The effects of neuron related disorders on the stability of the Hodgkin Huxley model

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1 Introduction

Neurons are the building blocks of our nervous system, they are responsible for receiving all our sensory inputs from the physical world around us. Touch, smell, sight and balance are all ways in which we experience objects, chemicals, photons and gravity, allowing us to navigate and survive in the world around us. Every action, emotion, thought and feeling is communicated via electrical signals at the same amplitude with all the information encoded in the frequency of these signals.
Sometimes we experience and react differently to stimuli, perhaps not in the evolutionary intended way. Certain psychoactive chemicals and nervous system diseases can alter our experience or the way in which we interact with the world. This premise makes the study of the neuron and the brain of great interest in the scientific as well as philosophical domain. In this paper we investigate the mechanistic changes that take place in individual neurons to induce certain aberrant electrophysiological functioning.

Epilepsy is a well known neurological disease of which there are many types. It is the fourth most common neurological disease and is characterized by unpredictable seizures, there are many types of epilepsy's with different causes (1). Studies have shown that mutations in the KCHQ5 gene of the inter-membrane potassium channel protein causes some forms of epilepsy, while mutations in the SCN1B gene coding for a sodium channel protein sub unit is responsible for other forms of epilepsy(2)(3).

Studying the sodium and potassium channels could give more insight to disease functioning (4). To investigate changes that could induce epilepsy in a quantitative manner one needs a suitable mathematical model. The great feat of Hodgkin and Huxley's model, discussed in the background section of this paper, provides an accurate mathematical description of a single neuron with sodium and potassium conductance parameters that will allow us to explore the conditions under which these diseases might occur.

Previously in 1995 Bedrov et al (5)(6) studied the relationship between the number of negative slope regions in the Voltage-current graph of the Hodgkin Huxley model to changes in maximal potassium and sodium conductance parameters, and found that the number of negative slope regions changes from 0 up to 2 by varying maximal sodium and potassium conductance parameters through the physiological excepted range (5)(6). More recently the effects of varying maximal sodium and potassium conductance's on the stability of the Hodgkin Huxley model was examined (7). It was found that the maximal sodium conductance parameter $\overline{g}_{Na}$, had a single bifurcation point, where the system was stable before this point and unstable after whereby the action potential fires continuously. For the maximal potassium conductance $\overline{g}_K$ two bifurcation points where found and the system was found to be unstable between these two points.

There has been many bifurcation studies of other parameters in the Hodgkin Huxley model but maximal sodium and potassium conductance parameters are seldom considered due to difficulties in experimentally obtaining data for different parameters values for $\overline{g}_{Na}$ and $\overline{g}_K$.(7)
By varying the maximal sodium and potassium conductance parameters, we can establish bifurcation points signifying the onset of an epileptic seizure (8).

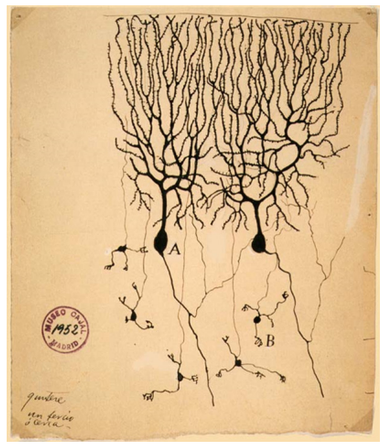
By studying the critical parameter range of $\overline{g}_{Na}$ and $\overline{g}_K$ for bifurcation onset it is possible to provide specific target areas for treatment function of sodium and potassium channel related epilepsy diseases.
In the following sections this paper will provide a brief historical background on the Hodgkin Huxley model as context for the model being used as well as a model description followed by a stability and bifurcation analysis taking maximal sodium and potassium conductance's separately and simultaneously as variables. Finally this paper will discuss and conclude the disease related implications, and possible treatment solutions.

Background on the Hodgkin Huxley model

The study of electrophysiology was first introduced over a century ago and the idea that signals where transmitted in living tissue electrically was first theorized by Luigi Galvani in 1791, a scholar from Bologna. He referred to this intrinsic electricity as "Animal electricity" (9).
He hypothesized that processes such as muscle contraction are due to electrically transmitted signals in the tissue. The problem was that "animal electricity" propagated far slower than electric fields (9). This got the attention of other scientists such as physicist Alessandro Volta, who disagreed with Galvini and tried to prove him wrong and subsequently developed the Electric Battery (9).

The First drawing of neurons where done by Cammilo Golgi who developed a superlative method for staining neurons which allowed for neurons to be viewed with never seen before detail. He stained a slicing of a dog's olfactory bulb and drew the network of neurons using a camera lucida projection in 1875. Cammilo Golgi theorized that the brain was a single unit network with no discrete parts, This was also previously theorized by Joseph von Gerlach in 1871 and was known as the "Reticular theory". Later in 1886 Santiago Ramon y Cajal used the same staining technique, and from his drawings theorized that the Brain was made of discrete individual cells, which was also theorized by others. This became known as the "Neuron doctrine" (10). Below are the famous drawings of Cammilo Golgi and Santiago Ramon y Cajal.

