Mathematical Modeling of the Dynamics of Voltage Gated Ion Channels & Ion Pumps

Khoi Le, Akansha Singh, Alvaro Rivas

***Abstract*— One of the most important features of a neuron is its ability to generate and propagate action potentials. There have been numerous studies on neuronal structures and mechanisms which gives insight into the various properties of a neuron. A major study on nerve cell excitability conducted by Alan Hodgkin and Andrew Huxley opened up alternative approaches to studying neurons, specifically through a more mathematical approach . From their study, a key discovery was made which was the Hodgin Huxley model which describes the dynamic characteristics of a neuron by modeling it as an equivalent circuit model with a capacitor in parallel with three branches where each branch contains a variable resistor and battery in series. The Hodgkin Huxley model enabled us to formulate a corresponding Simulink model of a neuron where different conditions can be adjusted and simulated in order to see their effects on the overall behavior of the action potential.**

Key words: Action potentials, ion channels, membrane potential, membrane current, sodium, potassium.

I. INTRODUCTION

Action potentials is a phenomenon in which rapid sequences of change in voltage, between the membrane of a neuron, is caused by constant influx and outflux of positive and negative ions. Action potential is the key to neuronal communication, whether it's from the CNS to PNS or CNS to the muscular system. To be elaborate further, influx and outflux of ions create an overall current that propagates down the axon. Once the current reaches the axon terminal, during a chemical synapse, the current triggers a release of neurotransmitters which travels across the synaptic cleft to bind to postsynaptic neurons. During an electrical synapse, there are gap junctions between pre and postsynaptic neurons that serve as a passage for the membrane current to travel down and through multiple neurons.

The neurotransmitters primarily responsible for an action potential, sodium and potassium play pivotal roles. The following will go into the mechanism as to how the flow of sodium and potassium influences the start, middle, and end leading to the overall structure of an action potential.

Sodium When an action potential is first introduced into a neuron, there is the activation of the sodium voltage gated channels. Firstly, going into the mechanism behind the sodium voltage gated channels, the channel itself has three different stages it can be in: activated, inactivated, and closed. Activated is when the sodium ions have the ability to travel through as the channel is open. Inactivated means the channel is open but the sodium ions cannot go through. An example of this is the ball and chain mechanism where the channel is open, but the ball will block the channel thereby inhibiting the movement of some ions across it. Closed is when the chanel is closed and no ions have the ability to travel across the membrane.

In regards to an action potential, the sharp rise seen in the beginning is due to the opening of the sodium ions. This has multiple different mechanisms to it: first being that the membrane potential has depolarized by reaching a membrane threshold thereby opening the sodium gated channels. This is seen in the beginning of the plot of an action potential. Moreover, it is with this stimulus that allows for the propagation of an action potential down a neuron. During this phase, the sodium voltage gated channels will open and sodium will travel into the cell. This will cause the cell membrane potential to depolarize and increase in voltage value, hence the sharp curve. Moreover, the mechanics of the sodium voltage gated action potentials open relatively quickly depicting this sharp increase. At the peak of the action potential is the highest value the membrane potential reaches. At this point the sodium voltage gated action potentials will begin to become deactivated allowing for the membrane potential to slowly drop as less sodium is traveling into the cell. [1]

Potassium In the action potential graph, the rise is due to the opening of the sodium voltage gated channels. The fall, or repolarization and hyperpolarization is due to the potassium voltage gated channels.

When the potassium voltage gated channels open, potassium will flow to the outside of the cell in accordance with the diffusion gradient and other electrochemical factors. This will drive the membrane potential of the cell down as potassium ions are leaving. This can be seen as the drop of the action potential graph where the sodium ions begin to leave the cell, hence driving the membrane potential down.

In comparison to the sodium voltage gated channels, the potassium voltage gated channels will activate slower. This explains why the fall, or repolarization, of the graph is slower in comparison to the sharp rise.

When looking into the hyperpolarization of the action potential graph, or the dip seen in an action potential, this mechanism is primarily driven by the potassium voltage gated ion channels. This occurs due to the slowing closing of the potassium voltage gated ion channels. Since the channels close slower, there comes a point when the membrane voltage potential surpasses the resting membrane potential and becomes more negative. Essentially, since the channel closes slower, more potassium ions will leave the cell, dropping the cell membrane to a value lower than that of its resting membrane potential. [1]

Leak Channels A leak channel can be defined as a channel that does not close and hence is always open. While leak channels for potassium, sodium, and chloride exist, the following research paper will take into account potassium leak channels into the biosystem.

