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Generation and Transmission of Action Potential in Nerve Cells and Neuron Populations Based on the Realistic Hodgkin-Huxley Neuron Model

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Abstract

There are several types of nerve cells in the central nervous system. Thanks to the synaptic connections, these cells form large and complicated networks. However, these cells have a stereotypical electrical activity called action potential (AP) or spike. In this work, the mechanisms of formation of this typical electrical signal and the methods of transferring from one cell to another were investigated using Hodgkin-Huxley neuron model. It has been seen that the formation of AP is based on the principle of "all or nothing law" and ion channel dynamics are critical in the typical form of AP. It has been shown that signal transduction between nerve cells is transmitted by post-synaptic potential and that these signals may be cell depolarizing or polarizing. Finally, it has been discussed that these electrical activities are quantities that can be measured by various methods at the micro and macro level.

1. Introduction

The brain and spinal cord that make up the central nervous system (CNS) have special cells called nerve cells or neurons, which are considered the smallest unit of the brain. The CNS consists of approximately 10^{12} nerve cells with complex synaptic connections with each other and almost 50 times as many cells called glia[1]. Glia cells' main task is meeting the energy requirement of the CNS and maintaining its stable structure [2].

Figure 1 shows Golgi-Cox staining of various types of cells in an adult mouse brain. Golgi-Cox staining images of cerebral cortex neurons and glial cells are shown in Figures 1A and Figure 1B. Hippocampal granule cells are seen in Figure 1C, Purkinje cell in Figure 1D, and dendritic spines in Figure 1E (scale bars are 500 µm in A, 50 µm in D, and 5 µm in E). As can be seen in Figure 1, it is seen that even neurons in a small cross-section have a rather complex structure. When the whole brain is considered, it is clearly understood how complex and enormous the brain is, with billions of neuron bodies and fiber connections in the form of a dense network.

In this study, comprehensive information about the general structure of nerve cells, electrical activity and how electrical activity occurs in neuron populations is presented. In order to demonstrate the generation and transmission of electrical signals between neurons, simulations involving single and multiple nerve cells were performed. In these simulations, pyramidal and interneuron neurons based on the realistic Hodgkin-Huxley neuron model are used. Thus, it was revealed how neurons transfer electrical signals to each other through synaptic connections. Although neurons have a very complex structure, it has been shown that the form of the electrical signal they create has a stereotyped structure in line with experimental studies. In addition, it has been revealed that this electrical signal is formed based on the all-or-nothing principle.

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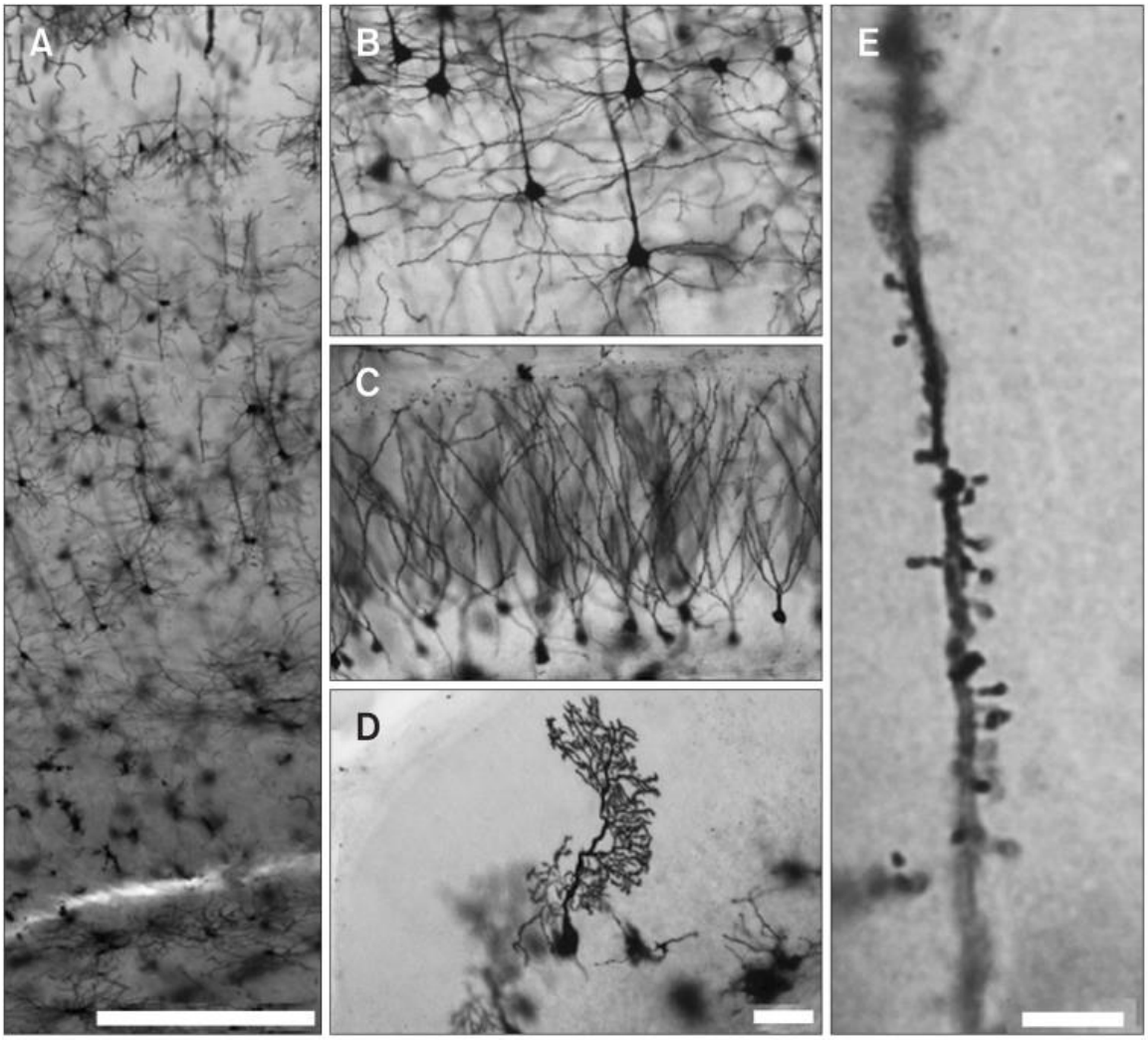