(a) Cammilo Golgi Drawing of a Dog's Olfactory bulb slicing (11)



(b) Santiago Ramon y Cajal drawing of a Purkinje cell (12)

Figure 1: First drawing of neural tissue by Cammilo Golgi and Santiago Ramon y Cajal which provided great insight to the structure of neural tissue and subsequently resulted in a joined Nobel prize

In 1897 Sir Charles Scott Sherrington Showed that neurons where connected by synapses which put the 'Reticular theory' to rest and left the "Neuron doctrine" as the accepted theory for explaining the structure of the nervous system (13).
In 1926 the "All or none law" was described by Edgar Douglas Adrian, whereby an electric impulse along a neuron called an action potential only occurred after a certain threshold of stimulus input and always produced a spike with the same amplitude, there was no graded intensity to the action potential.(5) In 1902 Bernstein described that membranes can be electrically excitable and that an action potential would occur at a certain electric potential

threshold across the membrane, whereby the membrane permeability greatly increased letting ions flow across, namely sodium and potassium.
The actual mechanisms through which the membrane permeability increased during an action potential was still unclear. It was in 1939 that Hodgkin and Huxley began there journey to discovering the set of equations describing the electrophysiological workings of neurons that revolutionized the field of electrophysiology.(7)
They first realized that the inner-membrane space became substantially more positive during an action potential which conflicted with Bernstein's theory. In 1945 Hodgkin and Huxley began discussing the mechanism for the increased permeability which turned out to be correct.
They hypothesized that the increase in permeability is highly specific for sodium ions which diffused inwards carrying the there positive charge into the cell. This hypothesis was observed to be true through experiments by Hodgkin and Katz in 1949 (4). Later on Hodgkin and Huxley went on to use patch clamp techniques in there experiments which allowed them to fix the potential and measure the current during an action potential.(7) Through numerous patch clamp experiments using a squid giant axon they eventually found 4 differential equations that accurately described the electrophysiological workings of neurons of which the solutions accurately represented the action potential of a firing neuron. This great feat is seen as an outstanding scientific achievement and is still used as the basis of electrophysiological models today. The Hodgkin and Huxley paper released in 1952 had finally brought an end to the 150 year old "animal electricity" problem and Hodgkin and Huxley received the Nobel prize for physiology or medicine in 1963.(7)

2 Model description

The Hodgkin and Huxley model is a set of nonlinear differential equations whose solutions accurately describe electrical excitation dynamics of a a neuron. It is a 4 dimensional system with a voltage state **V** and 3 gating channel states for sodium and potassium **m**,**h** and **n**. The Hodgkin and Huxley system is shown bellow.

$$
\begin{aligned}
\frac{dV}{dt} &= I_{inj} - \overline{g}_{Na} m^3 h (E_{Na} - V) - \overline{g}_K n^4 (E_K - V) - \overline{g}_l (E_l - V), \\
\frac{dm}{dt} &= \alpha_m(V)(1-m) - \beta_m(V) n, \\
\frac{dh}{dt} &= \alpha_h(V)(1-h) - \beta_h(V) n, \\
\frac{dn}{dt} &= \alpha_n(V)(1-n) - \beta_n(V) n,
\end{aligned}
$$

where

$$
\begin{aligned}
\alpha_m(V) &= \frac{0.1(V+40.0)}{1 - exp[-(V+25.0)/10]} \\
\beta_m(V) &= 4.0 exp(-\frac{V}{18.0}) \\
\alpha_h(V) &= 0.07 exp(-\frac{V}{20.0}) \\
\beta_h(V) &= \frac{1}{1 + exp[-(V+35.0)/10]} \\
\alpha_n(V) &= \frac{0.01(V+55.0)}{1 - exp[-(V+55.0)/10]} \\
\beta_n(V) &= 0.125 exp(-\frac{V+65}{18.0})
\end{aligned}
$$

The **m** and **h** state variables are the activation and inactivation state variables of the sodium gated channel. Where higher activation state values refers to the opening of the activation gate and higher inactivation state values refers to the opening of the inactivation gate.
The potassium channel only has one activation state variable **n** and no inactivation state. The activation and inactivation state variables are in the range 0-1 and imply the proportion

of open channels. The system and all of its biophysical components can be presented as an electrical circuit, where all of Kirchhoff's laws apply.

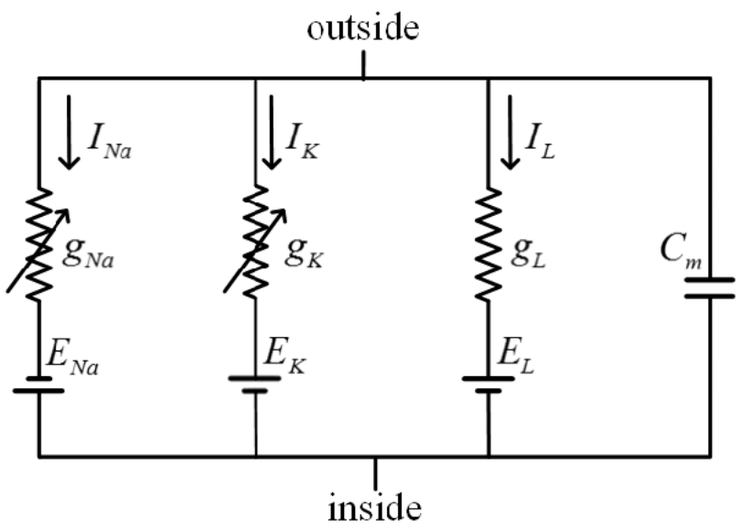


Figure 2: The electrical circuit equivalent of the Hodgkin Huxley model (14)

The voltage gated sodium and potassium conductance are represented by nonlinear functions

$$g_{Na} = \bar{g}_{Na} m^3 h$$

where $\bar{g}_{Na}$ is the maximum sodium conductance parameter, and

$$g_k = \bar{g}_K n^4$$

where $\bar{g}_K$ is the maximum potassium conductance parameter.

The electrochemical gradient driving the flow of ions across the membrane are represented by the parameters E_{Na} , E_K and E_L. The I_{inj} is the current introduced into the cell either from a synaptic transmission or artificially injected current in the case of experimentation. The bi-lipid layer of the cell membrane is represented as a capacitor Cm.

2.1 Parameter values

The parameter values have been taken from the Hodgkin and Huxley parameters found from the patch clamp experiments on the giant squid axon (15) where the temperature is set at $6.3°C$. Below are the parameter values used where I_{inj} is taken as zero for the stability analysis.

