Understanding the Hodgkin-Huxley Model

CS F433 Computational Neuroscience

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Index

Introduction

The Hodgkin-Huxley (H-H) theory of action potential, developed 50 years ago, is still regarded as one of biology's most significant successes and one of the most important conceptual innovations in neuroscience. The H-H theory laid the groundwork for contemporary computational neuroscience, along with the artificial neural networks of McCulloch and Pitts, the quantal theory of Katz, and the cable theory of Rall, all created around the same period.

Hodgkin and Huxley created two distinct double pulse procedures, the outcomes of which were crucial in creating their model, to illustrate the effectiveness of the voltage-clamp technique. To measure the voltage dependence and time constant of inactivation, which were inherent to the Na+ current but absent from the K+ current, they applied a variable first pulse followed by a second pulse to a potential at which the Na+ permeability pathway was open in their initial protocol. They used their knowledge of the Nernst equation and its implications in their second protocol to provide descriptions of permeability for the Na+ and K+ currents. They understood that ion X would cross the membrane in the direction that pushes the membrane potential towards EX when EX is far from the membrane potential and that the greater the distance between EX and the membrane potential, the larger the ion flux. The initial pulse depolarized the membrane to an open potential allowing permeability. After that, they moved to a set of potentials that extended to EX. Due to the instantaneous voltage clamp, the ion movement at the start of the second pulse would be governed by the difference between EX and the membrane potential. The linear instantaneous I-V relationship, a graphical representation of Ohm's law, was created by plotting the current's peak amplitude versus the second pulse's voltage. This gave the linear instantaneous I-V relationship, a graphical representation of Ohm's Law (I = gV), which was an integral model component and determined the current amplitude over a wide membrane area.

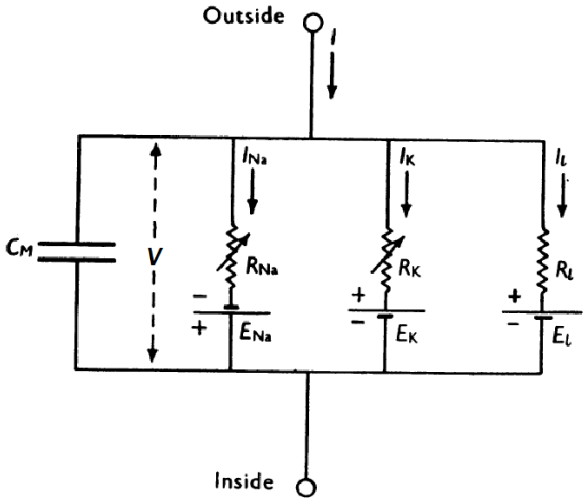


Fig: Representative Circuit Model of the Cell Membrane

In the paper, *Hodgin-Huxley revisited* [1], they investigated the capability of approximate Bayesian computation (ABC) to infer parameter distributions in the fundamental action potential model of Hodgkin and Huxley, for which there is a direct and established relationship to experimental findings. The accuracy of this early work is validated by ABC's ability to produce tight posteriors around the reported values for the gating rates of sodium and potassium ion channels. In contrast, the highly variable posteriors around some voltage dependency parameters indicate that voltage clamp experiments alone cannot constrain the entire model. Hodgkin and Huxley's estimates are nevertheless competitive with those generated by ABC. The inconsistent behavior

of posterior parametrized models under complicated voltage protocols shows that the model may be fully constrained with additional data. This work will serve as the basis for a thorough analysis of the identifiability of frequently employed cardiac models and as a model for instructive, data-driven parametrization of freshly proposed models. In this project, we have attempted to replicate some of the resultant plots obtained in the same paper by using NEURON as a library in Python for computational modeling.

Methodology

1. Anode Break

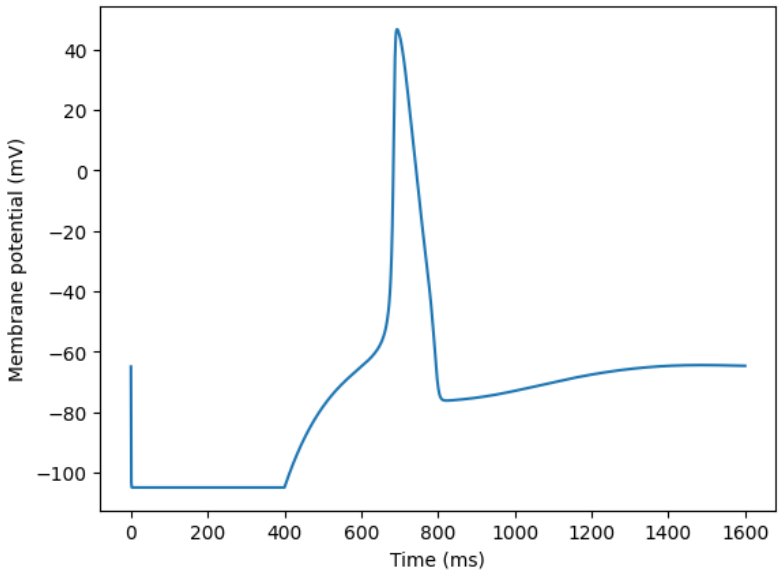


Fig 1: *Stimulus-response representation of the Voltage Protocol, Ref. Fig. 1(a), Anode Break* [2]

