UDC 621.386:616-073.7(045)

O. M. Klyuchko,
D. Yu. Sheremet

COMPUTER MODELLING OF BIOLOGIC VOLTAGE–ACTIVATED NANOSTRUCTURES

Aeronavigation Institute, National Aviation University, Kyiv, Ukraine
E-mail: iesy@nau.edu.ua

Abstract*—The results of our program modeling of biological "voltage-activated nanostructures" are suggested. Simulation was done on the base of experimental results of electrical currents studying in natural brain neurons.*

Index Terms—Program model, brain, neuron, molecular currents, nanostructure.

I. INTRODUCTION

The results of ion channel investigations in neuronal membrane one can find today in numerical manuals [1], [2], [4], [5], [8]. Such channels provide one of the mechanisms for support membrane electrical properties. It results, for example, that cortical pyramidal cells have a resting membrane potential in the absence of synaptic input of approximately –75 mV, thalamic relay neurons are at approximately –65 mV to –55 mV at rest in the waking animal, and retinal photoreceptor cells have resting membrane potential of approximately –40 mV. Some types of neurons do not have a true "resting" membrane potential in that they are spontaneously active even during the lack of all synaptic input. Rapid signaling in nerve cells is accomplished by brief changes in the membrane potential. Traditionally, the most characteristic type of signal has been considered to be the action potential, or nerve impulse (also referred to as a "spike"). All these phenomena require the movement of significant numbers of ions across the membrane in a relatively short period of time. The rapid rate of ionic flow occurring during the generation of an action potential is far too high to be achieved via an active transport mechanism. Rather it results from the opening of ion channels [1], [2]. The powerful combination of electrophysiological and molecular techniques has yielded valuable insights into the structure-function relationships of ionic channels. In present work we tried to develop computer model of some electrically activated molecular membrane structures functioning with aim to use this model in education process of students who study biophysics and other relative disciplines.

II. TASK STATEMENT

Basing on the results of electrical properties of natural brain neurons and their molecular channels studying to develop program models for some molecular membrane structures functioning.

III. TRANSMEMBRANE IONIC CURRENTS IN BRAIN CELLS AS PHENOMENA

Voltage-sensitive ionic channels appear to have several shared features. First, they are large proteins that span the 6–8 nm of the plasma membrane and are typically made up of subunits. Second, through protein folding, they form a cylinder surrounding a central water-filled pore that permits the passage of only certain classes of ions between the inside and outside of the cell. The selection of which ions are allowed to pass through each different type of ionic channel is based upon the size, charge, and degree of hydration of the different ions involved. Finally, voltage-gated ion channels possess one or more gates, or voltage-sensing regions, within the ionic pore, and the flow of ions through the channels is regulated by these gates.

Neurons in the nervous system do not simply lie at rest and occasionally generate an action potential. Neuronal membranes are in a constant state of flux due to the presence of a remarkable variety of different ionic currents. These currents are distinguished not only by the ions that they conduct (e.g., K^+, Na^+, Ca^{2+}, Cl^-) but also by their time course, sensitivity to membrane potential, and sensitivity to neurotransmitters and other chemical agents [1], [2], [4], [5]. As the various ionic currents were discovered, they were divided into two general categories: those that are sensitive to changes in membrane potential and those that are altered by neurotransmitters and internal messengers. Most currents that are sensitive to membrane potential are turned on (activated) by depolarization. The rate at which they activate and the membrane potential at which they start to become active (threshold) are important characteristics. Many voltage-dependent currents do not remain on once they are activated, even during a constant shift in membrane potential. The process by which they turn off despite a stable level of membrane potential in their activation range is known as inactivation. Inactivation is a state of the current and ionic channels that is distinct from

simple channel closure. Once a current becomes inactive, this inactivation must be removed before it can again be activated. Removal of inactivation is generally achieved by repolarization of the membrane potential. Like the process of activation, inactivation and removal of inactivation are time and membrane potential dependent. Together, all of these characteristics define the temporal and voltage domain over which the current influences the electrical activity of the neuron.

