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REPRESENTATION OF THE CARDIOMYOCYTES OF THE HEART MUSCLE IN THE FORM OF AN ELECTRICAL CIRCUIT ELEMENT

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Abstract**—***The article considers the simulation approach to describe the electrical functioning of the main heart muscle cell - cardiomyocyte, when instead of describing elements of different nature, whether electronic devices or biological objects, at the microphysical level of model ideas about the structure of matter, they are all considered from a single point of view in the sense that the nature of the application of these devices and objects is determined by the functions implemented at the available external inputs, while the degree of complexity of their internal structure has no significance for the operation of the system they belong to and whose operation is determined. A ferroelectric capacitor was chosen as a meaningful model for studying the mechanism of formation of electrical signals of the cardiomyocyte, because the mathematical description of its operation allows to model both nonlinearity and feedback of electrical processes occurring in the heart muscle. This model was mathematically formalized using the charge transfer equation in a nonlinear inertial system in the form of the balance equation, a delayed differential equation.*

Index Terms—Cardiomyocyte; algorithm; ferroelectric; modeling; differential equations.

I. INTRODUCTION

The sources of development of cardiac striated muscle tissue are symmetrical sections of the visceral leaf of the splanchnotome in the cervical part of the embryo – myoepicardial plates. During histogenesis, there are 5 types of cardiomyocytes – working (contractile), sinus (pacemaker), transient, conductive, and secretory.

Working cardiomyocytes form their chains. It is they who, by shortening, provide the force of contraction of the whole heart muscle. Working cardiomyocytes are able to transmit control signals to each other. Sinus – are able to automatically change the state of contraction to a state of relaxation in a certain rhythm. It is they who perceive control signals from nerve fibers, in response to which they change the rhythm of contractile activity. Sinus cardiomyocytes transmit control signals to transient cardiomyocytes, and the latter to conductive ones. Conducting cardiomyocytes form chains of cells connected by their ends. The first cell in the chain receives control signals from sinus cardiomyocytes and transmits them to other conducting cardiomyocytes. Cells that close the chain transmit a signal through transient cardiomyocytes to workers. Secretory cardiomyocytes perform a special function. They produce natriuretic factor (hormone), which is involved in the regulation of urination and in some other processes. All cardiomyocytes are covered with a basement membrane [1].

When a muscle fiber is stimulated by a chemical, electrical, or mechanical stimulus, the intracellular electrode registers an action potential (AP). It arises as a result of successive, rapidly alternating changes in the physicochemical properties of the cell membrane, which lead to a violation of its permeability to various ions and their transfer, which causes changes in membrane potential (the so-called Hodgkin–Huxley ionic hypothesis).

Action potential consists of two main phases: depolarization and repolarization (Fig. 1).

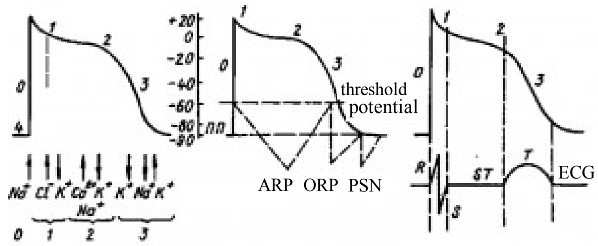

Fig. 1. Action potential of cells of contractile ventricular myocardium: 0 is the depolarization; 1, 2, 3 are phases of AP repolarization; PP is the rest potential; ARP is the absolute refractory period; ORP is the relative refractory period; PSN is a period of supernormality

II. PROBLEM STATEMENT

Let conside the current methods of modeling cardiomyocytes.

For example, the model of the heart, "as a continuous-pulse system combined with feedback control, perturbation and afterburner" [2], considers the myocardium at rest exhibiting viscoelastic properties. It can be represented by a 4-element rheological model. It is necessary to take into account the constantly shortened and constantly stretched sarcomeres, the variation of these ratios from contraction to contraction and their distribution in the anatomical structures of the heart. Also at reduction the myocardium develops the active tension depending on initial length of a muscle.

