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THE MODEL BEHAVIOUR OF FITZHUGH-NAGUMO SYSTEM

by

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Abstract

The application of models cannot be over emphasized in the field of science and engineering, since models are abstractions of real world. This paper is concerned with a nonlinear system called the FitzHugh-Nagumo system. We stated and defined all the parameters of the system and concentrated on the stability of the steady state of the system. Furthermore, after our investigation we observed that since our parameters must be greater than zero and γ *satisfying the inequality, thus both eigenvalues (*λ_1 *and* λ_2 *) are negative (which implies that the steady state of the system is stable) and complex (also meaning that the system also have spiral behaviour).*

Keywords: *FitzHugh-Nagumo System, Hodgkin-Huxley system, Excitable nature, Steady state, Conductivity.*

1. INTRODUCTION

In early 20th century, it was established in a major achievement in patch clamp experiments that many cell membranes are excitable, meaning that if sufficient current is being applied they exhibit large changes in potential. Nerve cells and some muscle cells are examples of such cells, for example see Olufsen (2015).

Hodgkin-Huxley, between 1948 and 1952 conducted an experiment on the giant squid axon, which was suitable for a large part of nerve tissue at that time. In an attempt to give mathematical clarification for the excitable nature, they constructed a model for the patch clamp experiment. They assumed that the electrical activity of the giant squid axon is dominated by the movement of sodium ion (Na^+) and potassium (K^+) ion across the membrane. Thus, Na^+ and K^+ used two different channels to go through. Furthermore a leakage channel through which chloride Cl^- and other ions can pass, were also included in the neuronal membrane of the model.(Keener and Sneyd, 1998).

2. THE NATURE OF EXCITABLE CELL SYSTEM- HODGKIN-HUXLEY MODEL

The equivalent circuit diagram for space-clamped axonal membrane of the Hodgkin-Huxleymodel is shown in the Figure 1.Here I is the currentand I_C, I_{Na}, I_K, and I_L represent the directions ofthe rate offlow of charge via the capacitance, sodium, potassium and Leakagechannels respectively. V is the voltage, C is the capacitance and g is the electrical conductivity.

The membrane act as a capacitor while the presence of channels can be modelled as resistors whose conductivities (inverse resistances) are g_{Na}, g_k and g_L for the sodium, potassium and Leakage potential channels respectively. On the other hand V_{Na}, V_K and V_K represent the potentials for each individual ion, which account for the ionic currents due to the concentration difference ofthe ions across the membrane.

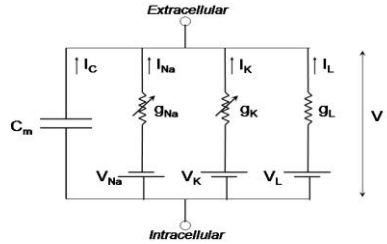

Figure 1: The equivalent circuit for space-clamped axonal membrane of the Hodgkin-Huxley model. (Edelstein-Keshet, 2005).

The conductivities of the Na^+ and K^+ channels are functions of time and the membrane potential, while the conductivity of the leakage channel is a constant and the change in the membrane potential do not affect it. (Gerstner and Kistler, 2002; Schwemmer, 2010).

The K^+ channel consists of four independent activation gates (i.e. four identical subunits) that open when the membrane potential is depolarised, allowing the flow of current through it. Thus, the current through these channels will then be given by

$$I_k = g_k n^4 (V - V_k) = \bar{g}_k n(t)^4 (V(t) - V_k)$$

where $\bar{g}_k$ is the maximum conductivity, a constant proportionality and $n = n(t)$ is the fraction of open activation gate at time t. In the same way, the Na^+ channel contains three activation gates which are independent of each other and opens when the neuron is depolarised, and also contains an activation gate that closes the channel when the membrane potential has been depolarised for some time t. Thus, the current through this channel can be given by

$$I_{Na} = g_{Na} m^3 h (V - V_{Na}) = \bar{g}_{Na} m(t)^3 h(t)(V(t) - V_{Na})$$

where $\bar{g}_{Na}$ is the maximum conductivity of the channel proportional to an additional fraction of open inactivation gates variable $h = h(t)$, and $m = m(t)$ is the fraction of open activation gates at time t. The gating variables $m(t)$ and $h(t)$ constitute the fraction of all the gating variables of the Na^+ channels in the open state at time t. (Mondeel, 2012).

