PHYSICAL SCIENCES

DERIVATION OF FITZHUGH-NAGUMO SYSTEM

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ABSTRACT
This paper is concerned with a nonlinear system called the FitzHugh-Nagumo system. We concentrated on the derivation of the system from the aspect of the nature of excitable cell model and gating model of Hodgkin-Huxley system. Furthermore, reduction of a Hodgkin-Huxley system to a FitzHugh-Nagumo system is also investigated and we concluded by depicting the two different variations of FitzHugh-Nagumo system that are widely used by researchers in the fields of neurophysiology and cardiac muscle model. This paper evaluates further ways in which this FitzHugh-Nagumo system can be applied.

KEYWORDS :*FitzHugh-Nagumo System, Gating Model, Excitable Cell Model.*

INTRODUCTION

Alan Lloyd Hodgkin and Andrew Huxley, between 1948 and 1952 conducted an experiment on the movement of action potential in the giant squid axon, which was suitable for a large portion of the nerve tissue at that time. In an effort to give mathematical meaning for the excitable nature, they constructed a model for the patch clamp experiment. Applying the Kirchhoff's conservation of current law and using the configuration of an equivalent circuit for space clamp axonal membrane, Hodgkin and Huxley formulated a differential equation called the Hodgkin-Huxley model Edelstein-Keshet, (2005).

The main analysis of Hodgkin-Huxley model was performed independently by Richard FitzHugh and Jin-IchiNagumo who noticed that they can, under some assumption, reduce the differential system to a 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 since mid 19th century. The FitzHugh-Nagumo system has been used in many different types of biological modelling (e.g. neurophysiology model, cardiac muscle model etc).

The dynamical behaviour of the FitzHugh-Nagumo system is very vital in the analysis and understanding of more difficult systems, so in this paper we focus on the system by investigating the reduction of the system from a differential system to a differential system.

NATURE OF EXCITABLE CELL MODELS-HODGKIN-HUXLEY MODEL

Conventionally, it was known that the cell membrane separates the internal working parts of the cell from its external parts, and it allows the passage of some materials and restricting the passage of others, thus controlling the movement of materials to and from the cell. A basic model for describing the aforementioned process is that of parallel capacitor and resistance, which has the form

$$C_m = \frac{dV}{dt} = -\frac{V - V_{eq}}{R} + I_{appl}. \quad \text{.....(1)}$$

Here C_m is the cell membrane capacitance, V the reversal potential (is the membrane potential at which there is no net flow of that particular ion from one side to the other of the membrane),V_{eq} is the resting membrane potential that balance the reversal potentials for the other ionic currents, R is the resistance, and I is the applied electric current Friedman and Kao (2014).

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, see for example Keener and Sneyd (2009).

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 squid giant axon is dominated by the movement of sodium and potassium ions across the membrane. Thus, Na^+ and K^+ use two different channels to go through. Furthermore a leakage channel through which chloride Cl^- and other ions can pass, are also included in the neuronal membrane of the model.

The equivalent circuit diagram for space-clamped axonal membrane of the Hodgkin-Huxley model is shown in the Figure 1. Here I is the current, 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 each individual ion, which account for the ionic currents due to the concentration difference of the ions across the membrane.

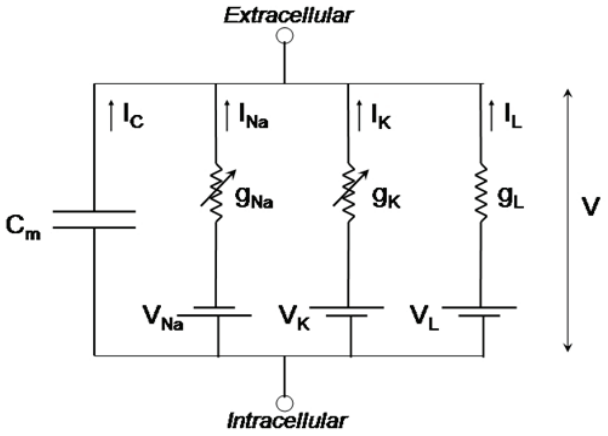

Figure 1: The equivalent circuit for space-clamped axonal membrane of the Hodgkin-Huxley model.

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 Kistlerl *et al.,* (2002).

The channel consists of four independent activation gates (i.e. four identical subunits) that opens 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 channel contain three activation gates which are independent of each other and opens when the neuron is depolarised, and also contain 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 is the maximum conductivity of the channel proportional to an additional fraction of open inactivation gates variable $h(t)$, and $m(t)$ is the fraction of open activation gates at time . 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 .

The Gating Model of the System

It was observed that the movement of sodium and potassium ions across the cell membrane of a neuron shows that sodium has a transient conductivity while potassium has a persistent conductance: see Figure 2 Mondeel, (2005).