Table 1: Hodgkin Huxley parameter values used in this paper

Parameter	**Values**
Cm	1.0 $\mu F/cm^2$
$\overline{g}_{Na}$	120 mS/cm^2
$\overline{g}_K$	36 mS/cm^2
$\overline{g}_l$	0.3 mS/cm^2
E_{Na}	50.0 mV
E_K	-77.0 mV
E_l	-54.387 mV

2.2 The action potential

An action potential is the quick rise and fall of the membrane potential at a specific location along the axon, it represents the pulse that sends the signal through the length of the neuron

called the axon. Figure 3 shows the experimentally obtained action potential by Hodgkin and Huxley (16).

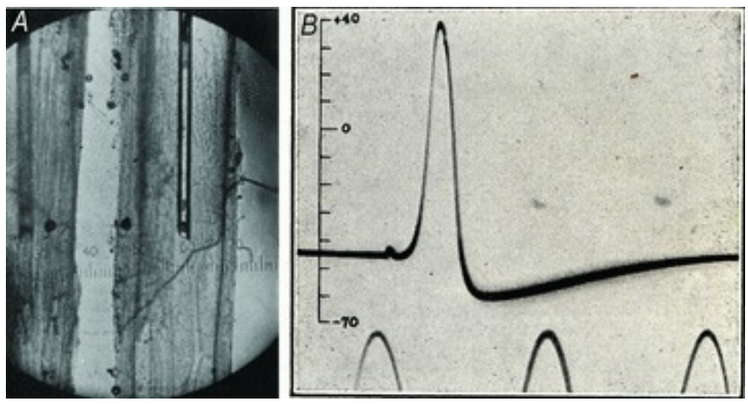


Figure 3: Intracellular recording of the squid giant axon as obtained by Hodgkin and Huxley and published in 1939 (16)(17)

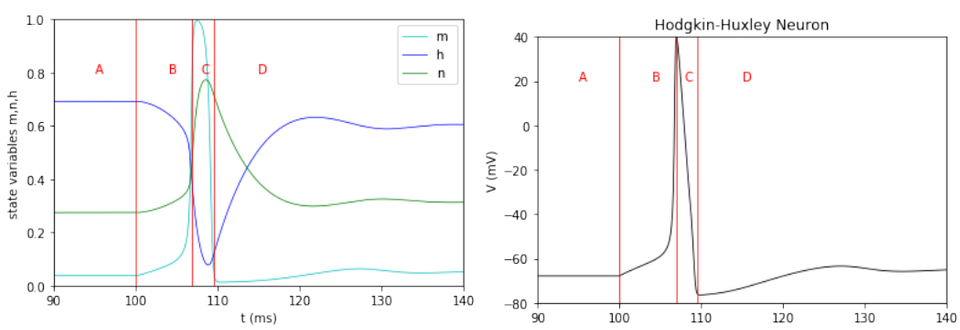
To understand how a mutation in the sodium or potassium channels might effect the firing of action potentials we should understand the dynamics of the channels during an action potential.

1. **Rest potential (A)**
   During the rest state depicted at **A** in figure 4(a-b) the Na^+ and K^+ activation gates are mostly closed and most inactivation gates are open. This is the period before the current is injected.

2. **Depolarization (B)**
   When a stimulus is applied the activation gates on some Na^+ gates open (illustrated in figure 5), the Na^+ influx through those channels cause an initial depolarization indicated at **B** in figure 4(a-b). If the stimulus is strong and induces a depolarization above the threshold, an action potential is produced. This is referred to as the all or nothing law mentioned in the background. If this happens most of the Na^+ activation gates open causing a further depolarization just below 40mV, as seen at **B** in figure 4(b).

3. **Re-polarization (C)**
   At this stage the inactive gates on most Na^+ channels are closed and most K^+ activation gates are open causing K^+ to move out of the cell resulting in re-polarization. This is depicted at **C** on figures 4 and 5.

4. **Hyper-polarization (D)**
   During this stage the membrane potential becomes more negative than the resting potential due to the latent out flux of K^+ ions. This is because the K^+ activation gate is slow to close, as can be seen by the green slop in D of figure 4(a). Eventually Some of the Na^+ activation channels open again and restore the membrane potential.



(a) Gating variable solutions (b) Action potential

Figure 4: Figure 4(a) shows the how the gating state variables change during an action potential and figure 4(b) shows the V-t solution or action potential

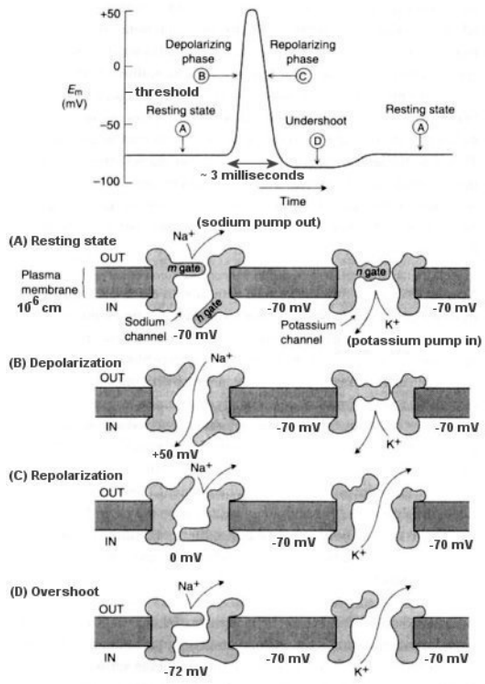


Figure 5: Biological depiction of the the gating dynamics during an action potential(18)

3 Analysis and Results

The equilibrium points of the Hodgkin Huxley model tell us where the system will end up. If the system is stable it will converge to a constant rest state given any initial condition, If unstable a trajectory will eventually oscillate in a periodic motion or become chaotic, with no periodic motion and no convergence. To find the equilibrium points we make

$$\frac{dV}{dt} = \frac{dm}{dt} = \frac{dn}{dt} = \frac{dh}{dt} = 0$$

where

$$0 = -g_{Na} m^{*3} h(V^* - E_{Na}) - g_k n^{*4}(E_K - V^*) - g_l(E_l - V^*) \tag{1}$$

$$m^*(V^*) = \frac{\alpha_m(V^*)}{\alpha_m(V^*) + \beta_m(V^*)}$$

$$h^*(V^*) = \frac{\alpha_h(V^*)}{\alpha_h(V^*) + \beta_h(V^*)}$$

$$n^*(V^*) = \frac{\alpha_n(V^*)}{\alpha_n(V^*)\beta_n(V^*)}$$

Since the equilibrium points of m^*, n^* and h^* are functions of V^* we have the set of all equilibrium points

$$\{V^*, m^*(V^*), h^*(V^*), n^*(V^*)\} \tag{2}$$

If we make the right side of equation (1) equal to $I(V^*)$ and solve for the roots of $I(V^*)$ we see that their is one equilibrium point, which is the resting potential of the system at -64.99637933 mV calculated using python as a tool.