IV. Mathematic model of electrical currents in excitable cells and their assembles

Some results of mathematic simulation of electric transmembrane currents were laid on the base of our model; let's observe some of such results [1], [2], [8]. The task of excitation spreading in myelinized fibers may be seen as a task with distributed parameters. If the maximum action potential significantly exceeds the threshold and if the rise front of potential is sufficiently narrow, i.e., the potential is growing very fast, it can be assumed that the excitation transfer occurs from one node of Ranvier to the nearby node and subsequent nodes have very little influence. It seems so, because the action potential is many times greater than the threshold, and the front rise of potential is 1.5–2 intervals between the nodes of Ranvier [1]. This case will be observed lower. The interval between the nodes is a distributed system and the potential change in it can be described by equation $\frac{d^2\varphi(\xi)}{d\xi^2} + vRC\frac{d\varphi(\xi)}{d\xi} - Ri(\xi) = 0,$ if current i is equal to zero and instead of R and C substitute resistance R_1 and capacitance C_1 per unit length of myelinized fiber parts. For simplicity in what follows we use dimensionless variables, namely, the coordinates are measured in intervals L, and the time t is in units of R_1C_1. Then the equation for the potential in intervals has much simpler look:

$$\frac{\partial\varphi}{\partial T} = \frac{\partial^2\varphi}{\partial X^2}, \quad T = \frac{t}{R_1C_1L^2}, \quad \mathrm{X}=\frac{x}{L}. \tag{1}$$

Suppose that at time $T = 0$ begins excitation of the node located at the point $X = 0$, and due to the mechanism of membrane potential changes in it according to law

$$\varphi(2,T) = \varphi_0(T). \tag{2}$$

Current generated by this node, charging capacity myelinized interval and capacity of the next node, located in $X = 1$. Assume that the charging node $X = 2$ almost did not occur until the time hopping excitation node $X = 1$. Therefore, as a boundary condition at $X = 2$ assume

$$\varphi(2,T) = 0. \tag{3}$$

Presence of lumped capacitance C_2 node of Ranvier at the point $X = 1$ reflects a simple condition

$$\frac{C_2}{C_1L}\frac{\partial\varphi(1,T)}{\partial T} = \frac{\partial\varphi(X,T)}{\partial X}I_{x=1+0} - \frac{\partial\varphi(X,T)}{\partial T}I_{x=1-0}. \tag{4}$$

As a starting point we take

$$\varphi(X,0) = 0. \tag{5}$$

This can be done due to significant difference between the threshold and action potentials; the presence of small initial charge on the fiber may not significantly affect the results.

The problem is solved under condition when time $0 < T < T_L$ where T_L is magnitudeless dimensionless time hopping from one node to another. The purpose of this task is to calculate that time, as the pulse velocity is inversely proportional to T_L.

Because of the lumped capacitance at the point $X = 1$ task should be divided into two parts: in the domain $0 < X < 1$, and in $1 < X < 2$.

Let's set designation

$$\varphi(1,T) = \psi(T). \tag{6}$$

This ratio can be regarded as a boundary condition for the two boundary value problems. Then, the solutions should be substituted into (4) and from it one can determine the unknown function $\psi(T)$.

$$\varphi(X,T) = 2\pi\sum_{n=1}^{\infty} n\sin(n\pi X)e^{-n^2\pi^2T} \times \int_0^T e^{n^2\pi^2\xi}\left[\varphi_0(\xi) - (-1)^n\varphi(\xi)\right]\xi. \tag{7}$$

In domain $1 < X < 2$ with boundary conditions (6) and (3) and the same initial condition we get

$$\varphi(X,T) = 2\pi\sum_{n=1}^{\infty} n\sin\left(n\pi(X-1)\right)e^{-n^2\pi^2T} \times \int_0^T e^{n^2\pi^2\xi}\varphi(\xi)\partial\xi. \tag{8}$$

For further calculations need to know the type of the function $\varphi_0(T)$, i.e. the change in the time of potential of working node. We approximate this dependence by a linear function

$$\varphi_0(T) = \frac{\varphi_2}{T_1}, \tag{9}$$

where φ_2 is maximum capacity; T_1 is rise time capacity. It is 1.5 – 2 times the time hopping T_L. For

the reasons stated above, the initial value of this function can be set equal to zero.