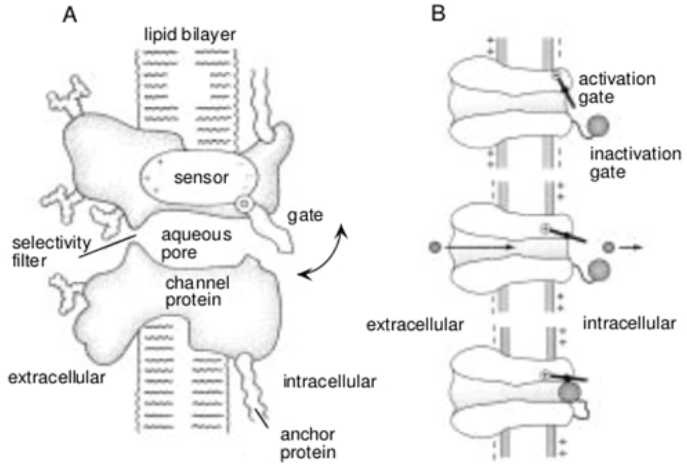

Figure 2: (A) is an example of a persistent conductance gate. The gate opens and closes by a sensor which responds to the membrane potential. (B) is an example of a transient conductance gate, the activation gate connect with a voltage sensor that functions like the gate in A Mondeel, (2005).

For the persistent conductivity gate to open a number of changes have to take place. The potassium channel, for example consists of four identical subunits, and for the channel to open, all four must experience a systemic change. This systemic change has to do with independent events. If b is identical, then independent events are needed to open a channel, and one of these events occurs with the probability n. Thus the conductance can be written as $g = n^b$ where n is a gating variable. If the present channels are many and they function independently of each other, then the fraction of channels open at any given moment is approximately equal to the probability that any of the channels is open. This is the implementation of the law of large numbers Mondeel, (2005).

If we assume that the n subunit gate controls the opening and closing state of the channel at a given time, then the probability that one of the subunit gate will be open is n and the probability that it will be close is 1-n. Therefore the transition of each subunit gate can be expressed as a first-order scheme in which the gating movement from closed to open occurs at a voltage-dependent rate $\alpha_n(V)$, and the reverse movement open to close occurs at a voltage-dependent rate $\beta_n(V)$. The probability that a subunit gate opens over a small period of time is proportional to the probability of finding the gate closed, 1-n, times the opening rate $\alpha_n(V)$. Conversely, the probability that a subunit gate closes over a small amount of time corresponds to the probability of finding the gate open n times the closing rate $\beta_n(V)$.

Thus the open probability for a subunit gate changes at a rate given by the difference of these two terms and so we derive the differential equation

$$\frac{dn}{dt} = \alpha_n(v)(1-n) - \beta_n \quad \text{..... (2)}$$

Where $\tau_n(v) = \frac{1}{\alpha_n(v) + \beta_n(v)}$, and $n_\infty(v) = \frac{\alpha_n(v)}{\alpha_n(v) + \beta_n(v)}$.

This equation actually implies that for a fixed voltage V, n tends to the value of $n_\infty(V)$ exponentially with time constant $\tau_n(v)$ Here $\alpha_n(V)$ and $\beta_\infty(V)$ are the opening and closing rate functions of voltage. All these are achieved by suitable experimental data based on a technique called voltage clamping which Hodgkin and Huxley used in their experiments Mondeel, (2005).

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

$$I_c + I_{Na} + I_k + I_L = I_{appl} \quad \text{.....(3)}$$

where is the applied current. Then equation (3) can be rewrite as

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

Hodgkin and Huxley proposed that n, m and h are the potential dependent gating variables that obey the voltage dependence described by the differential equations:

$$\frac{dn}{dt} = \alpha_n(v)(1-n) - \beta_n(v)n \quad \text{.....(5a)}$$

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

$$\frac{dh}{dt} = \alpha_h(v)(1-h) - \beta_h(v)h \quad \text{.....(5c)}$$

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

$$\alpha_m(v) = 0.1(v+25)\left(e^{(v+25)/10} - 1\right)^{-1}$$

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

$$\alpha_n(v) = 0.01(v+10)\left(e^{(v+10)/10} - 1\right)^{-1} \quad \text{.....(6)}$$

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

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

$$\beta_h(v) = \left(e^{(v+30)/10}\right)^{-1}$$

Equations (4), (5a), (5b) and (5c) represent a differential system called the Hodgkin-Huxley model Edelstein-Keshet, (2005). The model does lay a base for qualitative behaviour for the formation of action potential and basis for nearly all models of excitable cell membrane.