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When studying the mechanism of action potentials, students are often exposed to non-mathematical literature which consist of explanations regarding the importance of voltage gated channels and how they allow Na+ and K+ ions to travel through neurons but never really on how the voltage-gated channels are operated. Thus, modeling the system in accordance with the Hodgkin Huxley model becomes important to understand the mechanism behind what drives an action potential. [1]

The Hodgkin Huxley model is a model made to recreate the action potential considering voltage gated ion channels as a biosystem which can be used to study action potentials. This model includes factors such as resistance and conductance to replicate the characteristics of an action potential. The primary goal is to be able to display a graphical representation of the behavior of the action potential, both as a response to a single unit step of stimulus and a response to a stimulus applied at a certain frequency via the Hodgkin Huxley model.

II. METHODS

From the equivalent circuit model (Hodgin Huxley model), an equation for the membrane current was derived, shown below:

(1.)

$$I_M = C_M \frac{dV_m}{dt} + (V_M - V_{Na})G_{Na} + (V_M - V_K)G_K + (V_M - V_L)G_L$$

where $\boldsymbol{I_m}$ is the total transmembrane current being the sum of the sodium, potassium and leak current and the membrane capacitance. From equation (1.), a corresponding Simulink was created to represent the entire system, show below:

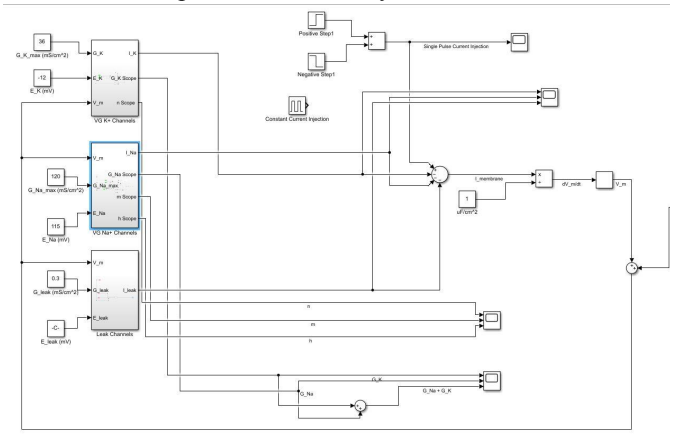

Figure 1: The simulink above represents the entire system which consists of multiple subsystems.

In order for the entire system to operate as desired, the three subsystems (represented by three boxes from figure 1) must be functional and working together. The first subsystem, voltage-gated potassium channels which produces a current:

(2.) $$\boldsymbol{I_K = G_K \cdot (V_m - V_K)}$$

where $\boldsymbol{G_K}$ represents the potassium conductance and $\boldsymbol{V_K}$ is the reverse potential of sodium. The potassium conductance is described as: :

(2a.) $$G_K = G_{K,max} n^4$$

where $\boldsymbol{G_{K,max}}$ represents the maximum potassium conductance and $\boldsymbol{n}$ is the gating variable where it requires 4 n particles to activate a voltage-gated sodium channel. Gating particle "n" is an activation particle and the total population of these n particles has the potential to change over time, depending whether the system is at steady state or during an action potential, which makes all gating variables voltage-dependent. The following ODE represents the change in n particles with respect to time. The ODE can be solved via Simulink.

(3.) $$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n$$

From equation (3.), $\boldsymbol{\alpha}_n$ and $\boldsymbol{\beta}_n$ are voltage-dependent variables which represent the transfer rate coefficients of gating channels from closed to opened state ($\boldsymbol{\alpha}_n$) and opened to closed state ($\boldsymbol{\beta}_n$). There are equations that represent these transfer rate coefficients which were derived experimentally:

(3a.) $$\alpha_n = \frac{0.1 - 0.01V'}{e^{(1-0.1V')} - 1}$$

(3b.) $$\beta_n = \frac{0.125}{e^{0.0125V'}}$$

With all of the equations above, a following Simulink was generated to illustrate the behavior of a voltage-gated potassium channel.