Figure 1. Golgi-Cox stained image of adult mouse brain (Retrieved from [5], based on open access policy)

2. Nerve Cell

There are quite many different types of nerve cells with different characteristics in the human brain, these cells are very similar in structure, as seen in Figure 2. However, it is stated that most of the brain functions in humans and other living things are related to the anatomical connections formed by these cells [3]. In the vertebrate cortex, each neuron usually has more than approximately 10^4 synaptic connections from neighboring neurons via the soma and its dendrites.

Neurons communicate with each other thanks to these large and complex network structures [2]. The synapses at these connections are usually in the form of chemical synaptic connections that replace the membrane potential of the neighboring neuron (post-synaptic neuron) with neurotransmitters. Cells such as muscle and cardiac cells have electrical synapses that communicate through the gap junction. The connection distance between cell bodies can be one (1) meter, as in a single axon in the human spinal cord, 1or a few millimeters, as in the brain. Axon thickness is in the range of about 1 μm to 500 μm, and thicker axons can transmit the signal faster [1]. Some axons are covered with a myelin sheath, an oil-like insulating material made up of regular spaces called nodes of Ranvier, which allows the signal to jump from one node to the next [3].

A typical nerve cell and neuron have a cell body called soma, dendrites that provide synaptic connections, an axon that transmits the signal formed in the cell body, and finally synaptic terminals that transmit this signal to other cells [2,3]. The soma is the largest component of a neuron. The main functions of the soma are to synthesize proteins, produce the necessary energy for the cell, and manage other vital functions of the cell. Another of the most important tasks of the soma is to transfer the signal/information it receives with the help of dendritic inputs to other cells via its synaptic terminals [5].

