

SIGNAL TRANSMISSION IN NEURONS

T. Kohnno

Institute of Industrial Science, University of Tokyo, Japan

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Summary

In the nerve system, electrophysiological activities of neuronal cells are playing fundamental roles in their information processing ability. The membrane potential, difference of voltages between the inside and the outside of the neuronal cells, varies dynamically in response to the external input or autonomously.

Its dynamics has been attracted interest of a number of researchers in both biological and mathematical fields as a key to understand the principle of the information processing in the nerve system.

This chapter reviews how the dynamics in the electrophysiological activities in the neuronal cells have been elucidated firstly by biophysical studies and then by mathematical approaches. Most of these modeling works have their root in the Hodgkin-Huxley model, the world's first model that successfully reproduces the membrane potential activities by describing the dynamics of the ionic channels using ordinary differential equations.

At first, the basic biophysical mechanism of the membrane potential is outlined by overviewing the experiments and the hypotheses utilized to constructed this model. Numerous improved models have succeeded it to describe more precisely the more complex behaviors such as autonomous burst firing. They are referred to as conductance-based models, two of which are covered in this chapter. Another group of the neuron models tries to reduce the complexity in their equations utilizing

mathematical techniques. They reproduce the behaviors of the membrane potential qualitatively utilizing simple and low-dimensional differential equations.

These features of the qualitative models allow us to utilize powerful techniques of the nonlinear dynamics such as the phase-plane and the bifurcation analysis, which have revealed the essential mechanisms in the various neuronal behaviors. Several qualitative models are covered in this chapter including the FitzHugh-Nagumo model, the first one that reproduces most behaviors of the Hodgkin-Huxley model. Finally, some 'restructured' models that are optimized to the implementation technologies are reviewed.

1. Introduction

Information processing in the nerve system including the brain is thought to be performed by the transmission of electrical signals in the network of neuronal cells. Each neuronal cell has single axon, the output line, whose endings connect to other neuronal cells.

These connections are called synapses, where electrical signals are transmitted by gradient of chemical transmitters or electrical potential. The neuronal cell to which the axon belongs and the targeted one, are termed presynaptic and postsynaptic cells, respectively. The effectiveness of transmission across the synapses changes depending on various conditions including the timing of the signals transmitted across them. This is thought to be the crucial mechanism for the robust, flexible, and autonomous information processing ability of the nerve system.

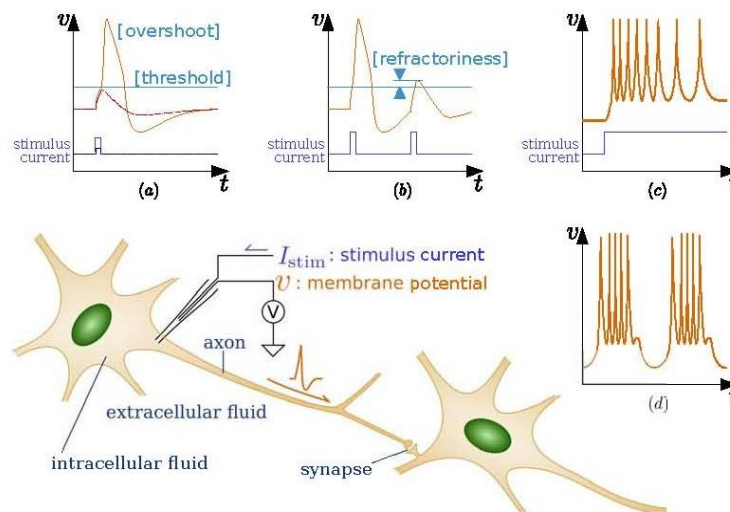


Figure 1. An overview illustration of signal transmission in the nerve system. The membrane potential v of the neuronal cell transports the electrical signal. (a) An action potential (overshoot of v) in response to a pulse of stimulus current. There is a threshold for v , which determines if an action potential is generated or not. (b) If two pulses of stimulus current of the same strength are applied successively and their interval is sufficiently short, the second action potential is smaller than the first one. This is caused by the refractoriness, the transient augmentation of the threshold. (c)

Some neuronal cells fire repetitively in response to a sufficiently strong sustained stimulus. In some cases, the frequency of the firing decreases as it continues firing (spike frequency adaptation). (d) Some neuronal cells produce burst firing patterns endogenously.

