SPONTANEOUS ACTIVITY OF ELECTRICALLY EXCITABLE PACEMAKER CELLS

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Abstract

We study a mathematical model of spontaneous activity of a cardiac pacemaker cell. The model includes five ionic membrane which are responsible for the spontaneous generation of an action potential of the pacemaker cell. These are the potassium, sodium and calcium ionic channels, the sodium-potassium pump and the sodium-calcium exchangers. The dynamics of intracellular concentrations of the main cations, responsible for the spontaneous activity of the pacemaker cell, was obtained. The computer simulation of the membrane potential and ionic currents was performed. The limit cycles oscillations were analyzed using the faze diagrams method. The pathology pacemaker activity during arrhythmia was simulated.

Introduction

The development of a mathematical model for electrochemical oscillators, such as cardiac pacemaker cells, is an important task of modern biophysics and electro-physiology of excitable membranes. This problem has been attracted much attention during last decades [1-9].

Denis Noble was the first who modified the classical Hodgkin-Huxley equations for the description of spontaneous activity of cardiac pacemaker cells [5]. Although the main results of the Noble's model are in good agreement with experimental findings, this model is based on modified empirical equations, which use a lot of parameters and thus the physics-chemical interpretation of the spontaneous activity of a pacemaker cell is much complicated. Furthermore, some of the results of the Noble's model (an amplitude of the action potential, a period of the limit cycle oscillations) are poorly coincide with experimental data [3]. Several models have been developed later [2-4], which have had more varied description of single channels [3] and another choice of pacemaker currents that drive membrane depolarization during diastole[2-5].

We have considered the recently proposed model [2] of spontaneous activity of a pacemaker cardiac cell of sinoatrial node. This model involves less varied description of ionic channels than most of existent models and uses more detail physics-chemical description of the processes which are responsible for the auto-rhythm oscillations of cardiac pacemaker cells. Thus, the model is rather useful for the simulation of interactions of biologically active agents with the excitable membrane of a cell and their influence on the auto rhythm oscillations of living cardiac cells.

Gating mechanisms of ionic channels

Let us consider a kinetic transition scheme between the open (O) and closed (C) states of an ionic channel, which is described by a Markov process

$$O \underset{\alpha}{\overset{\beta}{\Leftrightarrow}} C \tag{1}$$

where α and β are the rate constants, which depend on the transmembrane potential. The ionic channel is either entirely open or closed and randomly fluctuates between these two states. Let a variable x denotes the average fraction of open channels. The dynamics of ionic flux through an ensemble of open channels is described by the following differential equation

$$\frac{dx}{dt} = \alpha(1-x) - \beta x \equiv \frac{x_\infty - x}{\tau} \tag{2}$$

$$x_\infty = \frac{\alpha}{\alpha+\beta} \; ; \; \tau = \frac{1}{\alpha+\beta} \tag{3}$$

where x_∞ is the steady state fraction of open channels, τ is the relaxation time. Let the energy difference between the open and closed states of the channel is given by

$$\Delta E = E_O - E_C \equiv q(\varphi_x - \varphi) \tag{4}$$

where q is a gating charge, $q\varphi$ is the change in electrical potential energy due to the redistribution of charges during the transition, $q\varphi_x$ is the difference in conformational energy between the closed and open states of the ionic channel. At equilibrium $dx/dt = 0$ and the probability for a single channel to be open is given by the expression

$$\frac{x_\infty}{1-x_\infty} = \frac{\alpha}{\beta} \tag{5}$$

This probability is also given by the Boltzmann distribution

$$\frac{x_\infty}{1-x_\infty} = \exp\left(-\frac{\Delta E}{kT}\right) \tag{6}$$

Thus, from the expressions (4)-(6) with $q = +4e$ we obtain

$$x_\infty = \left[1 + \exp\left(\frac{4e\{\varphi_x - \varphi\}}{kT}\right)\right]^{-1} \tag{7}$$

The simplest choice for α and β is

$$\alpha = \lambda \exp\left(-\frac{2e(\varphi_x - \varphi)}{kT}\right) \tag{8}$$

$$\beta = \lambda \exp\left(\frac{2e(\varphi_x - \varphi)}{kT}\right) \tag{9}$$

where λ is the constant. The relaxation time as a function of the potential is given by

$$\tau = \left[2\lambda \cosh\left(\frac{2e\{\varphi_x - \varphi\}}{kT}\right)\right]^{-1} \tag{10}$$

Ionic flow and Nernst equilibrium potentials

There are two basic principles of a motion of charged particles. The first one is a diffusion, which drives the motion of all the particles (charged and non-charged). The second one is a motion of charged particles in an electric field, in our case this is the motion of ions in

a solution upon the action of an electric field. A simple diffusion is described by the empirical Fick's law

$$\vec{\Pi} = -ukT\nabla N \tag{11}$$

where $\vec{\Pi}$ is the ionic flow, N and u are the concentration and mobility of the particles. A motion of ions in an electric field is described by well known Ohm's law

$$\vec{\Pi} = -zeuN\nabla\varphi \tag{12}$$

where z is the valence, e is the elementary charge, φ is the electric potential.

