All-or-None Principle and Weakness of Hodgkin-Huxley Mathematical Model

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All-or-None Principle and Weakness of Hodgkin-Huxley Mathematical Model

S. A. Sadegh Zadeh, C. Kambhampati

Abstract—Mathematical and computational modellings are the necessary tools for reviewing, analysing, and predicting processes and events in the wide spectrum range of scientific fields. Therefore, in a field as rapidly developing as neuroscience, the combination of these two modellings can have a significant role in helping to guide the direction the field takes. The paper combined mathematical and computational modelling to prove a weakness in a very precious model in neuroscience. This paper is intended to analyse all-or-none principle in Hodgkin-Huxley mathematical model. By implementation the computational model of Hodgkin-Huxley model and applying the concept of all-or-none principle, an investigation on this mathematical model has been performed. The results clearly showed that the mathematical model of Hodgkin-Huxley does not observe this fundamental law in neurophysiology to generating action potentials. This study shows that further mathematical studies on the Hodgkin-Huxley model are needed in order to create a model without this weakness.

Keywords—All-or-none, computational modelling, mathematical model, transmembrane voltage, action potential.

I. Introduction

FOR biologists and neurophysiologists, mathematical and computational modelling are conceptually new, and these kinds of modelling may raise uncertainties. However, mathematical models basically serve the same purposes as real models. For instance, to analyse a neurological disease, in order to understand its process, the most investigations are done in animal models by scientists, rather than in the exact system of interest, i.e. the model of neuron or a network of neurons. It is true that these models are not exactly the same with the real human body, but these use necessary characteristics of the system of interest. These characteristics are irritability and conductivity. Irritability is the capability to reply to a stimulation and to change it into a nerve impulse and conductivity is the capability to convey the electrical signals to other cells. Individual neuron is the unit of structure and function of the nervous system, and the existence of its mathematical model contributes greatly to develop studies in the field of neuroscience.

The framework of the main foundation for modern neuroscience modelling in the past several decades was developed by two scientists, Allan Hodgkin and Andrew Huxley [1]. In the 50s, they provide a very detailed and

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complex set of electrophysiological experiments on the axon of squid giant that is very large (up to 1 mm in diameter).

The Hodgkin–Huxley model is a four-dimensional mathematical model. This model presents current flow via ion-selective channels in the membrane of the neuron. This model, by applying potassium (K+) and sodium (Na+) channels and through first-order ordinary differential equations, explains the behavior of intracellular membrane potential over time. Hodgkin and Huxley used voltage-clamp methods to obtain extensive quantitative experimental results and proposed a system of four-dimensional autonomous differential equations containing messy nonlinear functions. This model not only contains the voltage-clamped experimental data but also is remarkably successful in simulating action potential responses. It explains experimental phenomena accurately and quantitatively analyses the change of voltages and currents on the nerve cell membrane. Despite all the advantages, this model also has a weakness. The weakness is failure to execute all-or-none principle in the action potentials for different stimulations. The contribution of this paper focuses first on highlighting the lake of None-or-All principle in Hodgkin-Huxley model, and second, it focuses on the empirical analysis and results that illuminate this issue.

The rest of the paper is organized as follows. Section II briefly describes the all-or-none principle. The material and methods are presented in Section III. Simulation of Hodgkin and Huxley model follow by the results of the simulation are discussed in Section IV. Finally, Section V concludes this paper and provides study direction for the future.

II. All-or-None Principle

For the first time, the all-or-none principle was appointed by an American physiologist, Henry Pickering Bowditch, in 1871 [2]. The all-or-none principle in cell neurophysiology is a rule that persistently states that the strength by which a neuron responds to stimulates is completely independent of the strength of that stimulus. It means that the amplitude and velocity of an action potential are completely independent of the stimulus that created it. This law states that if the stimulus was greater than the threshold potential, then the neuron will give a full spike to that stimulus; otherwise, the exciting stimulus under threshold strength fails to draw out a propagated action potential [2].

