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Integrative Modeling of Electrical Properties of Pacemaker Cardiac Cells

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Abstract. This work represents modeling of electrical properties of pacemaker (sinus) cardiac cells. Special attention is paid to electrical potential arising from transmembrane current of Na^+, K^+ and Ca^{2+} ions. This potential is calculated using the NaCaX model. In this respect, molar concentration of ions in the intercellular space which is calculated on the basis of the GENTEX model is essential. Combined use of two different models allows referring this approach to integrative modeling.

1. Introduction

The cardiac muscle comprises typical and atypical pacemaker cardiac cells which form the cardiac conduction system. Excitation from the atrioventricular node under normal conditions is possible only in one direction. The most important condition for assurance of cardiac cells functioning is anatomical continuity of the whole conduction system. Topography of pacemakers and ionic mechanisms of ventricular connection and ventricular conduction system is not fully understood nowadays.

A great number of interrelated electrochemical processes with involvement of cardiac cells are conducted continuously in the heart, as a result of which action potential leading to cardiac contraction is generated. Disorder of this complex system leads to a wide range of cardiovascular diseases which are the main factor of mortality in advanced economies. Timely diagnostics of potentially adverse states might remedy the situation [1–4]. However, there are certain tasks which have not been settled yet by the modern technologies of experimental diagnostics, e.g. simultaneous measurement of dynamics of several transmembrane currents. There is a need to develop the area of mathematical modeling and comparative studies of electrophysiological arrangement of atrioventricular connection and ventricular conduction system cells.

The mathematical model will make it possible to explore general rules of cardiac muscle functioning more deeply and determine the disorder mechanism of the electrical and contractile function of cardiac cells.

2. Analysis of technologies

Conceptual models of the cardiac function have been developed since the 50s of the 20th century. Models of this class allow obtaining the qualitative idea of the studied phenomenon. They have relatively minor computational complexity, and their application is often not limited to the field wherefore they were elaborated. The example thereof is the FitzHugh-Nagumo model [5] which is

widely used not only for description of cardiac electrical activity, but also for other self-oscillating systems.

So called "detailed models", e.g. the family of Hodgkin-Huxley models [6], are applied in order to obtain qualitative estimates. Models of this class ensure design accuracy on the level of accuracy of experimental procedures which conditions their reasonable practicality. On the other hand, their resource intensity is substantially higher which is conditioned by complexity of the modeled system.

Computational complexity may be reduced significantly as part of the integrative approach that lies in synthesis of some relatively simple models describing different aspects of the studied system. Integrative modeling is most extensively used in the Physiome project [7], the purpose whereof is to build the complete human body model.

The most common models of intracellular ion concentration of ions in cardiac cells use calcium, sodium and potassium. Calcium concentration is important, and the majority of models elaborated since 1977 include at least some basic dynamics of intracellular calcium. Intracellular concentrations of sodium and potassium are easier to represent and updated only proportionally to the sum of transmembrane currents associated with each ion. Intracellular calcium models reproduce sophisticated dynamics of calcium inside the cell on some level. The increased level of intracellular calcium initiates the cell contraction process. Relatively small calcium influx through *L*-type calcium channels in the membrane raises calcium concentration in cytosol by approximately ten times. Calcium together with other cell compounds initiates the contraction process.

Cardiac muscle excitability arises under the influence of various stimuli, such as chemical, electrical, thermal ones etc., which condition the ability to shift to the excitation state. This phenomenon is based on negative electrical potential which arises at the primarily excited area. Functional cardiac cells in the excited tissue state have the polarized membrane. It has the positive charge on the outside and the negative one on the inside. Such a state is associated with different concentration of Na^+ and K^+ on both sides of the membrane. Different membrane permeability of cells plays a certain role for these ions. Na^+ ions do not penetrate through the cardiac cell membrane at rest. Potassium ions penetrate it only partially. Diffusion of K^+ ions escaping the cell increases the surface positive charge. Furthermore, the inner side becomes negatively charged. Sodium ions enter a cell under the influence of any stimulus. At this time the negative charge occurs on the cardiac cell membrane surface, and potential reversal is ensured. The amplitude of action potential of cardiac cells comprises around 10 mV and more. In its turn, this potential depolarizes membranes of adjacent cells. Eventually, they obtain their own action potentials, i.e. propagation of excitation occurs in other cardiac muscle cells as well.

Action potential of a functional cardiac cell is many times longer than that in skeletal muscles. Cardiac muscle cells do not get excited by the further stimuli during the period of development of action potential. This feature is essential for function of the heart as an organ. It is related to the fact that the cardiac muscle is able to draw only one action potential and can respond to repeated excitations only once. These phenomena create conditions for heart beating [6–8].

