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NEURON MODELING

Computational neuroscience as a tool for studying neurons

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ABSTRACT
OBJECTIVES: Computational neuroscience uses a neuron model to investigate the behavior of a neuron under different stimuli e.g. magnetic field. The aim of the study is to investigate the effect of conductivity change of sodium (Na^+) and potassium (K^+) ion channels on the generation and course of action potential, excitability and firing rate of neuron.
METHODS: HHSim (Hodgkin-Huxley) graphical simulator was used for investigation of generation and firing rate of action potential (AP) and investigation of neuronal excitability.
RESULTS: Na^+ channel downregulation of conductance reveals a decrease of AP amplitude, and upregulation an increase of amplitude. Higher conductance of Na^+ channel leads to higher firing rate from the value 53 HZ to 66 Hz. K^+ channel downregulation of conductance reveals an increase of AP amplitude. Lower conductance of K^+ channel leads to higher firing rate from the value 62 HZ to 68 Hz. K^+ channel upregulation of conductance shows a decrease of AP amplitude.
CONCLUSION: From the results it can be drawn that effect of conductivity change as a result of magnetic field is significant and can leads to change of neurons. uman brain cultures, often termed “glia-like” cells *(Tab. 4, Fig. 6, Ref. 21)*. Text in PDF www.elis.sk
KEY WORDS: ion channels, conductance, action potential, magnetic field.

Introduction

Computational neuroscience is an interdisciplinary field of computer science, mathematics and neuroscience focusing on the nervous system. The main building block in computational neuroscience is a neuron and its physical, biological and chemical properties. In a simplified neuron model, we can describe a neuron as a cell containing a cell body and axon. A neuron model determines development and course of action potential (AP), a conductance of specific ion channels or a specific external stimulus at a specific time. AP is a movement of sodium (Na^+), potassium (K^+) and chlorine (Cl^-) and calcium (Ca^{2+}) ions through the channels with a purpose to transmit information. Information on strength of stimulus can be encoded in a sequence of APs – firing rate. Applying physical laws and mathematical principles, we can design different models of neurons and study how altered conductance of ion channels affects AP over time. The first and most famous computation model of neurons was invented by Alen Hodgkin and Andrew Huxley in 1952. They proposed a mathematical model for APs in the form of a set of nonlinear differential equations (1). They were awarded for their discovery by a Nobel Prize in Physiology and Medicine in 1963. In their model, they propose an electric circuit that represents a neuron.

The main goal of computational neuroscience is understanding how the nervous system works, develops and responds to stimuli. However, computational neuroscience can bring new ideas regarding the prevention or treatment of various neural disorders, such as Parkinson’s disease, Alzheimer’s disease, autism, multiple sclerosis, schizophrenia or depression. It can also help to guide and predict expensive laboratory animal experiments.

Nowadays in the age of computers, it is much more possible to design various models of neurons and run practically an unlimited number of simulations at almost no cost. To create a simple computation model, a cell can be divided into discrete electrical circuits that can be mathematically described. The electrical circuit consists of voltage sources (E) representing the membrane potential and capacitor (C) representing cell membrane. Resistors (R) represents ion channels in cell membrane. The first well-known model used this representation and was represented only by a single circuit (2). Generally, neuron models can be divided into single or multi-compartment models. Single-compartment models consider the whole neuron as one unit. They usually abstract from morphological details such as dendrites or synapses of the neuron and assume, that its biophysical properties are uniform in the whole neuron. Multi-compartmental models consider that the neuron is divided into multiple compartments. Multi-compartmental models

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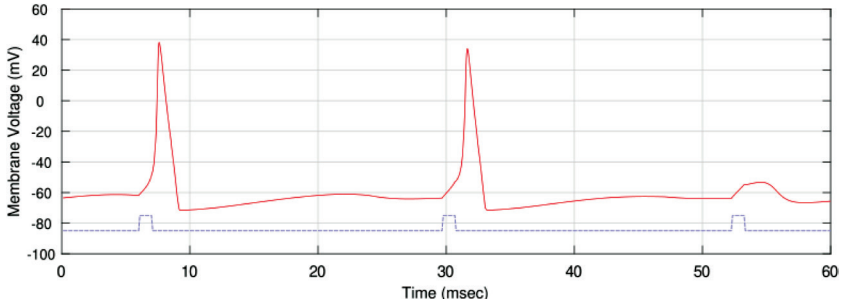

