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NONLINEAR MODEL
OF CALCIUM EXCITATIONS IN BIOMEMBRANES

A model is proposed to describe the calcium redistribution in biological substances. The model takes into consideration that calcium can be located inside or outside a cell. Calcium is redistributed due to its transport from the cell volume into the outer space and backward. The model makes allowance for the calcium diffusion into the outer space. It is shown that there are two modes of functioning of the system. In one of them, the initial perturbation of the calcium concentration in the extracellular space monotonically vanishes in time. In the other mode, this perturbation first grows, but afterward decreases to the zero value. The calcium concentration in the intracellular space is shown to be a critical parameter that governs the system operation mode.

K e y w o r d s: calcium, spark, biomembrane, diffusion.

1. Introduction

Even the simplest biological systems are difficult to be researched. Accordingly, their modeling, as well as the modeling of processes in them, requires a lot of efforts. As a rule, the progress can be achieved if the most common properties and relations are distinguished. This is a heuristic task that requires a thorough understanding of the functioning laws and principles of biological objects. In particular, when studying various systems involving biomembranes, it is often necessary to deal with calcium fluxes [1–3]. Calcium plays a significant role in many physiological processes, and it is a regulator responsible for important functions of complex organisms. A good example is the redistribution process of calcium ions in the extracellular space, when the cardiac muscle cells contract (see, e.g., work [4] and references therein). Let us consider the main stages of this process at the general level.

Cardiomyocyte, the cardiac muscle cell, is known to contain a reticulum that is a container, or a reservoir, to store calcium ions. This is calcium that is located in the intracellular space. It can transit into the outer space and return back. Such a transition takes place by means of special calcium channels, which are activated in the presence of an action potential. The peculiarity of the situation consists in that the re-

lease of calcium ions from the intracellular space into the extracellular one creates an additional potential, which stimulates the functioning of calcium channels, so that additional calcium is released. Hence, in this case, there exists a positive feedback. We should also take into account that the considered process is non-local owing to the calcium diffusion in the outer space [4–9].

Sparks, spontaneous events of calcium release into the extracellular space, are elementary signaling events. It is well known that sparks can form clusters or generate calcium waves [4, 10]. However, experimental data and theoretical calculations give grounds to assert that the appearance of calcium waves cannot be explained by a sporadic release of calcium into the extracellular space (see, e.g., work [4] and references therein). Although there is a significant body of various studies that explain or describe the mechanisms of calcium ion redistribution in the intra- and extracellular spaces, the task of creating a simple model at the qualitative level, which would explain the enhancement of initial calcium pertirbations in the extracellular space, remains challenging. The present work is devoted to the solution to this problem.

2. Researched System

While constructing a mathematical model, we maximally simplified the situation without losing the key issues. Our main assumptions were as follows:

• Calcium (calcium ions) can be in either of two states. First, calcium is accumulated in special vesicles (couplons) in the cells (in the intracellular space). Second, calcium can exist in the free state in the extracellular space.

• Calcium can transit from the intracellular space into the extracellular one and backward.

• The presence of calcium in the extracellular space stimulates a more intensive calcium release from the intracellular space.

• A positive feedback arises: the process of calcium release from the intracellular space into the extracellular one enhances itself. However, since the amount of calcium in the intracellular space decreases, this process is finite in time.

Below, we propose a simple mathematical model that allows the process of calcium redistribution in the intra- and extracellular spaces to be analyzed. In particular, let us consider a plane that separates the intra- and extracellular spaces. We are interested in the calcium distribution on the both sides of the plane, i.e. in the intra- and extracellular spaces. The whole system is considered as one-dimensional, i.e. the spatial dependence of the calcium concentration can vary along the axis x oriented normally to the plane. In other spatial directions, the calcium concentration is constant. On the one hand, this assumption substantially simplifies the analysis; on the other hand, it does not seem to be too unrealistic.