The heart is considered a 4-chamber reservoir. The relationship between the pressure in the cavity of each chamber of the heart with the voltage in the wall and the size of the cavity is determined by Laplace's law. Blood flow through the heart valves is determined by the pressure gradient, valve resistance and blood inertia, the structure of the outlet and inlet parts of the muscle cavities. The valve opens when the pressure on one side of the valve exceeds the pressure on the other side. Closing of the valve is caused by a return current (regurgitation) of some volume of blood.

The relationship of the above patterns, dependencies and phenomena are determined and subordinated to the self-regulation of muscle cavities: the heart as a whole monitors venous in-flow, providing blood flow corresponding to the tissue demand (metabolic demand), despite the disturbances.

Stress σ along the direction of the contractile threads: $\sigma = \sigma_e S_e + \sigma_c S_c$, where σ_c, σ_e are the stresses in the contractile threads and the elastic substance, respectively; S is the area of the considered area perpendicular to the direction of the contractile threads ($S = S_c + S_e$); S_c and S_e are parts of the area occupied by contractile threads and elastic material, respectively.

E_{PE}, k_{PE}, E_{SE}, are introduced – the parameters characterizing elastic properties of elastic substance and contractile threads. The stroke and final diastolic volumes (V_{st} and V_{fin}) of the ventricle are determined by the expression $V_{st} = k\cdot(V_{\text{fin}} - U_s)$, k is the pumping factor, which can be interpreted as the contractility factor, U_s is a parameter of linear approximation of the Starling dependence, V_{CE} is the volume of the cavity, which is due to the stretching of successive elastic elements.

The resistance of the valve will be determined by the logical relationship

$$\rho(\Delta) = \begin{cases} \rho^*, & \text{at } \Delta = 0, \\ \dfrac{2\rho^*}{1 + e^{-\beta\Delta}}, & \text{at } |\Delta| < \Delta^*, \\ 0, & \text{at } |\Delta| \geq \Delta^*. \end{cases}$$

Collectively, biophysical laws are subordinated to the system of self-regulation of the function of the left and right hearts separately, with the transfer function

$$K^{(n)}(z) = \frac{V_2^n(z)}{W^n(z)} = \frac{K(a_1 z - 1)z}{az^2 + (k - 1 - a_2)z - (k-1)a_2}$$

here neurohumoral influences are constant, frequency is close to norm (heart rate = 100 ± 20), venous pressure can vary from 5 to 15 mm Hg, the rate of change is less than 0.07 mm Hg. Between two heart contractions, the average blood pressure can vary from 40 to 150 mm Hg at a rate of 0.3 mm Hg for a blow [2]. Thus, the author concludes on modeling the structure of the heart self-regulation system.

Consider a "descriptive" approach to modeling, for example [3]. The starting point in the study, the authors take fibrillation – a condition in which cardiomyocytes contract inconsistently, asynchronously. As a result, the heart as a pump does not perform its function, there is oxygen starvation, which is especially dangerous for the brain – it lives in such conditions for only a few minutes.

Unexcited myocardial cells have a resting potential (–70 to –90 mV), which changes un-der the influence of various factors. It can become more negative, then the membrane is hyperpolarized, but it can also decrease when it is depolarized. The cations entering the cell (primarily Na^+ and Ca^{2+}) always depolarize the membrane, and the leaving ones (mainly K^+) hyperpolarize. The rapid shift of the resting potential in the positive direction is called the AP, which stimulates the heart cells to contract.

Direct dependence of cardiomyocyte contraction on its excitation (occurrence of AP), i.e. electromechanical coupling has already been studied in detail, but there were clinical data indicating the presence of feedback in the myocardium – changes in electrical processes under the influence of mechanical factors: myocardial distension and (or) changes in its contractile activity.

The total current flowing through the membrane of the cardiomyocyte also increases as the cell is stretched and disappears when its length returns to its original. The obtained results allow, according to the authors, to conclude that not only electrical excitation leads to contraction or relaxation of heart cells, i.e. to their mechanical change, but also on the contrary – to mechanical influence cardiomyocytes respond with electric activity. However, if the direct connection provides a normal heart rhythm, the reverse affects the opposite – a violation of rhythm.