3. Modeling

Integrative modeling is also applicable to pacemaker cardiac cells [9, 10]. One of the most important characteristics of these cells is transmembrane voltage which is characterized by the ordinary differential equation as part of the model [11]:

$$\frac{dV}{dt} = -\frac{I_{Na} + I_{Ca,T} + I_{Ca,L} + I_K + I_f + I_B + I_{NaK} + I_{NaCa} + I_{CaP}}{C_m} \tag{1}$$

where $V(t)$ is the voltage generated by a cardiac cell; C_m is the electric capacity; symbol I with different subscripts represents the concentration of relevant ions:

I_{Na} is the sodium current, $I_{Ca,T}$, $I_{Ca,L}$ are potassium currents T of L types, I_{CaP} is the calcium pump, I_{NaK} is the Na, K pump, I_{NaCa} is the exchanger, I_f is the activated current, I_B is the background current, and I_K is the potassium current.

Nowadays, experimental data represented by single cellular channels show that opening and closing of channels are described by random processes. As a cell has many functioning channels, models given below characterize the average ion concentration.

It is apparent that transmembrane current depends both on the ion concentration in the intercellular space and its geometry. These dependencies are reflected in the model [12] which represents the partial differential system:

$$\frac{\partial C_p}{\partial t} = -\frac{F_p L}{V_p}\frac{\partial C_p}{\partial x} - \frac{PS_g}{V_p}(C_p - C_{isf}) - \frac{PS_{ecl}}{V_p}(C_p - C_{ec}) - \frac{G_p}{V_p}C_p + D_p\frac{\partial^2 C_p}{\partial x^2} \quad (2)$$

$$\frac{\partial C_{RBC}}{\partial t} = -\frac{F_{RBC} L}{V'_{RBC}}\frac{\partial C_{RBC}}{\partial x} - \frac{PS_{RBC}}{V'_{RBC}}(C_{RBC} - C_p) - \frac{G_{RBC}}{V'_{RBC}}C_{RBC} + D_{RBC}\frac{\partial^2 C_{RBC}}{\partial x^2} \quad (3)$$

$$\frac{\partial C_{ec}}{\partial t} = -\frac{PS_{ecl}}{V'_{ec}}(C_{ec} - C_p) - \frac{PS_{eca}}{V'_{ec}}(C_{ec} - C_{isf}) - \frac{G_{ec}}{V'_{ec}}C_{ec} + D_{ec}\frac{\partial^2 C_{ec}}{\partial x^2} \quad (4)$$

$$\frac{\partial C_{isf}}{\partial t} = -\frac{PS_g}{V'_{isf}}(C_{isf} - C_p) - \frac{PS_{eca}}{V'_{isf}}(C_{isf} - C_{ec}) - \frac{PS_{pc}}{V'_{isf}}(C_{isf} - C_{pc}) - \frac{G_{isf}}{V'_{isf}}C_{isf} + D_{isf}\frac{\partial^2 C_{isf}}{\partial x^2} \quad (5)$$

$$\frac{\partial C_{pc}}{\partial t} = -\frac{PS_{pc}}{V'_{pc}}(C_{pc} - C_{isf}) - \frac{G_{pc}}{V'_{pc}}C_{pc} + D_{pc}\frac{\partial^2 C_{pc}}{\partial x^2} \quad (6)$$

where F_p is the flow of dissolved substance contained in plasma; PS_{RBC} is the surface area of red blood cells; PS_g is the surface area for passive transport through clearances or gaps between adjacent endothelial cells; PS_{ecl} is the clearance area for endothelial cells; PS_{eca} is the contact surface area; PS_{pc} is the surface area of parenchymal cells (myocytes); G_{reg} is the local ion rate; D_{reg} is the diffusion coefficient in the axial direction of the V_p area; V_p is the intracapillary plasma volume; V'_{RBC}, V'_{ec}, V'_{isf} and V'_{pc} are virtual volumes of red blood cells, endothelial cells, intercellular space and cardiac cells respectively.

The model (2)-(6) with natural initial and boundary conditions allows evaluating the ion concentration on the outside of cardiac cells. Modeling results are presented on figure 1.

Figure 1 shows modeling time from 0 to 10 seconds along the horizontal axis and the standardized ion concentration in dimensionless units along the vertical axis. It is obvious from this figure that concentration rises sharply starting from the 4th second which corresponds with model preset parameters. Concentration fades out starting from the 5th second, thereby showing the ion rate in the transmembrane current. Voltage of this current calculated according to the model [11] is given on figure 2.

Figure 2 shows the modeling time (0-10 seconds) along the horizontal axis and the standardized value of electric voltage generated by a cardiac cell in dimensionless units along the vertical axis. A single beat in the beginning of the 2nd second is caused by initial values of model parameters. Voltage fluctuations corresponding with the beginning of the transmembrane current occur from the 4th second (figure 1). The amplitude of these fluctuations grows smoothly at first, and then decreases sharply starting from the 8th second. This mode of fluctuations corresponds fully with the local ion rate in the intercellular space (figure 1).