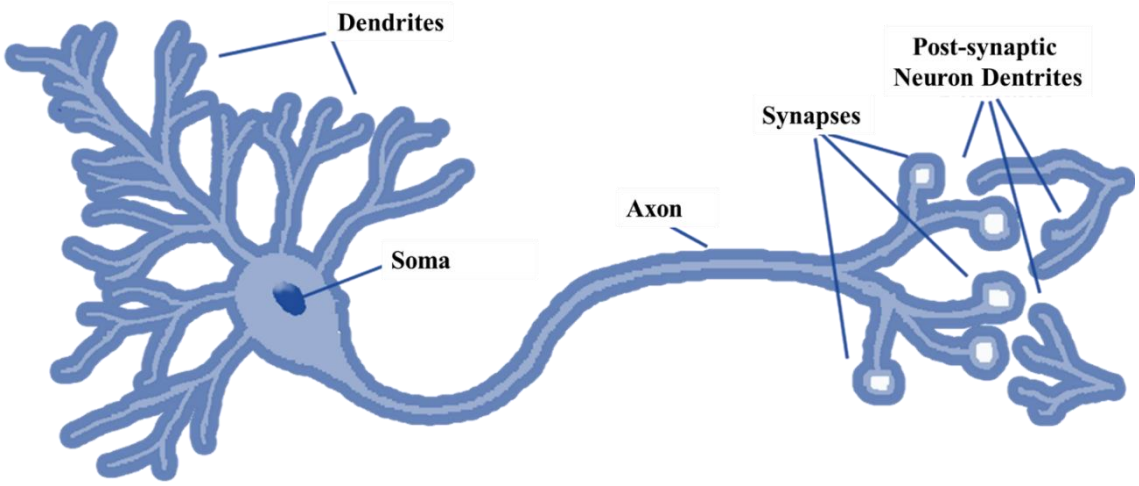

Figure 2. Schematic structure of an example nerve cell (motor neuron)

In addition, the cell body has a selectively permeable cell membrane called the membrane, which determines the basic characteristic of the electrical signal formed in the nerve cells. The selectively permeable porous structure of the cell membrane controls the transition of ionic molecules into or out of the cell. Dendritic and axonal projections of neurons, which are not found in other cells, enable the cell to communicate with other cells[1].

Although neurons make synaptic connections mostly by chemical and electrical mechanisms, they can also have ephatic synaptic connections[6]. They provide the transmission of the signal formed in the cell body as a result of synaptic connections, dendritic and/or axonal inputs to other neurons. Here, the source neuron that generates the signal is called the pre-synaptic cell, and the target neuron to which the signal is transmitted is called the post-synaptic cell[2]. Communication between pre-synaptic and post-synaptic cells takes place through structures called synaptic gap[3]. As shown in Figure 2, dendrites are structures that have many protrusions in a tree-like structure and that transfer a large number (thousands) of pre-synaptic inputs to the cell body thanks to this projection.

Although the main task of the dendrites is to transmit the signal transmitted from the pre-synaptic cell to the cell body, sometimes the incoming signal can be partially processed (gathered) in the dendrites and then transmitted to the soma[7]. But the main specialized cell unit for this process is the soma. The signal generated in the soma is carried to the synaptic terminals via the axon, which is longer than 1 m in humans[8]. Axons receive the action potential, which is a fast and transient electrical signal with an amplitude of about 100 mV and a period of 1 ms − 2 ms, from the cell body, and transfer it to the target cell via synaptic connections at a speed of about $0.5\ \mathrm{m/s}$ to $120\ \mathrm{m/s}$[1]. Thus, electrical signals produced in the soma can reach other associated neurons in the brain, or to the muscles through the innervation of effector muscles and glands via the motor cortex[5,9]. This electrical signal starts at the axon hillock and can be transmitted along the axon with almost no change[3]. Axons are divided into two types: whitish thick axons covered with myelin and thin axons without myelin[10]. Myelinated axons have several advantages such as faster conduction and less energy requirement[11]. There are many synaptic terminals called telodendria, which connect with the post-synaptic cell at the endpoints of axons[7].

3. Modeling and Simulation

In this study, simulations involving a single pyramidal nerve cell seen in Figure-3(A) were carried out to examine the nascency and form of AP. In addition, excitatory pyramidal (PY) cells and inhibitory interneurons (IN) were used in the cortical network (Figure-3(B)) designed to examine the transmission of electrical signals between neurons. The study was based on a single-compartment Hodgkin-Huxley neuron model with high biological reality for both PY and IN cell types. These mathematical models are generally expressed as follows[12–15]:

$$C\frac{dV}{dt} = I_{Na} + I_K + I_L + I \quad (1)$$

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

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

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

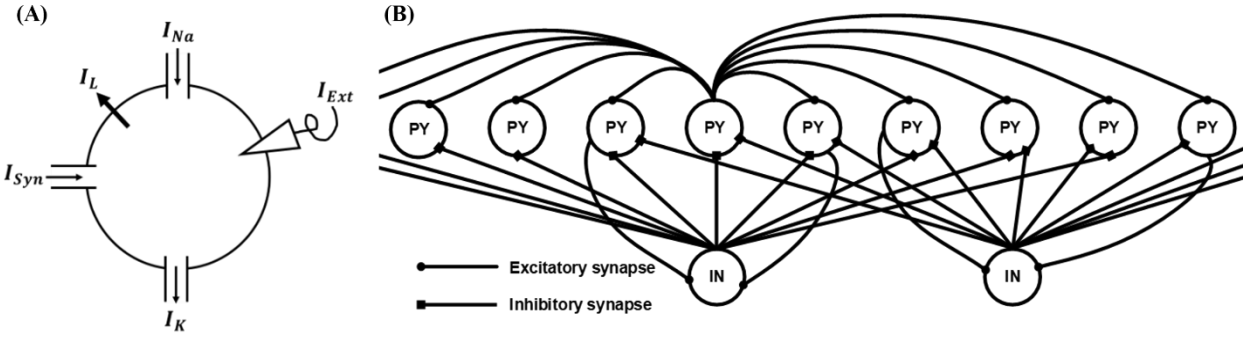

Figure 3. Schematic structure of single-cell and multi-cell applications

The voltage dependent channel currents given here are ionic currents, where I_{Na}, I_K and I_L represent sodium (Na^+), potassium (K^+) and leakage current, respectively. In addition, in the equations here, I denotes the sum of synaptic currents (I_{syn}) and/or external DC excitation current (I_{ext}), V denotes membrane voltage and $C = 1\mu F$ denotes cell membrane capacitance corresponding to unit area. The ionic current parameters $G_{Na} = 51.6$ mS, $G_K = 10$ mS, $G_L = 0.0452$ mS are the maximum values of sodium, potassium and leakage conductivities, respectively. E_{Na}, E_K, E_L are sodium, potassium, and leakage current reversal nernst potential values, respectively. On the other hand, m, h, and n gate dynamics are time-varying activation variables dependent on voltage-dependent ratio constants α_m, β_m, α_h, β_h, $\alpha_n$and β_n variables [13, 14].

In neuronal networks, the electrical potential generated by the pre-synaptic cell on the post-synaptic cell can be excitatory or inhibitory. In equation 1, which expresses the single-compartment cell model, the synaptic conductances caused by these potentials are represented by I_{syn} in the external current I and are generally expressed as follows[13–15].

$$I_{syn} = g_e(t)(V - E_e) + g_i(t)(V - E_i) \quad (5)$$

$$\tau_e \frac{dg_e}{dt} = -g_e \text{and} \tau_i \frac{dg_i}{dt} = -g_i \quad (6)$$

where V is the membrane voltage, time-dependent $g_e(t)$ and $g_i(t)$ are the excitatory and inhibitory synaptic conductivities, respectively. And $E_e = 0$ mV and $E_i = -75$ mV represent excitatory and inhibitory synaptic reversal potentials, respectively. Finally, $\tau_e = 2.7\,ms$ and $\tau_i = 10.5\,ms$ excitatory and inhibitory synaptic time constants, respectively [14].

In order to the cortical network model to be compatible with the anatomical and morphological bases, the study by Bazhenov et al. [16] was taken as reference and models were performed using 100 PY and 25 IN cells while maintaining the ratio of 4:1. Schematic representations of single-cell and multi-cell (cortical network) simulations are presented in Figure 3. As seen in Figure 3 (A), an external DC current (I_{ext}) was applied to examine the nascency and form of the AP. In order to examine the post-synaptic potentials, the cortical network whose schematic structure is presented in Figure 3(B) was created.

There are excitatory and inhibitory projections in the cortical network. Excitatory projections can be between PY cells (PY-PY) and from PY cells to IN cells (PY-IN), whereas Inhibitory projections can only be from IN cells to PY cells (IN-PY). Connection spreads are ±5%, ±1%, and ±5% for PY-PY, PY-IN, and IN-PY, respectively [16].

4. Action Potential

Nerve and muscle cells, which are excitable cells, have sodium (Na^+) and potassium (K^+) ion channels in their membranes. Thanks to the change in the internal and external (Na^+) and (K^+) concentrations of the ion channels, the electrical potentials on the membrane change. This electrical change is transmitted in waves along the cell axon and transferred to other cells, as in dominoes, via synaptic connections. As seen in Figure 4A, the resting membrane potential of a post-synaptic neuron that receives multiple pre-synaptic impulses (spike pulses) in a sufficiently strong external stimulus or in a short time window rises from a negative value (approximately -70 ∓ 10 mV) to a positive value (approximately $+40 \mp 10$ mV). Then it becomes negatively charged again by balancing the intracellular and extracellular ion concentration[2, 10, 17, 18].