We can rewrite each of the equation (5a)-(5c) in the form

$$z = \frac{-1}{\tau_z(v)}[z - z_0(v)]$$

for greater insight. Here z represent m, n or h. For any fixed voltage v, z tends to $z_0(v)$ with a time constant $\tau_z(v)$, where the asymptotic value $\tau_{z_0}(v)$ and the time constant are given by

$$\tau_{z_0}(v) = \frac{\alpha_z}{[\alpha_z(v) + \beta_z(v)]} \quad \text{and} \quad \tau_z(v) = \frac{1}{[\alpha_z(v) + \beta_z(v)]}$$

The parameters used are those specified by Hodgkin and Huxley, see Figure 3 and Figure 4 where the functions of $\tau_{z_0}(v)$ and $\tau_z(v)$ are shown Schwemmer, (2005).

THE FITZHUGH-NAGUMO MODEL

Reduction from a 4×4 to 2×2 a System

Fitzhugh and Nagumo noticed that they can under some assumption reduce the four by four differential system (4), (5a), (5b) and (5c) to a two by two differential system. The basic concept of the reduction can also be applied to that of neuron model with various ion channels. To perform this task, we have to eliminate two out of the four variables. We start with two qualitative observations in Figure 3 and Figure 4:

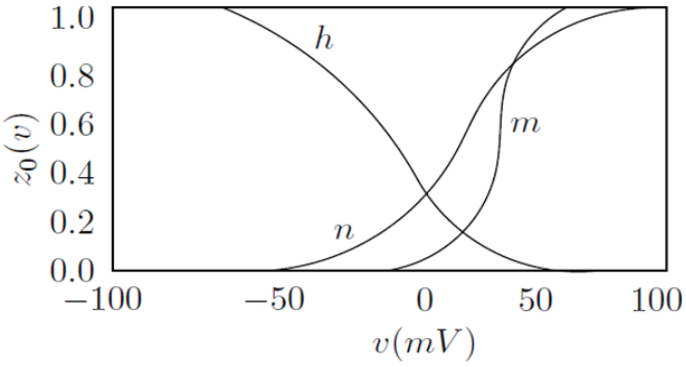

Figure 3: The equilibrium function for variables m, n, and h in the Hodgkin-Huxley Model. The resting potential is at v=0.

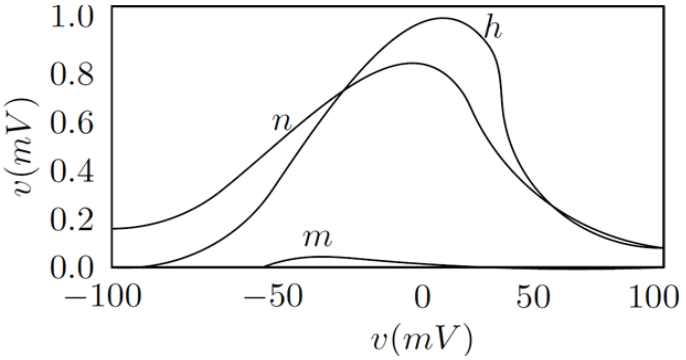

Figure 4: The time scale for variables m, n, and h in the Hodgkin-Huxley Model. The resting potential is at v=0.

In Figure 4 we notice that the kinetics of the gating variable m changes rapidly while that of the variables n, h and v changes relatively slowly, which is a consequence of τ_m being smaller than τ_n and τ_h (τ_m, τ_n , and τ_h are the time scales for m, n and h respectively). It also shows that m can be considered as an instantaneous variable that can be replaced in equation (4) by its steady-state value, $m(t) \to m_0(v(t))$, which is called the quasi steady state approximation Schwemmer, (2005). Furthermore, from Figure

4, we observe that the time scale $\tau_n(v)$ and $\tau_h(v)$ are close no matter the value of v, and even more there is similarity with the graphs of $n_0(v)$ and $1-h_0(v)$ in Figure 3. This shows that the variables n and 1-h can be approximated as a single functional variable w. To make it more universal, we take the linear approximation of d-h = bn, where d, and b are constants and we let $w = d-h = bn$. Now $h = d-w$,

$n = \frac{w}{b}$, $m = m_0(v)$. Then the system (4), (5a), (5b) and (5c) takes the form:

$$C\frac{dV}{dt} = -g_K\left(\frac{w}{b}\right)^4(V-V_K) - g_{Na}[m_0(v)]^3(d-w)(V-V_{Na}) - g_L(V-V_L)+I \quad \text{.....(7)}$$

or by introducing a new variable v, it can be written as

$$\tau_v\frac{dv}{dt} = F(v,w) + RI. \quad \text{.....(8)}$$

Where $R = \frac{1}{g_L}$, and $\tau_v = RC$ is actually the time scale of time of v while F denotes a function. Since m is regarded as constant, we are left with n and h which are lump together as a single functional equation

