

Simulation of an Action Potential using the Hodgkin-Huxley Model in Python

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Introduction:

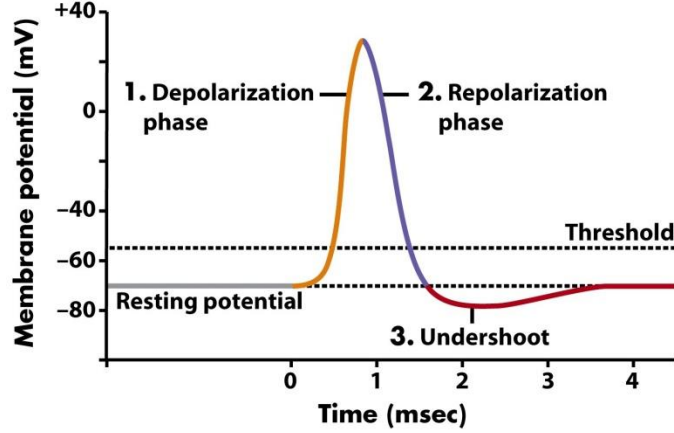
Computational modelling is fundamental to the scientific method providing a link between real world empirical evidence and conceptual predictions^[2]. Recent developments in neural biophysical modeling aim to use structural connectivity brain maps based on diffusion weighted imaging and positron emission tomography, to aid in predicting residual cerebral function in patients with disorders of consciousness after severe brain injury^[3]. The practicality and sophistication of these models are based on the integration of simpler tried-and-true simulations, such as the Hodgkin-Huxley model for an action potential. The purpose of this project is to develop an accurate computer simulation for ion gate behaviour, as well as, the initiation and propagation of an action potential based on the Hodgkin-Huxley model. Python programming language is used to develop the computer simulation. Similar coding projects, for example, in a recent paper published by Siciliano, at McGill University, tackles the same basic computational model^[7]. However, the simulation implements MATLAB programming language. The use of Python could simplify code development and code readability due the inherent nature of Python's syntax to be able to express ideas in fewer lines of code^[8]. The constants defined in the code will be based on empirical data of an action potential from a giant squid axon found in the original Hodgkin-Huxley paper. We aimed to test the accuracy of our model using qualitative and quantitative discrepancies between the action potential simulation and an action potential trace measured from a giant squid.

Theory:

The membrane potential of an animal cell is the difference in electrical potential between the intracellular compartment and the extracellular space^[1]. The difference in electrical potential is largely due to the imbalance between sodium (Na^+) and potassium (K^+) ions. This imbalance is maintained by the simultaneous active pumping of Na^+ ions out of the cell and K^+ ions in to the cell^[9]. Since the cell membrane is impermeable to ions a concentration gradient for Na^+ and K^+ ions is established. K^+ specific leak channels in the membrane allow K^+ to flow down its concentration gradient in to the extracellular space. This causes the intracellular compartment to become more negatively charged with

respect to the extracellular space. This tends to draw positively charged K^+ ions back in to the cell and, as a result, the diffusion force will eventually be opposed and balanced by an electrical force^[1]. At electrochemical equilibrium, this is called the resting membrane potential of the cell. This membrane potential represents a form of stored energy, and can be used to do work. Excitable cells such as neurons and muscle cells use the membrane potential to help initiate and propagate electrical signals called action potentials.

An action potential is a rapid reversal in the resting membrane potential of an excitable cell^[9]. This occurs when some mechanical, chemical or electrical stimuli causes a sufficient depolarization. A depolarization is an increase in positivity associated with a sudden influx of Na^+ ions in to the target cell^[9]. In Figure 1, the action potential features a 1ms depolarization phase. Following depolarization is the repolarisation and hyperpolarisation phases (undershoot). During these two phases the resting membrane potential is restored due the actions of Na^+/K^+ pumping, as well as, slow closing K^+ channels. Note that there exists a minimum threshold for depolarization before an action potential will fire. In Figure 1, the threshold potential is approximately $-55mV$. As mentioned above, when an action potential fires, the permeability of the cell for Na^+ and K^+ ions will change. The Hodgkin Huxley model for an action potential introduces a set of non-linear first order differential equations to model the behaviour of ion channels which are responsible for these permeability changes.