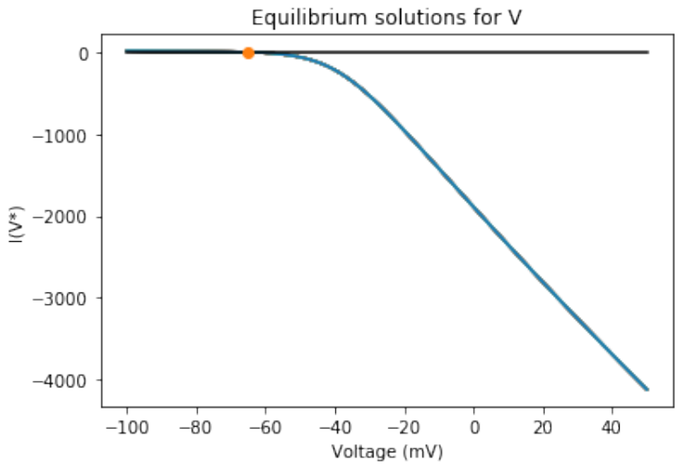


Figure 6: The graph shows the roots of the function $I(V^*) = -g_{Na}m^{*3}h(V^* - E_{Na}) - g_k n^{*4}(E_K - V^*) - g_l(E_l - V^*)$ where the roots are the equilibrium points of the system. The orange point is the intersection of the graph with the x axis and is the equilibrium point correlating to the resting potential

There are many stability criteria to study the stability of an equilibrium point. A key idea is to linearize the system near the equilibrium point to obtain the Jacobin matrix whose eigenvalues characterize the behaviour of the neighbouring points, this method of analysis uses Hartman Grobman's theorem (19). This idea is consistent with Lyapunov's theory of stability which loosely states that the trajectory of any initial point x_0 near the equilibrium will remain near the equilibrium point for $t \to \infty$ (20). The conditions for stability are that the real part of the eigenvalues are all negative. This method for establishing the stability of the equilibrium point of the system is demonstrated bellow.

$$J = \begin{bmatrix} \frac{dV}{dV} & \frac{dV}{dm} & \frac{dV}{dh} & \frac{dV}{dn} \\ \frac{dm}{dV} & \frac{dm}{dm} & \frac{dm}{dh} & \frac{dm}{dn} \\ \frac{dh}{dV} & \frac{dh}{dm} & \frac{dh}{dh} & \frac{dh}{dn} \\ \frac{dn}{dV} & \frac{dn}{dm} & \frac{dn}{dh} & \frac{dn}{dn} \end{bmatrix}$$

$$J_{(v^*,m^*,h^*,n^*)} = \begin{bmatrix} J_{11} & J_{12} & J_{13} & J_{14} \\ J_{21} & J_{22} & 0 & 0 \\ J_{31} & 0 & J_{33} & 0 \\ J_{41} & 0 & 0 & J_{44} \end{bmatrix}$$

Where the roots of the *characteristic equation*

$$det(J_{(v^*,m^*,h^*,n^*)} - \lambda I) = \begin{vmatrix} J_{11} - \lambda & J_{12} & J_{13} & J_{14} \\ J_{21} & J_{22} - \lambda & 0 & 0 \\ J_{31} & 0 & J_{33} - \lambda & 0 \\ J_{41} & 0 & 0 & J_{44} - \lambda \end{vmatrix}$$

are the eigenvalues.

3.1 Bifurcation analysis

Bifurcation plots are used to analysis the effects of varying $\overline{g}_{Na}$ and $\overline{g}_K$ parameters on the stability of the model. we take $\overline{g}_{Na}$ and $\overline{g}_K$ as variables and plot the relationship between the equilibrium point with $\overline{g}_{Na}$ and $\overline{g}_K$. Since all the equilibrium points depend on V* as shown in equation (2), we look at the relationship between the V* with $\overline{g}_{Na}$ and $\overline{g}_K$ and evaluate the bifurcation points where the equilibrium point (resting potential) becomes unstable. Matlabs Matcont software was used as a tool to do this.

3.1.1 V^* and $\overline{g}_{Na}$

Figure 7 shows the relation between V^* and $\overline{g}_{Na}$.