Let $u(t, x)$ and $v(t, x)$ be the calcium concentrations in the extra- and intracellular spaces, respectively. We consider the both concentrations as functions of the time t and the spatial coordinate x. The dynamics of the calcium concentrations in the extra- and intracellular spaces in the general case can be described by the following system of partial differential equations:

$$\frac{\partial u}{\partial t} = D_u \Delta u + k_1 uv - k_2 u, \tag{1}$$

$$\frac{\partial v}{\partial t} = D_v \Delta v - k_1 uv + k_2 u. \tag{2}$$

Here, Δ is the Laplace operator, D_u and D_v are the diffusion coefficients in the extra- and intracellular spaces, respectively, and k_1 and k_2 are phenomenological parameters of the model. In Eqs. (1) and (2), the first terms describe the diffusion processes (the calcium motion along the x-axis). The term $k_1 uv$ describes the calcium flux from the intracellular space

into the extracellular one. Here, we took into account that the intensity of this flux, on the one hand, should depend on the calcium concentration in the intracellular space (the source of calcium). On the other hand, the intensity of the calcium release into the extracellular space increases with the concentration of already released calcium. The term $k_2 u$ describes the calcium flux from the extracellular space to the intracellular one. We assume that this flux is proportional to the calcium concentration in the extracellular space.

For the further analysis, let us make our equations dimensionless. The following changes are made: $u \rightarrow u_0 u$, $v \rightarrow v_0 v$, $t \rightarrow t_0 t$, and $x \rightarrow Lx$, where L is a typical system size, $u_0 = v_0 = k_2/k_1$, and $t_0 = 1/k_2$. We also consulted the available experimental data, which testify that the calcium mobility in the intracellular space is substantially restricted, and put $D_v = 0$. Then we obtained the following system of equations that determines the calcium dynamics (its redistribution between the extra- and intracellular spaces):

$$\frac{\partial u}{\partial t} = a^2 \frac{\partial^2 u}{\partial x^2} + uv - u, \tag{3}$$

$$\frac{\partial v}{\partial t} = u - uv, \tag{4}$$

where the parameter $a^2 = \frac{D_u}{k_2 L^2}$ was introduced. These equations can be reduced to a single integro-differential equation,

$$\frac{\partial u}{\partial t} = a^2 \frac{\partial^2 u}{\partial x^2} + \varepsilon u \exp\left(-\int\limits_0^t u(\tau)d\tau\right), \tag{5}$$

in which the function $\varepsilon(x)$ is related to the initial calcium distribution in the intracellular space: $\varepsilon(x) = v(t = 0, x) - 1$. To solve Eq. (5), we also have to know the initial calcium distribution in the extracellular space $u(t = 0, x) = \varphi(x)$ and the boundary conditions for the function $u(t, x)$ at $x = 0$ and $x = 1$. We assume that calcium cannot transit into the extracellular space across the system boundary and put the corresponding conditions to be zero:

$$u(t, x = 0) = u(t, x = 1) = 0. \tag{6}$$

We also assume that the function ε does not depend on the spatial coordinate x, being a constant. However, it is clear that, even in this simplified formulation, the problem is not trivial and has to

be solved numerically. However, let us first consider some partial cases.

3. Analysis of Limiting Cases

One of the simplest cases is realized if there is no calcium diffusion in the extracellular space. In this case, we have to put $a = 0$. Then we obtain an ordinary differential equation that governs the dynamics of the calcium concentration in the extracellular space:

$$\frac{du}{dt} = u(t)(C - 1 - u(t)), \tag{7}$$

where C is the time-independent total calcium concentration for the intra- and extracellular spaces,

$$u(t) + v(t) = C. \tag{8}$$

The stable stationary solution looks like

$$u(t) \equiv C - 1, \tag{9}$$
$$v(t) \equiv 1 \tag{10}$$

in the case $C > 1$ and

$$u(t) \equiv 0, \tag{11}$$
$$v(t) \equiv C \tag{12}$$

in the case $C < 1$. It was rather easy to obtain precise analytical solutions for the dependences $u(t)$ and $v(t)$, but they are trivial and invoke no particular interest. The main conclusion that can be drawn on their basis and by analyzing the stability of stationary solutions is as follows: if the calcium concentration in the extracellular space at the initial time moment differs from the stationary value, then, in time, calcium becomes so redistributed that a stable stationary solution is realized. For the function $u(t)$, which describes the calcium concentration in the extracellular space, the stationary solution equals zero under the condition $C < 1$ and differs from zero if $C > 1$. Hence, there is a critical value for the total calcium concentration: if the actual amount of calcium is less than this value, there is no calcium in the extracellular space. In a sense, this result is important, but as will be shown below, the calcium diffusion in the extracellular space makes the situation even more interesting.

