

The Study of the Development of the Hodgkin-Huxley (HH) Neuron Model

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ABSTRACT: The brain is the material basis for human understanding of the external world and the self, and brain science research is considered one of the last frontiers of human science. The HH model successfully reproduces the experimentally observed firing activity of some neurons and opens the way to a theoretical model of neuronal firing. This paper presents a dynamic timeline of the development of the HH neuronal model and its future prospects, analyzing a large body of literature. It outlines the development of the most accurate but complex HH neuronal model and compares its strengths and weaknesses, introduces emerging developments in neurodynamics and bifurcation theories in terms of optimization, and argues that future developments will not be possible without the participation of multidisciplinary interdisciplinary field. The research on this neuronal model will make an impressive contribution to society.

1. INTRODUCTION

Compared to traditional computers, the human brain is undoubtedly a more powerful intelligence platform, with the ability to adapt itself to complex and even unfamiliar scenarios, acquire new information and skills, and interact and reason to make decisions. Brain science is one of the most important cutting-edge research fields in the 21st century. [1] At the end of the last century, countries around the world have put brain science research on the agenda, and the study of single neurons belonging to the micro-level has become a hot research topic. However, the traditional models of the past are no longer able to efficiently and concisely simulate the real-life activity of neurons in the face of advancing technology and emerging theories that will affect society as a whole in the future. The Hodgkin-Huxley was first proposed in the 1950s after Hodgkin and Huxley conducted extensive experiments on the firing of giant axons in the Atlantic squid using a voltage-clamp technique, and then analyzed and fitted the experimental data to a curve. [2][3][4] The high complexity of the structure and function of the nervous system requires multidisciplinary interactions, the integration of multiple techniques and the processing of large amounts of data, which is also an important condition and trend in neuroscience research.

This paper presents a review of a large body of literature, firstly using a chronological approach to introduce each of the optimization models of the neuronal model of the HH model, and then a comparative analysis to provide a summary view. This is followed by an introduction to neurodynamics and bifurcation theories, which have developed rapidly in recent years and will

change the neuronal model dramatically, and provides directions for future research on the neuronal model and predictions for future developments. This research will not only explain some of the hitherto unexplained experimental phenomena in neuroscience and quantitatively reveal the patterns behind some of the experimental data, but will also be able to predict some of the phenomena that neuroscience has failed to discover and will make a great contribution to the progress of human society.

2. CLASSICAL NEURON MODEL

2.1. Hodgkin-Huxley Neuron Model

In 1952, Hodgkin and Huxley published four consecutive papers describing experiments and models of nerve conduction. They used the voltage clamp technique invented by Cole to obtain extensive experimental data on the electrophysiological activity of squid axons and, based on these data, derived a mathematical model described by a four-dimensional system of non-linear differential equations called the Hodgkin-Huxley (HH) model. This model accurately explains the experimental results and quantitatively describes the process of voltage and current changes across the neuronal cell membrane. As this model not only replicates the voltage-clamp data itself but also simulates the propagating action potential, it has made a pioneering contribution to the quantitative study of the electrophysiological properties of excitable biological cells.

The HH model is the closest to biological reality in terms of neuronal properties and is widely used in computational neuroscience. The HH model accounts for

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the electrical activity of neurons at the ionic level, as the neuronal cell membrane contains different types of ion channels, including sodium channels, potassium channels and leaky channels that control a small number of inorganic salt ions. The distribution of gating proteins on the different ion channels, which constrain the passage of ions through the channels, allows the neuronal cell membrane to be selectively permeable to different ions, and it is this selective permeability of the neuronal cell membrane that allows the neuron to generate abundant electrical activity. At a mathematical level, the binding effect of the gating proteins is equated to ion channel conductance, which becomes a dependent variable that varies with the activation and deactivation variables of the ion channel. Ion channel conductance, ion channel reversal potential and membrane potential together determine ion channel current, sodium channel current, potassium channel current, leakage current and the current generated in the membrane capacitance due to changes in membrane potential. The sodium channel current, the potassium channel current, the leakage current and the current in the membrane capacitance due to the change in membrane potential together form a total current, and therefore the HH model also equates the cell membrane to a circuit diagram, as shown in Figure 1:

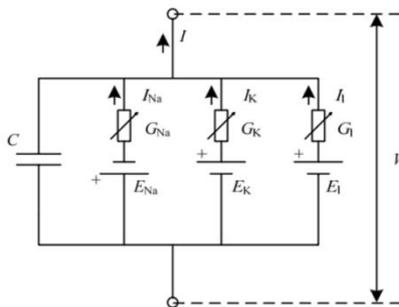


Figure 1 Equivalent circuit

I express the total current flowing through the membrane, which is made up of four branch currents: the sodium channel current, the potassium channel current, the chloride dominated leakage current and the current flowing through the membrane capacitor.[5]