Combining the expressions (11) and (12) we obtain the equation, which describes the total ionic flux upon the action of the electric field and the diffusion

$$\vec{\Pi} = -ukT\exp\left(-\frac{ze\varphi}{kT}\right)\nabla\left[N\exp\left(\frac{ze\varphi}{kT}\right)\right] \tag{13}$$

We can find an equilibrium Nernst potential by putting in (13) $\vec{\Pi} = 0$ and integrating from the external (e) to internal (i) side of the membrane

$$\int_{N^i\varphi^i}^{N^e\varphi^e}\int ukT\exp\left(-\frac{ze\varphi}{kT}\right)\nabla\left[N\exp\left(\frac{ze\varphi}{kT}\right)\right]dNd\varphi = 0 \tag{14}$$

Integrating (14) we obtain the following expression

$$\frac{N^i}{N^e} = \exp\left[-\frac{ze\left(\varphi^i-\varphi^e\right)}{kT}\right] \tag{15}$$

Solving (15) with respect to $\left(\varphi^i-\varphi^e\right)$ and introducing the notations $\varphi_T = {kT}/{e} = {RT}/{F}$, where F is the Faraday constant, we obtain the equilibrium Nernst potentials for the main cations of a cell

$$\varphi_K = \varphi_T \ln\frac{N_K^e}{N_K^i} \tag{16}$$

$$\varphi_{Ca} = \frac{\varphi_T}{2}\ln\frac{N_{Ca}^e}{N_{Ca}^i} \tag{17}$$

$$\varphi_{Na} = \varphi_T \ln\frac{N_{Na}^e}{N_{Na}^i} \tag{18}$$

Ionic channel currents

Let us consider the current through a single ionic channel with a length d and a cross section area $S(x)$. Let $x = -{d}/{2}$ denotes an internal membrane side and $x = {d}/{2}$ an external side. In case of a stationary flow the current trough all cross sections must be the same, and the flux is inversely proportional to the area

$$i = ze\Pi S = const \tag{19}$$

Using (19) for the flux and inserting it into (13) we obtain

$$\frac{i}{zeS} = -ukT\exp\left(-\frac{ze\varphi}{kT}\right)\nabla\left[N\exp\left(\frac{ze\varphi}{kT}\right)\right] \tag{20}$$

We multiply the resulting equation by $\exp\left(ze\left(\varphi-\varphi_0\right)/kT\right)$ and obtain

$$\frac{i}{S}\exp\left(\frac{ze(\varphi-\varphi_0)}{kT}\right)=-zeukT\frac{d}{dx}\left[N\exp\left(\frac{ze(\varphi-\varphi_0)}{kT}\right)\right] \tag{21}$$

where the constant φ_0 is chosen in such a way, that $\varphi(-d/2)=\varphi_0+\varphi/2$, $\varphi(d/2)=\varphi_0-\varphi/2$. In equation (21) $\varphi=\varphi(x)$, $N=N(x)$, $S=S(x)$ and all the others values do not depend on x. We integrate (21) from the inside side of the membrane $x=-d/2$ to the outside $x=d/2$ and obtain

$$i\cdot I=-zeukT\left\{N^e\exp\left(-\frac{\varphi ze}{2kT}\right)-N^i\exp\left(\frac{\varphi ze}{2kT}\right)\right\} \tag{22}$$

$$I=\int_{-d/2}^{d/2}\frac{\exp(ze(\varphi-\varphi_0)/kT)}{S}dx \tag{23}$$

We extract a factor $\sqrt{N^iN^e}$ and write the ratio of the concentrations in the Nernst potentials $\sqrt{N^i/N^e}=\exp(-ze\varphi/2kT)$ and obtain the following expression for the ionic current through the channel

$$i=\frac{zeukT}{I}\sqrt{N^iN^e}\left\{\sqrt{\frac{N^i}{N^e}}\exp\left(\frac{ze\varphi}{2kT}\right)-\sqrt{\frac{N^e}{N^i}}\exp\left(\frac{ze\varphi}{2kT}\right)\right\}=\frac{2zeukT}{I}\sqrt{N^iN^e}\sinh\left(\frac{ze(\varphi-\varphi_s)}{2kT}\right) \tag{24}$$