Despite the fact that the amplitude, velocity, and shape of an action potential are consistent over a time period for a given axon, but they almost vary from one neuron to another neuron. Thicker axons allow for faster conduction velocity of an action potential. It means that it can convey more action

potentials per second. The all-or-none principle puts the constraints on how an axon can convey a signal. Fig. 1 describes the concept of this principle more.
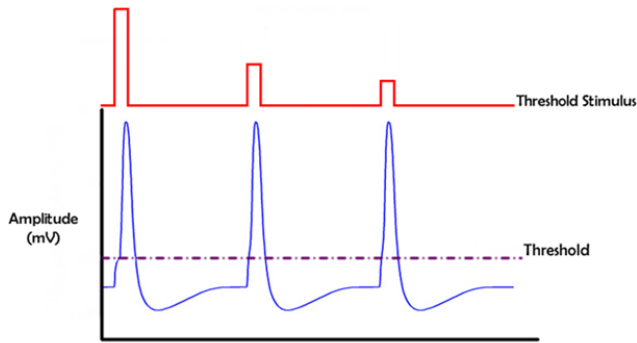

Fig. 1 Regard to all-or-none principle further increase in the stimulus does not cause an increase in the amplitude of the action potential. The other traces are on the same time scale. The dashed line shows the threshold voltage of the recorded neuron

III. MATERIAL AND METHODS

The full model. The mathematical model was made on the classical Hodgkin–Huxley formalism. Dynamic concentrations of sodium and potassium ions are applied in this model. The concentration of intracellular sodium ($[Na+]_i$) was checked by transient sodium current. On the other hand, the concentration of extracellular potassium ($[K+]_o$) was checked by transient potassium current. The equivalent electrical circuit employed by Hodgkin and Huxley is presented in Fig. 2. In this model, the membrane of the neuron is considered to be an electrical circuit composed of a capacitive element which is in parallel with ion conductance, and both types of elements are in series with the battery. The capacitor shows the lipid bilayer of membranes which have the dielectric properties. The batteries represent the electrochemical potential gradient and the conductance represent channels in the membrane.
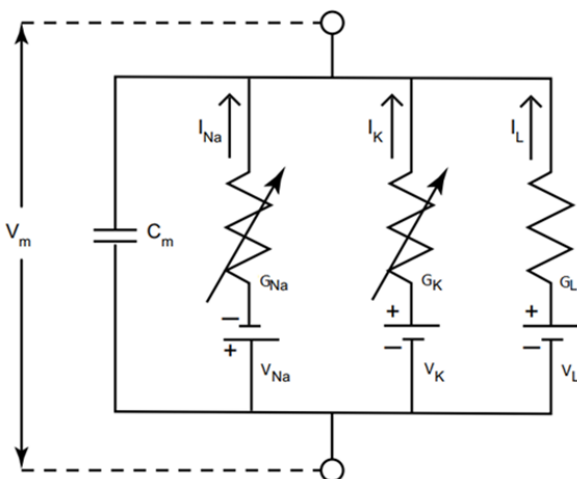

Fig. 2 The equivalent circuit which presented by Hodgkin and Huxley for the action potential. The circuit has three elements. The capacitive, the variable resistors, and the battery

Membrane potential dynamics. Activation of sodium channels leads to changes in the membrane potential in around 10^{-3} s, and this sharp change of voltage causes action potential. Action potentials are the method by which the brain receives, analyses, and conveys information. The project used a single compartment model including sodium currents, potassium currents, and specific leak currents for sodium, potassium and leakage ions, and also sodium and potassium pump current. The membrane potential, V, of the neuron is modelled by the below equations:

$$\frac{dV}{dt} = I_{inj} - I_m = \frac{1}{C_m}[I_{inj} - I_{Na} - I_K - I_L] \quad (1)$$

$$I_{Na} = G_{Na}m^3h(V - V_{Na}) \quad (2)$$

$$I_K = G_K n^4(V - V_K) \quad (3)$$

$$I_L = G_L(V - V_L) \quad (4)$$

$$\frac{dq}{dt} = \alpha_q(1 - q) - \beta_q q, q = m, h, n \quad (5)$$

where V represents the transmembrane voltage or membrane potential of the muscle cell that is produced because of the accumulation and transportation in the whole of membrane [3]. C_m is the *membrane capacitance* and I_{inj} represents the externally applied *stimulus current*, which is usually a tonic or a periodic forcing. This equation is a typical autonomous system or time-invariant systems because the right side of the equations does not explicitly depend on time variable, t [4]. There is an implicit view of switches controlling functionality to the ion channels in Hodgkin-Huxley equations. Hodgkin and Huxley termed these switches as *particles*. In the level of single channel, these particles represented by binary values which means that closing takes value of 0 and opening takes value of 1. Sodium and potassium channels are represented with four particles. About the potassium channel, any one of these particles have identical behaviors which represented as *n*. From a mathematical perspective, this fact is represented by a multiplication: $n*n*n*n=n^4$. About the sodium channel, there is one, *h* particle and three, *m* particle which is represented by m^3h. The values of *m,h* and *n* are between 0 and 1. As these values make the shape of action potentials, it seems that all-or-none principle should have affection on these values as well. V_{Na}, V_K and V_L represent the equilibrium potentials of sodium, potassium, and leak currents, respectively. G_{Na}, G_K and G_L are the maximum membrane conductance for Na^+, K^+ and leak currents [1], [5], [6]. The description of the parameters is mentioned in Table I.