At the next stage, let us take into account the diffusion of calcium in the extracellular space. We also assume that the parameter $\varepsilon > 0$ does not depend on

the spatial coordinate. Another assumption consists in that the solution $u(t, x)$ is small. This assumption does not seem to be false, because, in the case of zero initial condition for the function $u(t, x)$ and taking into account Eq. (5) and boundary conditions (6), we obtain the solution $u(t, x) = 0$. It is reasonable to assume that, if the initial calcium distribution in the extracellular space is negligibly small, then there is an opportunity for this concentration to remain small. If so, by substituting the exponential function in expression (5) by unity, $\exp\left[-\int_0^t u(\tau)d\tau\right] \approx 1$, we obtain the following equation:

$$\frac{\partial u}{\partial t} = a^2 \frac{\partial^2 u}{\partial x^2} + \varepsilon u. \tag{13}$$

It has the analytical solution in the form of an infinite series

$$u(t, x) = \sum_{n=1}^{\infty} U_n \exp(-\lambda_n t) \sin(\pi n x), \tag{14}$$

where the expansion coefficients U_n are determined from the initial condition $u(t = 0, x) = \varphi(x)$ by the formula

$$U_n = 2 \int_0^1 \varphi(x) \sin(\pi n x) dx, \tag{15}$$

and the parameters

$$\lambda_n = (\pi n a)^2 - \varepsilon. \tag{16}$$

It is easy to understand that if

$$\varepsilon > (\pi a)^2, \tag{17}$$

solution (14) contains terms that grow exponentially in time. This means that the initial assumption that the calcium concentration in the extracellular space remains negligibly low is invalid. Hence, we may assert that there is a critical value for the parameter $\varepsilon = (\pi a)^2$. If it is exceeded, the initial small deviations of the calcium concentration from the equilibrium value in the extracellular space will grow. In this case, no infinite increase of the calcium concentration in the extracellular space will take place, because, according to relation (5), the growth of $u(t, x)$ will increase the value of integral in the exponential function, so that the term that stimulates the growth of
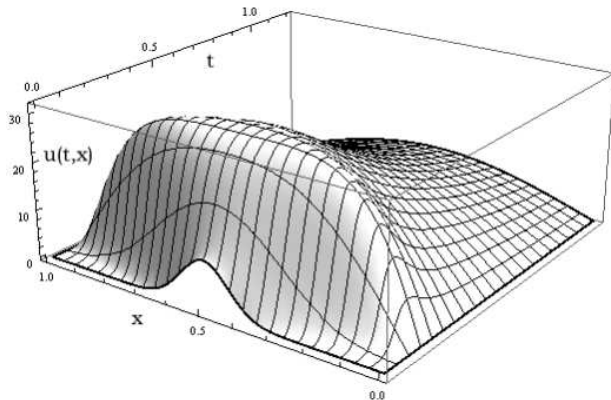
Fig. 1. Dependence $u(t,x)$ for the parameters $a = 0.4$, $\alpha = 100$, $A = 10$, and $\varepsilon = 33.6$
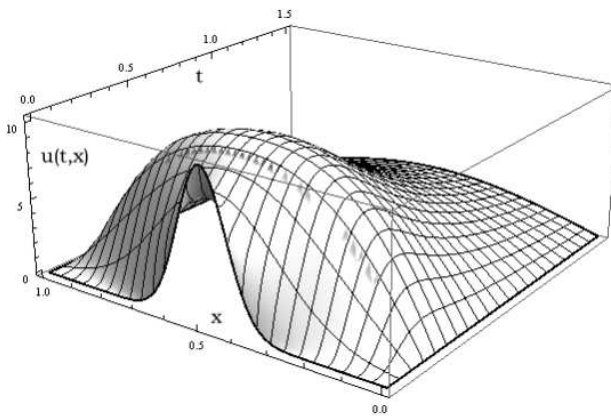