The integral (23) depends on the potential $\varphi=\varphi(x)$ as well as on the cross section of the channel $S=S(x)$. To determine the profile of the potential inside the channel we have to solve Poisson's equation for the potential, taking into account the real charge distribution inside the channel, which is not available at the moment. A commonly used approximation is that the potential inside the channel is linear, that is the electric field inside the channel is a constant $-d\varphi/dx=const$. With the assumption $S(x)=S_0$ we have

$$i=(ze)^2u\sqrt{N^iN^e}\frac{S_0\sinh(ze(\varphi-\varphi_s)/2kT)}{d\sinh(ze\varphi/2kT)} \tag{25}$$

The equation (25) is known as Goldman's constant field approximation. In the limit case $N^i=N^e$ it is reduced to the simple Ohm's law, since than $\varphi_s=0$. A more realistic situation when the integral (23) can still be calculated, is that of an ion channel with a constant cross section, except for a short and narrow pore with a radius $3\,\text{Å}$ and length $5\,\text{Å}$, which is a typical assumption for ionic channels [1]. If we will assume that the field is a constant, a pore length is εd, than the expression (23) after integration will have the following form

$$I=\frac{2kTd}{ze\varphi}\left\{\frac{1}{S_0}\sinh\left(\frac{ze\varphi}{2kT}\right)+\left(\frac{1}{S_p}-\frac{1}{S_0}\right)\sinh\left(\frac{\varepsilon ze\varphi}{2kT}\right)\right\} \tag{26}$$

In the limit case $\varphi\to 0$

$$I_0=d\left[\frac{1-\varepsilon}{S_0}+\frac{\varepsilon}{S_p}\right]\approx\frac{\varepsilon d}{S_p} \tag{27}$$

Assuming $I=const$ we obtain the expression for the current

$$i = k_S \sinh\left(\frac{ze(\varphi - \varphi_S)}{2kT}\right) \tag{28}$$

Were k_S is independent from φ

$$k_S = 2zeukT\sqrt{N^e N^i}\,\frac{S_p}{\varepsilon d} \tag{29}$$

If the flux through the potassium channels is given by (28), than the integral membrane current will be given by

$$i_K = k_K x \sinh\left(\frac{\varphi - \varphi_K}{2\varphi_T}\right) \tag{30}$$

$$\frac{dx}{dt} = \frac{1}{\tau_K}\cosh\left(\frac{\varphi - \varphi_x}{\varphi_T/2}\right)\left\{\frac{1}{2}\left[1 + \tanh\left(\frac{\varphi - \varphi_x}{\varphi_T/2}\right)\right] - x\right\}$$

where $\tau_K = 1/2\lambda$ is the maximum relaxation time, k_K is the conductance parameter, which is given by the expression (29).

The sodium and calcium channels have an inaction and activation mechanisms. These two mechanisms can be considered as two independent Markov processes. As the activation mechanism is a very fast, we can reduce the system of differential equations. The maximum time constant for the inactivation process of calcium and sodium channels have the same order (several hundreds of milliseconds), thus the currents of these channels have the following view

$$i_{Ca} = k_{Ca} f d_\infty \sinh\left(\frac{e(\varphi - \varphi_{Ca})}{kT}\right) \tag{31}$$

$$d_\infty = \frac{1}{2}\left[1 + \tanh\frac{2e(\varphi - \varphi_d)}{kT}\right] \tag{32}$$

$$\frac{df}{dt} = \frac{1}{\tau_{Ca}}\cosh\left(\frac{2e(\varphi - \varphi_f)}{kT}\right)\left\{\frac{1}{2}\left[1 - \tanh\left(\frac{2e(\varphi - \varphi_f)}{kT}\right)\right] - f\right\} \tag{33}$$

$$i_{Na} = k_{Na}\, h\, m_\infty \sinh\left(\frac{e(\varphi - \varphi_{Na})}{2kT}\right) \tag{34}$$

$$m_\infty = \frac{1}{2}\left\{1 + \tanh\left(\frac{2e(\varphi - \varphi_m)}{kT}\right)\right\} \tag{35}$$

$$\frac{dh}{dt} = \frac{1}{\tau_{Na}}\cosh\left(\frac{2e(\varphi - \varphi_h)}{kT}\right)\left\{\frac{1}{2}\left[1 - \tanh\left(\frac{2e(\varphi - \varphi_h)}{kT}\right)\right] - h\right\} \tag{36}$$

where k_{Ca} and k_{Na} are the parameter of the conductivity of calcium and sodium channels respectively, φ_d and φ_m are the half-activation parameters, φ_f and φ_h are the half-activation potentials.