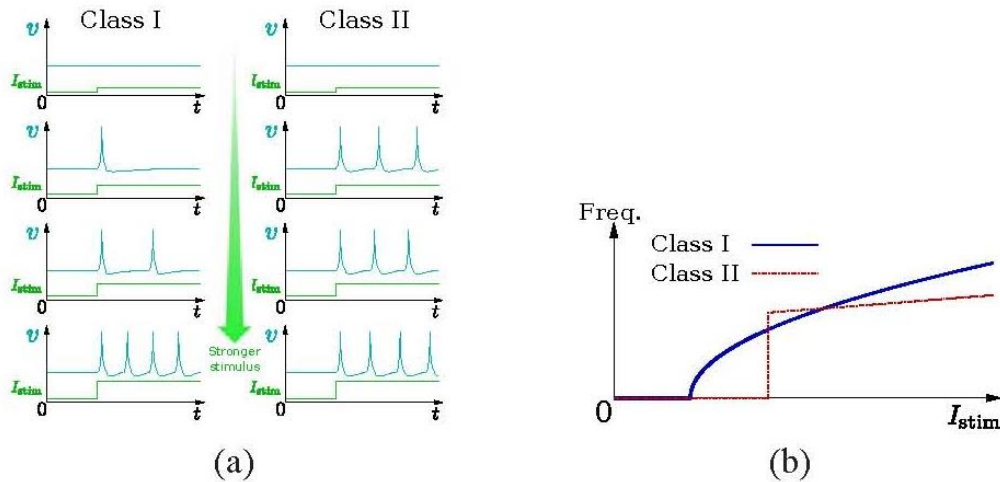


Figure 2. Hodgkin applied a sustained current of various values of strength to neuronal cells. Some neuronal cells start firing periodically in response to a sustained current stimulus when the amplitude I_{stim} is above a threshold. In a group of the cells, the periodical firing started with a very low spike frequency and it increased as I_{stim} is increased (Class I). In another, the frequency could not be lower than a certain value if I_{stim} was decreased (Class II). This is called the Hodgkin's classification. (a) and (b) illustrates it by the time waveform and the frequency plots.

The *cell membrane* of the neuronal cells transmits electrical signal actively consuming concentration gradient of various ions between inside (intracellular fluid) and outside (extracellular fluid) of the cell. This concentration gradient maintains potential difference between the intracellular and the extracellular fluids. The electrical potential of the former in comparison to the latter is called the membrane potential. When a cell is at resting state, it is stable around from -100 to -50 mV dependent on the ion composition of the fluids of each cell. If a pulse of stimulus current with a sufficient amplitude is applied to the cell, as shown in Figure 1(a), it fluctuates abruptly and produces a large spike-like time waveform (overshoot). They are called the resting membrane potential and the action potential, respectively. The signals transmitted in the nerve system are the pulses of the action potential, spikes, though there are several exceptions such as the cells in the *retina* where the information is coded in the value of the membrane potential. In retina, membrane potential of the *photoreceptor cell* gets lower gradually as strength of light input is increased. The *horizontal and the bipolar cells* also respond to applied input current gradually, the former decreases and the latter increases their membrane potential as the input current is increased.

When a neuronal cell produced an action potential, we say that the cell fired. One of the important features in the generation of the action potentials is the existence of a threshold. An action potential is generated only if a stimulus current increases the membrane potential above the threshold. We say that it is all-or-none if the amplitudes

of the generated action potentials are approximately independent of the strength of the stimulus current. In some neuronal models, it is very difficult to define the threshold voltage and the generation of the action potentials is not all-or-none. Another important nature is refractoriness. The threshold voltage of a neuronal cell is increased for a period after generation of an action potential. If we apply two successive pulse stimuli of a sufficiently short interval to a neuronal cell, the second response can be smaller than the first one as shown in Figure 1(b).

In 1948, Hodgkin [8] reported that some of the neuronal cells fired repetitively in response to a sustained stimulus current when its strength is above a threshold dependent on the cell. They were classified into two, Class I and II (Hodgkin's classification), according to the frequency of their repetitive firing (see Figure 2).

ion	Squid Axon		Mammalian muscular cell	
	Intracellular	Extracellular	Intracellular	Extracellular
K ⁺	400	20	155	4
Na ⁺	50	440	12	145
Cl ⁻	40 ~ 150	560	4	120
A ⁺	385		155	

Table 1. Ionic concentration in the intracellular and extracellular fluids (mM kgH₂O⁻¹).