As follows from the experimental data from [1], [2] such a linear approximation is not far from the truth. Substituting of (7) – (9) into (4), we obtain the equation for unknown function $\psi(T)$. For its solution it is convenient to use the Laplace transform. Omitting the intermediate steps, we give the final expression for the Laplace transform

$$\hat{\psi}(p) = \frac{\frac{\varphi_2}{p^2 T_2}\sum_{n=-\infty}^{\infty}\frac{(-1)^n}{p+n^2\pi^2}}{\frac{C_2}{C_1 L}+2\sum_{n=-\infty}^{\infty}\frac{1}{p+n^2\pi^2}}. \qquad (10)$$

Function $\psi(T)$ has a pole of second order at point $p=0$, stipulated by the multiplier $1/p^2$, and a number of poles of the first order, determined by the roots of the equation

$$2\sum_{n=-\infty}^{\infty}\frac{1}{p+n^2\pi^2} = -\frac{C_2}{C_1 L}. \qquad (11)$$

This equation has real roots. The left side of this equation is shown in the graph (Fig. 1). Roots of the equation are defined as the point of intersection of these curves with the horizontal line drawn at the level – C_2/C_1L. As seen from Fig. 1, all the roots of (11) are negative and lay to the left of $n^2\pi^2$. We denote the found roots $p_0, p_1, p_2, ..., p_k, ...$

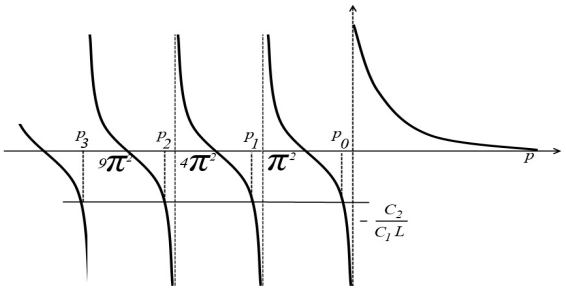

Fig. 1. The graph of the roots of equation (11)

From the known value T_L, defined by this equation, the v of the pulse can be calculated.

Because the true dimensional hopping time from one node to another is $R_1 C_1 L^2 T_L$, and the distance between nodes L, then velocity of the pulse is

$$v = \frac{1}{R_1 C_1 L T_L}. \qquad (12)$$

V. Modeling of voltage-activated nanostructure

All phenomena described above are provided by ion channels; electrical ionic currents flow there through molecules in neuronal membranes (nano structures). In present work we would like to demonstrate program model of functioning of such ion channels activity (voltage-activated nano-structure model). In some our previous publications we described few our program models – prototypes to the present one [3], [6], [7].

Numerical publications has been devoted to a detailed study of the laws of brain electrical activity [1], [2], others]. It was shown that electrical stimulation causes rapid relaxation of the surface of the cell membrane and reducing its capacity to an unsustainable level at which the excitation. The smallest current sufficient to cause this effect, called the excitation threshold. Neuronal membrane by itself behaves like a capacitor with leakage time constant is determined by its own resistance and capacitance. In order to boost short current could change the membrane potential; it must pass through a certain minimum amount of electricity (measured by the product of the current at the time). Important fact is that the membrane container is leaking and in need of some minimum current to cause the desired displacement of the transmembrane potential difference. On Fig. 2 the horizontal line "Steady" limits the activity of the neuronal membrane when no voltage applied: the membrane is in steady state.

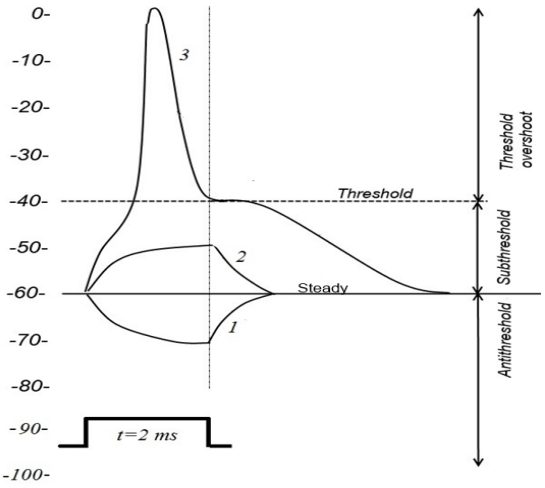

Fig. 2. Reaction of neuronal membrane on to the different shifts of transmembrane potential (spinal fiber, different limit settings)

Explanation of the program model functioning is given below. The classic representation of neuronal membrane reaction on to the different shifts of transmembrane potential is shown on Fig. 2. It is possible to see that overshoot of threshold causes the instability, appearance of quick inward current, and this electrical pulse (action potential) may carry a portion of information. Our program model demonstrates the development of such instability and action potential appearance. On each of following figures the different states of the system from Fig. 2 is shown (relative fragments of Fig. 2 are also present on figures below).