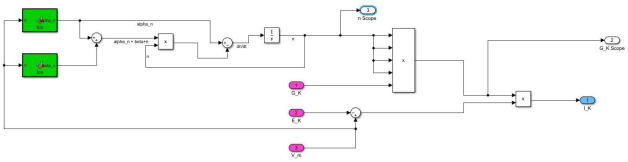

Figure 2: Simulink model representing a voltage-gated potassium channel. The inputs into the subsystem are the reverse potential of potassium, max conductance of potassium and membrane potential. The output of the subsystem is the potassium current.

The second subsystem illustrates the dynamic of a voltage-gated sodium channel. It can be described through its output current as:

(4.) $$\boldsymbol{I_{Na} = G_{Na} \cdot (V_m - V_{Na})}$$

where G_{Na} is the conductance of sodium and V_{Na} is the reverse potential of sodium. The equation that describes the conductance of sodium is:

(4a.) $$G_{Na} = G_{Na,max} m^3 h$$

where $G_{Na,max}$ is the max conductance of sodium and the gating variables being m & h. According to literature, a voltage-gated sodium channel requires three m particles for activation and one h particle for deactivation. The following ODEs below represents the change in proportion of m and h particles with respect to time:

(5.) $$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m$$

(6.) $$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h$$

Similarly, α and β from equation (5.) and (6.) are also voltage dependent variables which are represented through the following equations:

(5a.) $$\alpha_m = \frac{2.5 - 0.1V'}{e^{(2.5-0.1V')} - 1}$$

(5b.) $$\beta_m = \frac{4}{e^{\left(\frac{V'}{18}\right)}}$$

(6a.) $$\alpha_h = \frac{0.07}{e^{0.05V'}}$$

(6b.) $$\beta_h = \frac{1}{e^{(3-0.1V')} + 1}$$

From here, a Simulink for a voltage-gated sodium channel was created which is shown below.

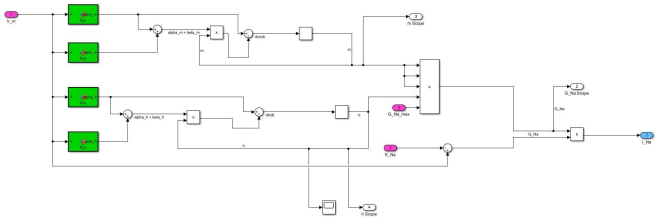

Figure 3: Simulink model illustrates a voltage-gated sodium channel via connections of functions, sum junctions, integrator, etc. The inputs into the subsystem are the reverse potential of sodium, max conductance of sodium and the membrane potential. The output of the subsystem is the sodium current.

The third subsystem is the leak channel which also contributes to the overall mechanism of an action potential. Unlike the first two subsystems, leak channels are voltage-independent, making the behavior of leak channels unpredictable since they open and close randomly. The output leak current is derived from Ohm's Law which states:

(7.) $$I_{leak} = G_{leak} \cdot (V_m - V_{leak})$$

Leak channels are important in terms of restoring the resting membrane potential since it serves as a negative feedback mechanism, creating a secondary passage for ions to flow through.

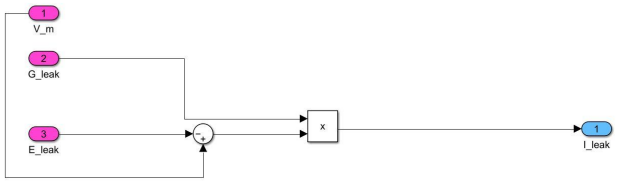

Figure 4: The dynamic of leak channels was modeled and simplified to be a constant subsystem where the leak current is derived from Ohm's Law. The inputs of the subsystem are the reverse potential of leak channels, conductance of leak channels and the membrane potential. The output is the leak current.

On top of the analysis and modeling of the Hodgkin Huxley model, another goal of the project was to model the dynamics of ion pumps which also play a role in re-establing the electro-chemical gradient between the membrane of the neurons. One major assumption from the Hodgkin Huxley model is that the model considers the reverse (Nernst) potential of ions to be a constant value. If we visualize, at a microscopic scale, the movement of ions between the membrane, there's always a consistent transferring of ions between the intra and extracellular fluid hence, the reverse potential of Na+ and K+ will fluctuate over time. The fluctuation is due to the Nernst equation which states:

(8.) $$V_{ion} = \frac{kT}{q} \ln\left(\frac{[ion]_o}{[ion]i}\right)$$

where k is the Boltzmann's constant (1.380649 × 10^-23 J/K), T is temperature in Kelvin, q is the charge of the ion in Coulombs, $[ion]_o$ and $[ion]_i$ are the extra and intracellular concentration of the ions, respectively.