The figure above shows the membrane potential of a single neuron over time in response to a current injection using the Hodgkin-Huxley model. The model includes inserting channels in the soma, which generate and propagate action potentials in neurons. In this simulation, a voltage clamp was applied to the neuron for 10 ms, holding the potential at -105 mV, 30 mV below resting potential. This clamp was then released, and the membrane potential was recorded every 0.1 ms for 30 ms. The resulting plot shows the membrane potential gradually depolarizing until it reaches the threshold for an action potential, triggering a rapid and transient spike in the potential, followed by a repolarization phase. The spike times are recorded using an APCount function that detects when the membrane potential reaches a certain threshold. The number of spikes recorded in this simulation can be seen as an indicator of the neuron's excitability under the given conditions.

2. Threshold Excitation

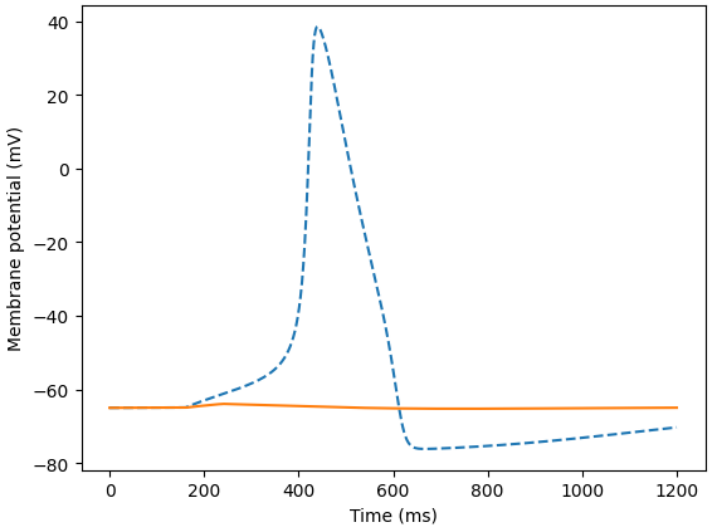


Fig 2: *Threshold Excitation, Ref. Fig 1(b)* [2]

The figure shows two plots of membrane potential as a function of time for two different stimuli in a neuron modeled using the Hodgkin-Huxley model. The neuron has been subjected to membrane depolarization, which increases the membrane potential from its resting state. Depolarization is induced by applying a current stimulus through an electrode placed on the neuron's soma. The first plot, shown with a dashed line, represents the membrane potential response of the neuron to a stimulus of 7 mV, which is sufficient to trigger an action potential (AP) in the neuron.

The second plot, shown with a solid line labeled "2" in yellow, represents the neuron's response to a lower stimulus of 2 mV, which is insufficient to trigger an AP. The depolarization of the neuron's membrane potential to a threshold value of 7 mV activates the voltage-gated Na+ channels, leading to a rapid influx of Na+ ions and a subsequent spike in the membrane potential, representing the AP. The depolarization to a lower value of 2 mV is insufficient to activate the Na+ channels and trigger an AP. However, it may lead to a slight increase in the membrane potential due to the activation of K+ channels.