[6]

Figure 1: Model action potential depicting depolarization, repolarization and hyperpolarization (undershoot) phases.

There are three different gating variables, n , m and h used to describe the behaviour of three ion gates, the K^+ channel gate, the Na^+ channel activation gate and the Na^+ channel inactivation gate, respectively. Note that there is both an activation gate and an inactivation gate in the Na^+ channel. Both gates must be open for Na^+ conductance to occur. The value of a gating variable is dimensionless and will vary between 0 and 1; 0 indicates that the channel is closed, whereas 1 indicates that the channel is open. The gating variable fraction is an indication of the conductance of a certain ion at a given time and membrane voltage. These gating variables are determined by Equations 1 – 3^[5] below,

$$\frac{dn}{dt} = \alpha_n(v)(1 - n) - \beta_n(v)n \quad (1)$$

$$\frac{dm}{dt} = \alpha_m(v)(1 - m) - \beta_m(v)m \quad (2)$$

$$\frac{dh}{dt} = \alpha_h(v)(1 - h) - \beta_h(v)h \quad (3)$$

Furthermore, in Equations 1 – 3, the variables α_x and β_x , where x denotes any gating variable, signify rate constants which depend only on membrane voltage. Both rate constants are based on empirical data and have units of $[\text{time}]^{-1}$ ^[4]. The variable, α_x , represents the rate of transfer of ions from the extracellular

space to the intracellular compartment. Accordingly, β_x , determines the rate of transfer of ions from the intracellular compartment to the extracellular space. Both α_x and β_x are functions which Hodgkin and Huxley fitted to data based on voltage clamp experiments and are provided below^[5],

$$\alpha_n(v) = \frac{0.01(V+10)}{(e^{(v+10)/10}-1)} \quad (4)$$

$$\beta_n(v) = 0.125e^{v/80} \quad (5)$$

$$\alpha_m(v) = \frac{0.1(V+25)}{(e^{(v+25)/10}-1)} \quad (6)$$

$$\beta_m(v) = 4e^{v/18} \quad (7)$$

$$\alpha_h(v) = 0.07e^{v/20} \quad (8)$$

$$\beta_h(v) = \frac{1}{(e^{(v+30)/10}+1)} \quad (9)$$

Now that these parameters have been defined, we continue with the full derivation of the Hodgkin-Huxley model.

The Hodgkin-Huxley model for an action potential takes in to consideration the behaviour of three ion channels separately. Note that this is not the same as the gating variables defined above. However, these gating variables play a role in modifying the ion channel conductance that will be covered in detail below. The current through each ion channel is summed, and the change in charge, and therefore, membrane potential can be calculated. The circuit diagram in Figure 1 describes current flow through the cell membrane:

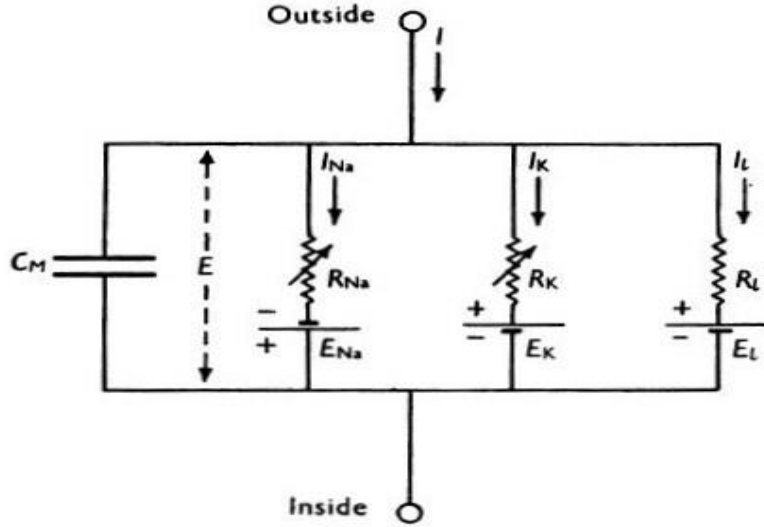


Figure 2: Circuit diagram representing a cell membrane

Based on Figure 2, the current is related to electrical potential by Ohm's Law which is given by