It is possible to model the ion pump by stating the variable V_{ion} is a function of the intracellular concentration of ion $[ion]_i$. We can derive this relationship by first analyzing the

change in V_{ion} with respect to time. The following ODE will enable us to do so:

(9.) $$\frac{dV_{ion}}{dt} = \frac{kT}{q} \cdot \frac{d}{dt} \ln\left(\frac{[ion]_o}{[ion]i}\right)$$

One thing to note is that with the ODE above, we assumed the extracellular concentration to be at a steady state (constant value) while the intracellular concentration changes with respect to time ($[ion]_i(t)$). A simulink can be created from equation (9.) in order to solve for the ODE, shown below:

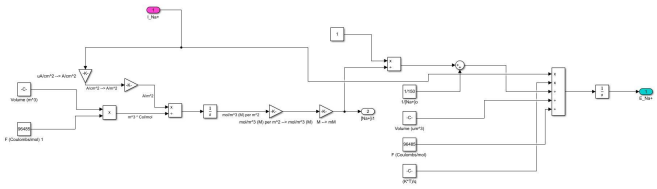

Figure 5: The simulink model above illustrates the ideal characteristic of an ion pump. The input into the subsystem is the ion current and the output is the reverse potential of the ion.

By showcasing that the behavior of ion pumps to be non-constant, this implies that the dynamics of ion pumps affect the ion's reverse potentials, making the reverse potential a function of intracellular and extracellular ion concentrations.

III. RESULTS

The transfer function of the expanded Hodgkin Huxley model was found by taking the laplace transform of the Hodgkin Huxley equations and modified Nernst equations as shown below.

$$H(jw) = \frac{L(Vm(s))}{L(Im(s))} = \frac{1 + \left(\frac{KT}{qF}\right)\left[\frac{1}{[Na]o} + \frac{1}{[Na]i} + \frac{1}{[K]o} + \frac{1}{[K]i}\right]}{SCm + Gna + Gk + Gl}$$

From the transfer function we can analyze the stability of the biosystem. The transfer function has a single pole when S is equal to the negative sum of the channel conductances divided by the membrane conductance as shown below.

$$\text{Pole at;} \quad s = -\frac{Gna+Gk+Gl}{Cm}$$

Because the conductances will always be a positive value, the pole will always be less than 0, indicating that the biosystem is stable. From this transfer function, the Bode plot was found by inputting values from literature.

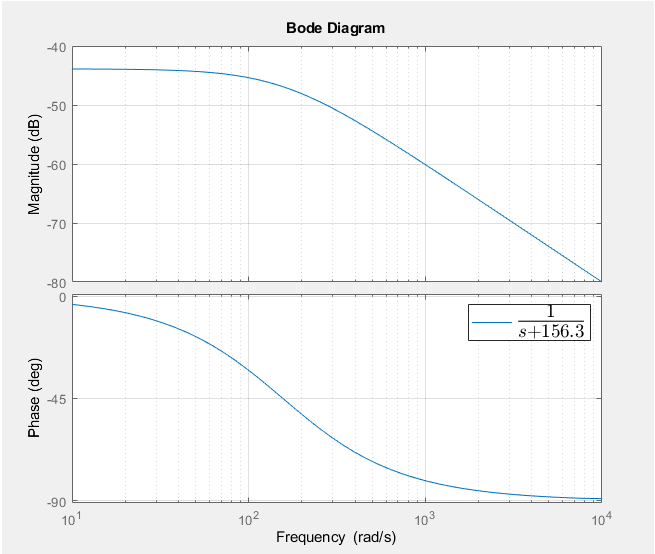

Figure 6: Bode plot of the transfer function of the biosystem Vm(s)/Im(s) with values from literature

From the Bode plot, we can see that the bandwidth increases as the channel conductances are increased and the membrane conductance is decreased. The bandwidth would then be decreased if the opposite condition were fulfilled. The Bode plot also has a phase margin of 90 degrees which also shows that the system is stable.

