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Mathematical and computer simulation of the electrophysical properties of a multicellular structure exposed to nanosecond electrical pulses

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Abstract. The article presents mathematical and computer models which allow to study the electrophysical properties (permittivity, impedance) of a multicellular structure exposed to nanosecond electrical pulses. The paper proposes a simulation approach that includes complex use of the classical theory of describing the electrodynamic properties of dispersed systems and the effective medium theory. We describe cell geometry using Gielis equations, which allow us to take account of the irregular shapes of cell membranes. We carry out a computational experiment with cell models to study the frequency dependences of permittivity and impedance exposed to nanosecond electrical pulses. The article considers the influence of membrane porosity on cell conductivity and permittivity as well. We carry out computer simulation of the plasma membrane electroporation mechanism. The obtained results will help to understand better the fundamental processes in the cell membrane exposed to electrical pulses and can be used in various practical applications, such as targeted drug delivery, incorporation of DNA and RNA genes into bacterial and mammalian cells, as well as the selective destruction of cancer cells.

Keywords: mathematical simulation, cellular membrane, electroporation, impedance, permittivity

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Математическое и компьютерное моделирование электрофизических свойств многоклеточной структуры при воздействии наносекундных электрических импульсов

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Аннотация. В статье приводятся математические и компьютерные модели, позволяющие исследовать электрофизические свойства (диэлектрическую проницаемость, импеданс) многоклеточной структуры при воздействии наносекундных электрических импульсов. В работе предлагается подход моделирования, включающий в себя комплексное использование классической теории описания электродинамических свойств дисперсных систем и теории эффективной среды. Для описания геометрии клеток используются формулы Джилиса, которые позволяют учитывать неправильные формы клеточных мембран. Проведен вычислительный эксперимент с моделями клеток по исследованию частотных зависимостей диэлектрической проницаемости и импеданса при воздействии наносекундных электрических импульсов. Изучено влияние мембранной пористости на проводимость и диэлектрическую проницаемость клетки. Проведено компьютерное моделирование механизма электропорации плазматической мембраны. Полученные результаты будут полезны для более глубокого понимания фундаментальных процессов, происходящих в клеточной мембране при импульсном электрическом воздействии, и могут использоваться в различных практических приложениях, таких как адресная доставка лекарств, включения генов ДНК и РНК в бактериальные клетки и клетки млекопитающих, а также избирательном уничтожении раковых клеток.

Ключевые слова: математическое моделирование, клеточная мембрана, электропорация, импеданс, диэлектрическая проницаемость

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Introduction

Field experiments which are carried out to study the cell membrane electroporation mechanism are time-consuming, expensive and require high-precision calibration of the equipment, as well as careful preparation of the object of study [1]. The main task during the experiment is to obtain the most reliable data at minimum cost. We find dependencies between factors as a part of the study, construct an approximation of the response function of various orders, perform a sensitivity analysis and determine the probability of one kind or other event.

Analysis of scientific literature [2–5] shows that short rectangular pulses are used in the overwhelming number of studies. For instance, Maxwell's equation is used to calculate the transmembrane electric potential induced by an external electric field in a spherical cell. As a consequence of the electric shock, temporary pores are formed in the cell membrane, thus increasing its permittivity. Electroporation conditions change depending on the type of substance introduced into the cells. The electroporation method [6], awarded the Nobel Prize in Chemistry 2003, is a needle-free alternative to classical mesotherapy. Seriousness of the method is confirmed by its active use in the field of medicine. Nowadays electroporation is the only non-injection effective method of transporting an active substance to skin cells while maintaining the maximum possible concentration — more than 90% [7].

Mathematical and computer simulation is a powerful tool for theoretical research in biophysics [8]. Development of mathematical models opens up a wide range of possibilities for a multimethod research of electroporation mechanism. It happens because parameter structure of mathematical models physically corresponds to the objects of study. Computer simulation as a research method denotes the concept of an iterative paradigm of the computational experiment, since we define a mathematical model more precisely, improve the computational algorithm and, in some cases, revise computational process organization in the experiment.