3. Positive Phase Depolarization

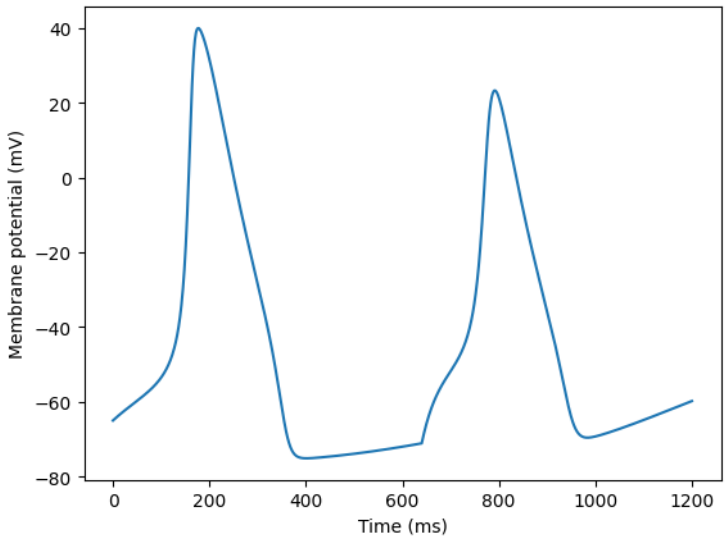


***Fig 3**: Positive phase depolarization, Ref. Fig 1(c)* [2]

The Hodgkin-Huxley model simulated a neuron's membrane potential in response to depolarizing current injections. A 15 mV depolarization is applied to the neuron first, and then an 8 ms time course simulation is applied. In response to the influx of Na+ ions through the voltage-gated Na+ channels, this causes the membrane potential to rise quickly and starts an action potential. A further depolarization of 90 mV is then applied to the neuron, which results in a greater influx of Na+ ions and a more significant action potential. The neuron then fires action potentials for the remaining 15 ms of the time course simulation. We can see that the duration and amplitude of the action potential increase in response to the more depolarizing current injection, consistent with the predictions of the Hodgkin-Huxley model.

4. Oscillation induction

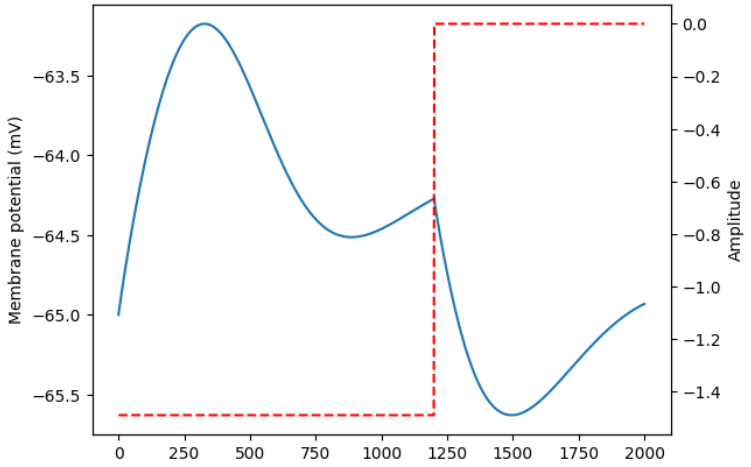


Fig 4: *The induced stimulus current (dotted red) and the resulting fluctuation in membrane potential. In all graphs, the models have reached steady-state by time t = 0 when the stimulus is applied.*
Ref. Fig 1(d) **[2]**

The figure shows the membrane potential response of a neuron model with Hodgkin-Huxley channels under an oscillatory induction protocol. After initially clamping the membrane potential to -75 mV, the model is subjected to a 15-ms current clamp with a constant current amplitude of -1.49 mA/cm^2. This causes the membrane potential to depolarize, which opens voltage-gated ion channels and, in turn, increases sodium and potassium conductances. This causes the membrane potential to rise to above 0 mV, producing an action potential.

The membrane potential returns to a resting state after the current clamp is released and the onset of the second action potential is delayed. The hyperpolarization of the membrane potential, which results in a decrease in potassium conductance and a slower repolarization of the membrane potential, is to blame for this delay.

The amplitude of the current clamp applied to the neuron model during the simulation is shown by the red dashed line in the figure. The time is shown on the x-axis in milliseconds, and the membrane potential is shown on the y-axis in millivolts.

5. Ionic Conductance of Potassium

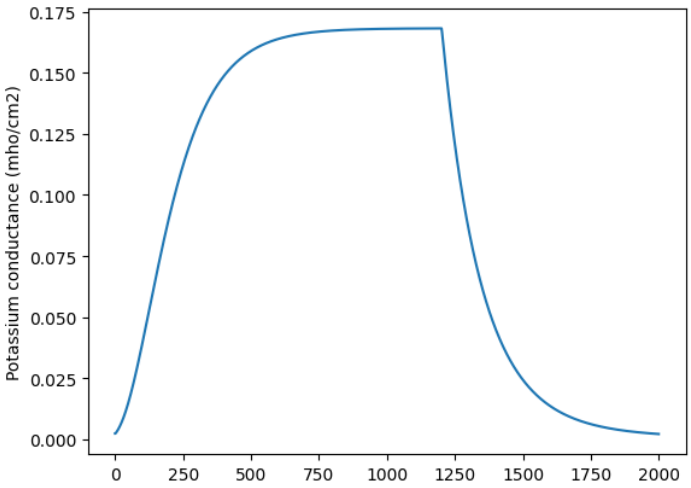


Fig 5: *Representation of distance calculation for potassium conductance between experimental data points and data simulated with functional curation for a single voltage clamp experiment (§3.1). Experimental data points are shown in red, while the simulated trace is shown in solid blue, with points corresponding to the time of experimental recordings marked with circles. Distances between these points and their experimental counterparts (shown in black lines) are used by equation (3.7) to calculate the objective function for ABC. Ref. Fig 2* [2]

The plot shows the simulated potassium conductance over time in a single-compartment neuron modeled using the Hodgkin-Huxley model. The code starts by creating a cell membrane and inserting the Hodgkin-Huxley channels in the soma. The potassium conductance parameter of the channel is set to 0.24, and the membrane potential is set to -25 mV at the center of the soma compartment.