The Simulink model of the axon produced graphs that exhibit the same behavior of an action potential with an input of a single pulse and a propagating wave input. The magnitude of these plots do not exactly match the plot of an action potential as shown in literature which may be due to errors found in the calculation of the gating variables as there are many approximations in the calculation of the alpha and beta values. The simulated action potential follows the same behavioral pattern as a naturally occurring action potential as it initially depolarizes, then repolarizes after reaching the peak voltage and hyperpolarizes back to steady state. Within our model the voltage begins at 0 mV instead of -70 mV which is an error that may be improved upon within future work

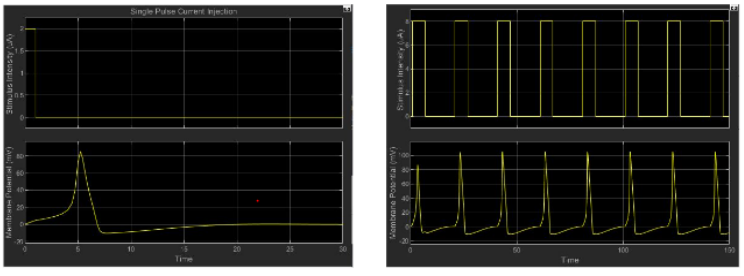

Figure 7: Simulink modeled action potential with a single pulse input of current at 2uA [left]. Response of model with a wave of current with magnitude of 8 uA at 53.3 Hz [right].

In order to further verify the accuracy of our model. The change in conductance over time of the sodium, potassium, and leak channels were plotted and compared to that which is found within literature. When comparing the

plots as shown in figure #, we see that the behaviors are the same but the magnitudes differ. Within literature, the peak magnitude of potassium conductance is nearly half of the peak conductance of sodium. Within our model the peak conductance for potassium is only slightly less than that of sodium. This difference may be caused by the variability within the approximation of gating variables as they are quite different in calculation across various sources of literature.

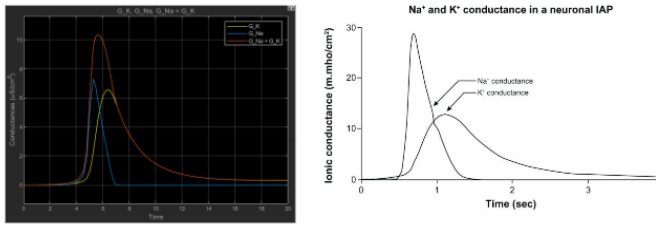

Figure 8: Plot of conductance vs. time for potassium, sodium and leak channels obtained theoretically from the Simulink model [left]. Plot of conductance vs. time for potassium, sodium and leak channels obtained experimentally from literature [right].

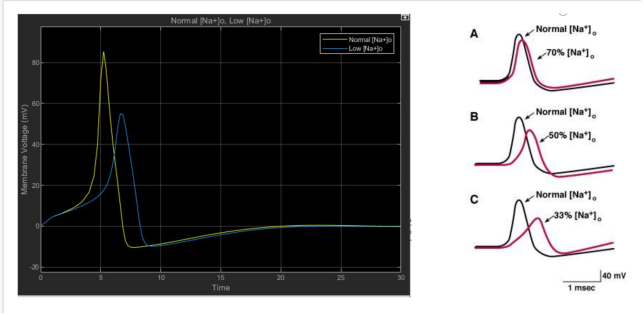

Figure 9: Theoretically modeled plot of extracellular sodium at nominal vs lowered concentrations [left]. Plot of extracellular sodium at nominal vs lowered concentrations derived experimentally [right] [5].

Building onto the original Simulink model, varying sodium concentration was modeled. By decreasing the sodium concentration. a medical condition, to be discussed in depth in the conclusion, can be modeled. The results are shown in figure 9.

In figure 9 shown, the left graph depicts two action potential curves: one curve with the default extracellular sodium concentration and the other curve with about ½-¾ of the default sodium concentration derived via Simulink. Analyzing this figure first, the main points include: the lowered peak for the action potential graph and the increased time duration of the action potential graph due to delay.