Analysis of such models allows to predict the most favorable conditions for their subsequent experimental study. In addition, it also allows to acquire new fundamental knowledge about dynamics of the cell membrane exposed to electromagnetic pulses. It helps to apply practical knowledge to medicine, cosmetology and other fields of science and technology in the future. Mathematical and computer modeling to study the effect of electrical pulses on biological objects is a relevant field of research, which allows to obtain detailed information about the object of study as well as data for further full-scale experiment and prediction of experiment results.

In the study we use a complex approach to carry out mathematical simulation of the electrophysical properties of cell membranes exposed to nanosecond electrical pulses. The approach includes the classical theory of describing the electrodynamic properties of dispersed systems and the effective medium theory [9].

1. Mathematical simulation of the electrophysical properties of a cell

The object of study is a multicellular structure exposed to uniform pulses of an electric field and consisted of arbitrarily shaped cells (Fig. 1), each of which has a plasma membrane and an intracellular organelle.

Every cell is described by the following values: ε_c — complex permittivity of a cell; σ_c — conductivity of a cell; ε_p — complex permittivity of a cell membrane; σ_p — conductivity of a cell membrane, ε_{org} — conductivity of a cell organelle, ε_{por} — complex permittivity of an organelle membrane. The following parameters simulate cell geomet-

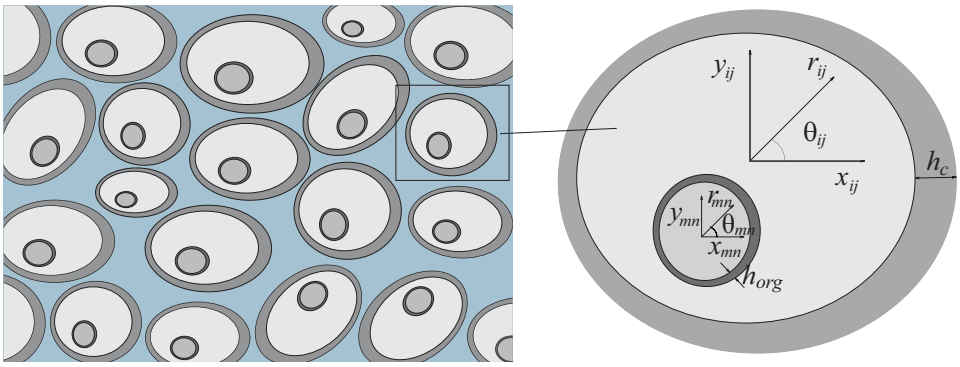

Fig. 1. Schematic image of a cell exposed to uniform pulses of an electric field

ry: $r_{i,j}$, $x_{i,j}$, $y_{i,j}$ — position vector and rectangular coordinates, which describe lateral view of a cell, $\theta_{i,j}$ — polar angle, which characterizes a local coordinate system of a membrane; $r_{m,n}$, $x_{m,n}$, $y_{m,n}$ — position vector and rectangular coordinates, which describe lateral view of an organelle, $\theta_{m,n}$ — polar angle, which characterizes a local coordinate system of an organelle, h_c — thickness of a plasma membrane, h_{org} — thickness of an organelle membrane.

We use Maxwell's equations in dispersed media to describe electrophysical properties of a multi-cell structure:

$$\nabla \times H = \varepsilon_0 \frac{\partial E}{\partial t} + \frac{\partial P}{\partial t} + \sigma E, \tag{1}$$

$$\nabla \times E = \mu_0 \frac{\partial H}{\partial t}. \tag{2}$$

The simulation approach is quite common and used in many studies, e. g. [10, 11]. The system of equations is rather difficult to solve for realistic multicellular structures. However, due to the small size of a cell, we can neglect the change in the magnetic field over time, hence $\nabla \times E = 0$. An electric field E can be derived from the scalar potential ϕ using the equation:

$$E = -\nabla\phi. \tag{3}$$

Substituting (3) for (1), we obtain the following partial differential equation:

$$\nabla \cdot \left(\varepsilon_0 \frac{\partial \nabla\phi}{\partial t} + \sigma\nabla\phi - \frac{\partial P}{\partial t}\right) = 0, \tag{4}$$

where σ is static ionic conductivity. The following boundary conditions are imposed to the mathematical model to satisfy the continuity equation $\nabla \times J = 0$:

$$\hat{n} \cdot (J|_{\Gamma^+} - J|_{\Gamma^-}) = 0, \tag{5}$$

where

$$J = \left(\sigma + \varepsilon_0 \frac{\partial}{\partial t}\right) E + \frac{\partial P}{\partial t}. \tag{6}$$

Γ^+ and Γ^- are outer and inner boundaries of cell membranes, respectively, $\hat{n}$ is normal vector, which is taken outside the membrane boundaries. The electric potential for each cell is calculated by root-finding algorithm (4). The transmembrane voltage $U_{i,j}$ is calculated as the difference between the electrical potential at the outer and inner boundaries ($\phi^-_{i,j}$ and $\phi^+_{i,j}$ respectively) of each cell membrane:

$$U_{i,j} = \phi^-_{i,j} - \phi^+_{i,j}. \tag{7}$$

We propose to use the effective medium theory to simulate complex permittivity of a multicellular structure. The study considers cells from 10 to 100 micrometers, frequency of the electromagnetic radiation wave is 3–30 GHz, the wavelength of the electromagnetic field is by an order of magnitude more than the cell size, so the simulation method is acceptable for use.

We can use the Rayleigh equation to describe complex permittivity of a multicellular structure [12]

$$\varepsilon_m = \varepsilon_c \left[1 + \frac{3V}{\frac{\varepsilon_h + 2\varepsilon_m}{\varepsilon_h - \varepsilon_m} V - 1.31 \frac{\varepsilon_h - \varepsilon_m}{\varepsilon_h + \frac{4}{3}\varepsilon_m^{3,33}} V} \right], \tag{8}$$

where ε_m is complex permittivity of a multicellular structure, ε_h is complex permittivity of the matrix, V is cell volume fraction in the medium. Permittivity of a cell is calculated by modifying the equations which were obtained in [13]:

$$\begin{gathered} \rho_1 \alpha \frac{\varepsilon_{org}\left(3\varepsilon_g + (\alpha-1)\left(\varepsilon_g + 2\varepsilon_{org}\right)\right) - \varepsilon_c\left(3\varepsilon_{org} + (\alpha-1)\left(\varepsilon_g + 2\varepsilon_{org}\right)\right)}{2\varepsilon_c\left((\alpha-1)\varepsilon_g + 2(\alpha+1)\varepsilon_{org}\right) + \varepsilon_{org}\left((\alpha+2)\varepsilon_g + 2(\alpha-1)\varepsilon_{org}\right)} + \\ + (1 - \rho_1\alpha)\varepsilon_h = 0, \\ \rho_2 \alpha \frac{\varepsilon_{org}\left(3\varepsilon_g + (\alpha-1)\left(\varepsilon_g + 2\varepsilon_{org}\right)\right) - \varepsilon_c\left(3\varepsilon_{org} + (\alpha-1)\left(\varepsilon_g + 2\varepsilon_{org}\right)\right)}{2\varepsilon_c\left((\alpha-1)\varepsilon_g + 2(\alpha+1)\varepsilon_{org}\right) + \varepsilon_{org}\left((\alpha+2)\varepsilon_g + 2(\alpha-1)\varepsilon_{org}\right)} + \\ + (1 - \rho_2\alpha)\frac{\varepsilon_g - \varepsilon_{org}}{\varepsilon_g + \varepsilon_{org}} = 0, \end{gathered} \tag{9}$$

where ε_g is permittivity of a cell nucleus, $\rho_1 = \frac{r_{i,j}^3}{(r_{i,j}+h_c)^3}$ is volume fraction of the plasma membrane to the total cell volume, $\rho_2 = \frac{r_{m,n}^3}{(r_{m,n}+h_{org})^3}$ is volume fraction of the organelle membrane to the total organelle volume, $\alpha = r_{i,j}^3 r_{m,n}^{-3}$.