Applying the Kirchhoff's conservation of current law and using the configuration of Figure 1, the Hodgkin-Huxley model can be written as

$$I_c + I_{Na} + I_k + I_L = I_{appl} \qquad (1)$$

where I_{appl} is the applied current.Then we can rewrite equation (1) as

$$C_m \frac{dV}{dt} = -\bar{g}_K n^4 (V - V_K) - \bar{g}_{Na} m^3 h (V - V_{Na}) - \bar{g}_L (V - V_L) + I. \qquad (2)$$

After many trial and error models, Hodgkin and Huxley found it necessary to introduce three variables and they proposed n, m and h as the potential dependent gating variables that obey the voltage dependence described by the differential equations:

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

$$\frac{dm}{dt} = \alpha_m(v)(1-m) - \beta_m(v)m \qquad (3b)$$

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

where the quantities $\alpha_m, \beta_m, \alpha_n, \beta_n, \alpha_h$, and β_h are assumed to be voltage dependent as follows:

$$\begin{aligned}
\alpha_m(v) &= 0.1(v+25)\left(e^{(v+25)/10}-1\right)^{-1} \\
\beta_m(v) &= 4e^{v/18} \\
\alpha_n(v) &= 0.01(v+10)\left(e^{(v+10)/10}-1\right)^{-1} \\
\beta_n(v) &= 0.125e^{v/80} \\
\alpha_h(v) &= 0.07e^{v/20} \\
\beta_h(v) &= \left(e^{(v+30)/10}\right)^{-1}.
\end{aligned} \qquad (4)$$

Equations (2), (3a), (3b) and (3c) represent a 4×4 differential system called the Hodgkin-Huxley model. (Edelstein-Keshet, (2005).

3. THE FITZHUGH-NAGUMO MODEL

The main analysis of Hodgkin-Huxley model was performed independently by Richard Fitzhugh and Jin-Ichi Nagumo who noticed that they can, under some assumption, reduce the four first order differential systemto a two first order differential system. The outcome of their experiment is what is now known as FitzHugh-Nagumo system. The FitzHugh-Nagumo system is the simplified form of the Hodgkin-Huxley system that explains the inner working process of the Hodgkin-Huxley system and a major model in the study of neuron physiology in the 20th century. The FitzHugh-Nagumo system has been used in many different types of biological modelling (e.g. neurophysiology model, cardiac muscle model etc.). (Aku et al. 2016).

The dynamical behaviour of the FitzHugh-Nagumo system is very vital in the analysis and understanding of more difficult systems. The FitzHugh-Nagumo system has been derived and written in different variations by researchers to suit their specific research work. In this paper we will focus on the one that will suit the current work.

Consider the phase portrait below

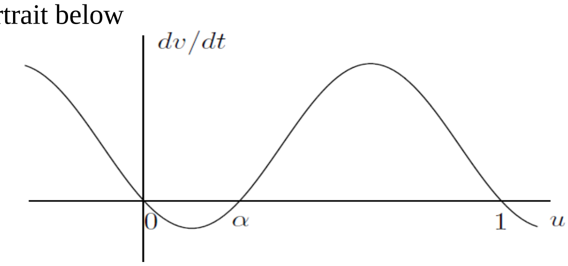

Figure 2: The profile of $\frac{dv}{dt}$ as a function of v. (Edelstein-Keshet, 2005).

As it is shown in Figure 2, v denotes the voltage of the action potential that has three critical values:

i. $v=0$, , as the resting potential.
ii. $v=\alpha$, as the threshold $(0<\alpha<1)$.
iii. $v=1$, asthe voltage level when Na^+ channels are closed.

We want to create a differential equation for v = v(t). To achieve that we have to express $\frac{dv}{dt}$ as a function of v. Since v =0 then $\frac{dv(0)}{dt} < 0$, but when the Na^+ start to open the voltage increases, so $\frac{dv}{dt} > 0$ and the more v increases, the neuron fires at $v = \alpha$, hence $\frac{dv(\alpha)}{dt} > 0$. Finally the voltage decreases such that the Na^+ channels closes at v = 1, so that $\frac{dv(1)}{dt} < 0$. The easiest description for $\frac{dv}{dt}$ as a function f(v) of v is expressed in Figure 2.(Edelstein-Keshet, 2005).