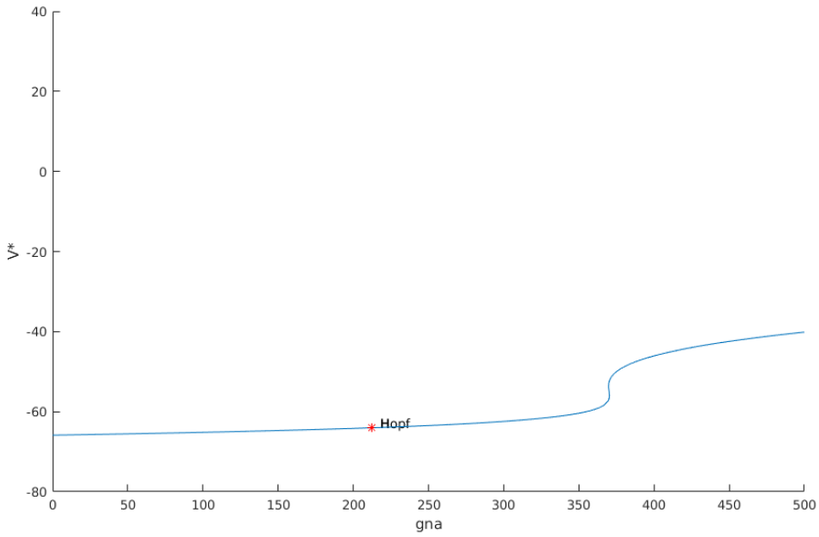
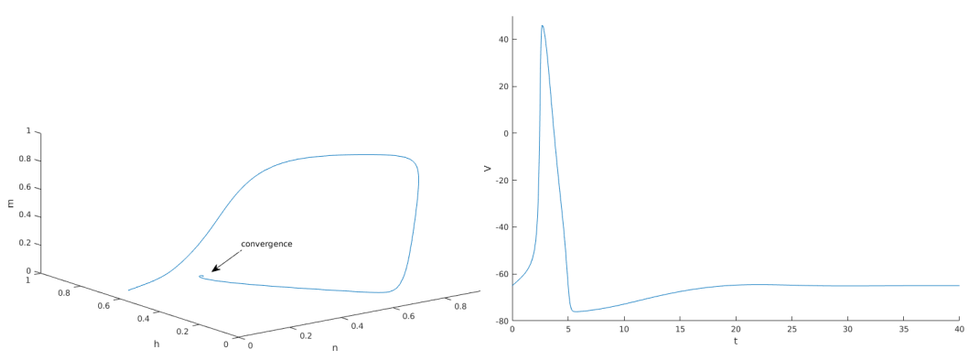


Figure 7: Relationship of V* with $\overline{g}_{Na}$ showing bifurcation points, saddle nodes and limit points where the equilibrium is not stable were not shown as after the first bifurcation point the solution lies on the limit cycle.

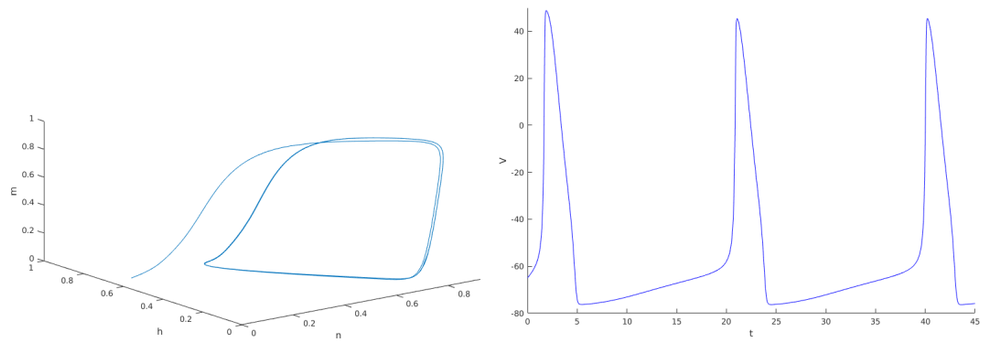
The bifurcation was found to be at $\overline{g^*}_{Na} = 212.648720656$, where the real parts of the eigenvalues $\lambda_{1,2,3,4}$ are negative before the bifurcation point, and there exist some positive real parts after the bifurcation point. Therefore according to the stability criteria mentioned previously, the equilibrium (resting potential) is stable for $\overline{g}_{Na} \in [0, \overline{g}_{Na})$ and unstable for $\overline{g}_{Na} \in (\overline{g}_{Na}, 500]$.

To analyze the bifurcation type at $\overline{g^*}_{Na}$ we plotted the the bifurcation using Matcont. The bifurcation type was found to be Andronov Hopf bifurcation which is the emergence of a limit cycle from an equilibrium point whereby the real part of a pair of eigenvalues disappears, leaving a pair of purely imaginary eigenvalues. Hopf bifurcation can be supercritical or subcritical whereby the limit cycle is stable or unstable respectively (21). The Lyapunov's coefficient calculated using Matcont, was used to determine the Hopf bifurcation type, where the coefficient is $\sigma > 0$ for subcritical Hopf bifurcation and $\sigma < 0$ for supercritical Hopf bifurcation. The Lyapunov coefficient was found to be positive for the bifurcation point and hence subcritical Hopf. For a closer inspection, the Hopf bifurcation was plotted and it was found that the subcritical Hopf moves back and eventually returns back from a saddle node (21) as a stable limit cycle over the unstable region of the equilibrium, with the cycle amplitude corresponding to an action potential. The Hopf bifurcation is shown in figure 10. The phase plots and action potentials showing the the stable equilibrium for $\overline{g}_{Na} < \overline{g}^*_{Na}$ and limit cycle of the Hopf bifurcation for $\overline{g}_{Na} > \overline{g}^*_{Na}$ is shown in figure 8 and 9. Figure 9(a-b) shows that the equilibrium resting potential is unstable for $\overline{g}_{Na} > \overline{g}^*_{Na}$ and so the system will not converge to the resting potential again, instead it oscillates continuously in a stable limit cycle.



(a) 3D-phase plot $\overline{g}_{Na} = 120 < \overline{g}^*_{Na}$, $\overline{g}_K = 36$ (b) V-t curve $\overline{g}_{Na} = 120 < \overline{g}^*_{Na}$, $\overline{g}_K = 36$

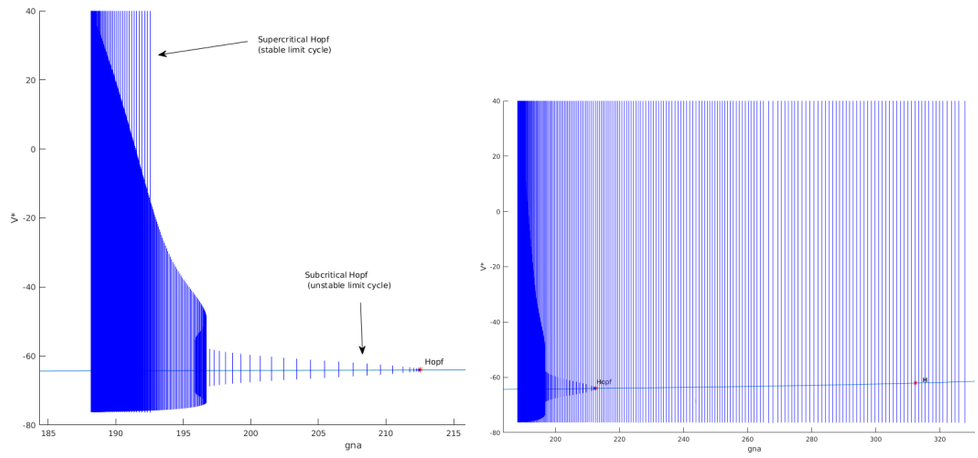
Figure 8: .