A voltage clamp protocol is then set up to stimulate the neuron with a 15 ms voltage step of 3 mV. The simulation is run for 25 ms with a time step of 0.01 ms. The recording vectors store the membrane potential and potassium conductance at each time step. The plot shows that the potassium conductance initially rises and then falls back to the resting level after the voltage step. This is due to the opening and closing of the potassium channels in response to the voltage clamp stimulus. The Hodgkin-Huxley model describes the ionic conductance of the neuron's membrane in terms of the four main ion channels: sodium, potassium, calcium, and chloride. The model assumes that the ionic conductance depends on the membrane potential, and the opening and closing of ion channels are described by activation and inactivation variables that depend on the voltage. This plot shows the potassium conductance results from the Hodgkin-Huxley model's simulation of the potassium channels' opening and closing dynamics in response to the voltage clamp stimulus.

6. Variation of Ionic Conductance of Potassium with different polarization

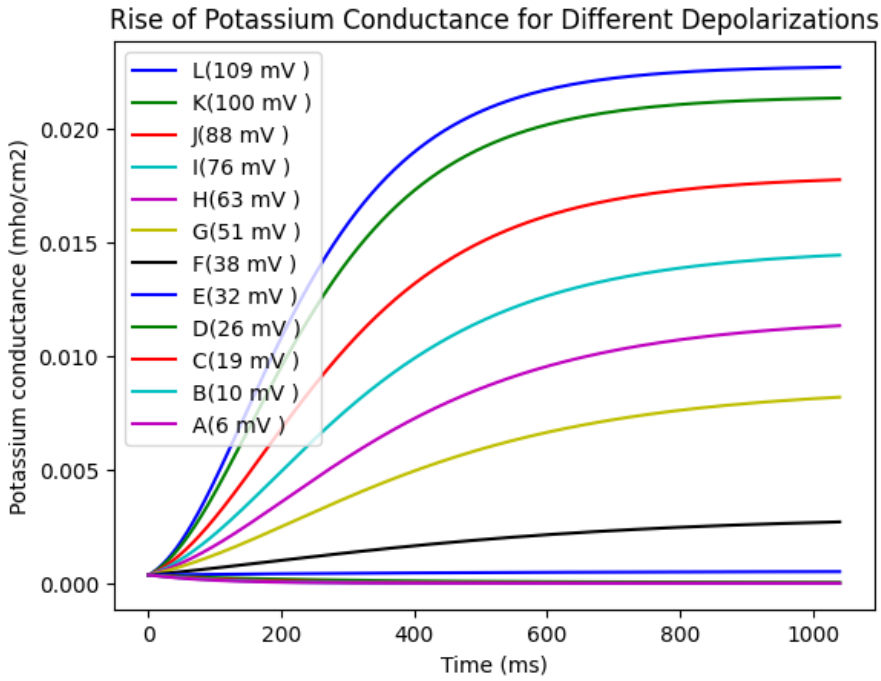


Fig 6: *Rise of potassium conductance associated with different depolarizations. The circles are experimental points obtained on axon 17, temperature 6-70 C, using observations in seawater and choline sea water (see Hodgkin & Huxley, 1952a). The smooth curves were drawn from eqn, (11) with 9KO==0 24 m.mho/cm2 and other parameters, as shown in Table 1. The time scale applies to all records. The ordinate scale is the same in the upper ten curves (A to J) and is increased fourfold in the lower two curves (K and L). The number on each curve gives the depolarization in mV. Ref. Fig 3 Pg. 508* [1]

The plot shows the rise of potassium conductance associated with different depolarizations, as predicted by the Hodgkin-Huxley model. The circles represent experimental data obtained by Hodgkin and Huxley themselves, while the smooth curves were drawn using equation (11) with the parameters shown in Table 1 of their paper. The time scale applies to all records, while the ordinate scale is the same for the upper ten curves (A to J) and increased fourfold for the lower two curves (K and L). Each curve gives the depolarization in mV, with the number one on each curve indicating the depolarization value. The Hodgkin-Huxley model is a mathematical model that describes the generation and propagation of action potentials in neurons. It is based on the properties of ion channels and their behavior in response to changes in membrane potential. The model assumes that the membrane of a neuron contains voltage-gated ion channels that open and close in response to changes in membrane generation and propagation of potential. The Hodgkin-Huxley model describes the kinetics of the voltage-gated sodium and potassium channels, which generate and propagate action potentials. This plot shows that the potassium conductance also increases as the depolarization increases. This increase in conductance is due to

the opening of voltage-gated potassium channels, which allow potassium ions to flow out of the cell and repolarize the membrane potential. This repolarization is necessary for the neuron to return to its resting state and to prevent sustained depolarization, which could harm the cell.