Cell geometry is simulated by Gillis equations:

$$x_{i,j} = A_{i,j} R_{i,j}\left(\theta_{i,j}\right)\cos\theta_{i,j}, \tag{10}$$

$$y_{i,j} = B_{i,j} R_{i,j}\left(\theta_{i,j}\right)\sin\theta_{i,j}, \tag{11}$$

$$R_{i,j}\left(\theta_{i,j}\right) = \left(\left[\frac{\cos(\frac{m_{i,2j-1}\theta_{i,j}}{4})}{\alpha_{i,2j-1}} \right]^{n_{i,2j-1}} + \left[\frac{\sin(\frac{m_{i,2j}\theta_{i,j}}{4})}{\alpha_{i,2j}} \right]^{n_{i,2j}} \right)^{-\frac{1}{b_{i,j}}}, \tag{12}$$

where $i = 1, ..., p$ and $j = 1, ..., q$ and $M = pq$ is a total number of cells and membranes, $\theta_{i,j} \in [-\pi; \pi]$ is a polar angle, which characterizes a local coordinate system, $m_{i,2j-1}$, $m_{i,2j}$, $n_{i,2j-1}$, $n_{i,2j}$ and $b_{i,j} \in R^+$ (positive real numbers), $\alpha_{i,2j-1}$, $\alpha_{i,2j} \in R_0^+$ (strictly positive integers), $A_{i,j}$, $B_{i,j}$ are scale parameters, $R_{i,j}$ is a position vector of the corresponding cell profile.

2. Computer simulation of the electroporation mechanism

We develop a computer model and carry out the computational experiment to study the electroporation mechanism of a multicellular structure. We use an algorithm for interpreting a full-scale experiment with an “ex vivo” method. Figure 2 shows a capacitor discharge circuit for generation of an exponentially decaying electric field pulse of a multicellular structure simulated using NI Multisim software package.

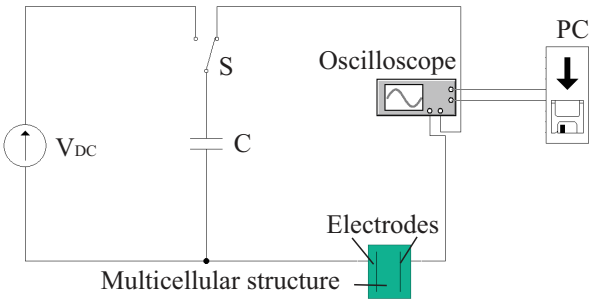

Fig. 2. Computer model of a capacitor discharge circuit for generation of an exponentially decaying electric field pulse to a multicellular structure

We use a multicellular structure with dimensions of 30x30x3 mm in the computational experiment. We use values in the range of 4–5 kOhm as the initial data of the impedance value of the object of study. The values are obtained as a result of a full-scale experiment in the research paper [14]. A computer model allows to study 160 samples, which are divided into 4 groups depending on the voltage applied to the object of study (230, 550, 750, and 1000 V for each group, respectively). If the electric properties change, the current which flows through a multicellular structure is calculated by the voltage change in the electrodes. We use a model of a 4-channel digital oscilloscope with the following characteristics: bandwidth (3.5 GHz), sampling frequency (10 GHz) in the computational experiment.