(a) 3D-phase plot $\overline{g}_{Na} = 250 > \overline{g}^*_{Na}$, $\overline{g}_K = 36$

(b) 3D-phase plot $\overline{g}_{Na} = 250 > \overline{g}^*_{Na}$, $\overline{g}_K = 36$

Figure 9: .



(a) Initital stage of Hopf Bifurcation

(b) Hopf Bifurcation plot

Figure 10: Figure 10(a-b) shows how the Hopf bifurcation starts and moves back and changes direction 3 times before it movies back past the bifurcation point with a stable limit cycle. Since there is a stable limit cycle over some of the stable equilibrium region the solution curve could have a completely different path for some other initial condition, but since the initial conditions are physiological restricted to the resting potential equilibrium point this is not likely to be observed naturally.

3.1.2 V^* and $\overline{g}_K$

In this section we looked at the relationship between V^* and $\overline{g}_K$ using the same method used to study $\overline{g}_{Na}$ and V^*. Figure 11 shows the the relationship of $\overline{g}_K$ and V^* with the bifurcation points indicated.

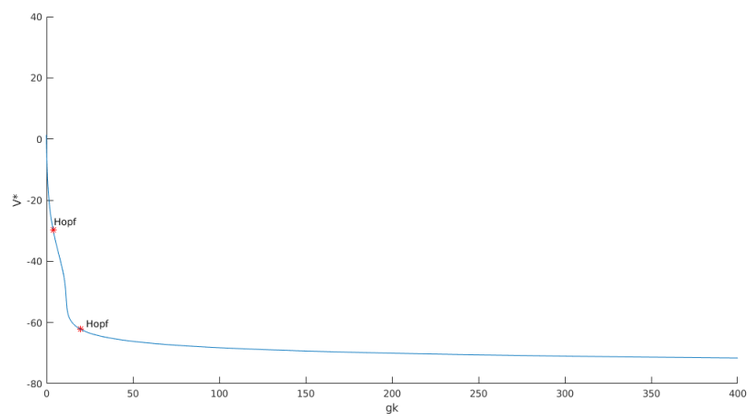
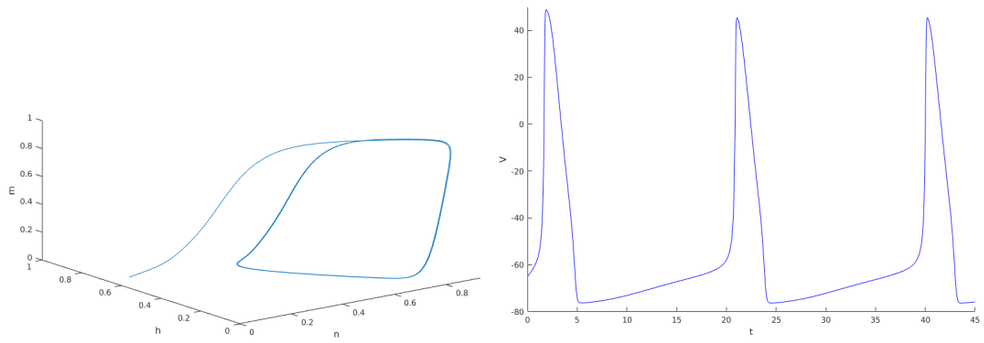


Figure 11: Relationship between V^* and $\overline{g}_K$ with Hopf bifurcation points indicated

The equilibrium point is sensitive for the range $\overline{g}_K \in [0, 25]$ where V* increases rapidly for decreasing values of $\overline{g}_K$. The bifurcation points are at $\overline{g}^*_{K_1} = 3.843499029$ and $\overline{g}^*_{K_2} =$

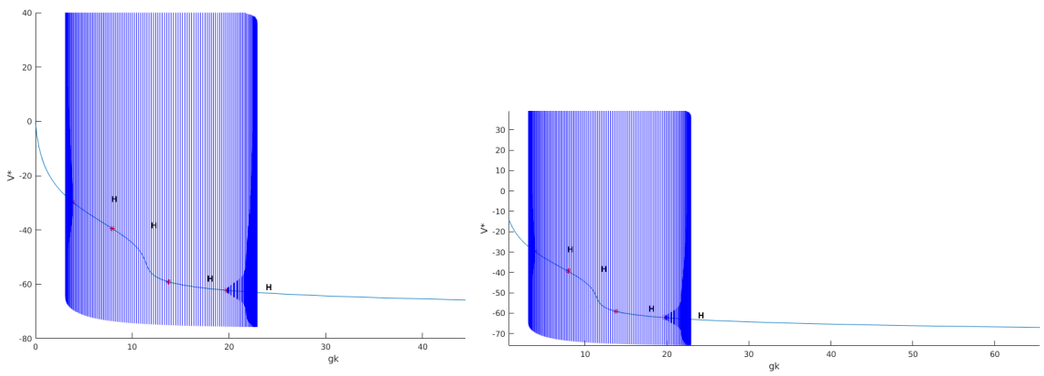
19.762260771, where V* is unstable for $\overline{g}_K \in (\overline{g}^*_{K_1}, \overline{g}^*_{K_2})$. Both bifurcation points are subcritical Hopf bifurcation that first progresses in the unstable equilibrium direction before returning with a stable limit cycle over the stable region in a similar way to the $\overline{g}^*_{Na}$ bifurcation. The bifurcation points and phase plots for some values between the bifurcation points are shown in figure 12 and 13.