Fig. 1. HHsim graphical simulator. The continuous line represents action potential. The conductance of the fast Na^+ channel was set gradually to the three different values. The first conductance is 120 µS, the second 90 µS and the last 60 µS. The dashed line represents three stimuli of size of 10 nA and duration of stimuli 1 ms in all three cases.

are more accurate than single-compartment models because they take into account that different parts (compartments) of the neuron can have different electrical properties. Some of the modeling techniques are pyramidal, cable or compartmental modeling. Pyramidal models focus on the morphology of the dendritic tree. Cable models assume that neurons can be modeled as cylindrical cables with uniform electrical properties. From the software perspective, there exist open-source tools that allow to model neurons and run simulations based on the specific model.

Neurons convert stimulus from dendrites into AP depending on intrinsic membrane properties such as conductance of ion channels or capacity of cell membrane. Properties play a crucial role in generation of action potential, firing rate and neuronal excitability. The aim of the study is to investigate the effect of conductivity change of sodium (Na^+) and potassium (K^+) ion channels on the generation and course of action potential, excitability and firing rate of neuron in HHSim graphical simulator.

Material and methods

HHSim is a Hodgkin-Huxley graphical simulator of AP. It is a pulse of electrical activity that transmits information. In the HHSim interface, one can configure Hodgin-Huxley parameters such as membrane parameters, temperature and ion concentration (3). The Hodgkin–Huxley model of the AP is a theoretical basis of computational neuroscience. AP is an electrical potential created by their uneven distribution in extracellular and intracellular space. As an input for neuron modeling a specific concentration of sodium (Na^+), potassium (K^+) and chlorine (Cl^-) ions can be used at a specific time. This one drives the flow of ions across the cell membrane. The neuron's intracellular space contains a higher concentration of K^+ and lower concentrations of Na^+ and Cl^- than does the extracellular space. It is maintained through ion-specific pumps that require energy (mainly sodium-potassium pump). In HH model, uneven distribution of ions is represented by voltage sources (E). By setting the concentration of K^+, Na^+ and Cl^- in intra- and extracellular space the size of membrane potential of neuron is determined. The external stimulus can be set by changing the conductance of ion channels.

Tab. 1. The peak amplitude for the specific Na^+ channel conductances.

Na^+ channel conductance (µS)	Peak amplitude (mV)
120	39.2
90	34.1
61	12.6
60	NA (AP was blocked)

Tab. 2. The peak amplitude for the specific Na^+ channel conductances.

Na^+ channel conductance (in µS)	Peak amplitude (mV)
120 with 10nA external stimuli	39.2
133 with 10nA external stimuli	40.6
133 without external stimuli	35.3
150 without external stimuli	41.4

Results

Figure 1 shows the downregulation of the conductance of the Na^+ channel. The spikes reveal the course of action potentials generated after stimuli at reduced conductance of fast Na^+ channel. The stimulus size was 10 nA and the duration of stimulus was 1 ms in all three cases. The first spike corresponds to the conductance of the fast Na^+ channel 120 µS, and the second spike to 90 µS. The conductance decreased to 60 µS caused blocking the generation of action potential after injecting the stimulus. Default Hodgkin-Huxley values were used in the experiment: the conductance of delayed rectifier K^+ channel 36 µS, capacitance C of neuron's membrane C=1 nF, resistivity R of ion channels in neuron's membrane R=5.1 MΩ, temperature T=6.3°C. It is observed that a decrease in conductivity of the Na^+ channel leads to a decrease of potential amplitude and can cause blocking of action potential (Tabs 1, 2). The conductance set to 61µS does not block the action potential, although it causes a reduction of the peak amplitude. At the same time, the value 60 µS and lower values cause blocking of the action potential (in our neuron configuration).