An expression that is compatible with the form of Figure 2 is given by

$$\frac{dv}{dt} = -v(v-\alpha)(v-1) \equiv f(v) \cdot \qquad (5)$$

Introducing the variable w that acts to diminish v into (5), we now have

$$\frac{dv}{dt} = -v(v-\alpha)(v-1) - w \equiv f(v) - w \cdot \qquad (6)$$

Introducing the applied electric current I to the right hand side of equation (6), and suppose that $\frac{dw}{dt}$ increases linearly in v and that w decreases linearly, then we get

$$\frac{dv}{dt} = -v(v-\alpha)(v-1) - w \equiv f(v) - w + I \qquad (7)$$

$$\frac{dw}{dt} = \varepsilon(\gamma v - w)$$

which is the FitzHugh-Nagumo model in dimensionless form, where v represents the fast variable (potential) and w denotes the slow variable (sodium gating variable). Besides $\alpha, \gamma,$ and ε are constants satisfying the conditions $0 < \varepsilon \leq 1$ and $0 < \alpha < 1$ which control some special behaviour of the system. The first term $\frac{dv}{dt}$ captures the basic dynamics of sodium and the leakage in the cell. The second term, -w, is the model of the potassium leaving the cell, seeEdelstein-Keshet, (2005). System (7) is the FitzHugh-Nagumo system we will focus on in thiswork.

4. Steady States of the FitzHugh-Nagumo System

To determine the steady state of the FitzHugh-Nagumo system, we must make the two differential equations (7) be equal to zero.

Thus, we define where $\frac{dv}{dt} = 0$ and $\frac{dw}{dt} = 0$:

$$w = -v(v-\alpha)(v-1)$$
$$w = \gamma v$$

These are known as the nullclines of the system.

Some critical facts about nullclines:

- Each point of intersection between the v-nullcline and the w-nullcline is an equilibrium state (steady state).

- As long as we move through a nullcline without traversing an equilibrium point, the course of the velocity vector remain unchanged. But if we traverse an equilibrium point, then the course of the velocity vector may change (from right to left, or up to down, reciprocally).
- Nullclines help to arrange and conceptualize directions of flows and determine the positions and types of steady states.

Hence to see where the nullclines intersect, we put their corresponding equations equal to each other:

$\gamma v = -v(v-\alpha)(v-1)$

Putting $v = 0$, gives the first steady state. If we assume $v \neq 0$, and dividing through by v gives

$-(v-\alpha)(v-1) = \gamma$

Expanding and rearranging gives

$v^2 - v(\alpha+1) + (\alpha+\gamma) = 0$

We now solve by quadratic formula:

$$v = \frac{-(\alpha+1) \pm \sqrt{(\alpha+1)^2 - 4(\alpha+\gamma)}}{2}$$

This gives the two other steady states.

Now the parameters (α and γ) of the system will determine if the solutions will be complex or real solutions. To have only real solutions, the discriminant have to be greater than zero:

$$(\alpha+1)^2 - 4(\alpha+\gamma) \geq 0$$

Rearranging gives

$$\frac{(\alpha+1)^2}{4} \geq \gamma$$

Thus, if γ is less than or equal to $\frac{(\alpha+1)^2}{4}$, this will give us 3 real steady states.

5. MODEL BEHAVIOR

5.1Stability of the Steady States of the system

In order to obtain the stability of the steady state point, we have to investigate the nature of the steady states where the nullclines intersect. We will use the technique of Jacobian matrix for the system to obtain the determinant. Furthermore, to determine the steady state's stability, we shall solve for the eigenvalues at each steady state.

First, we consider the following definitions:

$$F_1 = \frac{dv}{dt},$$

$$F_2 = \frac{dw}{dt}.$$

Then the Jacobian matrix is defined as:

$$J(v,w) = \begin{bmatrix} \frac{\partial F_1}{\partial v} & \frac{\partial F_1}{\partial w} \\ \frac{\partial F_2}{\partial v} & \frac{\partial F_2}{\partial w} \end{bmatrix}$$

Now computing the Jacobian of equations, we get:

$$J(v^*,w^*) = \begin{bmatrix} -3v^2 + (2\alpha+2)v - \alpha & -1 \\ \varepsilon\gamma & -\varepsilon - \lambda \end{bmatrix}_{(v^*,w^*)} = 0$$

Where (v^*, w^*) is the equilibrium state being evaluated.

Relating the eigenvalues and eigenvectors, we now have a way of obtaining a solution of the type

$M\vec{v} = \lambda\vec{v}$

Solving this equation, we get:

$\vec{v}(M - \lambda I) = 0$

Where M is the Jacobian matrix, *I*is the identity matrix, $\vec{v}$ is the eigenvector, and λ is the eigenvalue.