Fig. 2. Dependence $u(t,x)$ for the parameters $a = 0.4$, $\alpha = 100$, $A = 10$, and $\varepsilon = 11.2$
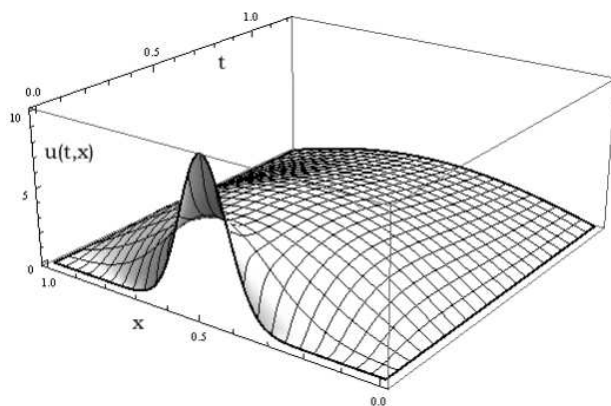

Fig. 3. Dependence $u(t,x)$ for the parameters $a = 0.4$, $\alpha = 100$, $A = 10$, and $\varepsilon = 4.8$

the initial disturbance will decrease. In other words, we have a negative feedback. In order to describe the features in the calcium redistribution in more details, we have to solve numerically the initial system of partial differential equations (1), (2).

4. Mode of Calcium Excitation Enhancement

The results presented above, which were obtained at a qualitative level, give grounds to expect that, in the case of initial calcium excitation (a release of an additional portion of calcium into the extracellular space), two scenarios are possible for the further redistribution of calcium in the system:

• the calcium spark monotonically vanishes,

• the calcium spark firstly grows and then vanishes.

In the framework of our research of the calcium redistribution, let us simulate system's response to the following initial perturbation of the calcium concentration in the extracellular space:

$$\varphi(x) = A \exp(-\alpha(x - 0.5)^2). \tag{18}$$

This is a Gaussian-like distribution around system's middlepoint, which corresponds to modern ideas about the stochastic release of calcium into the extracellular space. If the initial calcium distribution $\varphi(x)$ in the extracellular space is known, we can estimate the time derivative of the function $u(t,x)$ at the initial time moment:

$$\left. \frac{\partial u(t,x)}{\partial t} \right|_{t=0} = a^2 \varphi(x)'' + \varepsilon \varphi(x). \tag{19}$$

If the initial distribution $\varphi(x)$ is determined by formula (18), we obtain

$$\left. \frac{\partial u(t,x)}{\partial t} \right|_{t=0} = \varphi(x)\Big(\varepsilon + \alpha a^2(\alpha(2x - 1)^2 - 1)\Big). \tag{20}$$

It is evident that, for the initial perturbation to grow, it is sufficient (but not required) that the condition $\left. \frac{\partial u(t,x)}{\partial t} \right|_{t=0} > 0$ should be obeyed in a certain spatial interval. The indicated condition is obviously equivalent to the following one:

$$\varepsilon + \alpha a^2(\alpha(2x - 1)^2 - 1) > 0. \tag{21}$$

The expression on the left-hand side of this inequality has a minimum at $x = 0.5$ (the system middlepoint). At $x = 0.5$, condition (21) transforms into

the expression

$$\varepsilon > \alpha a^2. \qquad (22)$$

However, even if this condition is not satisfied, it does not mean that there cannot be any enhancement of the initial perturbation. The calcium concentration may firstly decrease. Afterward, the stage of calcium concentration growth in the extracellular space begins. This scenario is confirmed by the results of a numerical simulation. To obtain numerical solutions, a standard method of lines was used. It is based on the spatial discretization of original equations. As a result, the original problem is reduced to the solution of a system of ordinary differential equations.