The ion channels in the Hodgkin-Huxley model are mainly sodium channels, potassium channels and leaky channels that control a few inorganic salt ions. The biological significance of the parameters of each channel is clear and they play a crucial role in the electrophysiological activity of neurons. The leaky channels, which mainly control small amounts of inorganic salt ions, can be combined with the corresponding gating variables to describe the electrical activity of the neuron. The current flowing across the cell membrane depends mainly on the impedance of the ion channels and the capacitance of the cell membrane, with the total ion current consisting mainly of Na^+ , K^+ and Cl^- . The electrophysiological activity of neurons in the HH model can be described using the following set of equations. [6]The role of the leaky current in the HH model is to maintain a fixed cell membrane resting potential in the absence of any depolarisation occurring,

and it does not contain activation-type covariates in its conductance; the conductance of the sodium channel current contains two covariates, the inactivation variable h and the activation variable m , which are sodium channel gating variables; n is a potassium channel gating variable, and they are controlled by three first-order differential equations.

$$C \frac{dv}{dt} = G_{Na} m^3 h (E_{Na} - V) + G_K n^4 (E_K - V) + G_l (E_l - V) + I \quad (1)$$

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

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

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \quad (4)$$

V is the neuronal membrane potential, C is the membrane capacitance, I is the sum of the currents through the membrane, G_{Na} , G_K and G_l are the maximum conductivities of the sodium, potassium and leaky channels respectively, m is the activation parameter of the sodium channel, h is the inactivation parameter of the sodium channel and n is the activation parameter of the potassium channel. α and β functions are time-independent rate functions related to the membrane potential. Hodgkin and Huxley fitted the α_m , β_m , α_h , β_h , α_n and β_n curves to the experimental transmembrane currents at different clamp voltages to obtain the following expressions for each rate function:

$$\alpha_m = \frac{0.1(V+40)}{1 - \exp\left(-\frac{(V+40)}{10}\right)} \quad (5)$$

$$\beta_m = 4 \exp\left(-\frac{(V+65)}{18}\right) \quad (6)$$

$$\alpha_h = 0.07 \exp\left(-\frac{(V+65)}{20}\right) \quad (7)$$

$$\beta_h = \frac{1}{\exp\left(-\frac{(V+35)}{10}\right) + 1} \quad (8)$$

$$\alpha_n = \frac{0.01(V+55)}{1 - \exp\left(-\frac{(V+55)}{10}\right)} \quad (9)$$

$$\beta_n = 0.125 \exp\left(-\frac{(V+65)}{80}\right) \quad (10)$$

2.2. HH-Like Neuronal Models

2.2.1. FitzHugh-Nagumo Neuron Model

The HH model is a mathematical model that describes how neuronal action potentials are generated and transmitted, thus explaining the ionic mechanism of action potential initiation and transmission in the giant axon of the squid, based on the measurement of the temporal characteristics of the membrane and ionic conductance of the squid. Later, Fitzhugh simplified the HH model in 1961 to produce a simpler mathematical model of neural excitation. [7] In 1952 Nagumo et al. subsequently designed, implemented and analyzed an equivalent circuit. The simplified second-order nonlinear model of FitzHugh was simulated experimentally:

$$\frac{dV}{dt} = V - \frac{V^3}{3} - W + I_{ext} \quad (11)$$

$$\tau \frac{dW}{dt} = V + a + bW \quad (12)$$

Where the variable V represents the membrane potential of the neuron, and it is a fast variable. The parameter I_{ext} is the externally applied current, and W is the recovery variable, which is a slow variable representing the combined effect of sodium channel inactivation and potassium channel inactivation. Here a , b and τ are positive constants. The FHN model consists of two coupled nonlinear ordinary differential equations, one describing the rapid evolution of neuronal membrane voltage and the other representing the slow "recovery" effects of sodium channel inactivation and potassium channel inactivation. The model describes "regenerative self-stress" in terms of a nonlinear positive feedback membrane voltage and "regenerative self-stress" in terms of a linear negative feedback gate voltage.