Figure 2 shows the upregulation of the conductance of the Na^+ channel. The three spikes reveal the course of action potentials generated after the stimulus at enhanced conductance of the fast Na^+ channel. The stimulus size was 10 nA and the duration of stimulus was 1 ms. The spikes correspond to the conductance of the fast Na^+ channel enhanced to 133 µS. Default values were used in the experiment: the conductance of delayed rectifier K^+ channel 36 µS, capacitance C of neuron's membrane C=1 nF, resistivity R of ion channels in neuron's membrane R=5.1 MΩ, temperature T=6.3°C. It can be observed, that enhancement in conductivity of the Na^+ channel from 120 µS to 133 µS leads to an increase of potential amplitude. In addition, continuous spontaneous generation of spikes is observed (without any additional external stimulus) (Tabs 3, 4). Firing rate is about 53 Hz.

Figure 3 shows the upregulation of the conductance of the Na^+ channel. The spikes reveal the course of action potentials generated

after setting the conductance of the fast Na^+ channel to 150 μS without injecting any external stimulus. Default values were used in the experiment: the conductance of delayed rectifier K^+ channel 36 μS, capacitance C of neuron's membrane C=1 nF, resistivity R of ion channels in neuron's membrane R=5.1 MΩ, temperature T=6.3°C. Continuous spontaneous generation of spikes can be observed (without injecting any external stimulus). However, conductance of Na^+ channel increased to 149μS does not cause spontaneous (without the need of any external stimulus) spikes firing (Tab. 2). Firing rate is about 66 Hz.

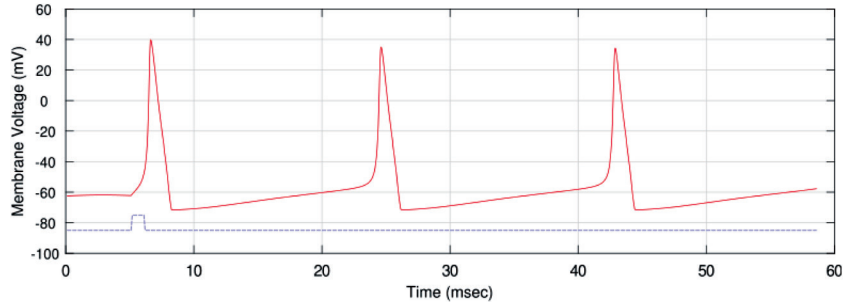

Fig. 2. HHsim graphical simulator. The continuous line represents action potential. The conductance of the fast Na^+ channel is set to 133 μS. The dashed line represents stimulus size of 10 nA and duration of stimulus 1ms.

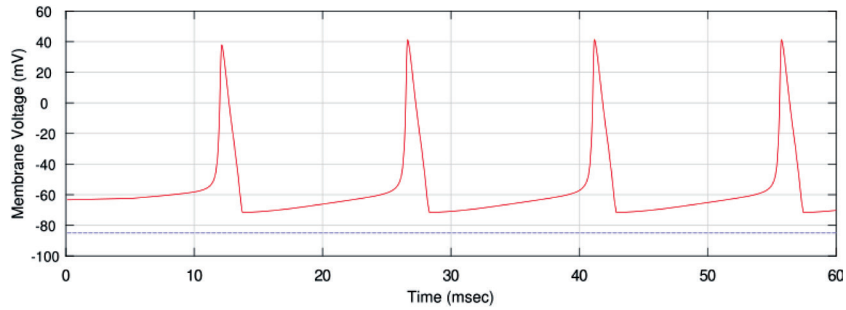

Fig. 3. HHsim graphical simulator. The continuous line represents action potential. The conductance of the fast Na^+ channel is set to 150 μS and even no stimulus was injected, continuous spontaneous generation of spikes is observed.

