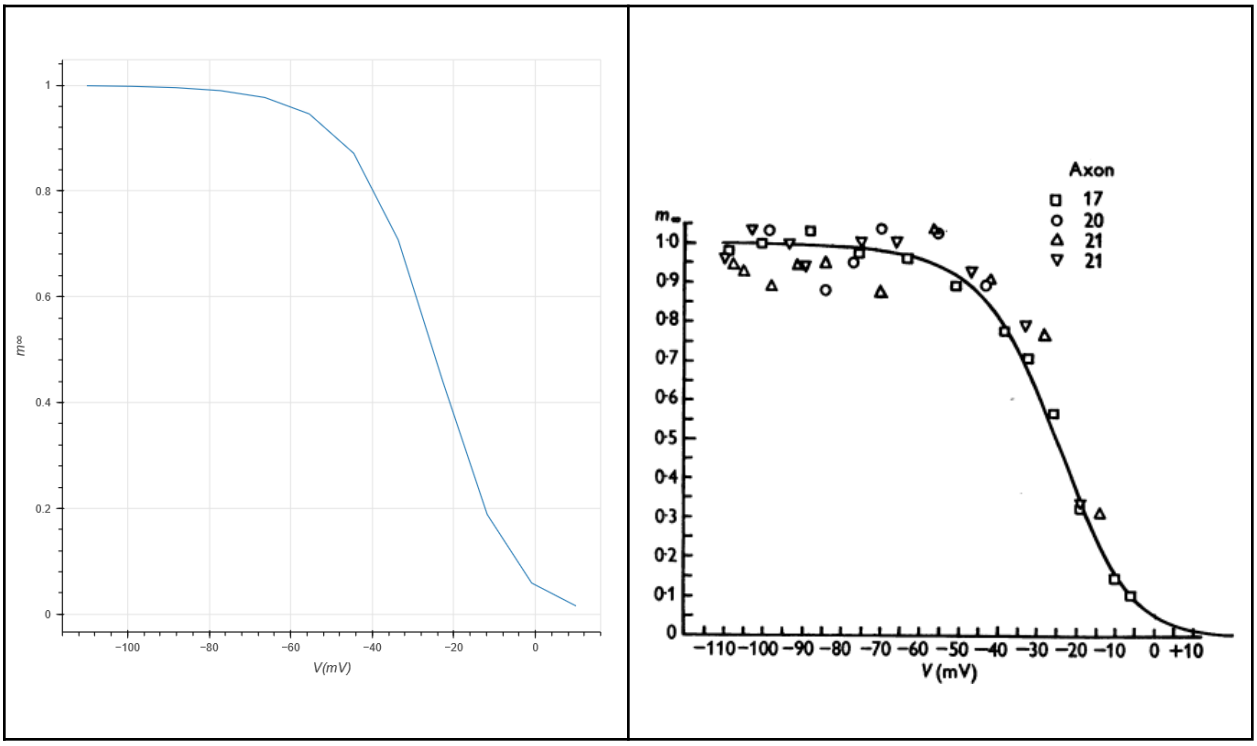
The value of α_m ans β_m are calculated using the equations -

$$\alpha_m = \frac{0.01(V+25)}{[exp\frac{V+25}{10}-1]} \text{ ------ (16)}$$

$$\beta_m = 4\, exp(V/18) \text{ -------(17)}$$

It can be inferred from the graph that the value of α_m decreases and β_m increases as the membrane potential becomes more and more positive i.e as the membrane is depolarized, which means the rate of transfer from outside to inside decreases and in turn the transfer from inside to outside increases as the depolarization increases.

Fig 12 m_∞ i.e. Fraction of sodium ions inside the membrane at infinite time vs. membrane potential in mV.