Variables m, h, and n are the activation and inactivation variables. The amount of these variables varies between 0 and 1. These variables indicate the fraction of ion-selective channels in the open-close states. Opening and closing rates of the ion channel are represented by αm, βm, αh, βh, αn, and βn. These parameters are dependent on membrane potential V.

$$\alpha_n(V) = \frac{0.01\,(V+55)}{1 - exp[-(V+55)/10]} \quad (6)$$

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$$\beta_n(V) = 1.125\, exp\left[-\frac{V+65}{80}\right] \tag{7}$$

$$\alpha_m(V) = \frac{0.01\,(V+40)}{1-exp[-(V+40)/10]} \tag{8}$$

$$\beta_m(V) = 4exp[-(V+65)/18] \tag{9}$$

TABLE I
THE DESCRIPTION OF PARAMETERS

Parameter name	Parameter description
V	= Membrane potential
I_{inj}	= Sum of external and synaptic currents entering the cell
I_{Na}	= Sodium current
I_K	= Potassium current
I_L	= Leak current
I_m	= Membrane current
m, n, h	= State variables
V_{Na}	= Equilibrium potential at which the net flow of Na ions is zero
V_K	= Equilibrium potential at which the net flow of K ions is zero
V_L	= Equilibrium (or reversal) potential at which leakage is zero
C_m	= Membrane capacitance
g_{Na}	= Sodium channel conductivity
g_K	= Potassium channel conductivity
g_L	= Leakage channel conductivity
$\alpha_{m,n,h}$	= Suitable rate coefficients
$\beta_{m,n,h}$	= Suitable rate coefficients

$$\alpha_h(V) = 0.07exp[-(V+65)/20] \tag{10}$$

$$\beta_h(V) = \frac{1}{1+exp[-(V+35)/10]} \tag{11}$$

The reversal potentials of Na+ (V_{Na}), and K+ (V_K), are given by Nernst equations:

$$V_{Na} = 26.64\, ln(\frac{[Na^+]_o}{[Na^+]_i}) \tag{12}$$

$$V_K = 26.64\, ln(\frac{[K^+]_o}{[K^+]_i}) \tag{13}$$

where $[.]_i$ and $[.]_o$ represent concentrations inside and outside the cell, respectively.

Numerical Methods. The equations are solved using the Ode45 method which is based on an explicit Runge-Kutta method, with a time step of 0.01 ms. Codes reproducing key results are available upon request from authors. The equilibrium potential applied for sodium is 50 mV, for potassium is -71 mV, and for leakage is -51 mV. The channel conductivity for sodium is 120 ms/cm^2 for potassium, is 36 ms/cm^2 and for leakage is 0.3 ms/cm^2. The injected current varies from 10 nA, to 75 nA for the five same neurones.