The output of the membrane voltage is expressed as depolarization (discharge) and its decrease again as repolarization (charge) (Figure 4A). This charge and discharge event takes place due to the displacement of ionic substances, mainly Na^+, K^+,

Ca^{++} and Cl^{-}, along the cell membrane from the outside to the inside and from the inside to the outside, and the concentration difference between the intracellular and the extracellular. In this displacement process, ion pumps using adenosine triphosphate (ATP) energy also play an active role[18]. This electrical signal, in the form of a pulse with an amplitude of about 100 mV, formed in this way is called Action Potential (AP) or spike[2]. These electrical signals are of great importance for the cell, and they have a critical importance in the communication of nerve cells with each other, and thus in the realization of many body functions. Although AP is caused by many different environmental factors, it has a very stereotypical structure in the entire nervous system. For this reason, a signal carrying visual information and a signal carrying information about smell are similar to each other [3].

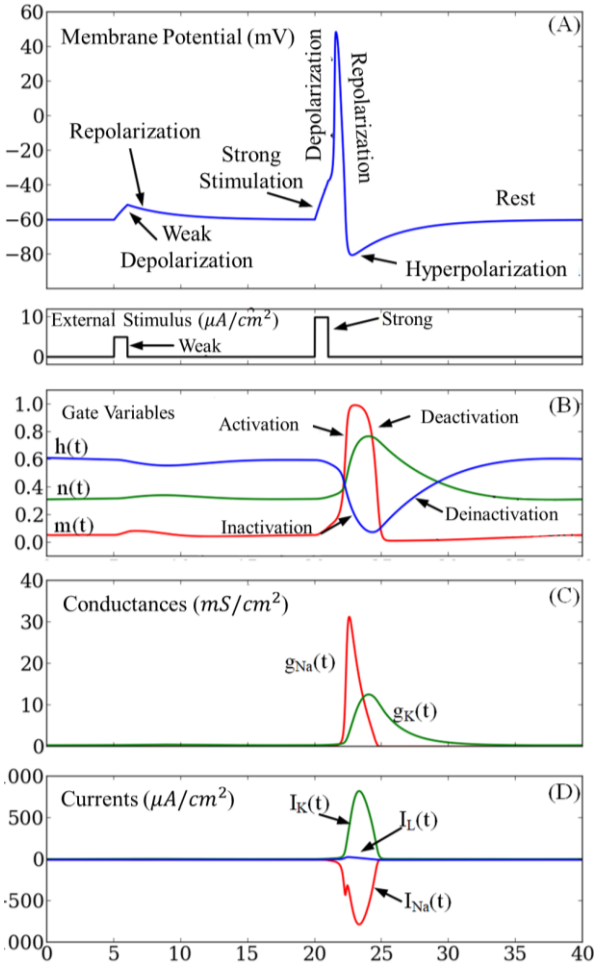

Figure 4. Action Potential and ionic channel dynamics according to the Hodgkin-Huxley model

Figure 4 shows the variations of a simulated AP and other ionic dynamics using mathematical models derived from a series of studies by Hodgkin and Huxley. The graphics in the figures are fully compatible with the work of Hodgkin and Huxley and were obtained as a result of our simulation-based on these models.

As seen in Figure 4A, with a sufficiently large excitation, the membrane voltage depolarizes by exceeding the critical voltage value. In the depolarization phase, the activation variables m and n increase, while the inactivation variable h decreases (Figure 4B). Since the Na^+ activation gate time constant $\tau_m(V)$ is faster than the others, the variable m is also faster than the others. The rapidly activated Na^+ channels depolarize the membrane voltage (V), increasing it up to the E_{Na} level. After the membrane voltage has reached its peak, the slower gate variables (n and h) come into play; the inactivation variable $h \to 0$ causes the Na^+ current to be passive, and the activation variable $n \to 1$ causes the outward K^+ current to be activated slowly. As seen in Figure 4C, the variation of sodium conductivity rises and falls rapidly, while potassium conductivity has a slower activity. This situation is related to the rate of change of the time constants seen in Figure 5. Then, the membrane voltage is repolarized towards the V_{rest} level with the effect of K^+ current and leakage current. The curves of the changes in channel currents are given in Figure 4D.