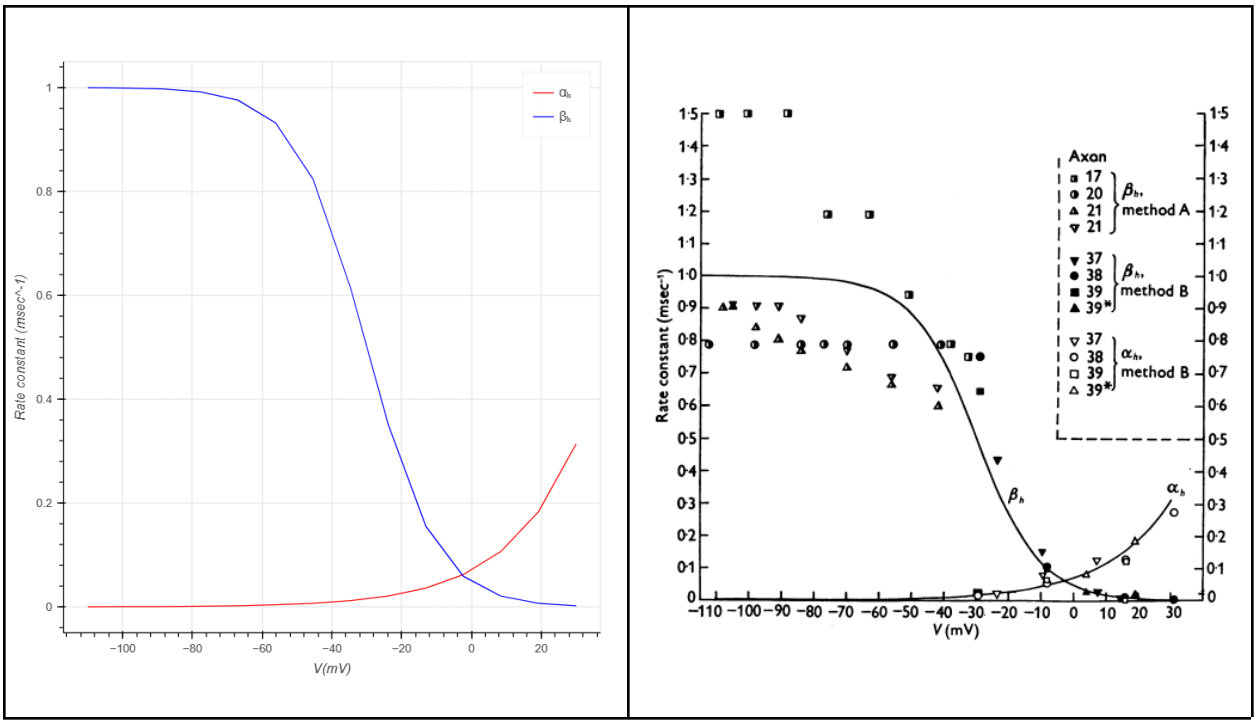
X-axis: The membrane potential minus resting potential in seawater.
Y-axis: m_∞ - represents the proportion of activating molecules on the inside of the membrane at infinite time, that is in the correct

m_∞ is calculated from the steady potassium conductance by the equation -

$$m_\infty = \alpha_m/(\alpha_m + \beta_m)$$

It can be inferred from the above graph that the value m_∞ decreases as the depolarization increases. This means the number of particles to allow the flow of sodium ions through the ion channels decreases, thereby decreasing the conductivity of sodium ions.

Fig 13 Rate constants α_h and β_h in msec^{-1} vs. membrane potential in mV.



Y-axis: Rate constants of inactivation (α_h and β_h)

X-axis: Membrane potential (V) in mV

The rate constants for the inactivation process were calculated from the expressions:

$$\alpha_h = h_\infty / \tau_h$$

$$\beta_h = (1 - h_\infty)/\tau_h$$

The smooth curves were calculated using

$$\alpha_h = 0.07 exp(V/20)$$

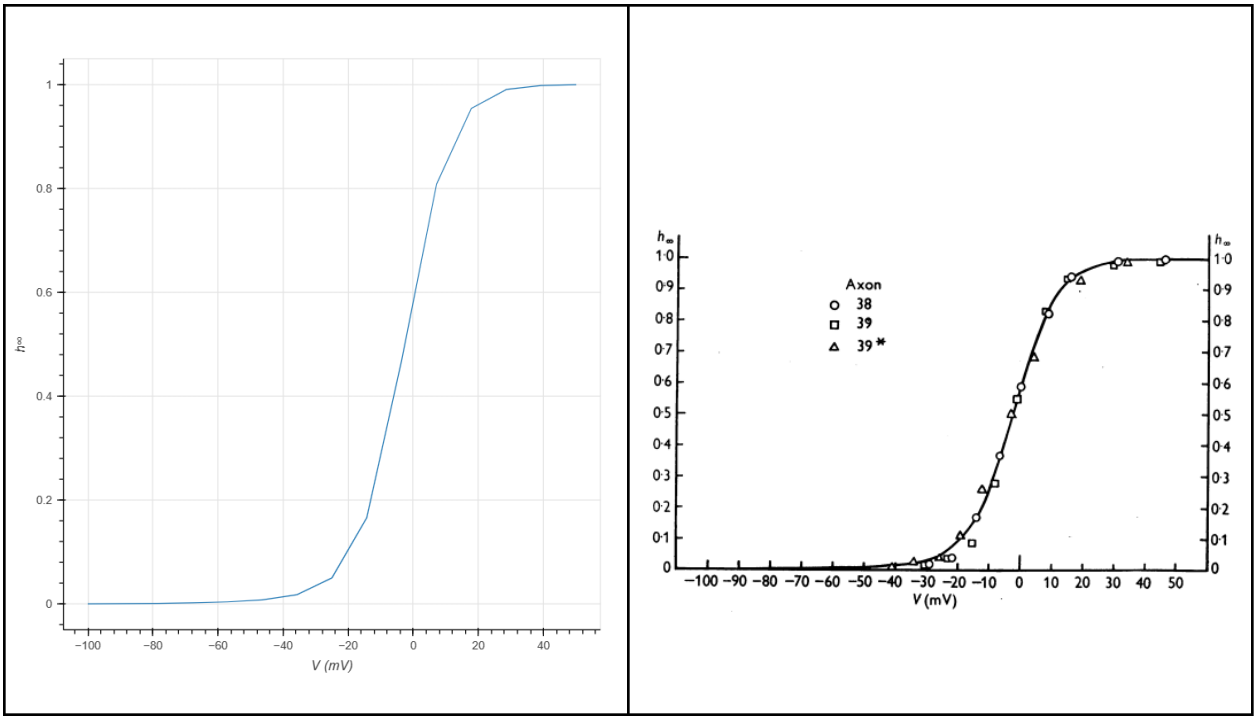
$$\beta_h = \frac{1}{exp(\frac{V+30}{10})+1}$$