Cardiomyocytes effectively convert mechanical stimulation into electrical responses, with the work of the first cells modulated by the second. In a healthy heart, the stretching of cardiomyocytes, which leads to depolarization of their membrane, and the stretching of fibroblasts, which causes hyperpolarization, are in equilibrium. At pathology reaction to such mechanical irritation is expressed especially strongly, but differently in those and other cells. If the amount of fibroblast hyperpolarization is greater than the depolarization of cardiomyocytes, the heart rate becomes less frequent and may even stop. Conversely, if the latter predominates, arrhythmia begins and fibrillation may develop.

Finally, consider the "computational" model. An example of such a model is the development of a computational technique designed to study blood circulation in the body [4] under the action of a periodically contracting heart. The authors draw attention to the mutual influence of various organs (primarily the kidneys) on the pressure in the circulatory system. The study of the influence of various factors associated with deviations from the norm of the functional characteristics of the vessel on the state of the system as a whole, as well as ways to compensate for vascular defects, such as shunting.

The circulatory system is formally described by a graph consisting of edges and vertices. The edges of the graph correspond to individual large vessels of the circulatory system or bundles of functionally homogeneous small vessels. The tops of the graph are attributed to the functional properties of either the branches of blood vessels, or muscle tissue, or individual organs of a living organism. The description of the movement of blood in the circulatory system is based on the laws of conservation of mass and momentum (amount of movement). Vessels are considered to be quite elongated in comparison with their transverse dimensions (diameter), which al-lows the quasi-one-dimensional approximation to be used for their mathematical description.

The length of the arc (axis of the vessel) passing through the centers of the circular sections of the vessel is chosen as the spatial coordinate x. The cross-sectional area $S(x, t)$ depends on the x-coordinate and time t. The speed of blood flow is considered to be directed along the axis of the vessel and is denoted by $U(x, t)$. Blood pressure – $p(x, t)$. Blood density ρ is considered constant (incompressible fluid). The law of conservation of momentum (amount of motion) leads to a differential equation

$$\frac{\partial uS}{\partial t}+\frac{\partial}{\partial x}(u^2S)+\frac{S}{\rho}\frac{\partial p}{\partial x}=SF_{\mathrm{g}}+SF_{\mathrm{fr}}. \qquad (1)$$

Here F_{g} is the gravitational force density, which in the simplest case is equal to $F_{\mathrm{g}} = g\cdot\cos\varphi$, where φ is the angle between the axis of the vessel and the direction of the acceleration vector of free fall, the magnitude of which is equal to g. The force F_{fr} is the force of viscous friction against the vessel wall [5].

After the transformations, equation (1) is reduced to the form

$$\frac{\partial u}{\partial t}+\frac{\partial}{\partial x}\left(\frac{u^2}{2}\right)+\frac{1}{\rho}\frac{\partial p}{\partial x}=F_{\mathrm{g}}+F_{\mathrm{fr}}.$$

The elastic-mechanical properties of vessels are taken into account in the approximation of the simplest model of an isotropic thin shell. Next, we consider inhomogeneous equations of hemodynamics for one vessel of the species

$$\begin{aligned}&\frac{\partial s}{\partial t}+\frac{\partial us}{\partial x}=0,\\&\frac{\partial u}{\partial t}+\frac{\partial}{\partial x}\left(\frac{u^2}{2}+\frac{p}{\rho}\right)=\frac{1}{\rho}q_{\mathrm{f}},\\&s=s(p),\end{aligned}$$

here $g_{\mathrm{f}}(x, t)$ is the bulk density of the external force. Given that

$$\frac{\partial s}{\partial t}=\Theta(p)\frac{\partial p}{\partial t},\quad \frac{\partial s}{\partial x}=\Theta(p)\frac{\partial p}{\partial x},\quad \Theta(p)=\frac{ds(p)}{dp}$$

get the characteristic form of recording the system of equations of hemodynamics:

$$\pm\frac{1}{\rho c(p)}\left(\frac{\partial p}{\partial t}+\lambda^{\pm}\frac{\partial p}{\partial x}\right)+\frac{\partial u}{\partial t}+\lambda^{\pm}\frac{\partial u}{\partial x}=\frac{1}{\rho}q_f.$$

As a result of modeling, the authors of [6] obtained dependences that represent graphs of the flow function $q(t)$ in the arteries of the left and right arm and right leg during two cardiac periods.