In comments to Fig. 3 it is necessary to mention that each condition of the neuronal membrane corresponds to zones “steady”, “antithreshold”, “subthreshold”, “threshold overshoot” and set by limits -100 ... -60 mV, -60 ... -40 mV, -40 ... 0 mV. With help of regulator, we set the amount of voltage applied to the brine, in order to choose in which zone we examine the membrane. Chart denoted as “1” describes the case, when we examine the membrane in zone -100 ... -60. For that case, we set the limit to -60 mV and apply testing pulse duration of which is 2 ns and magnitude of which is -10 mV. As the charge hits the membrane and E-CRCs, no current flows inside the neuronal membrane. Only charged particles near the membrane from neuron inside start to regroup (see Fig. 2). It is explained by the great resistance of E-CRCs across the membrane (6000 MOhm) and electromagnetic effect. This condition of neuronal membrane is called “Hyperpolarization”. Obtained results for this experiment, performed in zone -100...-60 are represented on Fig. 4.

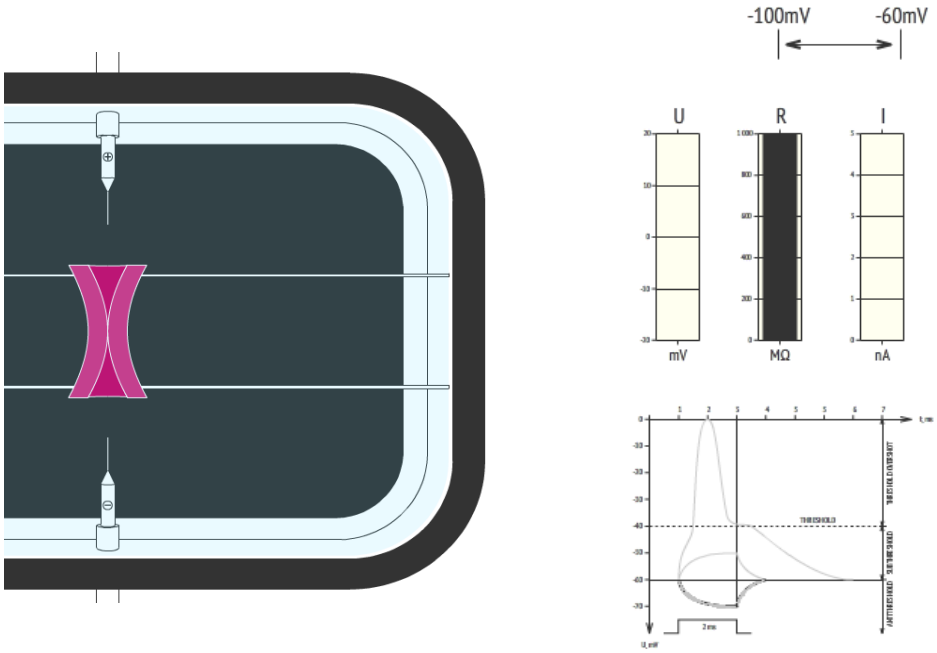