In Class I neurons, it is very low when the stimulus I_{stim} is just above the threshold. As I_{stim} is decreased nearer to the threshold, the frequency gets lower down to zero. In Class II neurons, however, it cannot be lower than a certain value. If I_{stim} is decreased, the repetitive firing ceases instead of firing slower. In some neuronal cells, the frequency decreases as the cell continues to firing as shown in Figure 1(c), which is called spike frequency adaptation. In this case, Hodgkin's classification can be applied to the onset of the repetitive firing. It is thought to account a kind of roles of a neuronal cell in the nerve system. For example, Class I neurons are thought to be playing a role of leaky integrator.

Some neuronal cells such as the pacemaker neurons endogenously fire periodically without any stimulus current. They are thought to be one of the sources of rhythms in the nerve system that are playing crucial roles in the information processing in the brain and the generation of motion patterns in the *peripheral nerve system* including heartbeat and *bowel peristalsis*. A neuronal cell is called a bursting neuron (or burster) if it repeats alternation of tonic firing and silent phases as shown in Figure 1(d). One of the best known bursters is the leech heart interneuron, an element in the heartbeat-generating neural network [6].

In this chapter, we will see several milestones of the mathematical models that describe the behavior of the membrane potential. Note that they are space-clamped models that describe its behavior at a narrow region on the cell membrane. In many cases where the simplicity of the model is emphasized, a space-clamped model is substituted for a neuron model (single compartmental model), whereas, multiple space-clamped models

are connected to each other to model a single neuron when a detailed model is required (multi-compartmental model).

2. Conductance-Based Models

The cell membrane is basically a *lipid bilayer*, which repels any ionic particles. It contains a diversity of *functional proteins* including ionic pumps and channels (see Figure 3(b)). The former transmit ionic particles actively consuming *adenosine triphosphates* (ATPs) to maintain the ionic concentration difference between the intracellular and the extracellular fluids (see Table 1). In the extracellular fluid, the concentration of sodium (Na^+) ion is high and that of potassium (K^+) ion is low, whereas it is opposite in the intracellular fluid.

The ionic channel transmits a specific ion passively dependent on both the electrical and the concentration gradients. Because ionic particles have their own electrical charge, their transportation produces an electrical current across the cell membrane. It is called an ionic current. For example, the sodium channel transmits sodium ions but no other ionic particles and produces the sodium current. The ionic current is dependent on balance between the electrical force produced by the membrane potential and the diffusion force produced by the concentration gradient across the cell membrane. The Nernst equation formulates the electrical potential E that equilibrates with the concentration gradient of an ion as follows:

$$E = \frac{RT}{ZF} \ln \frac{a^{(o)}}{a^{(i)}}, \quad (1)$$

where R, T, Z , and F are the constants that represent the universal gas constant ($8.314 \text{ J K}^{-1} \text{ mol}^{-1}$), the absolute temperature, the charge of the ion, and the Faraday constant ($9.648 \times 10^4 \text{ C mol}^{-1}$), respectively. The variables $a^{(o)}$ and $a^{(i)}$ are the chemical activities of the ion. The chemical activity is a kind of the effective concentration in the perspective of thermodynamics where the forces of attraction between the particles are taken into account. It is approximately equal to and can be replaced by the concentration when it is sufficiently small. This potential is referred to as the reversal potential or the equilibrium potential. It is because if the membrane potential equals to E the ionic particles are not transmitted across the ionic channel (ionic current is zero), and the direction of the transmission is reversed when the membrane potential crosses E (see Figure 3(a)). The ionic current I can be represented as follows:

$$I = g \times (E - v), \quad (2)$$

where g is the conductance of the ionic channel and v is the membrane voltage. An equivalent circuit is shown in the inset of Figure 3(a).

Because the cell membrane does not transport the ionic particles, it is an insulator from the electrical point of view and thus has capacitance, which is referred to as membrane capacitance. The ionic currents charge or discharge the membrane capacitance and

affect the voltage across this capacitor, the membrane potential v , directly (see Figure 4). This is described by the current balance equation,

$$C \frac{dv}{dt} = \sum_j I_j + I_{stim}, \tag{3}$$

where I_j is a ionic current, I_{stim} is a stimulus current externally applied.