$$I = \frac{V}{R} \quad (10)$$

where I denotes the current, V is the potential and R is the resistance. To calculate the value of the potential contributing to Na^+ , K^+ or leak channel ion flow we take the difference between the potential and the Nernst potential. The Nernst potential is the membrane potential at which there is no ion flow between the intracellular space and the extracellular space^[4]. The Nernst potential is denoted by the variable V_y , and modifies Ohm's Law as follows,

$$I = \frac{V - V_y}{R} \quad (11)$$

both V , I and R have the same physical meaning as described previously. Finally, this equation is simplified using conductance which is defined as the reciprocal of the resistance that a current encounters^[4]. In Figure 2, this is indicated by R_{Na} , R_{K} and R_{L} , which are the resistances to ion flow in the Na^+ , K^+ and leak channels, respectively. Qualitatively, conductance is the ease at which current will pass through a resistor. It is defined by the constant \bar{g}_y and modifies Equation 11 as follows,

$$I = \bar{g}_y(V - V_m) \quad (12)$$

Equation 12, determines the amount of current as a result of ions passing through an open Na⁺, K⁺ or leak channel in to the intracellular compartment. In the Hodgkin-Huxley model, the gating variables n, m and h act on Equation 12, and modifies ion conductance with respect to membrane voltage. The total current which passes from the extracellular space in to the intracellular compartment is given by^[5],

$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l) \quad (13)$$

In Equation 13, note that C_M is a capacitance that represents the lipid bilayer. The right hand side equation represents the total ion current which passes in to the intracellular space^[5].

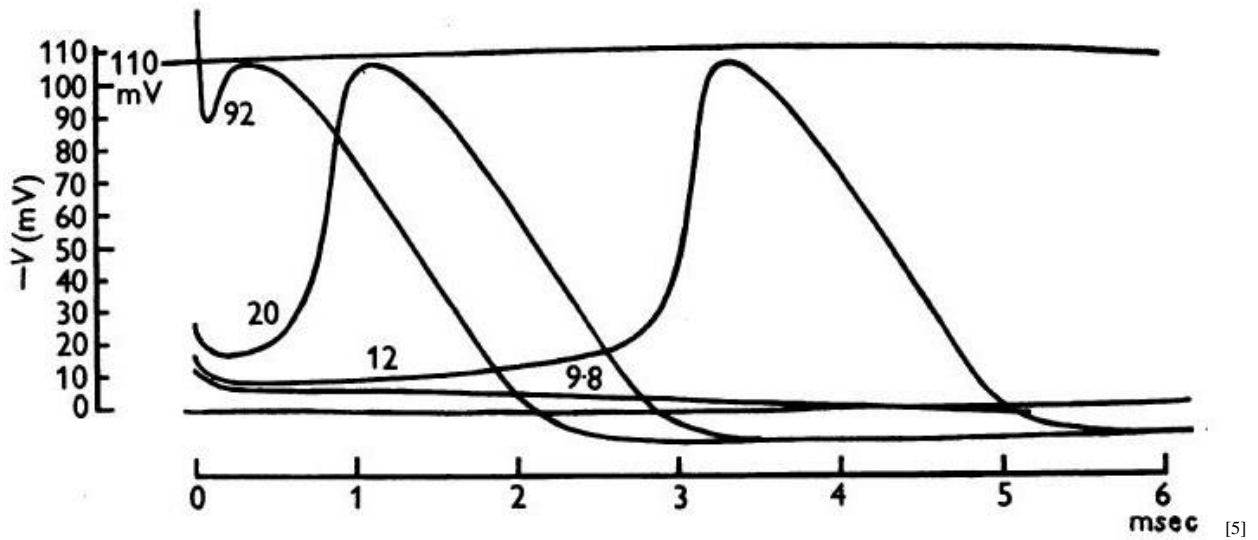


Figure 3. Measured Membrane Action Potential trace for a Giant Squid Axon at 6.3°C with 15mV depolarization