Fig. 3. The neuronal membrane is in the steady condition

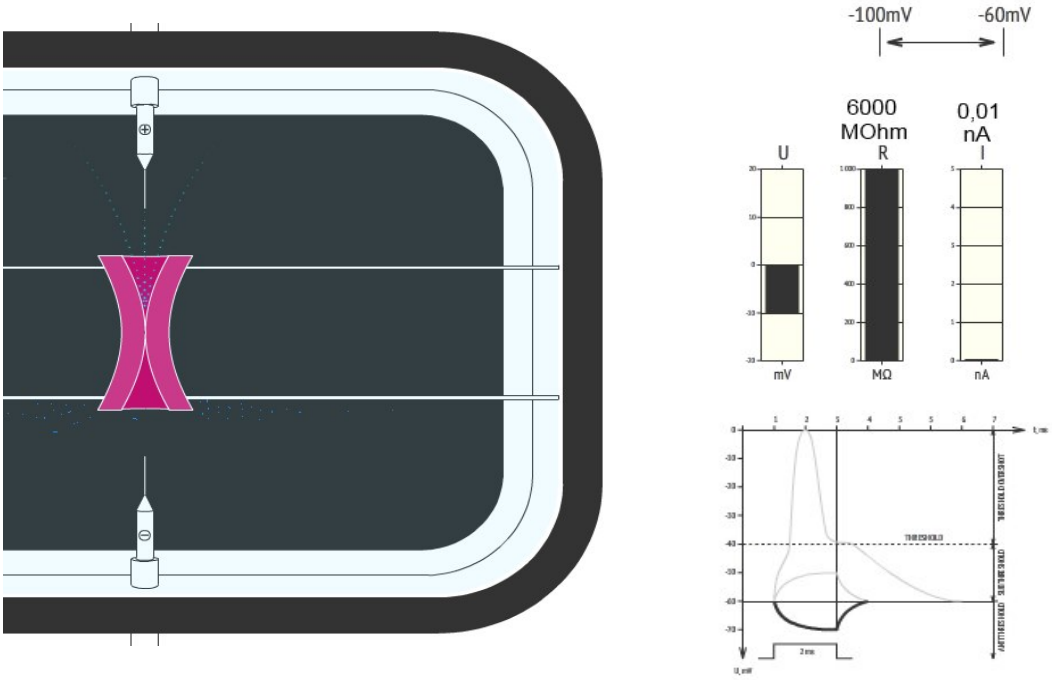

Fig. 4. Hyperpolarization V=-10 mV: R = 6000 MOhm, I = 0,01 nA

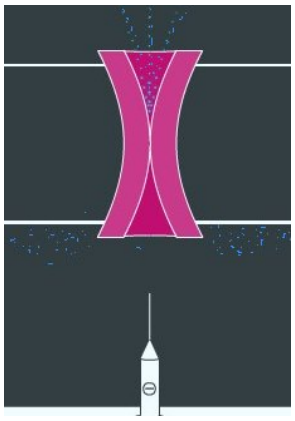

Fig. 5. Demonstration of electromagnetic effect inside the neuronal membrane during hyperpolarisation

At Fig. 5 are demonstrated charged particles (ions) that flow through a “channel” from the inner side of membrane being influenced by electromagnetic field.

The case, when the scientist examines the neuronal membrane in zone -60...-40 is described on Fig. 6. The limit is still set to -60 mV and testing pulse of 2 ns and magnitude of -10 mV is applied. Due to these conditions, permittivity grows, and ions pass the channel. The ions flow through the channel more intensive then in case on Fig. 4 (asymmetry for electrical currents). This condition of neuron (and respectively, its membrane) is called "Ready for excitation". At this interval the depolarization of neuronal membrane is registered. Obtained results for this experiment, performed in zone -60...-40 are represented on Fig. 6.