IV. RESULTS OF SIMULATION

The results of simulation are shown, along with the parameters that control them. The reported graphs are presented in Figs. 3-5. As shown in Fig. 3, the amplitude of action potentials has decreased by increasing the rate of stimulation currents. By increasing the strength of injection current, the height of the amplitude is shorter and shorter, so that the highest amplitude is for the injection current with 10 nA strength and the shortest amplitude is for the injection current with 75 nA strength.
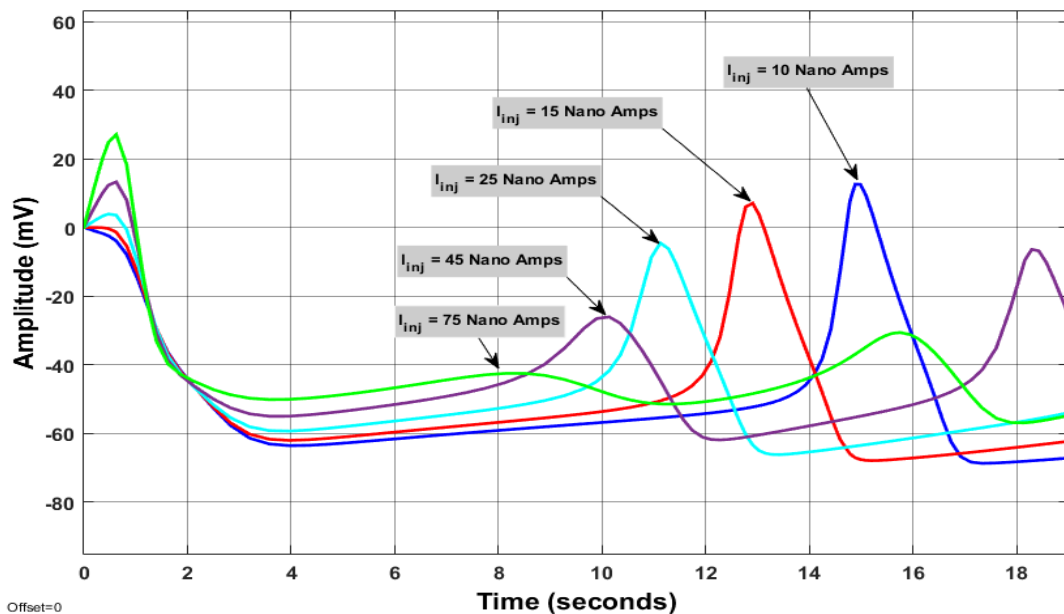

Fig. 3 The action potential represented by different stimulation from 10 to 75 nA. The amplitude of each action potential is different from other action potential with different stimulations

On the other hand, the frequency of action potential is increased by increasing the injection current (Fig. 4). The resting membrane potential also became less negative (hyperpolarized) with increasing the injection current as is shown in Fig. 5.

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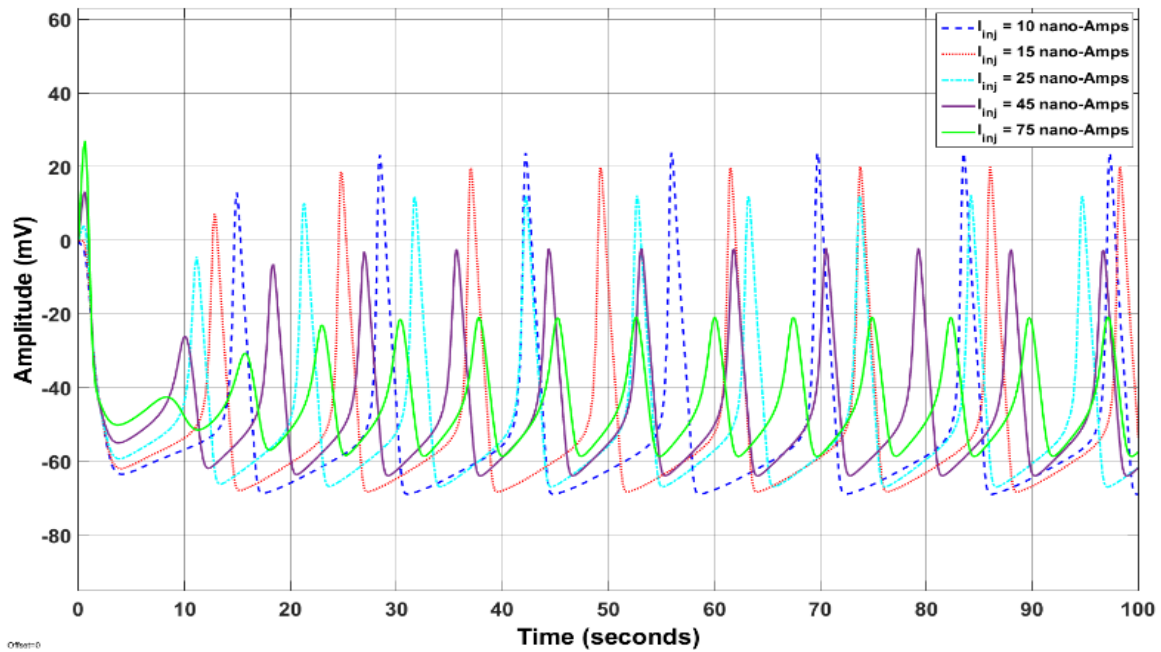Vol:11, No:11, 2017