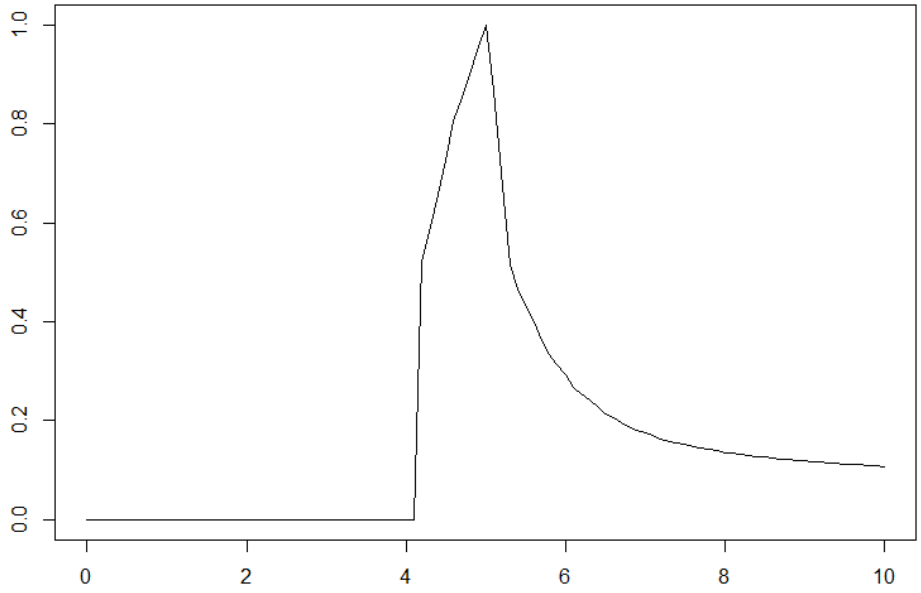

Figure 1. Dependence between ion concentration on the outside of a cardiac cell and time.

The specified results were obtained on the office computer with CPU frequency of 3.2 GHz and RAM of 8 Gb under control of the 64-bit operating system of the Windows family. Calculation time comprised approximately 20 seconds for each model. Thus, the integrative approach allows obtaining qualitative estimates of electrical activity of cardiac cells under random conditions. At the same time, fewer computation capacities are required as opposed to detailed models.

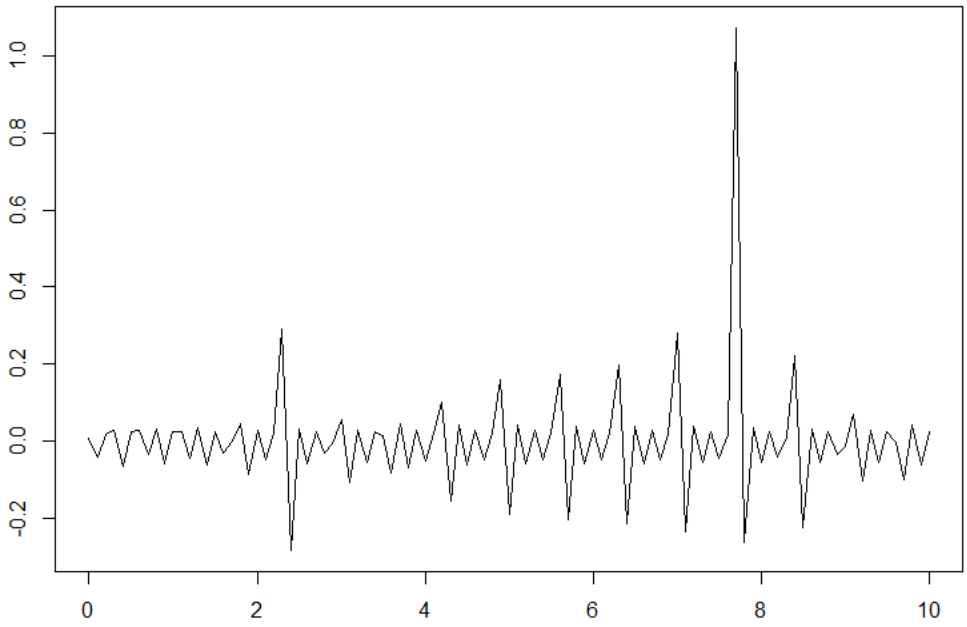

Figure 2. Dependence between cardiac cell electric voltage and time.

4. Conclusion

It is obvious that cardiac cells represent quite a sophisticated contractile "machine". Its arrangement principles and behavior may be predicted only using complex mathematical modeling. At present there are certain developments, and various mathematical models which describe subsystems of the cardiac muscle/cardiac cells with different degree of detail are elaborated. Models of passive mechanical properties of cardiac cells, models of their active mechanical behavior as well as the model of electrical activity of myocytes are described. However, there is still a considerable lack of integrative models which characterize the existing subsystems with account of direct links and feedback between them.

The mathematical model not only allows investigating rules of cardiac muscle behavior in the active mode thoroughly, but also enables to determine the disorder mechanism of the electrical and contractile function of cardiac cells which accompany different cardiac pathologies, as well as elaborate and implement new methods of treatment of various disorders. Possibilities of integrative methods for clinical practice are demonstrated by examples of analysis of arrhythmia mechanism and treatment methods which arise in case of calcium overload of cardiac cells that happens in many heart diseases. This model makes it possible to predict the role of mechanical and electrical links in pathogenesis of cardiac arrhythmia [13].

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