III. Experiment Description

It is easy to see that the mathematical model of the circulatory system on the graph of elastic vessels is very sensitive to the setting of the initial data and the values of the parameters of vessels and conjugation nodes. In particular, the poor choice of parameters of nodes and vessels can lead to the phenomena of non-physical resonance in vessels, the effects of "locking" in nodes, etc.

Instead of describing elements of different nature, whether electronic devices or biological objects, at the microphysical level of model ideas about the structure of matter, in engineering practice it is more appropriate to use another approach based on the fact that the variety of phenomena and properties on which the simulated systems, all of them are considered from a single point of view in the sense that the nature of the application of these devices and objects is determined by the functions implemented at the available external inputs, although the degree of complexity of their internal structure does not matter for the system and the work of which is determined.

The theory of electric circuits is based on this approach, the methods of which can be used to model the most complex physical and physiological structures, without specifying their internal structure. Consider the equation of state – the functional relationship between the parameters of the state, corresponding, in the general case, to a given kind of interaction of the system with the environment. One of the parameters is the cause of the processes in the system under study, the other is its response to the impact of this kind.

To describe the functional relationship between the state parameters, a one-dimensional model [7] – [9] is used in the form of a special form of writing the balance equation with respect to some state coordinate Q.

$$\frac{dQ(t)}{dt}+\frac{1}{\tau_r(Q)}Q\left(t-\tau_0\right)=\sum_{k=1}^{n}x_k(Q)F_k(t). \qquad (2)$$

The values in formula (2) have the following meaning. If we denote any of the extensive properties of the system at time t and the point r of the elementary physical volume dr by $G(t, r)$, then the variable $Q=\int_V G(t,r)dr$ can be called the number of properties in the volume V. In this case, Q means a macroscopic value averaged over the system of corresponding particle characteristics.

The value that determines the external source is expressed in terms of the input effect $F_k(t)$. The input characteristic of the system is x_k. The value of τ_r – called the relaxation time – reflects the relationship between the conservative and dissipative components of the system, thus determining its dynamic inertia.

Model (2) is an equation with a deviating argument τ_0, thus reflecting the motion Q in space with a finite velocity, that is, describing the process with aftereffect.

Equations of this kind are used when in the problem under consideration the state of the system depends not only on the factors affecting it at the present time, but also on the state of the system at some point in time preceding the one under consideration.

In what follows, we will consider as an electric resonator such an element of the electric circuit as a ferroelectric capacitor, which is caused by nonlinear characteristics similar to the objects we are considering in this paper. In itself, "in pure form", the model of the ferroelectric capacitor has, basically, theoretical value as, in itself elements are applied extremely seldom. Since any electronic component is only one of a large number of components of the device, which it is included along with other components, and the physiological object interacts with many surrounding objects.

Consider the case of inclusion of a ferroelectric capacitor in the simplest electrical circuit, designed primarily to remove its characteristics.

The scheme of such a circuit is shown in Fig. 2.

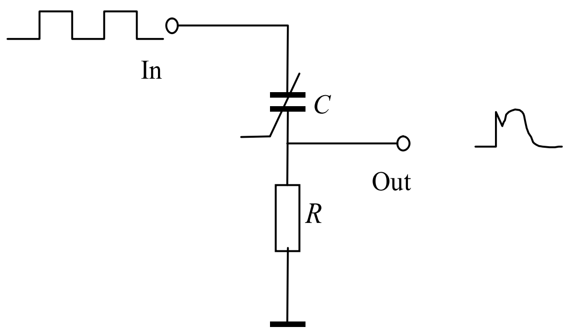

Fig. 2. Investigated scheme

Taking into account the resistance of the circuit connected in series with the capacitor, the model equation is transformed into the form:

$$\begin{cases} U_c(t)=U(t)-R\dfrac{dq}{dt}, \\ \dfrac{dq(t)}{dt}+\dfrac{1}{\tau_r(q)}q(t)=\sigma(q)u(t). \end{cases}$$

The study of forced oscillations in such a circuit allows us to obtain AP graphs of the form shown in Fig. 3, which allow us to obtain an acceptable description of electrical processes under different initial conditions of the model.