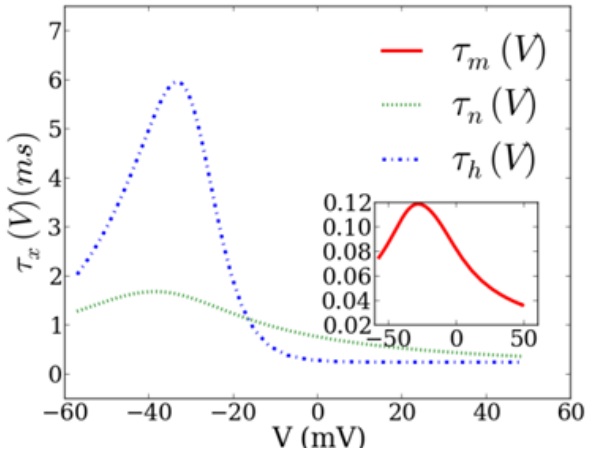

Figure 5. Time constants of activation and inactivation gates according to the Hodgkin-Huxley model

When the membrane voltage is $V \approx V_{rest}$, as seen in Figure 5, since voltage dependent $\tau_n(V) \cong 1.1\text{ms}$ and $\tau_h(V) \cong 2\text{ms}$ have relatively larger values than $\tau_m(V) \cong 0.08ms$, the improvement/correction variables n and h are slower. Accordingly, even when the membrane voltage is at about rest level ($V \cong V_{rest}$) in the continuation of the AP, the K^+current continues to be active and causes the membrane voltage to become hyperpolarized by pulling it below the rest level. At the end of the AP activity, the

membrane voltage of the hyperpolarized cell is brought back to the resting potential by the Na^+sodium-potassium ion pump. When the Na^+ current is inactivated (h is low), it cannot be used for a new regenerative function and a second AP cannot be triggered, this period is called the absolute refractory period. On the contrary, the period in which the current is de-inactivated, in which the system can generate a new AP with a sufficient (greater than normal) excitation is called the relative refractory period[19].

5. Electrical Activity in Neuron Populations

In general, it can be said that the potential difference and AP formation across the membrane is due to the concentration difference of K^+, Na^+ cations and Cl^- and large organic anions (Figure 7). However, the electrical activity that emerges as a result of these ionic channel activities in a post-synaptic nerve cell is shaped by some factors. These factors are the APs that emerge by exceeding the threshold value in pre-synaptic cells, and the sub-threshold potentials (PSP, post-synaptic potentials) created by these APs in the post-synaptic cell. In vivo synaptic conductances can be excitatory or inhibitory. If synaptic activity produces an excitatory potential in the postsynaptic cell, it is called excitatory post-synaptic potential (EPSP), and if it generates an inhibitory potential, it is called inhibitory post-synaptic potential (IPSP)[14].

As stated in Chapter 4, AP formation generally begins with rapidly increasing Na^+ ion permeability, and as a result of the influx of Na^+ ions into the cell due to the concentration difference, the intracellular potential rises rapidly. After a certain voltage value, the Na^+ ion permeability decreases. On the contrary, the permeability of K^+ ions increases and these ions flow from inside the cell to the outside, causing the inside of the cell to become negative again compared to the external environment. Thus, AP, which is a stereotypical signal lasting 1-2 ms, or in other words, a spike is formed. It processes the formation of this electrical signal according to the "all or nothing" law[10]. As seen in Figure 6A, this was demonstrated by Weidmann [20] applying square-shaped stimuli to Sheep Purkinje cells. On the other hand, Figure 6B shows the simulation results using the Hodgkin-Huxley neuron model. Both experimental and model results show us that AP occurs according to the all-or-nothing law.

PSPs are also associated with events occurring at the post-synaptic membrane. When the AP reaches the synapse, it changes the permeability of the next post-synaptic membrane by releasing some chemicals called mediators or transmitters, and as a result, ions cross the membrane and create a potential across the membrane. As can be seen in Figure 7 inner graph, if this potential depolarizes the membrane voltage, an EPSP will occur, increasing the probability of spike firing. If the membrane voltage is polarized, as can be seen in Figure 7 inner graph, IPSP will occur on the contrary. The form of PSPs is not stereotyped like APs and depends on the rate of neurotransmitters released. A typical PSP has an amplitude of 5mV to 10mV and a period of 10ms to 50ms. Therefore, multiple PSPs must occur in succession at appropriate times for supra-threshold stimulation required to generate AP in the post-synaptic cell soma. In other words, phase coherence between post-synaptic and pre-synaptic cells is vital for the formation of AP in the cell. Therefore, efficient signal transmission between nerve cells is possible only if there is phase synchronization [21].