In figure 9 on the right is a depiction of varying levels of extracellular sodium channels and its influence on the action potential pulled from literature. It can be seen from this graph that by decreasing the extracellular sodium concentration, the max cell membrane potential achieved at the peak of the action potential curve is lower compared to that of the default. Moreover, the duration of the action potential is increased as well, i.e., more time needed for the depolarization, repolarization, and hyperpolarization. Thus, the model can be confirmed and so can the hypothesis, to be explained in the discussion. [5]

One key note to make is the difference in values. Given that the original action potential graph produced from Simulink had values that were off (i.e., graph did not start at -70 mV and the peak value was different when compared to that against literature), the voltage values produced with this lowered extracellular sodium concentration should be taken with precaution. It is most likely that the voltage values are indeed wrong if this model was created in an actual neuron. However, given that the overall trend of the graph matches, the model can be verified and validated.

IV. DISCUSSION & CONCLUSION

Many medical conditions arise from the irregular functionality of neurons in focus with the sodium and potassium concentrations. One particular way neurons may function abnormally is through varying levels of sodium concentrations. [3]

The sodium voltage gated channels can be quite susceptible to changes in their morphology or structure. Given genetic disorders, the sodium voltage gated channel NavCHs may incur mutations or polymorphisms that influence the structure and functioning of the channel. If the channel is unable to function properly, the sodium ions may not be able to travel into the cell when depolarization is supposed to happen. This channel is particularly prone to early phases of closing, hence allowing for less sodium ions to travel from outside the cell into the cell. This can occur if there is slow inactivation of the D3-D4 linker, a channel protein that lies on the membrane of the cytoplasm. Given this information, the NavCHs channel can have profound impacts on the functioning of an action potential by working to limit the amount of sodium that may enter the cell due to premature closing. [3]

This condition was modeled in the MATLAB simulink to analyze the effects of low extracellular sodium on the action potential.

It was hypothesized that if the extracellular sodium concentration were to decrease, less sodium ions would be able to travel into the cell. This proposes two results: a lower action potential peak and a longer time duration for the action potential.

Going into the former hypothesis, this was theorized because if there were less full functioning sodium ion channels, less sodium ions would be flowing into the cell. Hence, there would be less ions to drive up the cell membrane potential. While the cell membrane potential would still increase, the peak value for the cell membrane in the action potential would not be as high as it would be for a default concentration of extracellular sodium.

Going into the later hypothesis, this was theorized because there would be less fully functioning sodium ion channels available for the diffusion of the sodium ions. As a result,

the sodium ions would have less of a chance to go through a fully functioning ion channel. It was theorized that in order for an action potential to occur, more time would be needed since less channels are available for the sodium ions to diffuse through.

In comparison to the results from modeling this medical condition, the presented model for the malfunctioning of the sodium channel NavCHs can be confirmed. Even though the voltage values may be off, the general trend for lowered extracellular sodium concentration matches up with that of literature. This confirms the hypothesis and validates the Simulink model.

For future applications, it would be important to be able to accurately model the ion pumps. By incorporating the pumps into the main action potential model, a more accurate model for action potential to see the dynamics and cooperation of different subsystems.

V. ASSUMPTIONS & LIMITATIONS

Within our model there are errors that root from many possible reasons. One possibility is the assumptions used to simplify complex particle behaviors into the model such as the conductance of leak channels. The conductance of leak channels are assumed to be a constant within all literature as the leak channels are not the primary focus of neuronal research. These leak channels have a constant exchange of ions due to concentration gradients which indicates that the conductance of these leak channels should naturally vary even if it is slight as these particles pass in and out of a neuron. Another source of error are the gating variables used within the Hodgkin Huxley model which vary significantly across literature. These gating particles and their behaviors are approximated using probability distributions which cannot fully describe the behavior of these particles as it is used to only predict it. Other biological assumptions include, assuming that the geometry of an ion channel closely resembles that of a truncated cone in order to calculate the volume.

VI. ACKNOWLEDGMENT

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Constant Variable	Numerical Value	Units
$V_{Initial}$	0	mV
$V_{Resting}$	-70	mV
E_{Na}	115	mV
E_K	-12	mV
E_{Leak}	10.613	mV
C_M	1	$\mu F/cm^2$
G_{Na}	0.3	mS/cm^2
G_K	120	mS/cm^2
G_{Leak}	36	mS/cm^2

** values obtained via literature