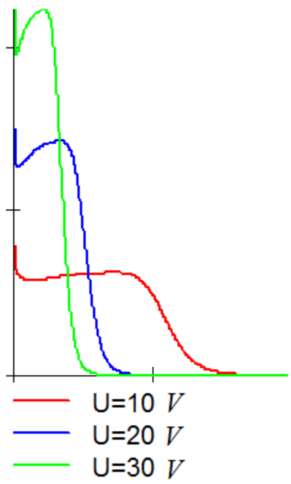

Fig. 3. Action potential for different case

IV. CONCLUSIONS

The proposed modeling principle will allow henceforward, by changing various initial parameters of the model equation, to simulate certain features of the behavior of the cardiomyocyte, depending on the various conditions of its physiological functioning. Carrying out full-scale experiments will allow us to correlate the input values with the obtained solutions of the model equation using the same approach that was developed and proposed in the article for the input electric action in the form of a rectangular pulse.

This approach will allow moving from "in vivo" experiments to "in vitro" experiments and improve understanding of the work of the heart muscle.

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Д. Є. Мельніков. Представлення кардіоміоцитів м'яза серця у вигляді елемента електричного кола
У статті розглянуто підхід імітаційного моделювання для опису електричного функціонування основних клітин серцевого м'яза – кардіоміоцита, коли замість опису елементів різної природи, будь-то електронних пристроїв, або же біологічних об'єктів, на мікрофізичному рівні модельних уявлень про побудову речовини, всі вони розглядаються з єдиної точки зору у тому сенсі, що характер застосування даних пристроїв та об'єктів визначає реалізацію на доступних зовнішніх входах функцій, при тому, що ступінь складності їх внутрішньої структуру не має жодного значення для робочої системи, у яких вони входять, і роботу, якої визначають. У якості змістовної моделі для дослідження механізму формування електричних сигналів кардіоміоцитів вибраний сегнетоелектричний конденсатор, що завдяки математичному опису його функціонування дозволяє моделювати як нелінійність, так і зворотній зв'язок електричних процесів, що відбуваються у серцевому м'язі. Ця модель була математично формалізована за допомогою рівнянь переносу заряду в нелінійній інерційній системі у формі рівняння балансу – диференціального рівняння із затримкою. Застосування такого підходу для моделювання електричних процесів у досліджуваному елементі дозволить у подальшому змоделювати потенціал дії в залежності від патології серця, за допомогою змін початкових умов рівнянь моделі.
Ключові слова: кардіоміоцити; алгоритм; сегнетоелектрик; моделювання; диференційні рівняння.

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Д. Є. Мельников. Представление кардиомиоцитов мышцы сердца в виде элемента электрической цепи
В статье рассмотрен подход имитационного моделирования для описания электрического функционирования основной клетки сердечной мышцы - кардиомиоцита, когда вместо описания элементов различной природы, будь то электронных устройств, или же биологических объектов, на микрофизических уровне модельных представлений о строении вещества, все они рассматриваются с единой точки зрения в том смысле, что характер применения данных устройств и объектов определяется реализующимися на доступных внешних входах функциями, при том, что степень сложности их внутренней структуры не имеет никакого значения для работы системы, в которую они входят, и работу которой определяют. В качестве содержательной модели для исследования механизма формирования электрических сигналов кардиомиоцита выбран сегнетоэлектрический конденсатор, поскольку математическое описание его функционирования позволяет моделировать как нелинейность, так и обратную связь электрических процессов, протекающих в сердечной мышце. Эта модель была математически формализована с помощью уравнения переноса заряда в нелинейной инерционной системе в форме уравнения баланса - дифференциального уравнения с запаздыванием. Применение данного подхода для моделирования электрических процессов в исследуемом элементе позволит в дальнейшем смоделировать потенциал действия в зависимости от патологии сердца, при помощи изменения начальных условий уравнения модели.
Ключевые слова: кардиомиоциты; алгоритм; сегнетоэлектрик; моделирование; дифференциальные уравнения.

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