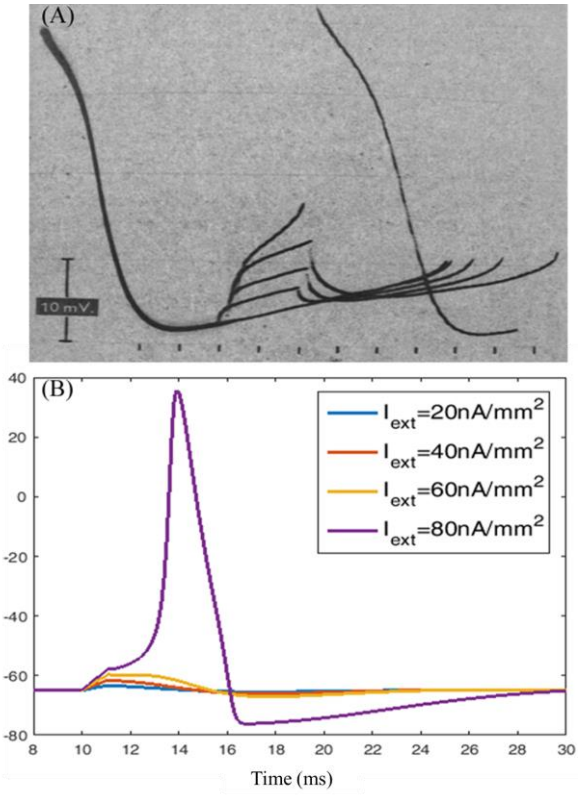

Figure 6. The all-or-none law. (A) Sheep Purkinje cell AP forms [20], (B) AP forms according to the Hodgkin-Huxley neuron model

Due to the various types of ionic channels, many ionic currents occur across the nerve cell membrane towards the inside and/or outside of the cell. In this case, due to ionic currents, massively magnetized parallel directional dipoles (double poles) appear. The synchronization of the electrical activity created by these oppositely charged dipoles allows the

electric field formed in the cell membrane to be monitored at a macroscopic level [22].

The most known method of measuring brain electrical activity is Electroencephalography (EEG), which is recorded from the scalp [22, 23]. Richard Caton (1842-1926) is considered the first scientist to investigate brain potentials. He studied cat and rabbit brains and measured electrical current activities with a galvanometer. Later, Napoleon Cybulski (1854-1919) graphically demonstrated the electroencephalogram by adding a photographic addition to the galvanometer, and was the first to observe epileptic EEG activity with electrical stimulation in a dog [24]. The first electroencephalogram recording from the human skull was made in 1929 by Hans Berger [25]. In 1935, electroencephalography emerged in today's clinical field and the modern era of EEG recording (Grass Model I) began. However, since the spatial resolution of EEG is low, more advanced techniques are used today. Some of these are electrocorticography (ECoG) which can be measured from the surface of the cortex, micro-EEG (or LFP) which can be measured from deep brain tissue, or techniques with a very high spatial resolution that can be directly measured intracellularly[26].

The formation of synchronized electrical activities in the CNS is made possible by various distant and/or near projections. For example, vertical pyramidal cells [27] arranged in the form of columns in the neocortex are synchronized by thalamocortical projections from the thalamus[28]. In addition, it is stated that astrocytic signaling has critical importance in maintaining synchronization and modulates sleep states and sleep/wake transitions [29]. These synchronized electrical signals, which can be observed macroscopically, can be measured by electroencephalography (EEG) from the skull surface or by electrocorticography (ECOG) method directly from the cortical surface inside the skull. An important point to know here is that the contribution of APs to these electrical signals is almost nonexistent and that these signals are composed of post-synaptic potential sums formed in a synchronized manner [30]. While the contribution of synchronized neurons in the measurement region to the electrical signals in question is directly related to the number of these neurons, the contribution of nonsynchronous neurons is proportional to the square root of their number [22].