Fig. 4 The action potential represented by different stimulation from 10 to 75 nA. The time interval of each action potential is different
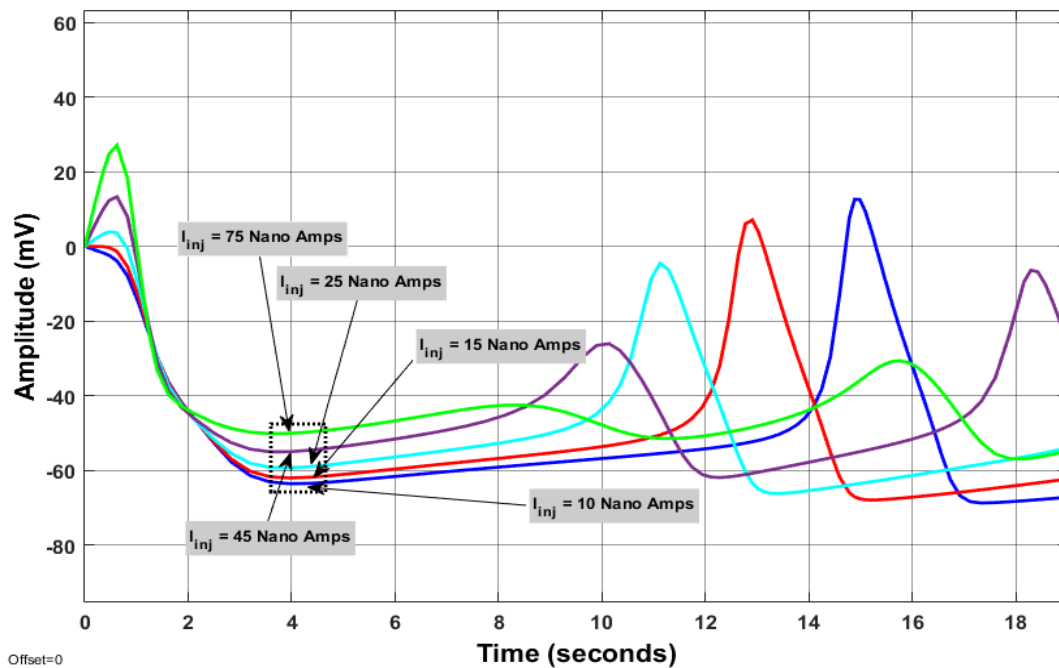

Fig. 5 The action potential represented by different stimulation from 10 to 75 nA. The resting membrane potential of each action potential has different value from others

V. DISCUSSION

Important features of the neuronal action potential are depolarization, overshoot, peak, repolarization, and finally hyperpolarizing. From signal processing point of view these characteristics are divided into importance features, i.e. signal amplitude and signal frequency. Amplitude of a spike is its height or magnitude of that spike which is the most basic and inherent characteristic of any spike representing in action potential of a neuron. The number of cycles that the spike completes in the form of oscillation in a single second is called frequency which is another basic characteristic of any action potentials. On the other hand, from neurophysiology point of view, as mentioned in Section II, the amplitude and velocity of an action potential are completely independent of the stimulus that initiated the action potential. It implies that, to sending an action potential, the difference between a weak stimulus and a strong stimulus, the axon cannot send bigger or faster action potentials. The timing of an action potential is the speed of

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action potential propagation along a given axon which is frequency of action potential. So, the weak or strong of a stimulation can affect just the frequencies.

Following our implementation of mathematical model of Hodgkin-Huxley, the results of experiments demonstrated in Section III. Different stimulation with different intensities have been applied on the computational model. The intensities of stimulations are varied from 10 to 75 nA. As shown in Figs. 3-5, all major characteristics of an action potential by applying different strength of stimulations have been changed. From mathematical point of view, these changes are completely reasonable. However, from the neurophysiology point of view and by considering the all-or-none principle, changing the amplitudes and resting membrane potential is not acceptable. An implicit view of switches controlling functionality for the ion channels in Hodgkin-Huxley model has been discussed in Section III.

It seems that implicit view of switches controlling functionality has a connection to the principle of all-or-none. The reason for that is the formative role that this functionality has on the shape of the action potential. So, further research on the defining of activation and deactivation sodium channels and activation of potassium channels needs to solve this problem on Hodgkin-Huxley model. Although this model is the basis of many studies in neuroscience, failure to comply with this law is considered as one of its weaknesses which essentially needs a mathematical solution.

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