Sodium - potassium pump

The reaction of Na^+, K^+ pump is fully described by the following equation

$$ATP + 3Na_i^+ + 2K_e^+ \underset{\beta}{\overset{\alpha}{\Leftrightarrow}} ADP + 3Na_e^+ + 2K_i^+ + P_{io} \tag{37}$$

where ATP, ADP, P_{io} are adenosine triphosphate, adenosine diphosphate and inorganic phosphate respectively. The energy, which is required for the active transport of 3 cations Na^+ and 2 cations K^+ against the electrochemical gradient

$$\Delta G_{Na} = -3e(\varphi - \phi_{Na}) \tag{38}$$

$$\Delta G_K = +2e(\varphi - \phi_K) \tag{39}$$

The change in Gibbs energy is described by

$$\Delta G = \Delta G_{ATP} + \Delta G_{Na} + \Delta G_K = e(\varphi_{ATP} + 3\varphi_{Na} - 2\varphi_K - \varphi) \tag{40}$$

where ΔG_{ATP} is the energy, associated with the breakdown of ATP, $\varphi_{ATP} = \Delta G_{ATP}/e$. The sum of forward and backward rates can be equaled to a constant

$$\alpha + \beta = \lambda \tag{41}$$

At equilibrium the forward and backward reactions must occur at the same frequency, that is

$$\frac{\alpha}{\beta} = \exp\left(-\frac{\Delta G}{kT}\right) \tag{42}$$

Solving the equations (41) and (42) for α and β we obtain

$$\alpha = \frac{\lambda \exp\left(-\frac{\Delta G}{kT}\right)}{1 + \exp\left(-\frac{\Delta G}{kT}\right)} \tag{43}$$

$$\beta = \frac{\lambda}{1 + \exp\left(-\frac{\Delta G}{kT}\right)} \tag{44}$$

The difference

$$\alpha - \beta = \lambda \frac{\exp\left(-\frac{\Delta G}{2kT}\right) - \exp\left(\frac{\Delta G}{2kT}\right)}{\exp\left(-\frac{\Delta G}{2kT}\right) + \exp\left(\frac{\Delta G}{2kT}\right)} = \lambda \tanh\left(-\frac{\Delta G}{2kT}\right) \tag{45}$$

gives the total current of Na^+, K^+ pump

$$i_{NaK} = Me(\alpha - \beta) = k_{NaK} \tanh\left(\frac{\varphi + 2\varphi_K - 3\varphi_{Na} - \varphi_{ATP}}{2\varphi_T}\right) \tag{46}$$

where $k_{NaK} = Me\lambda$.

Sodium-calcium exchanger

The reaction which describes the sodium-calcium exchanger has the following view

$$Ca_i^{2+} + 3Na_e^+ \underset{\beta}{\overset{\alpha}{\Leftrightarrow}} Ca_e^{2+} + 3Na_i^+ \tag{47}$$

The energy, which is necessary to extract one cation Ca^{2+} against the electrochemical gradient, is produced during moving of three cations Na^+ along the electrochemical gradient

$$\Delta G_{Na} = +3Na(\varphi - \varphi_{Na}) \tag{48}$$

$$\Delta G_{Ca} = -2Na(\varphi - \varphi_{Ca})$$

The total work is given by

$$\Delta G = \Delta G_{Na} + \Delta G_{Ca} = e(\varphi - 3\varphi_{na} + 2\varphi_{Ca}) \tag{49}$$

The ratio α to β has the same form as in (42), but as opposite to sodium-potassium pump the saturation effect is not expected, and thus

$$\alpha = \lambda \exp\left(-\frac{e(\varphi - 3\varphi_{Na} + 2\varphi_{Ca})}{2kT}\right)$$

$$\beta = \lambda \exp\left(\frac{e(\varphi - 3\varphi_{Na} + 2\varphi_{Ca})}{2kT}\right) \quad (50)$$

where λ is a constant. For the total current of n sodium-calcium exchanger we have

$$i_{naCa} = -ne(\alpha - \beta) = k_{NaCa} \sinh\left(\frac{e(\varphi - 3\varphi_{Na} + 2\varphi_{Ca})}{2kT}\right) \quad (51)$$

where $k_{NaCa} = 2ne\lambda$.

The membrane potential

Suppose that the electr0chemical activity of a cardiac cell is defined by three K^+, Na^+, Ca^{2+} channels, Na^+K^+ pump and Na^+Ca^{2+} exchanger, and all the other currents can be neglected. The standard differential equation for the membrane potential and the conservation laws for the intracellular ionic concentrations of the main cations have the following view

$$\begin{aligned}
\frac{d\varphi}{dt} &= -\frac{1}{C}\left(i_{ca} + i_{Na} + i_K + i_{NaK} + i_{NaCa}\right) \\
\frac{dN_K^i}{dt} &= \frac{2i_{NaK} - i_K}{FV} \\
\frac{dN_{Ca}^i}{dt} &= \frac{2i_{NaCa} - i_{Ca}}{2FV} \\
\frac{dN_{Na}^i}{dt} &= \frac{-i_{Na} - 3i_{NaKa} - 3i_{NaCa}}{FV}
\end{aligned} \quad (52)$$

where C is the membrane capacitance , F is the Faraday constant. Solving the equation system (52) we obtain the expressions for i_K, i_{Na}, i_{Ca}

$$\begin{aligned}
i_K &= -FV\frac{d}{dt}N_K^i + 2i_{NaK} \\
i_{Ca} &= -2FV\frac{d}{dt}N_{Ca}^i + 2i_{NaCa} \\
i_{Na} &= -FV\frac{d}{dt}N_{Na}^i - 3i_{NaK} - 3i_{NaCa}
\end{aligned} \quad (53)$$