2.2.2. Morris-Lecar Neuron Model

The Morris-Lecar model is a simplified and action potential generating biophysical model proposed by Morris and Lecar.[8] The model has three example channels: the K^+ ion channel, the Ca^{2+} ion channel, and the leakage current channel. Since the rate of the Ca^{2+} current is much faster than the rate of the K^+ ion current, Morris and Lecar assume that Ca^{2+} reaches its steady-state value at the moment of activation, thus transforming the original model into a simplified two-dimensional model of the following form:

$$C_m \frac{dV}{dt} = -g_{Ca} m_\infty 3h(V - V_{Ca}) - g_K n(V - V_K) - g_l(V - V_l) + I \quad (13)$$

$$\frac{dV}{dt} = \Phi \frac{n_\infty(V) - n}{\tau_n(V)} \quad (14)$$

Of which:

$$m_\infty(V) = 0.5 \left[1 + \tanh\left(\frac{V - V_1}{V_2}\right) \right] \quad (15)$$

$$n_\infty(V) = 0.5 \left[1 + \tanh\left(\frac{V - V_3}{V_4}\right) \right] \quad (16)$$

$$\tau_n(V) = \left[\cosh\left(\frac{V - V_3}{2V_2}\right) \right]^{-1} \quad (17)$$

In the above equation, V represents the membrane voltage, $n \in [0, 1]$ is the activation variable of K^+ , the parameters g_{Ca} , g_K , g_l are the maximum conductance of Ca^{2+} , K^+ and the leakage current, V_{Ca} , V_K , V_l are the balance voltages of the corresponding currents, the external input current is denoted by I , and the constant Φ determines the value of the K^+ channel opening rate.

2.2.3. Hindmarsh-Rose Neuron Model

As early as 1982, Hindmarsh and Rose proposed a model of the HR neuron based on the extensive data obtained from voltage-clamp experiments on snail nerve cells, assuming a linear dependence of the rate of change of the

membrane potential on the current z and the internal current y through the electrode and a non-linear dependence on the membrane potential x , which was then modified in 1984 by Hindmarsh and Rose.[9] Hindmarsh and Rose obtained a large amount of data from experiments on the visceral ganglion of the pond snail, and in 1984 they modified the original model by introducing another differential equation with a slow time scale to regulate the transition between a cluster of repeatedly discharging states and the resting state. The modified model of the HR neuron is as follows:

$$\frac{dx}{dt} = y - ax^3 + bx^2 - z + I_{ext} \quad (18)$$

$$\frac{dy}{dt} = c - dx^2 - y \quad (19)$$

$$\frac{dz}{dt} = r[S(x - x_{rest}) - z] \quad (20)$$

The HR neuron model is designed to study the membrane potential futile behaviour observed in single neuron experiments. Where x , y , and z are variables concerning time t , and x denotes the neuronal membrane potential, expressed in dimensionless units. The other two variables with y and z have to do with ion channel transmission, y is a recovery variable associated with internal currents (e.g. K^+ and Na^+), called spike variables, and z is a recovery variable associated with Ca^{2+} is the slow-varying regulatory current associated with the activated K^+ current, referred to as the burst variable. a , b , c , d , r , S are constants, and x_{rest} is the resting potential set by the system, I_{ext} is the stimulation current entering the neuron.

Among the many neuronal models, the HH model is the most accurate in describing the electrophysiological properties of neurons, and the physiological parameters are the most explicit. It can accurately simulate the changes of various parameters such as membrane potential, ion channel conductance, ion channel current and membrane current in real neurons during external current stimulation. The FHN and MR models are two-dimensional mathematical models that simplify the HH model and retain some of the features of the HH model for better analysis of a specific study object. The HR model has been simplified to include a time scale, making it a three-dimensional model for the study of membrane potential.

3. NEW DEVELOPMENT THEORIES

3.1. Neurodynamics

Since Professor Walter Freeman, a molecular neurobiologist at the University of Berkeley, introduced the concept of neurodynamics more than 20 years ago, the use of dynamical theories and methods to study the activities of cognitive and neural systems has become a new field of research, and research results have proliferated.[10]

The basic ideas of neurodynamics have increasingly permeated and are reflected in neuroscience, artificial

intelligence, brain-like computing, bioinformatics, medical diagnosis, image processing, control science, complex networks, and engineering applications. A typical example is the extension of the classical mechanic's approach to modeling dynamical systems to neuronal systems and the creative construction of a new neuronal model equivalent to the HH model.[11] This has revealed a new mechanism of neuronal activity that has never been discovered before, and this new mechanism has revealed two patterns of neuronal activity. The first is that there is a unique correspondence between neuronal membrane potential emission and neural energy; the second is that neuronal activity below the threshold is dominated by energy consumption, while above threshold activity is dominated by both energy absorption and energy consumption. The first pattern reveals a unique correspondence between the functional acquisition of neuronal membrane potentials and the energy function, a finding that is strongly supported by the H-H model. The second pattern validates an experimental phenomenon that is currently unexplained by neuroscience, namely that blood flow increases by 31% after activation of brain regions, while oxygen consumption increases by only 5-6%. The new neuronal model, based on experimental data, has led to an original concept and theory of energy coding.