Type of action potential	Temperature (°C)	Stimulus	Spike height (mV)
Propagated Membrane	18.5	—	90.5
Membrane	18.5	15 mV depolarization	96.8
Membrane	6.3	100 mV depolarization	108.8
Membrane	6.3	90 mV depolarization	108.5
Membrane	6.3	15 mV depolarization	105.4
Membrane	6.3	7 mV depolarization	102.1
Membrane	6.3	Anode break	112.1 ^[5]

Table 1: Measured Spike Heights for Membrane Action Potential traces at Varying Temperatures and Stimuli Strength

The action potential simulation and measured action potential trace will be compared based on qualitative features such as curvature and slope, as well as, quantitatively using spike height. Figure 3, shows the measured membrane action potential traces for a 15mV depolarization at 6.3°C. The computer simulation will attempt to replicate this action potential specifically. Finally, the spike height of the simulation will be compared to the measured spike height using a percentage error calculation. Percentage error is given by,

$$\% \text{ Error} = \frac{|\text{Experimental} - \text{Accepted}|}{\text{Accepted}} \times 100 \quad (14)$$

This error calculation will show how well the Hodgkin-Huxley model can replicate the height of a true measured action potential trace.

Methods:

Coding Procedure Summary. The computational simulation of an action potential and ion gate behaviour is written using Python programming language. Spyder, a Python development environment, is used to assemble and run the code. A summary of the coding procedure will be outlined below.

All of the constants listed in Table 1, are defined in Python. These numbers fall in to the range of experimental values provided in the original Hodgkin and Huxley model.

<i>Constant</i>	<i>Chosen Value</i>
$C_M (\mu F / cm^2)$	<i>1.0</i>
$V_{Na} (mV)$	<i>-115</i>
$V_K (mV)$	<i>+12</i>
$V_l (mV)$	<i>-10.613</i>
$\bar{g}_K (mmho/cm^2)$	<i>120</i>
$\bar{g}_{Na} (mmho/cm^2)$	<i>36</i>
$\bar{g}_l (mmho/cm^2)$	<i>0.3</i>

[5]

Table 1: Constants defined in Python based on range of values defined in the Hodgkin-Huxley model

These values were chosen so that qualitative and quantitative analysis can be performed using a membrane action potential trace measured at 6.3°C. The constant V_l , is an exact value to make the ionic current zero at the resting membrane potential^[5]. The resting membrane potential is 0mV. Voltage is defined as a range of evenly spaced integer values between -100 and 250. Time is defined as a range of evenly spaced integer values between 0ms and 35ms with a time step of 0.005ms. Equations 1-9, 13 must be declared as vectors in the code. This allows mathematical operations to be applied to the coded equations. The initial input stimulus is 10uA/cm². Gating variables are plotted as a function of membrane voltage and membrane potential is plotted as a function of time.

Results:

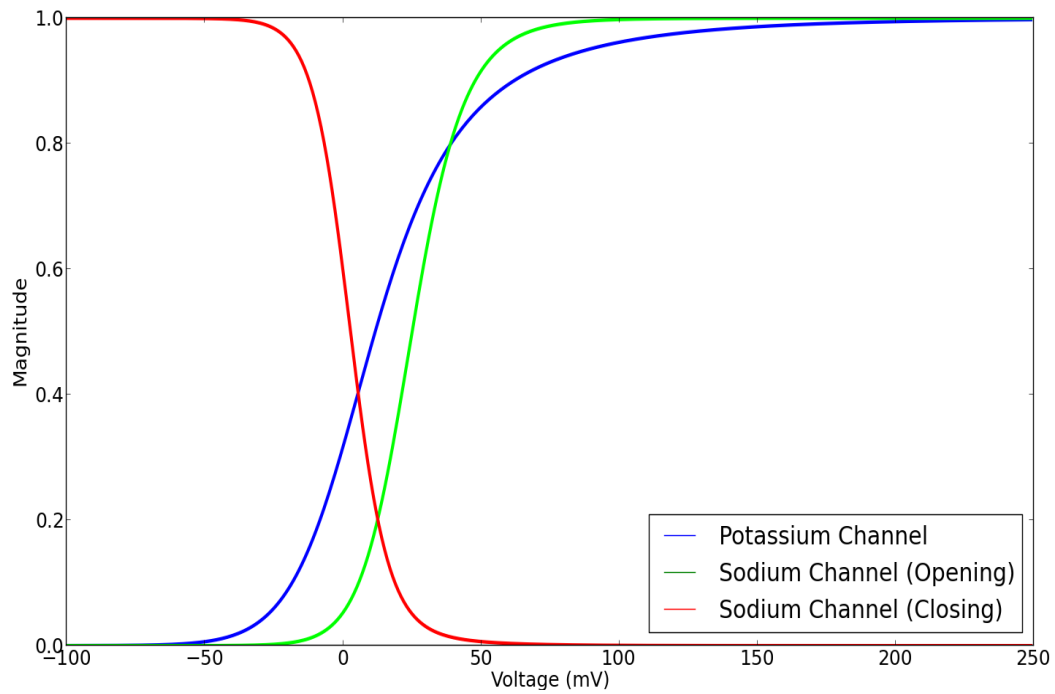


Figure 4: Ion channel gating variables with respect to membrane voltage (where 0 = close and 1 = open)

Figure 4, shows that for increasing voltage, the value of the potassium channel and sodium channel (activation gate) gating variables increases. In contrast, increasing membrane potential causes the sodium inactivation gate variable to approach zero.

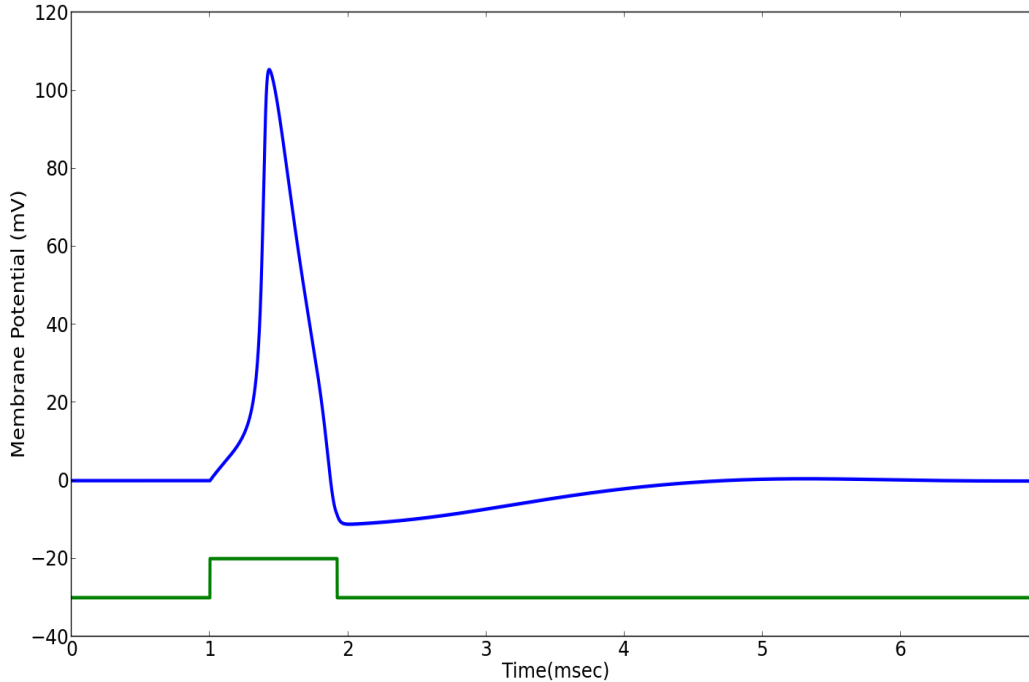


Figure 5: Change in membrane potential with respect to time (Hodgkin-Huxley Model)

The simulated action potential trace in Figure 5 is calibrated such that the resting membrane potential is set to 0mV. The total input impulse is less than 2msec. The membrane potential returns to resting state after 5msec. The maximum membrane potential is 1.05400725e+02mV.