Figure 4 shows the downregulation of the conductance of the K^+ channel. The three spikes reveal the course of action potentials generated after the stimulus at reduced conductance of delayed rectifier K^+ channel from default value 36 μS to lower value 32 μS. The stimulus size was 10 nA and the duration of the stimulus was 1 ms. Default values were used in the experiment: the conductance of fast Na^+ channel 120 μS, capacitance C of neuron's membrane C=1 nF, resistivity R of ion channels in neuron's membrane R=5.1 MΩ, temperature T=6.3°C. Additional continuous spontaneous generation of spikes was observed (without injecting any additional external stimulus). Firing rate was about 62 Hz.

Figure 5 shows the downregulation of the conductance of the K^+ channel. The spikes reveal the course of action potentials generated after reducing the conductance of the delayed rectifier K^+ channel from a default value of 36 μS to a lower value of 30 μS. Default values were used in the experiment: the conductance of fast Na^+ channel 120 μS, capacitance C of neuron's membrane C=1 nF, resistivity R of ion channels in neuron's membrane R=5.1 MΩ, temperature T=6.3°C. Continuous spontaneous generation of spikes was observed (without injecting any external stimulus). Firing rate was about 68 Hz.

Figure 6 shows the upregulation of the conductance of the K^+ channel. The two spikes reveal the course of action potentials generated after stimuli at increased conductance of delayed rectifier K^+ channel from default value 36 μS (the first spike) to increased values of 54 μS (the second spike). However, the injection of the third stimulus did not fire action potential when the conductance was set to 75 μS. Each stimulus size was 10 nA and the duration of stimulus was 1 ms. Default values were used in the experiment: the conductance of fast Na^+ channel 120 μS, capacitance C of neuron's membrane C=1 nF, resistivity R of ion channels in neuron's membrane R=5.1 MΩ, temperature T=6.3°C. It was observed that upregulation can decrease potential amplitude and also cause blocking of the action potential.

Discussion

Deposition of iron in some neurological diseases such as Parkinson disease, Alzheimer disease and multiple sclerosis is observed (4–7). Under some conditions iron can mineralize to magnetite particles and their magnetic field could affect the function of neurons. There are several possible mechanisms. One mechanism is the impact of magnetic field on the movement of Na^+ and K^+ ion

Tab. 3. The peak amplitude for the specific K^+ channel conductance.

K^+ channel conductance (μS)	Peak amplitude (mV)
36 with 10nA external stimuli	39.2
33 with 10nA external stimuli	39.5
32 with 10nA external stimuli	39.7
32 without external stimuli (spontaneous spikes)	36.0
30 without external stimuli (spontaneous spike) – first spike	36.5
30 without external stimuli (spontaneous spikes) – other spikes	38.3

Tab. 4. The peak amplitude for the specific K^+ channel conductance.

K^+ channel conductance (μS)	Peak amplitude (mV)
36 with 10nA external stimuli	39.2
54 with 10nA external stimuli	36.2
74 with 10nA external stimuli	27.9
75 with 10nA external stimuli	NA (AP was blocked)

through ion channels by the Lorentz force. It is the force acting on charged particles moving in the presence of magnetic field. The trajectory of ion in magnetic field of particles is deflected and therefore the friction between ions and wall of ion channels could lead to reduction of conductance through ion channels (8). Another possible mechanism which could influence the conductance of ions channels is alteration of membrane structure (9, 10). Molecules of neuron membranes are weakly repelled by magnetic field of particles in their vicinity (11, 12). Result of this effect is deformation of membrane and ion channels located in it and subsequently changed conductance of ions through them. Altered conductance of Na^+ and K^+ ion channels changes the course of action potential and in turn the function of neuron cell. To test the effects of magnetic field on neuronal excitability, we used a Hodgkin-Huxley-based model to simulate the course of action potential.