Substituting obtained expressions into the equation for the potential we have

$$\frac{d\varphi}{dt} = \frac{FV}{C}\frac{d}{dt}\left(N_K^i + 2N_{Ca}^i + N_{Na}^i\right) = 0 \quad (54)$$

This equation can be written as

$$\frac{d}{dt}\left(\varphi - \frac{FV}{C}\left(N_K^i + 2N_{Ca}^i + N_{Na}^i\right)\right) = 0 \quad (55)$$

Integrating (55) we obtain

$$\varphi - \frac{FV}{C}\left(N_K^i + 2N_{Ca}^i + N_{Na}^i\right) = A \quad (56)$$

where the constant A is found from the condition, that the membrane potential is equal to zero, when the inside and outside cation concentrations are equal. Thus, the equation for the membrane potential has the following view

$$\varphi = \frac{FV}{C}\left(N_K^i - N_K^e + 2(N_{Ca}^i - N_{Ca}^e) + N_{Na}^i - N_{Na}^e\right) \tag{57}$$

The parameters used during computer simulations

We have used the following parameters to simulate numerically the pacemaker activity of a sinoatrial node cell [2]: the conductance parameters k_{Ca} =26.2 pA, $k_{b,Ca}$=0.01645 pA, k_{Na} =112.7 pA, k_K=32.9 pA, k_{NaCa}=1400 pA, k_{NaK}=11.46 pA, the extracellular ionic concentrations N_K^e=5.4 mM, N_{Na}^e=140 mM, N_{Ca}^e=2 mM, the temperature $T = 310$K, the capacitance of a membrane C=10 pF, the volume of a cell $V = 10\mu m^3$, the relaxation time $\tau = \tau_K = \tau_{Na} = \tau_{Ca} =$ 200 ms, the half-activation potentials φ_x = -25.1 mV, φ_d = -6.6 mV, φ_f =-25 mV, φ_m = -41.4 mV, φ_h = -91 mV, φ_{ATP} = -450 mV.

Numerical results and discussion

The electro-physiological spontaneous activity of real pacemaker cells is reasonably described by above described theory. In particular, we have simulated the spontaneous activity of a rabbit sinoatrial node cell using this model. The simulated membrane action potential of the pacemaker cell is shown in Fig.1.

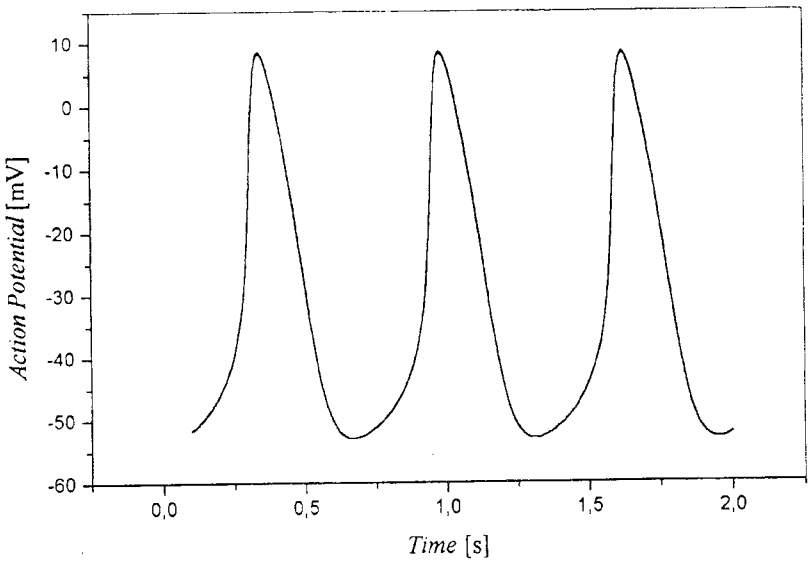

Fig. 1 Simulated membrane action potential of a pacemaker cell

The waveform and amplitude of the simulated action potential reasonably coincide with experimental results [6]. Using this theory we can predict experimentally observable ionic currents, which underlie the spontaneous activity of alive pacemaker cells. Furthermore, we

can get some physics-molecular meaning of the processes which drive auto-rhythmic oscillations in the pacemaker cell. The dynamics of the ionic currents K^+, Na^+, Ca^{2+} is shown in Figs 2 - 4.