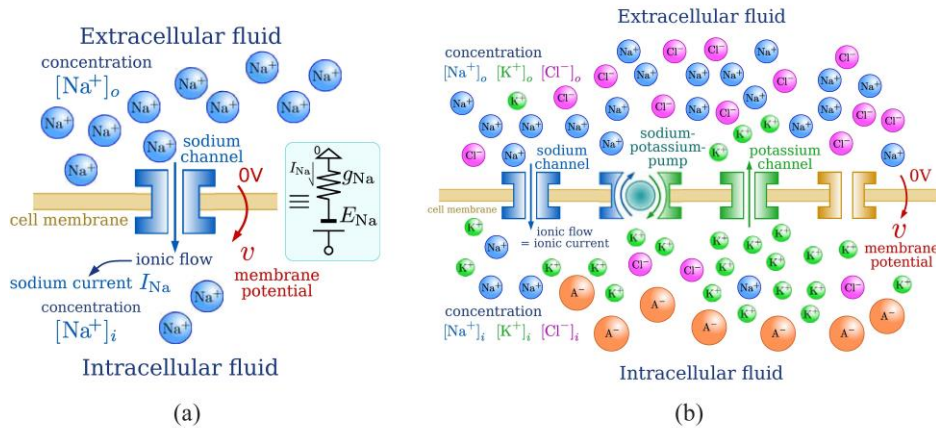


Figure 3. (a) Sodium channel and sodium current I_{Na} . The equilibrium circuit of I_{Na} is shown in the inset. (b) Multiple ionic channels, pumps, and gradients exist across a cell membrane.

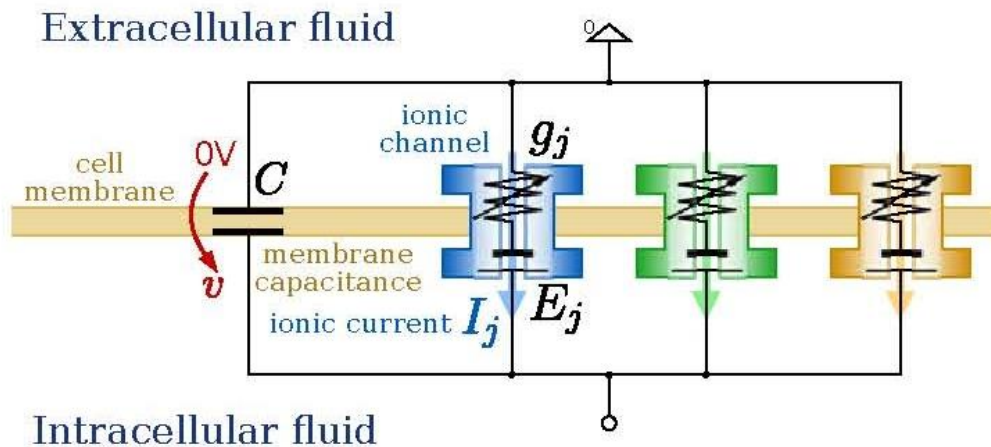


Figure 4. The equivalent circuit for the membrane potential, where C and v are the membrane capacitance and potential, respectively. The ionic current of the j -th ion I_j is determined by v and the conductance g_j and the equilibrium potential E_j of the i -th ion. according to the Eq. (2). The conductance g_j varies dependent on the membrane potential v (voltage-dependent conductance).

The membrane potential v is stable when the sum of all the ionic currents (membrane current) is zero, whose condition when $I_{stim} = 0$ is formulated by the Goldman-

Hodgkin-Katz equation [10]. This equation gives the membrane potential that makes the sum to zero:

$$E_{\text{GHK}} = \frac{RT}{F} \ln \frac{\sum_i p_i^+ a_i^{+(o)} + \sum_j p_j^- a_j^{-(i)}}{\sum_i p_i^+ a_i^{+(i)} + \sum_j p_j^- a_j^{-(o)}}, \quad (4)$$

where $a_i^{+(o)}$ and $a_i^{+(i)}$ are, respectively, the chemical activities of the i -th ion with positive charge in the extracellular and intracellular fluids, $a_j^{-(o)}$ and $a_j^{-(i)}$ are those of the j -th ion with negative charge, and p_i and p_j are the permeability for the i -th and the j -th ions, respectively.

If we give specific values to these variables, the membrane capacitance is charged or discharged by the ionic currents until the membrane potential v reaches E_{GHK} . Note that each of the ionic currents is not zero even in the stable state. They consume the ionic concentration gradients, which is replenished by the ionic pumps.

When the cell membrane is at its resting state, the ionic permeabilities (p_i and p_j) are constant and thus the membrane potential v is stable at E_{GHK} . This is the resting membrane potential. If a stimulus current is applied, the charge of the membrane capacitor and thus the membrane potential are varied.

When this variation is sufficiently large, the membrane potential does not go back to its prior value monotonically after the stimulus current is removed. It produces a spike-like time waveform, the action potential.