We will first discuss the downregulation of the conductance of the Na^+ channel without changing any other membrane parameters. Na^+ channels (voltage-gated) are the most important ion channels responsible for neuronal excitability and generation and propagation of action potentials in neurons. Any disturbance to conductance of the Na^+ channel could have downstream effects on excitability. After receiving the stimulus by a nerve cell, that is strong enough, it changes the action potential primarily by changing the permeability of Na^+ channels. Voltage-gated Na^+ channels open and Na^+ ions enter the neuron (depolarization phase) and action potential under physiological conditions changes from the value of about –70 mV (resting potential) to about +30 mV. Our results from simulations show that downregulation of the conductance of the Na^+ channel without changing any other membrane parameter at first leads to a slight decrease of amplitude of action potential (hypoexcitability) and later the blocking of the action potential. Ghovanloo et al. investigated the effect of cannabigerol (a non-psychotropic phytocannabinoid) on excitability of neurons. They found that inhibition of Na^+ channel (Na_v 1.7 channels) by cannabigerol in dorsal root ganglion neurons may lead to neuronal hypoexcitability (13).

Neurons should be able to alter their firing rates as a response to the input they receive. That is achieved by altered ion channels conductance across the membrane. Magnetic field of endogenous particles can also enhance the conductance of Na^+ channel located in neuronal membrane. Matzner and Devor used the Hodgkin-Huxley model in the squid giant axon to predict the effect of altering maximal Na^+ conductance on

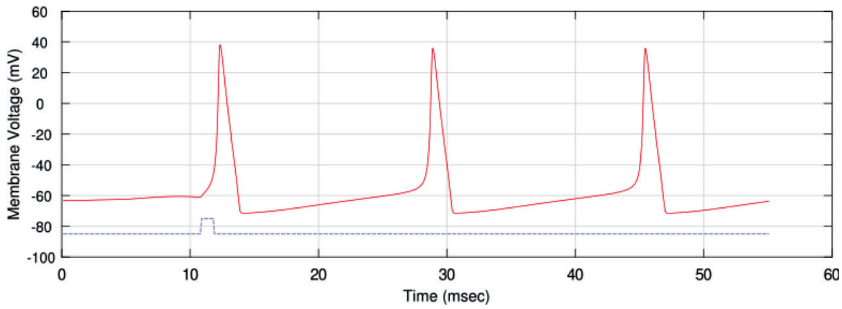

Fig. 4. HHsim graphical simulator. The continuous line represents action potential. The conductance of delayed rectifier K^+ channel is set to 32 µS. The dashed line represents stimulus size of 10 nA and duration of stimulus 1 ms.

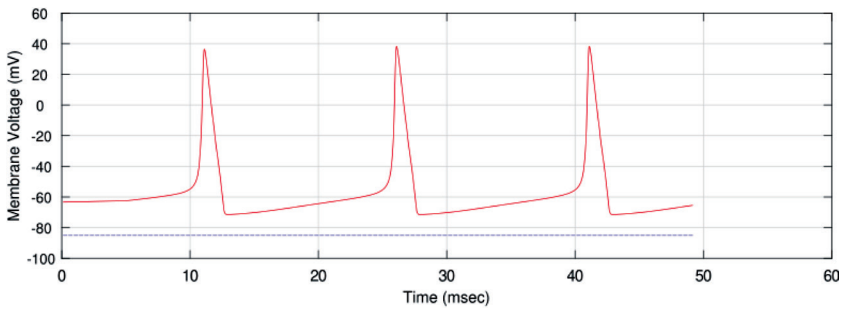

Fig. 5. HHsim graphical simulator. The continuous line represents action potential. The conductance of delayed rectifier K^+ channel is set to 30 µS and even no stimulus was injected, continuous spontaneous generation of spikes is observed.