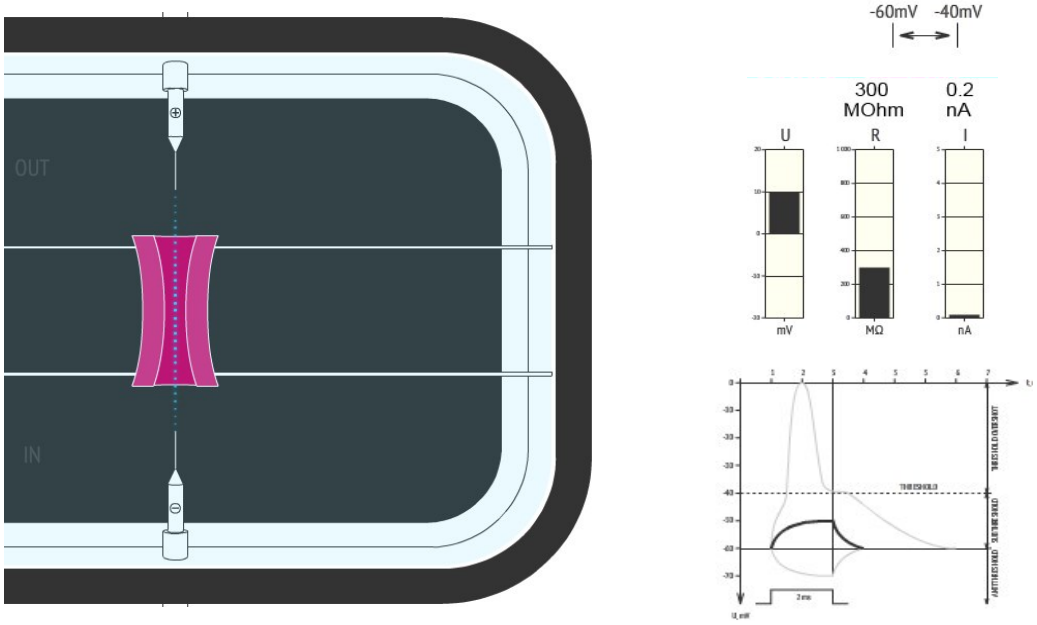

Fig. 6. Depolarization V = 10 mV: R = 300 Mohm; I = 0,2 nA

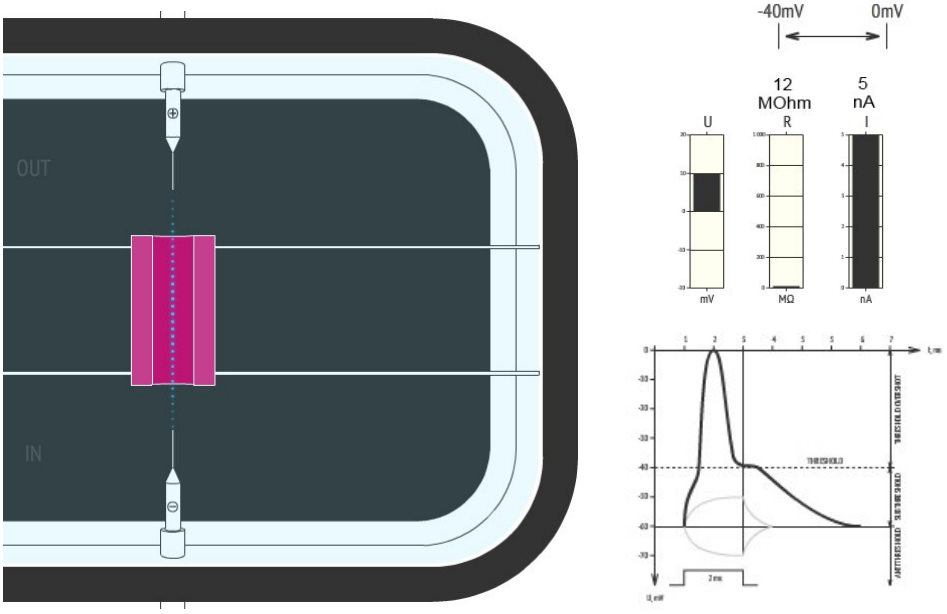

Fig. 7. Threshold is crossed – action potential appeared. V=10 mV: R=12 MOhm, I=5 nA

On Fig. 7 the case, when the scientist examine the membrane in zone -40 ... 0 is represented. The limit is set to -40 mV and testing pulse of 2 ns and magnitude of -10 mV is applied again. Due to these conditions, membrane resistance falls to the minimum, ion influx inside the neuron is a maximal one. This condition of neuron (and its membrane) is called "Threshold is crossed" or "Action potential". Obtained results of this experiment performed in zone -40 ... 0 are represented on Fig. 7.

VI. CONCLUSIONS

In present article the results of program modeling of biological "voltage-activated nano-structures" are presented. At the beginning of the article the brief description of examined phenomena is given. Further following results are represented.

1. Mathematic model of electric events as well as current pulses propagation in brain cell membranes are given.
2. Original program model of biological "voltage-activated nano-structures" functioning is described.
3. This model will be useful for the demonstration during university lections in "biophysics", "biotechnology" and other related courses.

REFERENCES

[1] Kostyuk, P. G.; Kryshtal, O. A. Mechanisms of nervous cell electrical excitability. Moscow. Nauka. 1981. 204 p. (in Russian).

[2] Sigworth, F.; Sackman, B.; Neher, E. Single channel registrations. Moscow. Mir. 1987. 448 p. (in Russian).

[3] Shutko, V. M.; Klyuchko, E. M. "Liquid crystal nanostructures in neurons and the development of screens for television systems on their base." *Vistnyk of Engineer Academy of Sciences*. 2012. no. 3–4. pp. 170–173. (in Ukrainian).