The rate constant α_h represents the rate of transition of the inactivation gating particle h from the open state to the closed state. It increases with depolarization of the membrane potential and is usually a steeply increasing function of voltage. This is because the inactivation gating particle h becomes more likely to enter the closed state as the membrane potential becomes more positive.

The rate constant β_h represents the rate of transition of the inactivation gating particle h from the closed state to the open state. It decreases with depolarization of the membrane potential and is typically a slowly decreasing function of voltage. This is because the inactivation gating particle h becomes less likely to leave the closed state and re-enter the open state as the membrane potential becomes more positive.

At resting membrane potentials, both α_h and β_h are relatively low, indicating that the inactivation gating particle h is mostly in the open state. As the membrane potential depolarizes, α_h increases and β_h decreases, which causes an increase in the fraction of inactivation gating particles in the closed state and a reduction in the availability of sodium channels for activation.

Figure 14 h_∞ i.e. steady state inactivation fraction vs. membrane potential in mV.



Y-axis: h_∞ i.e. steady state inactivation fraction

X-axis: membrane potential in mV.

The smooth curve is calculated from the relation:

$$h_\infty = \alpha_h/(\alpha_h + \beta_h)$$

If V > - 30 mV, this expression approximates to the simple expression used in a previous paper

$$h = \frac{1}{1+exp(V_h - V)}$$

where V_h is about -2 and is the potential at which h_∞ = 0.5.

The paper notes that this equation is similar to describing how the ratio of negatively charged particles on the outside of a membrane to the total number of such particles on both sides of the membrane changes with potential. This similarity suggests that the inactivation of sodium channels may be due to the movement of a negatively charged particle that blocks the flow of sodium ions when it reaches the inside of the membrane.

HH clarify that this physical theory does not by itself lead to satisfactory functions for α_h, β_h and additional assumptions are necessary to derive these functions.

The h_∞ vs V graph as shown plots the steady-state inactivation of the voltage-gated sodium channels as a function of membrane potential. In the Hodgkin-Huxley model, the inactivation gating variable h represents the fraction of sodium channels that are inactivated (closed) at a given membrane potential. This inactivation occurs when the membrane potential becomes depolarized, meaning that it becomes more positive than the resting potential of the cell.

This graph typically has a sigmoidal shape, with a midpoint voltage, V_h, at which half of the sodium channels are inactivated. The slope of the curve represents the steepness of the voltage dependence of the inactivation process.

At resting membrane potentials, the inactivation gating variable h is usually low, indicating that most of the sodium channels are available for activation. As the membrane potential becomes more depolarized, h_∞ increases rapidly, indicating that more and more sodium channels are becoming inactivated. This means that fewer channels are available for activation, which helps to limit the peak amplitude of the action potential and prevent it from becoming too large.

1) **Action Potential Generation**: The Hodgkin-Huxley model demonstrated that the action potential, the electrical impulse in neurons, arises from the interplay of voltage-gated ion channels. By measuring and modeling the conductance of potassium (gK) and sodium (gNa) channels, they showed how the dynamics of these ion channels contribute to the generation and propagation of action potentials.

2) **Ionic Basis of Excitability**: The voltage clamp experiments revealed the voltage dependence of ion channel conductance, providing insights into the ionic basis of neuronal excitability. They found that the conductance of sodium channels increases rapidly during depolarization, allowing sodium ions to flow into the cell and depolarize the membrane. Conversely, the conductance of potassium channels increases slowly, contributing to the repolarization and restoration of the resting state.

3) **Computational Modeling**: The Hodgkin-Huxley model provided a mathematical framework for simulating and understanding the electrical behavior of neurons. By quantifying the conductance changes of potassium and sodium channels and their voltage dependencies, computational models could be developed to simulate the behavior of neurons and neural networks accurately. This model laid the foundation for subsequent computational neuroscience studies.

4) **Neuronal Information Processing**: The findings from the Hodgkin-Huxley experiments and subsequent computational models have deepened our understanding of how neurons process and transmit information. The precise control of ion channel conductance allows neurons to generate and propagate electrical signals with remarkable precision, enabling complex computations and information integration within neural circuits.

The figures and findings from the Hodgkin and Huxley 1952 papers provided crucial insights into the biophysical mechanisms underlying neuronal excitability and led to the development of computational models that continue to be widely used in understanding neural dynamics and information processing in computational neuroscience today. All our replicated images demonstrate these points about the HH model and thus justify it.

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