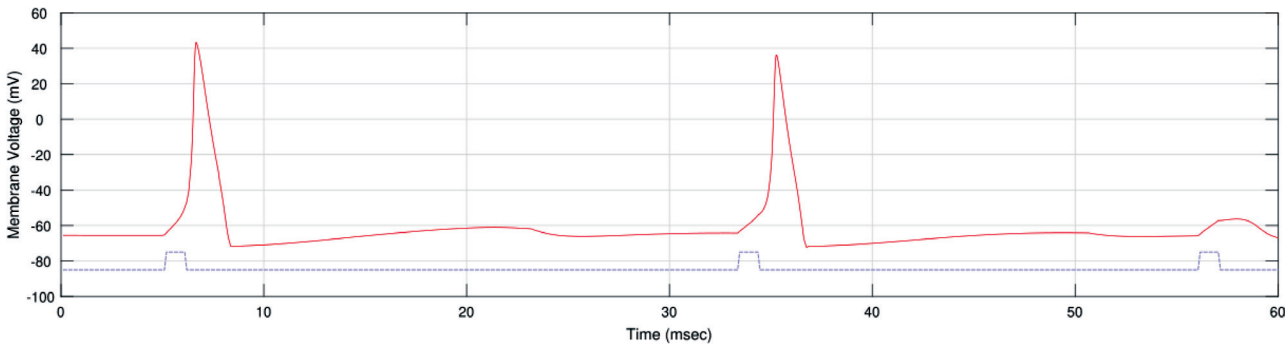

Fig. 6. HHsim graphical simulator. The continuous line represents action potential. The conductance of delayed rectifier K^+ channel was set gradually to three different values. The first conductance is 36 µS, the second 54 µS and the last 75 µS. The dashed line represents three equal stimuli each of size of 10 nA and the duration of one stimulus was 1 ms.

the repetitive firing process. They observed that increasing of Na^+ channel conductance without changing any other membrane parameter reduced the threshold current required to evoke repetitive firing. It means the neuron is more excitable (14). Similarly, Kispersky et al detected higher firing rates at higher conductance of Na^+ channel (15). Our result shows a slight increase of potential amplitude with upregulation of Na^+ conductance with external stimulus and continuous spontaneous generation of spikes without any additional external stimulus. The biophysical mechanism underlying the spontaneous generation of spikes is interaction of intrinsic currents depolarizing the cell membrane to threshold and current repolarizing the membrane to negative potentials and in turn the next spike can fire (16).

One of the K^+ channels' role is to decrease the membrane potential during the action potential. Channels are responsible for regulating neuronal excitability. When they open, the potassium ions flow out to extracellular space and reduce excitability. A dysfunction of K^+ channels can be associated with various diseases such as long-QT syndromes, episodic ataxia/myokymia, familial convulsions, hearing and vestibular diseases, Bartter's syndrome, familial persistent hyperinsulinemic hypoglycemia of infancy, cardiac hypertrophy and failure, apoptosis and oncogenesis, and other neurodegenerative and neuromuscular disorder (17). The downregulation of K^+ channels causes, that potassium ions leave the cell membrane slowly. The amplitude of action potential increases slowly after receiving the stimulus. We observed that decreased conductance of the delayed rectifier K^+ channel leads to continuous generation of spikes at a fixed firing rate after external stimulus. Firing rate without external stimulus increases from the value 62 Hz to 68 Hz. Womack et al. found in Purkinje neurons that block of calcium-activated potassium ion channels increased the irregular firing rate (18). Finally, we discuss the upregulation of the conductance of the K^+ channel without changing any other membrane parameter. As the potassium ions leave the neuron membrane faster after upregulation, the membrane potential should repolarize faster. That could lead to a decrease in the AP amplitude or even block the action potential. Ni et al. observed that enhanced A-type potassium conductance decreased neuronal excitability in pyramidal neurons (19). Gilly et al. experimentally observed that an increase in K^+ channels conductance by about 50% leads to higher firing rate and increased rate of repolarization. They propose that this effect can result from phosphorylation of squid K^+ channels (20).

Conclusion

Regardless of the fast progress in technologies, there are still many challenges in neuron modeling. The human body contains more than 86 billion neurons and each of the neurons can look differently and have different behavior. Creating a model that would reflect the real behavior would require extreme computation power. Results show that altered conductance of ion channels as a result of effect of magnetic field has significant consequences on neuron behavior. This effect is positive and can be used in therapy – transcranial magnetic stimulation or negative from the view of various disorders (21).

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