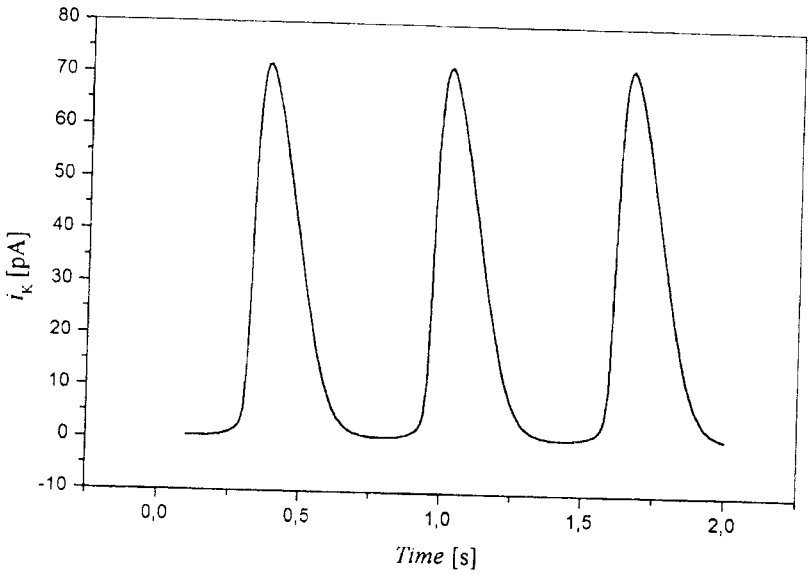

Fig. 2 The outward delayed rectifying potassium current of a pacemaker cell

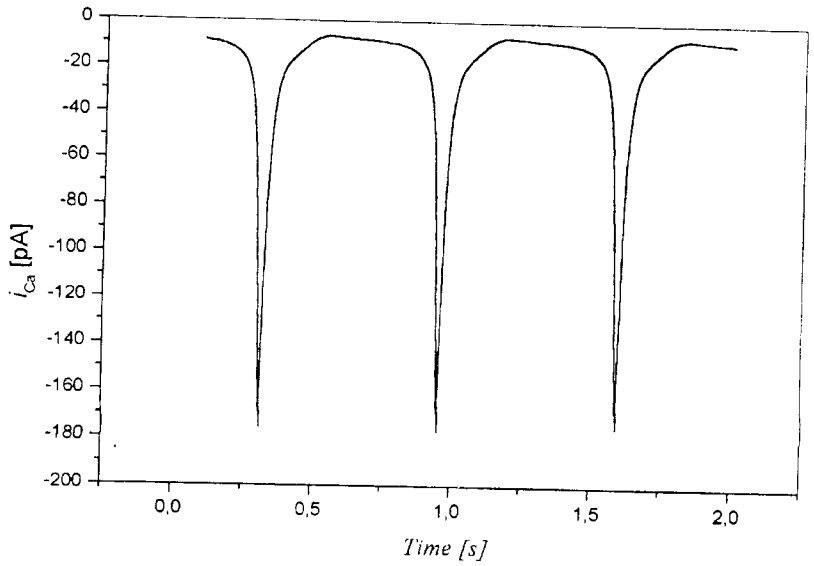

Fig. 3 The inward calcium current of a pacemaker cell

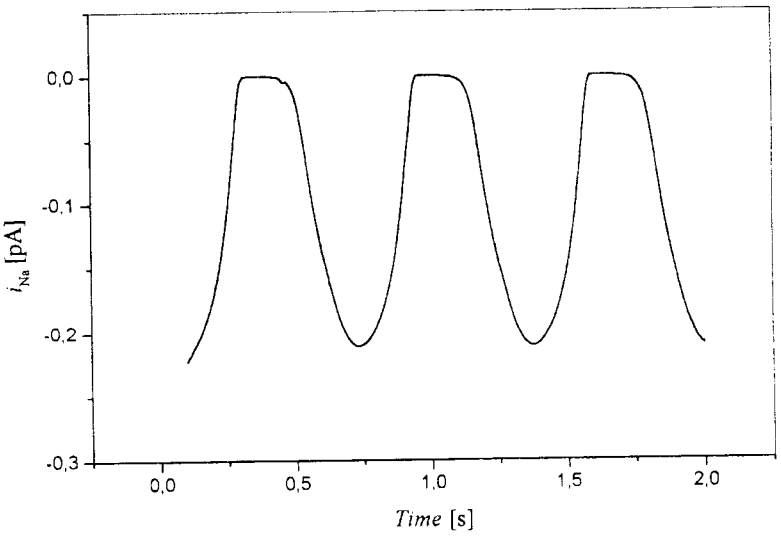

Fig. 4 The inward sodium current of a pacemaker cell.

The long-time simulation of the membrane potentials with the equal starting intracellular and extracellular ionic concentrations is shown in Fig.5.