This new concept and coding theory can not only explain some of the hitherto unexplained experimental phenomena in neuroscience but also quantitatively reveal the patterns behind some experimental data. This demonstrates the impact of mechanics on the advancement of neuroscience and the existence of neurodynamics in neuroscience, life sciences and even in society.

3.2. Bifurcation Theology

Bifurcations are often found in the mathematical study of dynamic systems and are small but continuous changes in the parameters of the system (bifurcation parameters) that result in a sudden change in the nature or topology of the system.[12] Bifurcations can occur in continuous systems (described by ordinary differential equations, time lag differential equations or partial differential equations) or in discrete systems (described by mappings). From a mathematical point of view, bifurcation theory focuses on the effect of parameters in non-linear equations (differential equations, integral equations, difference equations, etc.) on the qualitative properties of the solutions. Among these, the relationship between the parameters and the fundamental properties of the solution, such as stability, periodicity and equilibrium position, is the focus of the study. As early as 1885, Poincaré proposed a theory of the relationship between equilibrium states and parameters of planar dynamical systems. In the 1950s, the Soviet scholar A.A. Andronov generalized Poincaré's results and applied them to the theory of non-linear vibrations. Later, the theory of bifurcation in higher-dimensional Euclidean or Banach spaces was investigated, but the results are not yet available.

The electrical activity of neurons, such as resting, subthreshold oscillations, peak discharges, cluster discharges and mixed oscillations (mixed oscillations are

alternating between subthreshold oscillations and peak discharges), is determined by the intrinsic properties of the neuron itself and by external inputs and plays an important role in the information processing of the nervous system. Using the methods and theories of nonlinear dynamics, it is possible to reveal the inherent properties of neurons and the differences in their response to external inputs. For example, the different dynamics around the bifurcation of the saddle junction on the invariant circle and the Hopf bifurcation can explain not only the different firing frequencies of type 1 and type 2 excitatory neurons, but also the different responses of neurons to stimuli such as noise, impulse input and synaptic input.

The study of neuronal firing patterns, as well as bifurcation and chaos, is generally conducted under single-parameter conditions and differs significantly from the joint action of multiple parameters in real physiological systems, so the global bifurcation and multi-level bifurcation structure of the system need to be further investigated. In addition, neurons in real neural systems are always affected by internal and external noise. Therefore, when studying the firing patterns of real neurons, the role of stochastic factors needs to be considered in addition to the deterministic kinetic model.

4. EVALUATION OF FUTURE DIRECTIONS AND RESEARCH

The development of neuronal models today is not just a field of study, but a multidisciplinary crossover, accompanied by an unprecedented influx of biological data on the brain and nervous system, while the concepts of computation, physics, and bifurcation theory are increasingly commonly applied to the analysis of cognitive processes, attracting outstanding scientists from cross-disciplinary disciplines to enter the field and strengthen the crossover, not only by the rational application of existing techniques, but also by the commitment to develop new techniques and methods for the rational applications, but more importantly to raise new scientific questions and major needs and to work on the development of new technologies and methods for brain science research. The use of basic research results in neuroscience to promote and serve the solution of some urgent social needs has increasingly permeated and manifested in many aspects of neuroscience, artificial intelligence, brain-like computing, bioinformatics, medical diagnosis, image processing, complex networks and engineering applications. Neuronal models, as the most fundamental foundation, must, on the one hand, approximate as closely as possible the behavioural patterns of biological neurons, so that one can build large neural networks and explore the response mechanisms and working principles of biological nervous systems. On the other hand, neuronal models must be structured in the simplest possible way to achieve the appropriate functions according to the circuit and algorithmic requirements, thus enabling large-scale integration and production. The development of neuronal models is closely related to the development of neuroscience. As research on biological neurons and neural networks progress, the mathematical

representation and physical implementation of neuronal models are constantly being improved and enriched.

5. CONCLUSION

Among a large number of neuronal models, the HH model adequately reproduces the changes in the parameters of the human neuron during stimulation and provides the most accurate description of the firing characteristics of the neuron, but it also increases the computational workload and is extremely difficult to compute and analyze. This is why a more simplified and efficient model is proposed to optimize the neurons. With the further development of neural dynamics and bifurcation theories, newer iterations of neuronal models have been developed to better fit real neurons' properties more accurately. This thesis has analyzed a large body of literature, for which some aspects are still unsatisfactory and some methods and models have not yet developed a concrete theory that is widely accepted. The present authors believe that there will be great scope for development with the continuous updating and development of mathematical models and neurocomputing devices. Neuronal models are not only important for bionics, memory design, logic operations and signal processing, but also for the analysis of the dynamics of the nervous system and brain science, and even for human understanding of ourselves and the world.

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