Substituting our Jacobian matrix for M and simplifying, we obtain

$$\vec{v} = \begin{bmatrix} -3v^2 + (2\alpha + 2)v - \alpha & -1 \\ \varepsilon\gamma & -\varepsilon - \lambda \end{bmatrix} = 0$$

To solve for the eigenvalue of the system, we evaluate the determinant and simplify to get:

$$\lambda^2 + \lambda(\propto + 3v^2 - 2(\propto + 1)v + \varepsilon) + \varepsilon(3v^2 - 2(\alpha + 1)v) + \alpha + \gamma) = 0$$

To solve for λ , we use the quadratic formula:

$$\lambda = \frac{-\left(\alpha + 3v^2 - 2(\alpha + 1)v + \varepsilon\right) \pm \sqrt{\left(\alpha + 3v^2 - 2(\alpha + 1)v + \varepsilon\right)^2 - 4\varepsilon\left(3v^2 - 2(\alpha + 1)v + \alpha + \lambda\right)}}{2}.$$

We get the two eigenvalues, λ_1 and λ_2 .

If we let Δ be the discriminant of the λ equation and depending on sign of the determinant, we obtain the following stability cases for the set of the real eigenvalues:

Case 1: If $\Delta \geq 0$ (real eigenvalues)

- λ_1 , λ_2 are both >0: Unstable node
- λ_1 , λ_2 are both <0: Stable node
- λ_1 and λ_2 are opposite signs: Unstable Saddle node

Case 2: If $\Delta < 0$ (complex eigenvalues)

- Real parts of λ_1 and λ_2 are both >0: Unstable Spiral
- Real parts of λ_1 and λ_2 are both <0: Stable Spiral
- Real parts of λ_1 and λ_2 are both = 0: test is inconclusive (The corresponding linear system has a centre at (0; 0) with closed solution orbits around it and is stable).(Dobrushkin, 2014).

5.2Stability of the Zero State of the System

We have already explored that at $v = 0$ the system is in a steady state, regardless of the parameter values. Now, to find out more about its stability, we substitute $v = 0$ into the general equations for the eigenvalues. If both eigenvalues are negative, then $v^* = 0$ is stable. Substituting $v = 0$ in the system, gives:

$$\lambda_1 = \frac{-\alpha - \varepsilon + \sqrt{(\alpha + \varepsilon)^2 - 4\varepsilon\alpha - 4\varepsilon\gamma}}{2}$$

$$\lambda_2 = \frac{-\alpha - \varepsilon - \sqrt{(\alpha + \varepsilon)^2 - 4\varepsilon\alpha - 4\varepsilon\gamma}}{2}$$

Simplifying the two equations, gives:

$$\lambda_1 = \frac{-\alpha - \varepsilon + \sqrt{(\alpha + \varepsilon)^2 - 4\varepsilon\gamma}}{2}$$

$$\lambda_2 = \frac{-\alpha - \varepsilon - \sqrt{(\alpha+\varepsilon)^2 - 4\varepsilon\gamma}}{2}$$

Since our parameters must be greater than zero,then λ_1 and λ_2 will be negative. Thus, $v^* = 0$ is a stable steady state.

Furthermore, it is possible for the eigenvalues to be complex. For this to be achieve, the discriminant must be less than zero.

$$(\alpha+\varepsilon)^2 - 4\varepsilon\gamma < 0$$

Solving it gives:

$$\gamma > \frac{(\alpha+\varepsilon)^2}{-4\varepsilon}$$

Hence, if γ satisfies this inequality, the eigenvalues will be negative (stable steady state) and complex (spiral behaviour).

6. Phase Plane Analysis of the FitzHugh-NagumoSystem

Phase plane analysis helps us to visually see the behaviour of a system. We use phase plane analysis to study and apprehend the FitzHugh-Nagumo system (7).

This technique is extensively used to understand qualitative behaviour of different excitable systems other than the FitzHugh-Nagumo system.Since we have knowledge of some facts about nullclines and steady states where the nullclines intersect. If we set the two differential equations (7) to be equal to zero, i.e.

$\frac{dv}{dt} = 0$ and $\frac{dw}{dt} = 0$.

We get;

$w = -v(v-\alpha)(v-1)$

$w = \gamma w$

Since the equations satisfies the conditions $\frac{dv}{dt} = 0$ and $\frac{dw}{dt} = 0$, (meaning v and w are not changing). These are known as the nullclines of the system, see Figure 3.Whenever the two nullclines intersect, the system experiences what is called a steady state (i.e. v and w are not changing). (Segel and Edelstein-Keshet, 2013;Friedman and Kao 2014).