7. Ionic Conductance of Sodium

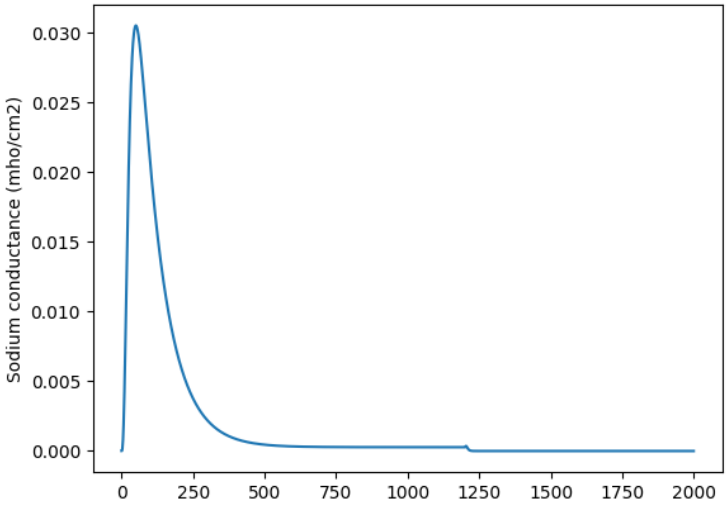


Fig 7: *The plot shows the simulation results of a Hodgkin-Huxley neuron model with a voltage-clamped membrane with the depolarizing potential set to 25 mV. The neuron membrane potential and sodium conductance are recorded and plotted over time. The membrane potential starts at -75 mV and is stepped up to +3 mV for 15 ms by the voltage clamp. As a result, the neuron depolarizes, and sodium channels open, increasing sodium conductance. The sodium conductance curve starts at zero, rises rapidly to a peak, and then declines back to zero as the voltage clamp turns off.*

The Hodgkin-Huxley model describes the behavior of neurons in terms of ionic currents flowing across the neuron membrane. The model assumes that the neuron membrane contains ion channels selectively permeable to different ions, such as sodium and potassium. The opening and closing of these ion channels are voltage-dependent, meaning that they respond to changes in the membrane potential. The figure shows sodium conductance increases rapidly when the neuron is depolarized, reflecting the opening of voltage-gated sodium channels. This increase in sodium conductance triggers the action potential, which is the fundamental mechanism for neuronal communication. Thus, the plot illustrates how the Hodgkin-Huxley model captures the essential biophysical processes underlying neuronal activity.

8. Variation of Ionic Conductance of Sodium with different polarization

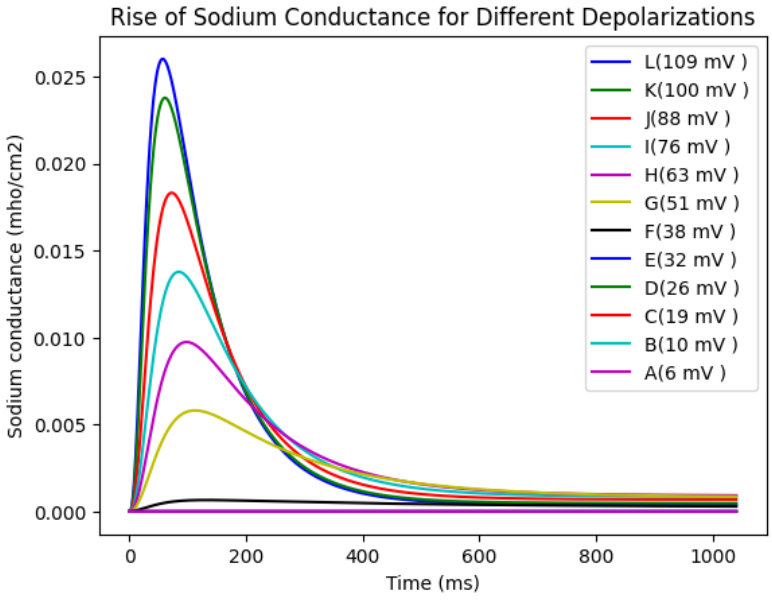


Fig 8: *Changes of sodium conductance associated with different depolarizations. Lines A to H drawn from eqn. 19, I to L from 14, 17, 18 with* g_{Na} *= 70*7 m.mho/cm*^{2}*. The ordinate scales on the right are given in m.mho/cm*^{2}*—the numbers on the left show the depolarization in mV. The time scale applies to all curves. Ref. Fig. 6, Pg. 513* [1]

The plot shows the rise of sodium conductance for different depolarizations in a neuron modeled using the Hodgkin-Huxley model. The Hodgkin-Huxley model describes the behavior of ion channels in the neuronal membrane, which are responsible for generating action potentials. In this model, the membrane potential is governed by the flow of ions through sodium and potassium channels.