[4] Krishtal, O.; Kiskin, N.; Tsyndrenko, A.; Klyuchko, E. "Pharmacological properties of amino – acid receptors in isolated hippocampal neurons." *Walter de Gruyte*. Berlin (Germany), Receptors and ion channels. 1987. pp. 127–137.

[5] Akaike, N.; Kawai, N.; Kiskin, N. I.; Klyuchko, E. M.; etc. "Spider toxin blocks excitatory amino-acid responses in isolated hippocampal pyramidal neurons." *Neuroscience Letters*. 1987. vol. 79. pp. 127–137.

[6] Klyuchko, E. M.; Hairutdinov R. R. "Modeling of electrical signals transmission along the neuron and its nanostrucrures." *Electronics and control systems*. 2011. no. 2(28). pp. 120–124. (in Ukrainian).

[7] Klyuchko, E. M.; Pashkivsky, A. O.; Sheremet, D. U. "Computer modeling of some nanoelements for radiotechnic and television systems." *Electronics and control systems*. 2012. no. 3 (33). pp. 102–107. (in Ukrainian).

[8] Cherny, V. V., Chismadzhev, Yu. A. Membrana: ion channels. Edited Yu. A. Chismadzhev. Moscow. Mir. 1981. 320 p. (in Russian).

Received 13 March 2014

Klyuchko Olena. Ph.D. in Biological Sciences (biophysics). Docent.
Aeronavigation Institute, National Aviation University, Kyiv, Ukraine.
Education: National University named after Taras Shevchenko, Kyiv (1981), National Aviation University(2003), Kyiv, Ukraine.
Research area: biophysics, brain sciences, bioinformatics, ecology.
Publications: 126.
E-mail: iesy@nau.edu.ua

Sheremet Dmytro. Bachelor of Engineering Sciences.
Aeronavigation Institute, National Aviation University, Kyiv, Ukraine.
Education: National Aviation University, Kyiv, Ukraine (2013).
Research area: wireless technologies, nanotechnologies.
Publications: 1.
E-mail: iesy@nau.edu.ua

О. М. Ключко, Д. Ю. Шеремет. Програмне моделювання біологічних потенціал-активованих наноструктур

Наведено результати програмного моделювання біологічних потенціал-активованих наноструктур, яке було виконано на основі експериментальних результатів з дослідження електричних струмів у природних нейронах мозку.

Ключові слова: програмна модель; мозок; нейрон; молекулярні струми; наноструктура.

Ключко Олена Михайлівна. Кандидат біологічних наук. Доцент.
Інститут аеронавігації, Національний авіаційний університет, Київ, Україна.
Освіта: Національний університет ім. Тараса Шевченка, Київ (1981), Національний авіаційний університет (2003).
Напрям наукової діяльності: біофізика, науки про мозок, біоінформатика, екологія.
Кількість публікацій: 126.
E-mail: iesy@nau.edu.ua

Шеремет Дмитро Юрійович. Бакалавр.
Інститут аеронавігації, Національний авіаційний університет, Київ, Україна.
Освіта: Національний авіаційний університет, Київ, Україна(2013).
Напрям наукової діяльності: бездротові технології, нанотехнології.
Кількість публікацій: 1.
E-mail: iesy@nau.edu.ua

Е. М. Ключко, Д. Ю. Шеремет. Программное моделирование биологических потенциал-активированных наноструктур

Приведены результаты программного моделирования бологических потенциал-активируемых наноструктур, которое было выполнено нами на основе экспериментальных результатов по исследованию электрических токов в природных нейронах мозга.
Ключевые слова: программная модель; мозг; нейрон; молекулярные токи; наноструктура**.**

Ключко Елена Михайловна. Кандидат биологических наук. Доцент.
Институт аэронавигации, Национальный авиационный университет, Киев, Украина.
Образование: Национальный университет им. Тараса Шевченко, Киев(1981), Национальный авиационный университет(2003).
Направление научной деятельности: биофизика, науки о мозге, биоинформатика, экология.
Количество публикаций: 126.
E-mail: iesy@nau.edu.ua

Шеремет Дмитрий Юрьевич. Бакалавр.
Институт аэронавигации, Национальный авиационный университет, Киев, Украина.
Образование: Национальный авиационный университет, Киев, Украина(1969).
Направление научной деятельности: беспроводные технологии, нанотехнологии.
Количество публикаций: 1.
E-mail: iesy@nau.edu.ua