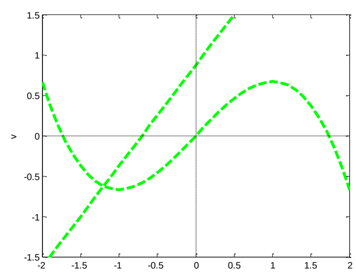

Figure 3: The nullclines of theFitzhugh-Nagumo system with $\alpha = 0.25$ and $\gamma = 0.2$.

The qualitative behaviour of the system for various parameter values can basically be deduced by observing the structure and movement of the flow field of the nullclines graph. In Figure 4, we present a graph of v and w nullclines of Fitzhugh-Nagumo system (7) with parameters γ and ε kept as constant while α changes.

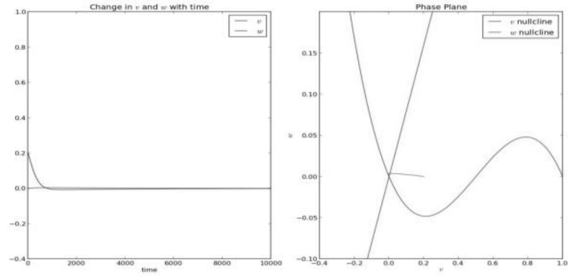

Figure 4(a): Simulations with $\alpha = 0.5$.

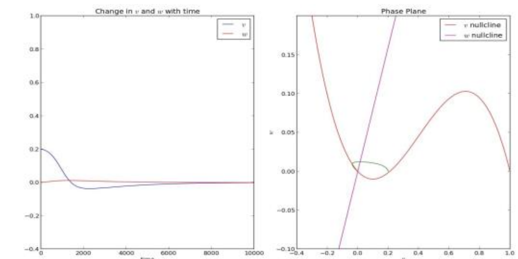

Figure 4(b): Simulations with $\alpha = 0.21$

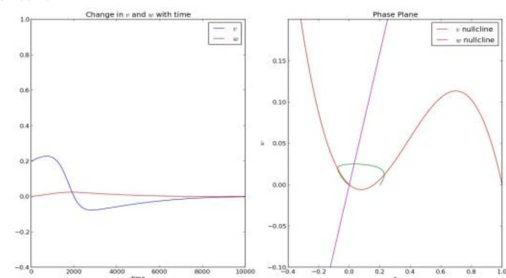

Figure 4(c): Simulations with $\alpha = 0.16$

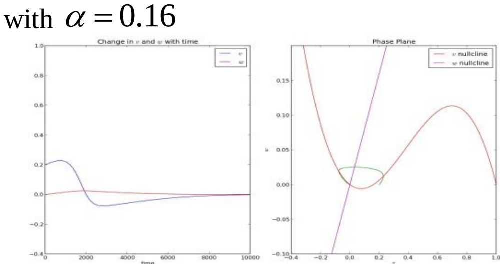

Figure 4(d): Simulations with $\alpha = 0.1$

7. DISCUSSION OF RESULTS

The focus of this work was to analyse the model behaviour of FitzHugh-Nagumo system.We observed that whenever the v and w nullclines of the system intersect, it results to a unique solution orbit (trajectory) also known as steady state, since at that point the v and w nullclines are not changing. This shows that at that point the system has a stable solution see Figure 4a. We also notice in Figure 4 how the threshold value α affect the behaviour of the

system. If we increased α above the initial voltage v_0 an action potential is not generated, as shown in Figure 4a. If we set α just above v_0 an action potential is still not generated, but the action potential moves back to rest with a more gradual slope as illustrated by Figure 4b.
However, if we set α slightly below v_0, a full action potential is still not generated, but a delay occurs before the action potential returns to rest, as shown in Figure 4c. Lastly, if the value of α is substantially below v_0, an action potential is generated, as depicted in Figure 4d.

8. CONCLUSIONS

We observed from our investigation of the stability of the steady state of the FitzHugh-Nagumo system, that since our parameters must be greater than zero and γ satisfying the inequality, then both eigenvalues (λ_1 and λ_2) are negative (which implies that the steady state of the system is stable) and complex (meaning the system also exhibited spiral behaviour).We further observed that the qualitative behaviour of the system for various parameters can basically be deduced by the structures and movement of the flow field of the nullclines.
Lastly, we also noticed that with the changes in the parameters, there are threshold behaviour, steady action potentials and the spread of the action potentials was also exhibited.

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