As the depolarization increases, the sodium channels open, allowing more sodium ions to flow into the neuron, rapidly increasing sodium conductance. This rapid increase in conductance is seen as a sharp rise in the plot. The peak of the rise in sodium conductance varies with the level of depolarization, with higher levels of depolarization leading to a higher peak.

An increase follows the rise in sodium conductance in potassium conductance, which brings the membrane potential back to its resting state. The potassium conductance peak occurs after the sodium conductance peak, reflecting the time delay in opening potassium channels.

Overall, the plot shows how changes in depolarization lead to changes in sodium and potassium conductance, which in turn affect the membrane potential and the generation of action potentials.

The Hodgkin-Huxley model provides a mechanistic understanding of these processes and has been widely used to study the dynamics of neuronal signaling.

9. Relationship between m_∞ and V

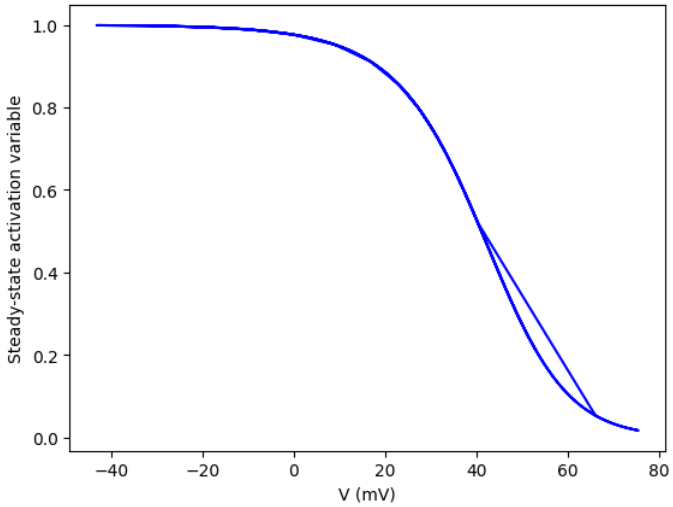


Fig 9*: Abscissa: membrane potential minus resting potential in seawater. Ordinate: mt obtained by fitting curves to observed changes in sodium conductance at different depolarizations (e.g., Fig. 6 and Table 2. The smooth curve is drawn according to eqn. (22). The experimental points are proportional to the cube root of the sodium conductance, which would have been obtained without inactivation. Ref. Fig 8, Pg 516* [1]

The plot shows the steady-state activation variable of the Hodgkin-Huxley sodium channel model as a function of membrane potential. The steady-state activation variable represents the probability that the sodium channels are open at a given membrane potential. As the membrane potential increases, the steady-state activation variable increases and approaches a maximum value, which indicates that more sodium channels are open at higher membrane potentials.

The Hodgkin-Huxley model describes the electrical properties of excitable cells such as neurons and muscle cells. It is based on the idea that the cell membrane contains ion channels that selectively allow ions to flow across the membrane, thereby generating electrical signals. In the model, the sodium channel is described by a set of differential equations that relate the membrane potential to the opening and closing of the channel. The steady-state activation variable is one of the critical variables in the model, and it determines the behavior of the sodium channel in response to changes in the membrane potential.

The smooth curve in the plot represents the theoretical prediction of the steady-state activation variable based on the Hodgkin-Huxley model equations. The experimental points are obtained from measurements of the sodium conductance at different depolarizations, which are

proportional to the cube root of the sodium conductance obtained if there were no inactivation. The agreement between the theoretical prediction and the experimental points indicates that the Hodgkin-Huxley model provides a good description of the electrical properties of excitable cells and that the steady-state activation variable is a valuable concept for understanding the behavior of ion channels.