As can be seen from the long-term simulation the Nernst equilibrium potentials are reached roughly after 750 c (12.5 minutes). These long-time simulations confirm a hypothesis on the limit cycle oscillations in the simulated sinoatrial node cell. The importance of the presented model as well as others reasonable models lies in the possibility of applying of the model for investigation of some pathologies, which have well defined clinical manifestation. One of such heart disease is an ischaemia[1,7]. The simulated action potential at different extracellular concentrations of K^+, as it takes place during ischaemia, is shown in Fig.6.

As it can be seen from Fig.6 the arrhythmia pathology takes place with increasing of extracellular potassium concentration. Although some evident success in describing of the pacemaker activity during ischaemiapathology, the model falls to predict all the possible extracellular K^+ concentrations, that can take place during this disease [7-9]. The problem can lie partly in that fact, that the model involves only three main cations K^+, Na^+, Ca^{2+}, and does not include for instance Cl^- anions. This is a subject of the following investigations, as it can be mentioned from electro-neutrality requirements of the intracellular and extracellular salt aqueous solutions, which have not been considered in the model.

It is known, that the spontaneous oscillations in a pacemaker cells have the limit cycle character. To analyze this phenomenon we have simulated the phase diagram of the spontaneous oscillations using the model. The phase diagram of the limit cycle oscillations is shown in Fig. 7.

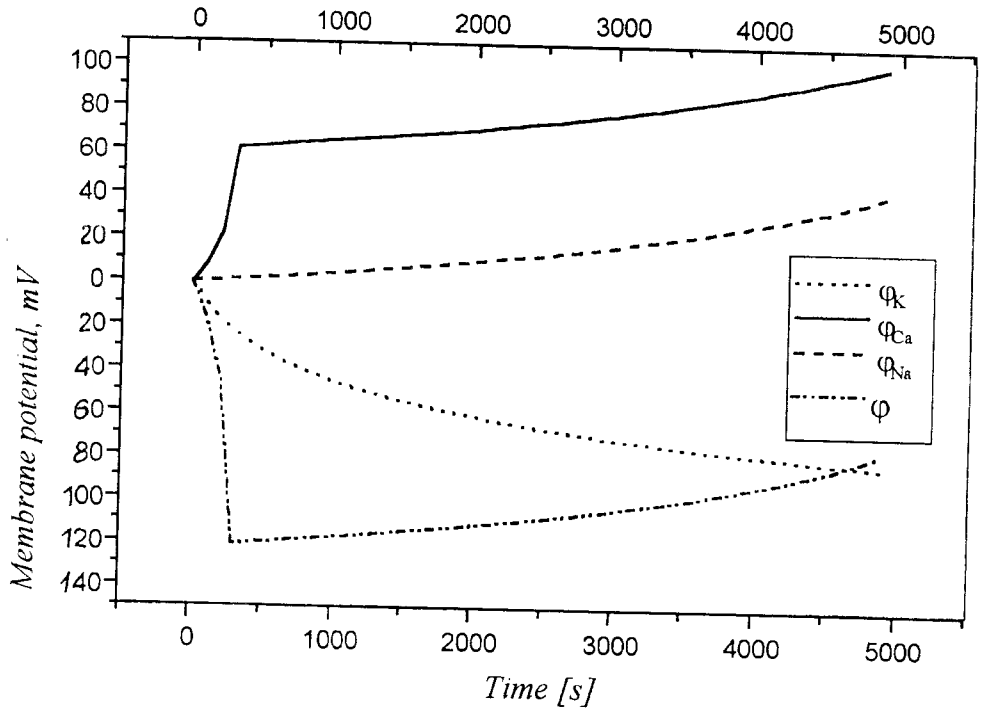

Fig. 5. Long-time simulation of the membrane potentials of a pacemaker cell

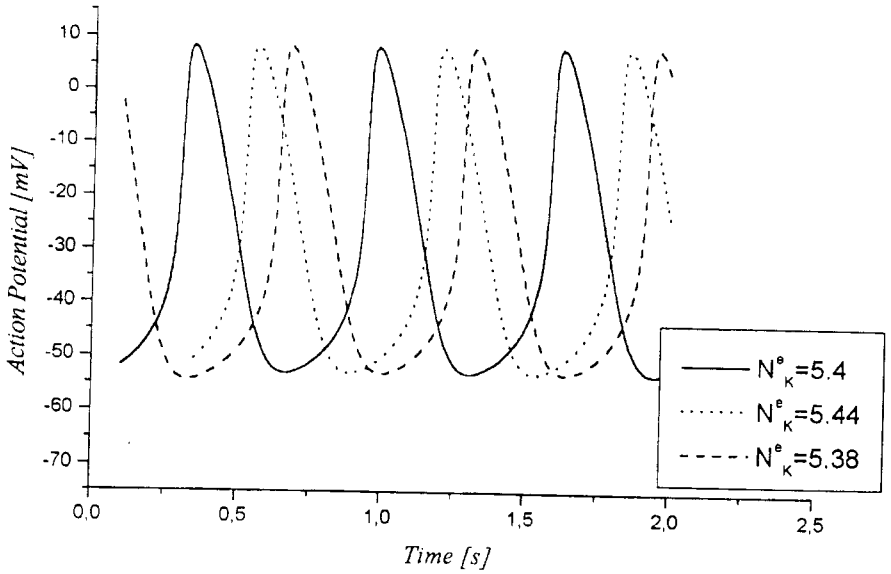

Fig. 6 An influence of an extracellular potassium concentration on the arrhythmia of a pacemaker cell