This is because some of the ionic permeabilities are dependent on the membrane potential (we may use the expression “voltage-dependent” to represent anything related to the dependence of ionic permeability on the membrane potential). Conductance-based models describe quantitatively the electrical aspect of this mechanism of the membrane potential in the form of differential equations. The equivalent circuit for the membrane potential is shown in Figure 4. In these models, ionic permeability is represented electrically by conductance of ionic channels.

The conductance-based models describe the dynamical relationship between the membrane potential and the ionic currents that are dependent on it as exactly as possible based on the data of the electrophysiological experiments. They can predict the behavior of the membrane potential in the target neuronal cell accurately and precisely. It allows the researchers in various fields to explore the cell’s behavior under various conditions using computers, which mightily facilitates the understanding of its characteristics.

Among the numerous conductance-based models developed based on the results of diligent experimental studies, we are reviewing three representative studies in historical order. Beginning with the founding work of Hodgkin and Huxley, we proceed to the single-neuron exploration era and then finally look at a fine model of the day that is developed to simulate a specific neural network.

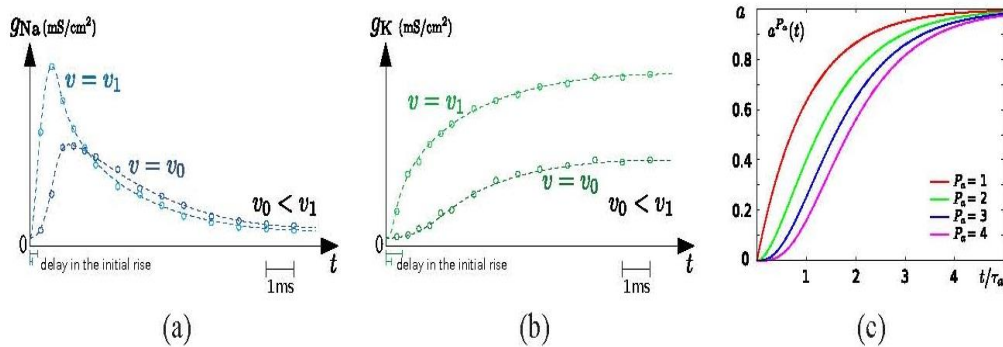


Figure 5: Time series examples of (a) sodium conductance, (b) potassium conductance. In (a) and (b), the membrane voltage v is changed at $t = 0$ from v_r to v_0 or v_1 , where v_r is the resting membrane potential. Delay is observed in the initial rise in the every curve. (c) The red curve ($P_a = 1$) is the solution $a(t)$ of Eq. (5) when $a_0 = 0$ and $a_\infty(v) = 1$. Those for $P_a = 2, 3$, and 4 draw $a^{P_a}(t)$ under the same condition.

2.1. The Hodgkin-Huxley Model

In 1952, Hodgkin and Huxley published the world premiere quantitative model [9] that described the ionic dynamics in a neuronal cell. The Hodgkin-Huxley (H-H) model achieved so great success that it has been one of the most important bases of the researches on the neuron models until now.

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Biographical Sketch

Takashi Kohno, M.D., Ph.D., received the B.E. degree in medicine and the Ph.D. degree in mathematical engineering from University of Tokyo, Japan, in 1996 and 2002, respectively. After experiencing designing of medical care information systems in Hamamatsu University School of Medicine, took the job of a group leader in Aihara Complexity Modeling Project, Exploratory Research for Advanced Technology (ERATO), Japan Science and Technology Agency (JST), Japan. He is currently an associate professor in Institute of Industrial Science, University of Tokyo, Japan. His research interests include the nonlinear dynamics in the models of the neuronal cells and the synapses and the silicon neural network, an artificially realized nerve system. Based on his knowledge over the three academic fields, applied nonlinear mathematics, neurophysiology, and electronic circuit design, he is realizing a simple, compact, and low-power consuming silicon neuron circuit whose dynamics is qualitatively equivalent to several classes of neuronal cells and can be selected at run-time. His main interest is moving to construction of small silicon neural networks and autonomous regulation of the silicon neuron circuit. The final goal of his research is to realize a brain-like computing system that is at least comparable to the human brain. In his private life, he has a long history of developing digital circuits including an original microprocessor and electronics development tools such as a logic analyzer and a ROM emulator. He started it in the mid-1980s and got his first personal FPGA device board in the early 1990s. He has a number of contributions to Japanese industry journals on digital circuit design.