10. Time Course Of Inactivation And Delayed Rectification

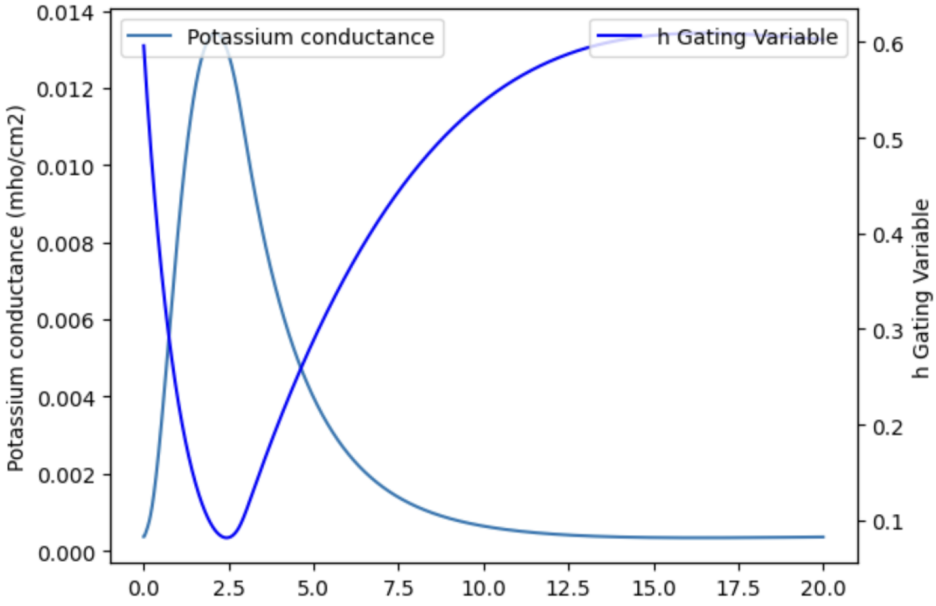
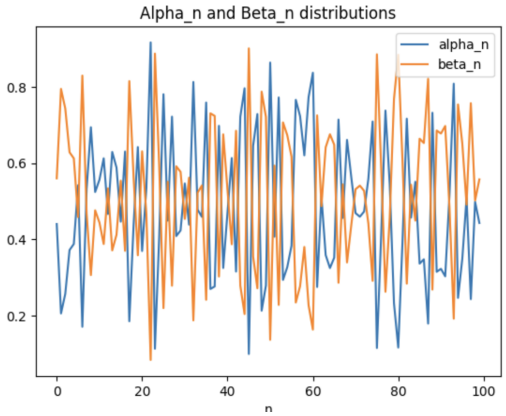


***Fig 10**: Numerical solution of eqn. (26) for initial depolarization of 15 mV and temperature of 6° C. Upper curve: membrane potential, as in Fig. 13. Lower curves show a time course of 9E and h during action potential and refractory period.*

The figure shows the time course of the h gating variable and the potassium conductance during an action potential and refractory period in the Hodgkin-Huxley model. The lower curves represent the h-gating variable responsible for the sodium conductance's slow inactivation during the action potential. The h variable shows a rapid increase during the depolarization phase and then slowly decreases during the repolarization phase, reaching its resting value during the refractory period. The upper curve represents the potassium conductance, which shows a sharp increase during the repolarization phase of the action potential, reaching a peak value during the refractory period. The figure demonstrates the complex interplay between ion channels and gating variables in generating and terminating an action potential.

11. Visualising α_n and β_n

variable(s)	prior distribution	kernel distribution
α_n, β_n	uniform(0, 1)	$\mathcal{N}(0, 0.1)$



$$\alpha_n(V) = \frac{k_{\alpha_n 1}\left(V + k_{\alpha_n 2}\right)}{\exp\left(\frac{V + k_{\alpha_n 2}}{k_{\alpha_n 3}}\right) - 1},$$

$$\beta_n(V) = k_{\beta_n 1} \exp\left(V / k_{\beta_n 2}\right),$$

***Fig 11**: Visualization of α_n and β_n*

In this figure, we have tried to visualize the values of α_n and β_n. Here prior distribution is generated from a normal distribution with a mean of 0 and a standard deviation of 1. The kernel distribution is generated from a normal distribution with a mean of 0 and a standard deviation of 0.1. The posterior distribution is obtained by adding the prior and kernel distributions.