(a) 3D-phase plot $\overline{g}_{Na} = 120$, $\overline{g}_K = 3 < \overline{g}^*_{K_1}$

(b) V-t curve $\overline{g}_{Na} = 120$, $\overline{g}_K = 10 < \overline{g}^*_{K_1}$

Figure 12: .



(a) Hopf bifurcation area

(b) Hopf bifurcation over the entire computed range

Figure 13

3.1.3 $\overline{g}_{Na}$ and $\overline{g}_K$ parameter plane

In this section we take $\overline{g}_K$ and $\overline{g}_{Na}$ as variables and plot the set of bifurcation points for varying values of $\overline{g}_K$ and $\overline{g}_{Na}$, where the system undergoes bifurcation on the plotted line. Figure 14 shows the continuous set of hopf bifurcation points corresponding to varying $\overline{g}_K$ and $\overline{g}_{Na}$ values. On figure 14 area A and B is divided by the bifurcation line, area A contains all the points $(\overline{g}_{Na}, \overline{g}_K)$ where the equilibrium is stable and area B contains all the points $(\overline{g}_{Na}, \overline{g}_K)$ where the equilibrium is unstable and the system is in a stable limit cycle. Our results are contradictory to the interpretation of Yue Zhang et al (7) where they explain that the stable region is in B. This is however not possible because the model with physiological Hodgkin Huxley parameter points $\overline{g}_K = 36$ and $\overline{g}_{Na} = 120$ should be stable and in fact lie in area A.

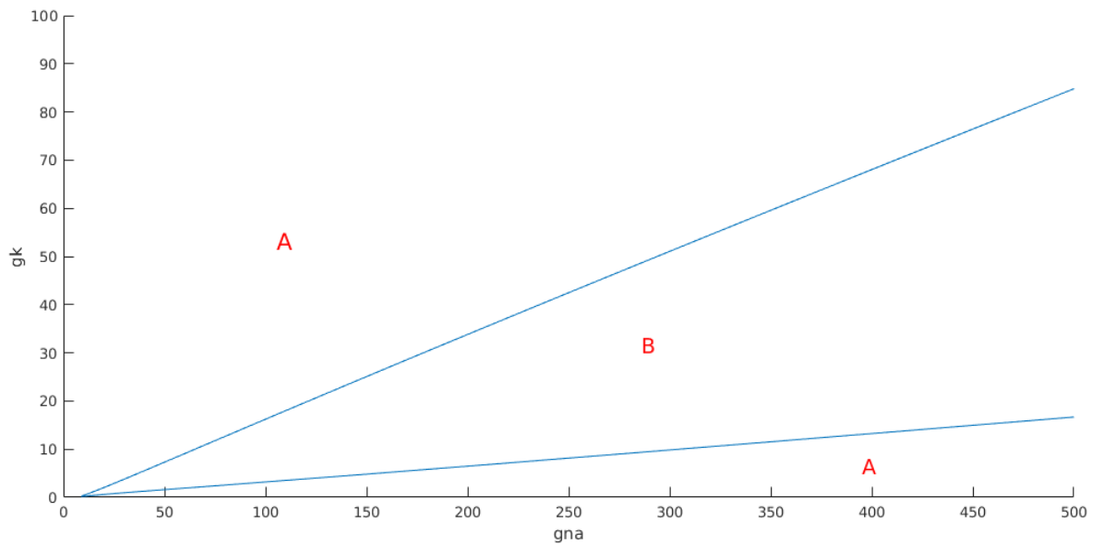


Figure 14: $\overline{g}_{Na}$ and $\overline{g}_K$ parameter plane

As a case study KCHQ5 and SCN1B mutations were studied with the $\overline{g}_{Na}$ and $\overline{g}_K$ parameter plane results for validation. In figure 15 the potential mutational shifting effect for KCHQ5 and SCN1B mutations on the potassium and sodium channels has been indicated. The mutational effects are explained and discussed later in this paper. Point **P** on figure 15 indicates the physiological parameter position where $\overline{g}_K = 36$ and $\overline{g}_{Na} = 120$.

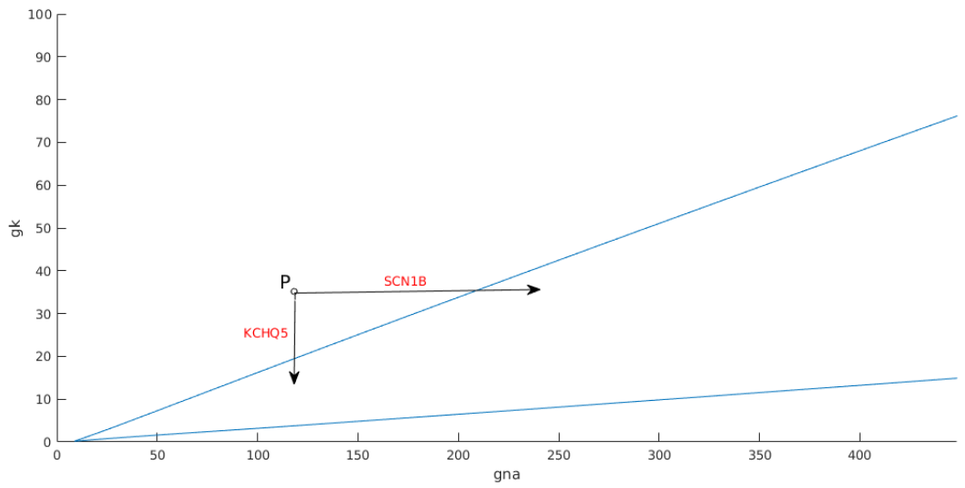


Figure 15: $\overline{g}_{Na}$ and $\overline{g}_K$ parameter plane indicating Possible KCHQ5 and SCN1B mutational shifting effect