3. Results and discussions

Figure 3, *a* shows a dependency graph of voltage on the time of exposure to an electric field pulse for each sample group. The graph shows that voltage increases significantly in the range of 25–30 ns until it reaches its maximum value and then exponentially decreases. It means that the electrophysical properties of a multicellular structure can significantly change under the influence of electrical nanopulses. Figure 3, *b* shows dependence of the impedance of a multicellular structure on the volume fraction of cells in the medium.

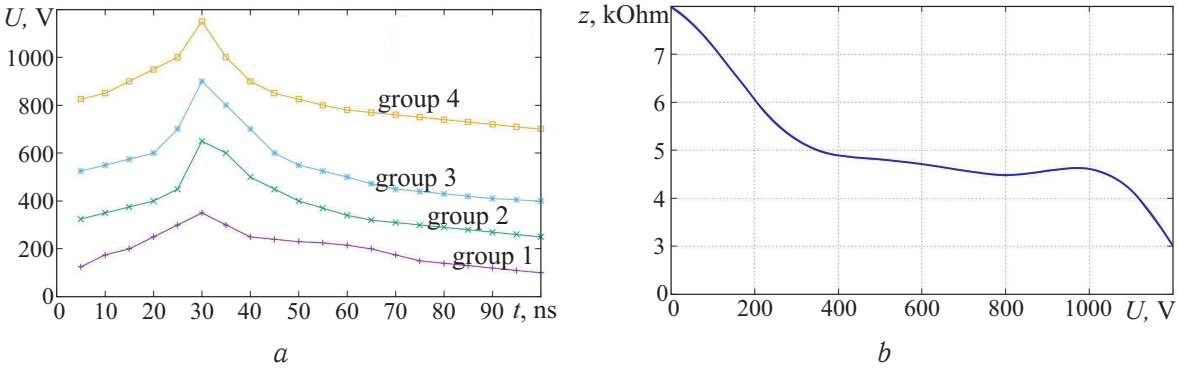

Fig. 3. Dependence of voltage on the time of exposure to an electric field pulse (*a*) and dependence of the impedance of a multicellular structure on the volume fraction of cells in the medium (*b*)

The computational experiment shows that impedance drops significantly near the peak of the electric field pulse and then changes insignificantly. High intensity of electrical pulses results in slower impedance recovery. Hence, time values of electrical pulses of 40–100 ns approximately have a greater effect on the cell membrane recovery.

Figure 4 shows dependence of permittivity of a multicellular structure on the wavelength of external factors. Simulation results show resonant bursts which can be connected to relaxation phenomena of the nuclear membrane and plasma membrane polarization.

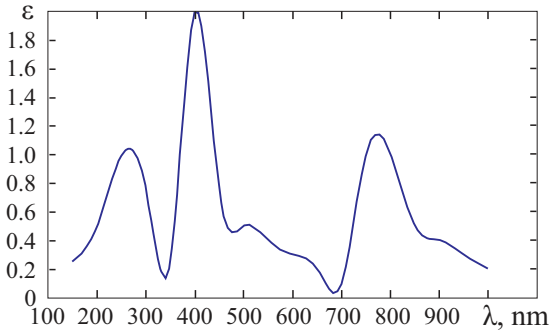

Fig. 4. Dependence of permittivity of a multicellular structure on the wavelength of external factors

Conclusion

The paper presents a simulation approach that includes complex use of the classical theory of describing the electrodynamic properties of dispersed systems and the effective medium theory. Gielis equations provide a wide range of possibilities for simulation of multicellular systems of various geometric configurations. As a result of the study, we find out that the electrophysical properties of a multicellular structure exposed to electrical nanopulses can significantly change. We study the dynamics of the electrophysical properties of a multicellular structure against the frequency of external force and the duration of the electric field pulses as well. We set time values of electrical impulses which have a greater effect on the cell membrane recovery. The obtained results will help to understand better the fundamental processes which occur in the cell membrane exposed to electrical pulses and can be used in various practical applications, such as targeted drug delivery, the incorporation of DNA and RNA genes into bacterial and mammalian cells, as well as the selective destruction of cancer cells.

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