12. Understanding Approximate Bayesian Computation

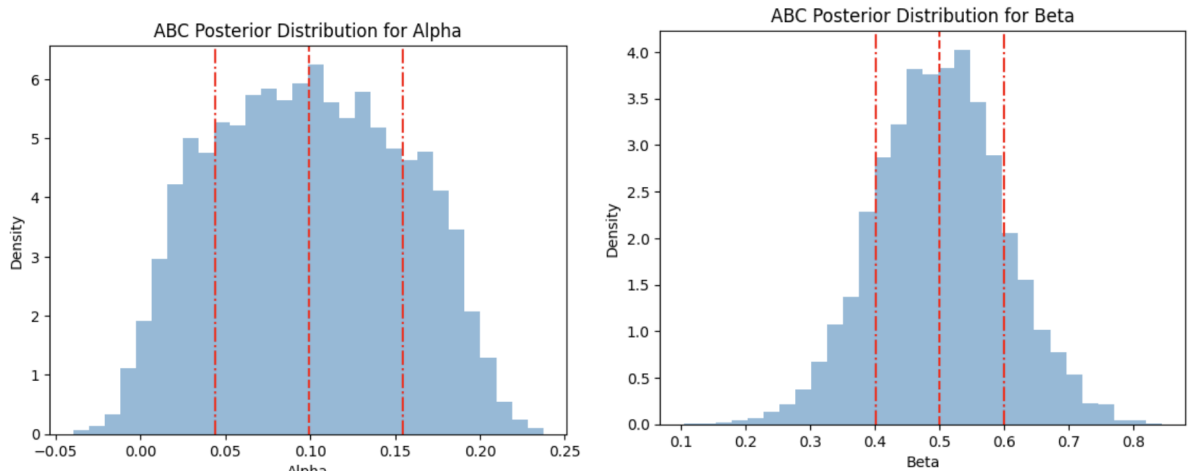


***Fig 12**: ABC Posterior Distribution of* α_n *and* β_n

Approximate Bayesian Computation (ABC) is a statistical inference method used to estimate a model's posterior distribution given some observed data without explicitly computing likelihood functions. Model output is simulated using parameters continuously sampled from a predetermined prior distribution.

The algorithm proceeds by generating parameters and then simulating data from those parameters, and then accepting or rejecting the proposed parameters based on the distance between the summary statistics of simulated and observed data. The accepted parameters are then used to approximate the posterior distribution. The implementation used here uses a normal distribution to generate the parameters and calculates the mean and standard deviation of the accepted ones. Finally, the results are visualized by plotting the histograms of accepted α_n and β_n (parameters) values with vertical lines showing mean and standard deviation.

Conclusion & Inference

The Hodgkin and Huxley model is still pivotal to understanding how neurons function in neuroscience. Hodgkin and Huxley's description of the mechanism underlying action potentials in neurons through this model laid the groundwork for our understanding of the nervous system. We built a similar neuron with Hodgkin-Huxley channels using Python and the NEURON simulator, which allowed us to reproduce the behavior of a neuron as Hodgkin and Huxley described it. We were able to simulate several experiments and watch the expected behavior, such as the conduction of action potentials and the impact of changes in membrane potential on the gating of ion channels, by altering the model's parameters.

The fact that our findings agreed with those reported in Hodgkin and Huxley's 1952 papers served to support our methodology. The Hodgkin-Huxley model's drawbacks and potential for improvement were also examined, as well as the potential for more sophisticated computational methods like Approximate Bayesian Computation (ABC). This method generates constant values against voltage using formulas, probability, and number generation. A later paper revisited the Hodgkin and Huxley Model and used ABC to make predictions about the characteristics of a squid cell's neuron. This strategy still has some drawbacks, such as defining prior distributions, but it points in a promising direction for future computational neuroscience research.

Our study highlights the advantages of using computational models to research intricate biological systems like neurons. We can better understand the underlying mechanisms and the potential for enhancing existing models by fusing theory with experimental findings. We can anticipate the creation of even more complex models and simulations as technology and computational power advance, which will improve our knowledge of the nervous system and its function in behavior and cognition.

Relevant Code:

- Github - https://github.com/alphaNewrex/CSF433-CompNeuro-Assignment
- Google Colab - https://colab.research.google.com/drive/1tNEwKauawKbkCNM9EGiRjhXrL9-7qggY?usp=sharing

References:

[1] 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

[2] Daly Aidan C., Gavaghan David J., Holmes Chris and Cooper Jonathan 2015 Hodgkin–Huxley revisited: reparametrization and identifiability analysis of the classic action potential model with approximate Bayesian methods R. Soc. open sci.2150499150499 http://doi.org/10.1098/rsos.150499

[3] Bologna LL, Smiriglia R, Lupascu CA, Appukuttan S, Davison AP, Ivaska G, Courcol JD, Migliore M. The EBRAINS Hodgkin-Huxley Neuron Builder: An online resource for building data-driven neuron models. Front Neuroinform. 2022 Sep 26;16:991609. doi: 10.3389/fninf.2022.991609. PMID: 36225653; PMCID: PMC9549939.

[4] Peyrard M. How is information transmitted in a nerve? J Biol Phys. 2020 Dec;46(4):327-341. doi 10.1007/s10867-020-09557-2. Epub 2020 Oct 10. PMID: 33037976; PMCID: PMC7719126.

[5] https://www.neuron.yale.edu/neuron/static/py_doc/index.html

[6] https://nrn.readthedocs.io/en/8.2.2/