<i>Measured Peak Height (mV)</i>	<i>Simulation Peak Height (mV)</i>	<i>Percentage Error</i>
<i>105.40mV</i>	<i>105.40</i>	<i>0%</i>

Table 2: Percentage error of the measured peak height and the simulation peak height

The peak height of a measured action potential trace in the giant squid axon at 6.3°C based on Hodgkin & Huxley (1952) was compared to the simulation action potential peak height. The simulated peak shows a 0% error in comparison to the measured peak.

Discussion:

The shape of the curves in Figure 3 can be described in terms of ion conductance as a result of changing voltage after the onset of an action potential. During the depolarization phase, sodium and potassium ion conductance increases leading to an increase in membrane potential. However, after

+50mV, the sodium gate becomes inactivated and Na⁺ channels close. This marks the end of the depolarization phase. Each gating variable modifies ion conductance to produce the action potential shown in Figure 4. This action potential will be compared to the measured membrane action potential trace in Figure 1.

Based on the percentage error calculations, it was determined that a 10uA/cm² input pulse would be the best simulation for a measured membrane action potential with a 15mV depolarization. That being said, the computer simulation in Python is by no means, a perfect representation of a measured action potential. Qualitatively, there are some portions of the curve in the simulation that do not appear in the measured action potential. First, in the simulated axon potential, there is a sharp initial depolarization. However, in the measured membrane potential, the depolarization phase is much smoother. In fact, the curvatures of both the highest peak and the hyperpolarized minimum of the simulation are much greater and produce sharper peaks. The measured action potential trace is much smoother in general. The tendencies of the simulation to produce these errors are due to Equations 1 – 9, which describe the gating variables. This is a characteristic of the Hodgkin-Huxley model itself and not the constants defined in Table 1. Another, set of characteristics which these equations impose on the simulation are steeper slopes for the depolarization and repolarisation phases. This is another marked difference between the action potential simulation and the action potential recording. Finally, Equations 4 and 6 in particular, cause a saddle point during the repolarisation phase in the simulation. This is due to division by zero errors that can occur in both equations. A discontinuity in the simulated action potential was resolved using l'Hôpital's Rule to evaluate the limit for those equations. Accordingly, the value of the limit is plotted along with the rest of the simulation to produce a continuous action potential trace.

The implications of a simulation of the Hodgkin-Huxley model in Python are considerable. Since the model is a good representation of a true measured action potential in the giant squid axon this computer simulation can be used to facilitate the study of the ion gating mechanisms which are dependent on membrane voltage. Furthermore, this model can be applied to many different biological models of

excitable cells because the underlying mechanisms of ion transport do not change^[8]. The use of this programming language enhances the accessibility of this model for researchers in different fields of science due to good code readability and the simplicity in modifying the code^[8].

Some future research that should be considered is the modification, as well as, simplification of this model to fit the shape of a true action potential. In addition, computer simulations for specific cell types can be created so that they can provide better predictions for a cell subjected to hypothetical conditions.

Conclusion:

A model for an action potential in a giant squid axon at 6.3°C, with stimulus strength 15mV, can be created using a set of non-linear differential equations proposed by Hodgkin-Huxley. The constant values proposed by Hodgkin-Huxley, applied in conjunction with a 10uA/cm² input stimulus can produce an action potential with identical spike height to the measured membrane action potential. This model was fully implemented in to Python programming language and an action potential simulation was produced. This simulation was good, however, showed some differences with the original membrane trace recording upon qualitative analysis.

References:

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