In order to obtain numerical solutions for the system of equations (1) and (2), we used the following values of the parameters: $a = 0.4$, $\alpha = 100$, and $A = 10$. Then the critical value of the parameter ε calculated according to formula (17) equals 1.56. The value of αa^2 on the right-hand side of inequality (22) equals 16. Figure 1 demonstrates the dependence $u(t, x)$ calculated for the parameter value $\varepsilon = 33.6$. It is quite expected that, in this case, we have a growth of the initial perturbation, which is associated with the presence of calcium in the extracellular space. However, in time, this perturbation, as was predicted, vanishes.

A similar situation takes place in the case depicted in Fig. 2. The figure illustrates the dependence $u(t, x)$ calculated for the parameter value $\varepsilon = 11.2$. The specific feature of this scenario consists in that the initial perturbation firstly decreases, and, only afterward, the amplification stage begins. Finally, the calcium concentration in the extracellular space returns back to zero.

As the value of the parameter ε decreases, the maximum amplitude of the calcium concentration profile in the extracellular space also decreases. In Fig. 3, the dependence $u(t, x)$ for the parameter $\varepsilon = 4.8$ is shown. Now, there is no enhancement of the initial perturbation. If the parameter ε decreases further, the time dependence of the calcium concentration becomes monotonically decreasing.

A more distinct apprehension about the changes in the process of calcium redistribution is given by Fig. 4. This figure demonstrates the time evolution of the calcium concentration at the middlepoint (at
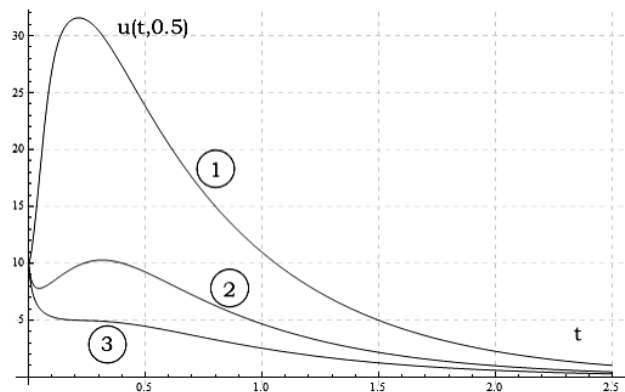

Fig. 4. Dependence $u(t, x = 0.5)$ for various ε-values: 33.6 (*1*), 11.2 (*2*), and 4.8 (*3*)

$x = 0.5$) for all three cases considered above. As was marked above, the calcium concentration in the extracellular space ultimately vanishes. However, a temporary growth of this parameter in the extracellular space may occur.

5. Conclusions

To summarize, the proposed model describes the process of calcium redistribution in the extracellular space. The model makes allowance for the calcium diffusion in the extracellular space and for the nonlinear mechanism that stimulates calcium to transit from the intracellular space into the extracellular one. The most important result of our theoretical analysis and numerical calculations is that an insignificant sporadic release of calcium into the extracellular space of the examined system can be enhanced. The corresponding mode is realized, if the calcium concentration in the intracellular space exceeds a certain threshold. This conclusion is in good agreement with the results of other studies (see, e.g., work [4]). This can be important for the explanation of processes associated with the formation of calcium clusters and the generation of calcium waves.

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НЕЛІНІЙНА МОДЕЛЬ
КАЛЬЦІЄВИХ ЗБУДЖЕНЬ В БІОМЕМБРАНАХ

Р е з ю м е

Пропонується модель, яка описує процес перерозподілу кальцію в біологічних тканинах. В моделі враховано, що кальцій може знаходитись в зовнішньоклітинному або внутрішньоклітинному просторі. Перерозподіл кальцію відбувається за рахунок його переходу із внутрішньоклітинного простору у зовнішньоклітинний, і навпаки. Також у моделі враховано дифузію кальцію у зовнішньоклітинному просторі. Показано, що існує два режими функціонування такої системи. В першому режимі початкове збурення концентрації кальцію у зовнішньоклітинному просторі монотонно з часом зменшується до нульового значення. В другому режимі початкове збурення концентрації кальцію підсилюється (однак зрештою все одно повертається до нульового значення). Критичною характеристикою, яка визначає режим функціонування системи, є концентрація кальцію у внутрішньоклітинному просторі.