$$\tau_w\frac{dw}{dt} = Q(v,w) \quad \text{.....(9)}$$

where τ_w is the time scale of w. The equations (8) and (9) define a neuron model Schwemmer, (2005). Replacing the four equations of Hodgkin and Huxley by the two equations (8) and (9), FitzHugh and Nagumo obtained sharp pulse like oscillations that are similar to that of action potentials by describing the functions F(v, w) and Q(v, w) as

$$F(v,w) = v - \frac{v^3}{3} - w$$

$$Q(v,w) = b_0 + b_1 v - w$$

where v is the membrane voltage, and w is the recovery variable. F and Q are linear in w and the cubic term in v is non-linear. So we finally obtain the system

$$\tau_v\frac{dv}{dt} = v - \frac{v^3}{3} - w$$

$$\tau_w\frac{dw}{dt} = b_0 + b_1 v - w \quad \text{.....(10)}$$

where b_0 and b_1 are positive constants. The system (10) is an example of FitzHugh-Nagumo System Schwemmer, (2005).

Two Different Variations of FitzHugh-Nagumo System

The FitzHugh-Nagumo system has been derived and written in different variations by researchers to suit their specific research work. In this section we look at two different formulations and then focus on the one we will use in the current work.

Firstly, we consider two variables x and y and model properly the FitzHugh and Nagumo system. We define the variable x as the measure of excitation (such as voltage in a neuronal setting), hence x is the fast variable (replacing variables V and m in the Hodgkin-Huxley system) and use y as the slow recovery variable (replacing variables n and h in the Hodgkin-Huxley system), which damps out the excitation of x when increased. Making the equation simple enough for the rate of change for x and y, we assume that x and y satisfies the linear kinetics,Segel and Edelstein-Keshet (2013):

$$\frac{dx}{dt} = c\left(x - \frac{x^3}{3} - y + d\right) \quad \text{.....(11a)}$$

$$\frac{dy}{dt} = \frac{1}{c}(x + a - by) \quad \text{.....(11b)}$$

System (11) is the FitzHugh-Nagumo system we will focus on in this work. Here the parameters c and $\frac{1}{c}$ are introduced to create a symmetry that makes x faster and y slower whenever c is increased. The parameters a, b, and c are all positive, and satisfy the conditions $1-\frac{2b}{3} < a < 1$ and 0 < 1. The parameter d denotes the stimulus and can have any sign, Segel and Edelstein-Keshet (2013).

In the second formulation of the FitzHugh-Nagumo system, we consider the phase portrait below

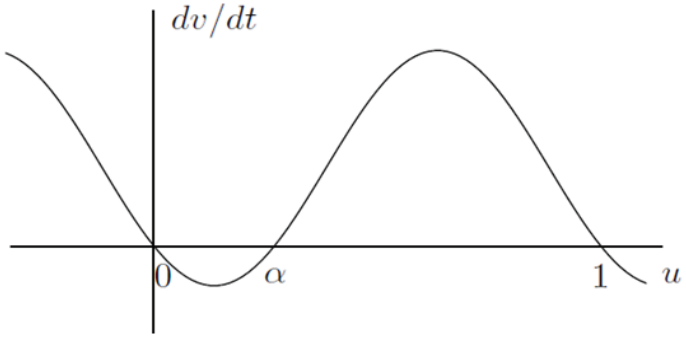

Figure 5: The profile of $\frac{dv}{dt}$ as a function of v Olufsen, (2015).

As it is shown in Figure 5, v denotes the voltage of the action potential that has three critical values: v = 0, as the resting potential, $v = \alpha$, as the threshold

$(0 < \alpha < 1)$ $v = 1$, as the 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, $\frac{dv}{dt} > 0$ so and the more v increases, the neuron fires at $v = \alpha$, hence . Finally the voltage decreases such that the Na^+ channels closes at $x = 1$, 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 5 Olufsen, (2015).

An expression that is compatible with the form of Figure 5 is given by

$$\frac{dv}{dt} = -v(v-\alpha)(v-1) = f(v) \quad \text{.....(12)}$$

Introducing the variable w that acts to diminish v into (12), we now have

$$\frac{dv}{dt} = -v(v-\alpha)(v-1) - w = f(v) - w \quad \text{.....(13)}$$

Introducing the applied electric curren $\frac{dw}{dt}$ o the right hand side of (13), and suppose that increases linearly in v and that w decreases linearly, then we get

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

$$\frac{dw}{dt} = \varepsilon(v - \gamma w) \quad \text{.....(14)}$$

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 $0 < \alpha < 1$ and $0 < \alpha \leq 1$ Olufsen, (2015).

CONCLUSION

Hodgkin-Huxley system was used to study an excitability phenomenon for nonlinear system which resulted to FitzHugh-Nagumo system. The paper focused on the derivation of the system and its reduction from differential equation to a differential equation. The paper also investigated all the mathematics in the reduction and depict the two most widely used variations of the system by researchers in the fields of neurophysiology, cardiac muscle model etc.

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