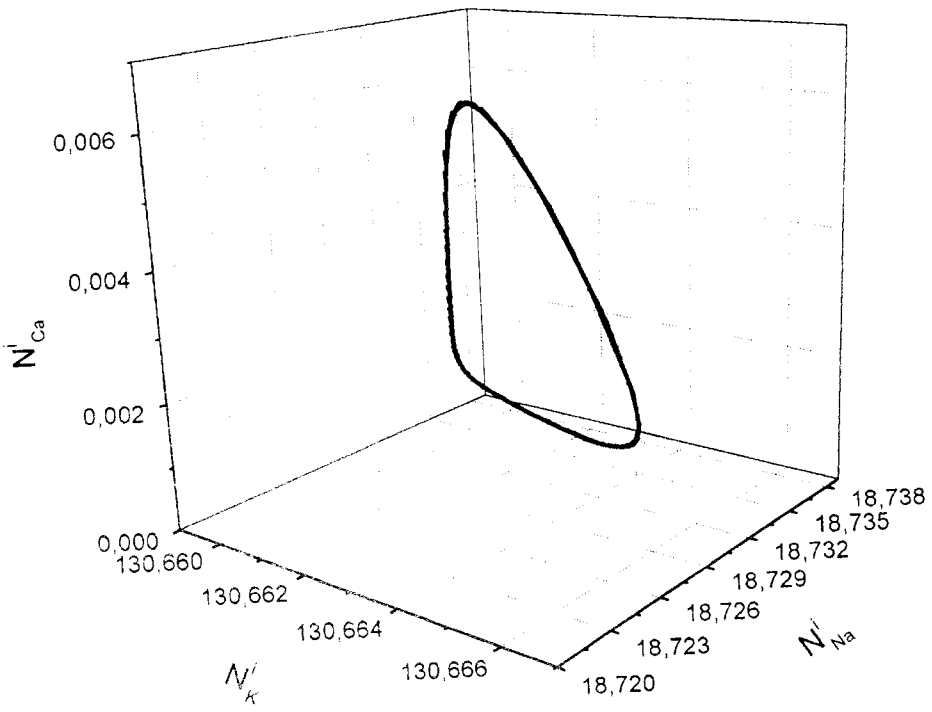

Fig. 7 Limit cycle oscillations of a pacemaker cell

If the starting intracellular concentration of main cations is changed in the limit cycle range, the trajectory of the phase diagram asymptotically approaches the limit cycle, while at the concentrations $K^+ > 5.44$ mM the trajectory of the limit cycle follows to infinity.

References

1. Hille B. Ionic Channels of Excitable Membranes. - 2nd ed. – Massachusetts: Sinauer Associates Inc, 1991. – 624 p.
2. Endersen L.P., Hall K., Hoye J.S. and Myrheim J., A theory for the membrane potential of living cells // European Biophysical Journal. – 2000. - V. 29. - P. 90-103.
3. Docos S., Celler B. and Lovell N., Ion Currents Underlying Node Pacemaker Activity: A New Single Cell Mathematical Model // Journal Theoretical Biology. – 1996. - V. 181. - P. 245-272.
4. Noble D. The initiation of the heartbeat. Oxford: Oxford University Press, 1979. – 412 p.
5. Noble D., Noble S. A model of sino-atrial node electrical activity based on a modification of the DiFrancesco-Noble equations // Proc. R. Soc. Lond. B. – 1984. - V. 222. - P.295-304.
6. DiFrancesko D. Pacemaker mechanisms in cardiac tissue // Annual Rev. of Physiology. – 1993. - V. 5. – P.455-472.

7. Ch'en F.F., Vaughan-Jones R.D., Clarke K., Noble D. Modeling myocardial ischaemia and reperfusion // Progress in Biophysics and Molecular Biology. – 1998. - V. 69. - P. 515-538.
8. Lei M., Brown H., Noble D. What role do T-type calcium channels play in cardiac pacemaker activity // Proceedings from the International Electrophysiology Meeting (Basel, Switzerland, 1996). - P. 103-109.
9. Han X., Sen L., Smith T., Functions of T-type calcium channels in rabbit atrioventicular node and cardiomyopathic hamster ventricle // ibid. - P. 110-122.