4 Discussion and Conclusion

Most Neurological diseases that are caused by altered excitation dynamics in neurons have no definitive cure, In fact epilepsy has no specific cause, and seizures can be induced in a healthy individual by varying physiological conditions. For example, sleep deprivation, stress and electric shock can induce seizures in a normal brain (8).
Epilepsy can arise from other neurological disorders that bring the equilibrium closer to a bifurcation point. There are no cures for epilepsy but there are numerous treatments that help prevent the onset of a seizure event. These treatments include medication and diet to regulate biochemical conditions, nerve stimulation implants to interrupt the onset of seizures or surgery to remove parts of the brain or connections responsible for the seizures (22). Seizures can be classified by the onset and offset of bifurcations (8), thus epilepsy can be seen as the effect of bringing the equilibrium closer to a bifurcation boundary. Knowing and understanding the bifurcation range for varying parameters can give insight into possible treatment solutions for epilepsy. In this study we investigated the neural excitation

dynamics using the Hodgkin Huxley model to plot the steady state V^* with the bifurcation parameters $\overline{g}_K$ and $\overline{g}_{Na}$. The stable and unstable regions where found for varying $\overline{g}_K$ and $\overline{g}_{Na}$ values were the unstable regions had a constant limit cycle indicating a seizure event. It was found that there was a parameters region for ($\overline{g}_K$,$\overline{g}_{Na}$) points where the system is always in a limit cycle and it can be inferred that individuals with parameter values close to this region are at a higher risk of having an epileptic seizure when conditions are varied. As a case study, mutations KCHQ5 and SCN1B known to cause epilepsy were studied in relation to the results of this paper. There are 4 mutations in the in the KCNQ5 gene of the potassium channel that are known to cause epilepsy, 3 of which cause loss of function and 1 gain of function (23). The results of this paper account for the loss of function mutations but not for the increase in function mutation. This may be due to some other biological mechanisms that are not accounted for in our model, which is suggested by (23). A decrease in function should cause an increase in maximal conductance as the gates are slow to close with the mutation in effect, instead the mutation mostly causes a decrease in channel expression entirely which overall reduces the current flow, lowering $\overline{g}_K$. This is in line with the results of this paper as a decrease in $\overline{g}_K$ brings the equilibrium closer to the bifurcation boundary, This is illustrated in figure 15.
More recently, mutations in the SCN1B gene have been found to cause epilepsy. According to (2,3) The SCN1B mutations indicate a loss of function which causes a long lasting Na^+ current. This could be due to slow inactivation and closing of the activation channel which would increase the maximal conductance. The results of this paper agree with the supposed mutation consequence and are illustrated in figure 15. Since these presumed mutational effects correspond to the results of this paper, one could look at the parameter space ($\overline{g}_K, \overline{g}_{Na}$) to infer possible treatment function to correct mutations. A sodium channel mutation could be corrected by decreasing the $\overline{g}_{Na}$ or by increasing or decreasing the $\overline{g}_K$ conductance to move the ($\overline{g}_{Na}, \overline{g}_{Na}$) position back to a stable region indicated by area A in figure 14. A $\overline{g}_K$ mutation causing decrease in maximal conductance could be corrected by further decreasing $\overline{g}_K$ or by increasing the maximal conductance. The mutation could also be corrected by targeting the $\overline{g}_{Na}$, decreasing the $\overline{g}_{Na}$ so that ($\overline{g}_{Na}, \overline{g}_{Na}$) lies further from the bifurcation boundary.

Additionally it was found that the bifurcation points for $\overline{g}_K$ and $\overline{g}_{Na}$ where both Hopf subcritical that ultimately proceeded as a stable limit cycle over the unstable equilibrium region with constant amplitude corresponding to the action potential range. This allows for the all or none law of action potentials (referred to in Background) to apply even under unstable conditions whereby the continual action potential firing maintains a constant amplitude. The subcritical Hopf is complex and was studied in (24), this complex stability structure could be further studied with respect to the evolutionary design of the neuron in maintaining a constant action potential amplitude.

There are numerous limitations to this study that could be improved in future studies. This study used The Hodgkin Huxley model with squid giant axon parameter values, using parameter values for other neuron cell types could give more reliable results but in general the model dynamics remains relatively consistent and thus still useful for this study. Another consideration is the use of conductive based current kinetics in the Hodgkin Huxley model. Evidence suggests that the gating variables are coupled and the activated and inactivated states work cooperatively. Using drift diffuse currents would include these kinetics in which case the system could undergo bifurcation through different mechanisms (25). The Hodgkin Huxley model does not include some other channels that have a minor role but could still vary bifurcation results to some extent as for the case of the functional decrease mutation in the potassium channel that could not be explained by this papers findings. This study also assumes that other parameter values are not directly effected by varying $\overline{g}_K$ and $\overline{g}_{Na}$ parameter values which is also noted in (8) who communicated that it was reasonable to keep other parameter values the same.

The findings of this paper open up various target areas for epilepsy medication. The mutational effects on $\overline{g}_{Na}$ and $\overline{g}_K$ could infer the functionality of future epilepsy treatments. For drug discovery, further studies could investigate the effects of chemicals on maximal sodium and potassium conductance to find potential drugs to counteract mutational effect.

From this study it is evident that changes in sodium and potassium channels can increase the likelihood of seizure onset. In this paper the Hodgkin Huxley model was used to show how changes in maximal sodium and potassium conductance's can produce a seizure, and how the parameter plane of $\overline{g}_{Na}$ and $\overline{g}_{K}$ can be used to investigate possible treatments for epilepsy caused by mutations in potassium and sodium channels. The premise that bifurcation characterized the onset and offset of seizure events was used to evaluate the parameter plane for individuals who are more likely to have epileptic seizures. Future Epilepsy medication could target these conductance parameters to relieve epileptic symptoms.

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