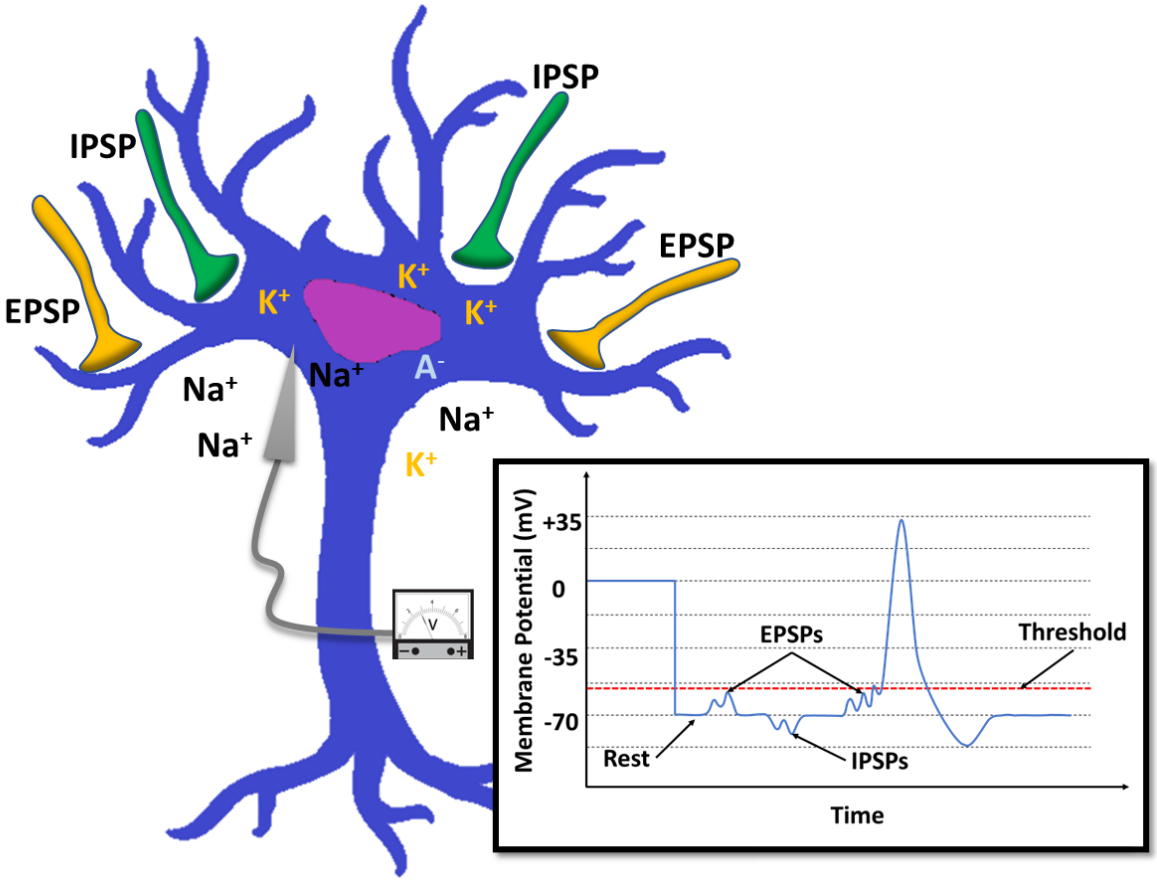

Figure 7. Electrical charge difference between inside and outside of the cell and PSP inputs

Accordingly, in the case of measuring with the electroencephalography method, it is assumed that there are approximately 10^8 neurons in the area where the electrode is placed. Accordingly, let's assume that the proportion of cells with synchronized activity is 10% of the total number of cells (i.e. 10^7 cells). In this case, from the expression $10^7/\sqrt{10^8} = 1000$, it can be said that the contribution of synchronized cells to the measured electrical signal is 1000 times more than nonsynchronous cells.

6. Discussion and Conclusion

In this study, the general structure of the nerve cell, its electrical activity, and how electrical activity occurs in neuron populations are focused on. The simulations results showed that although nerve cells have a very complex structure, AP has a stereotyped form in nerve cells and is formed according to the "all or nothing" principle. This principle is of critical importance and demonstrates that realistic neuronal models can also be applied to digital circuits An example of hardware designs made for this purpose is the I&F-based Memristive Integrate-and-Fire (MIF) model[31]. Furthermore, considering the computational cost, various reduced HH-based models such as FitzHugh–Nagumo, Hindmarsh–Rose, Morris–Lecar, I&F, or Izhikevich can be used for this purpose[32].

It has been observed that ion channel gate dynamics have a critical role on the form of AP. It has been observed that neurons conduct/transmit this electrical signal to each other through synaptic connections, and depending on the type of synaptic connection, this signal can create an effect that depolarizes (EPSP) or polarizes (IPSP) membrane voltage in the post-synaptic cell. Finally, how the electrical activities of large populations of neurons are measured at micro or macro scales, and the methods used for this purpose are discussed.

According to this study, neurons show that they process information with the AP signal, which is a stereotyped signal formed according to the "all or nothing" principle. Accordingly, it seems possible to develop integrated circuits in which neurons can be imitated. Thus, digital neuronal networks can be created with these electronic neurons. As a result, digital systems can be designed that mimic the cognitive functions of the brain.

Statement of Research and Publication Ethics

The study is complied with research and publication ethics.

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