MODELLING OF REGULATION MECHANISMS OF CARDIOVASCULAR SYSTEMS

HIDIROVA MOHINISO BAHROMOVNA

Received March 26, 2003

Abstract. The importance of taking into account the spatial-separated processes at modelling of excitement origin and wave propagation on cardiac tissues is demonstrated. The possibility of mathematical modelling the consequent activation of cardiac cells by means of the delay-differential equations is shown. This equations allow to take into account the temporary relations in the system of cardiac regulation. Due to complexity of considered system for delay-differential equations, the methods for construction of their model systems are offered for model studies. In this work the results of the qualitative analysis of developed equations for cardiac tissue excitement and using this equations for mathematical and computer modelling of cardiovascular system regulatory mechanisms are given.

Despite the fact that the study of cardiac activity has a centuries-old history, the first mathematical model for human heartbeat was offered by van der Pol and van der Mark in 1928. This equations is still the investigation object for a mathematicians and allows to understand the common, simple laws for processes of activation and relaxation in the cardiac tissue. The equation is known as the van der Pol equation and is reduced to the second-order differential equation:

$$\ddot{u} - \alpha(1 - u^2)\dot{u} + \omega^2 u = 0$$

α describes the way in which voltage flows through the system, ω describes how much voltage is injected into the system. The equation describes the periodicity of heartbeat with two distinct phases: a slow recovery trajectory and a fast relax trajectory.

The Hodgkin and Huxley discovery in the early 1950's, describing the action potential of squid giant axon, provided the next direction in modeling of the cardiac activity. Based on the Hodgkin and Huxley model, the FitzHugh-Nagumo model (1961-1962), the Noble model (1962) of cardiac Purkinje fibres, the Beeler-Reuter model (1977) of the action potential of ventricular myocardial fibres, the Luo-Rudy model (1991) of the cardiac ventricular action potential were developed. This models are the basis for the modern investigations in cardiac activity at the norm and anomalies. The results of experimental and model researches [1-5] have shown a complex space-temporary variety of excitement processes in heart tissues. It can be noted that the models of cardiac activity with taking into account the feedback are very actual. In this case the heart is represented as excitable media, consisting of the regulatory cells (pacemaker) and the feedback system, allowing to control of heart rhythm. In this work the possible simplest equations of heart tissues excitement are considered. In the equations the spatial-separated processes of activation origin and excitement propagation are taken into account. In works [6-8] the results of cardiac activity modelling based on the consequent quantitative description of cardiac tissue excitement taking into account the above-mentioned regimes are given. According to the

2000 *Mathematics Subject Classification.* 34K35, 34K60.

Key words and phrases. regulatory mechanisms, differential-delay equations, qualitative study, cardiovascular system, quantitative analysis.

given methodology, system of heart muscle fibres is considered as an excitable medium with the rhythm driver (pacemaker) in sinus node. Cardiac activation occurs due to propagation of activity waves on the heart surfaces. Pacemaker activity is regulated by means of the neuro-hormonal factors. Let x_1 be the excitement value of muscle fibre at the moment t_0; x_2 be the excitement value of muscle fibre at the moment $t_0+\tau$; x_n be the excitement value of muscle fibre at the moment $t_0+(n-1)\tau$. The excitement wave propagation on sinus node of heart tissue muscles can be described by the following delay-differential equations [8]:

$$\frac{dx_1(t)}{dt} = \alpha_{i-1}x_{i-1}(t-\tau) - b_{i-1}x_i(t); \qquad i = 2,...,n, \tag{1}$$

where α_i is coefficients expressing the velocity of excitement activity in $i+1$ layer of cardiac tissue muscle; b_i is coefficients expressing the repression velocity in $i+1$ layer of muscles fibre. Note that $b_i > \alpha_{i+1}$, and value $b_i - \alpha_{i+1}$ expresses the loss of power.

Then the excitement wave covers both auricles which have common musculature:

the right auricle

$$\begin{aligned} \frac{dy_1(t)}{dt} &= \beta_1 x_n(t-\tau) - c_1 y_1(t); \\ \frac{dy_i(t)}{dt} &= \beta_i y_{i-1}(t-\tau) - c_i y_i(t); \\ & \qquad i = 2,...,m, \end{aligned} \tag{2}$$

the left auricle

$$\begin{aligned} \frac{dz_1(t)}{dt} &= \beta_1^{'} x_n(t-\tau) - c_1^{'} z_1(t); \\ \frac{dz_i(t)}{dt} &= \beta_i^{'} z_{i-1}(t-\tau) - c_i^{'} z_i(t); \\ & \qquad i = 2,...,m, \end{aligned} \tag{3}$$

where $y_i(t), z_i(t) \quad (i = 1,2,..,m)$ are amounts of excited muscle fibres of right and left auricles at the moment t. $\beta_i, c_i, \beta_i^{'}, c_i^{'}, \quad (i = 1,2,:,m-1)$ are coefficients like ones in the equation (1).

Further excitement wave propagation on ventricle muscle fibres can be expressed by the following differential-delay equations:

the right ventricle

$$\begin{aligned} \frac{d\theta_1(t)}{dt} &= \gamma_1 y_m(t-\tau) - d_1\theta_1(t); \\ \frac{d\theta_i(t)}{dt} &= \gamma_i \theta_{i-1}(t-\tau) - d_i\theta_i(t); \\ & \qquad i = 2,...,k, \end{aligned} \tag{4}$$

the left ventricle

$$\begin{aligned} \frac{d\eta_1(t)}{dt} &= \gamma_1^{'} z_m(t-\tau) - d_1^{'}\eta_1(t); \\ \frac{d\eta_i(t)}{dt} &= \gamma_i^{'} \eta_{i-1}(t-\tau) - d_i^{'}\eta_i(t); \\ & \qquad i = 2,...,k, \end{aligned} \tag{5}$$

where $\theta_i(t), \eta_i(t) \quad (i = 1, 2, ..., k)$ are amount of excited muscular fibres of the right and left ventricles, accordingly. The $\gamma_i, d_i, \gamma_i^{'}, d_i^{'} \quad (i = 1, 2, .., k)$ coefficients are like ones in equations (1).

Let us consider the construction of equations for heart tissues excitement in sinus node at the beginning the cardiac cycle. The muscles fibre excitement degree depends on power supply, effective functioning of auricles and ventricles during the previous stage of the cardiac cycle and the state of heart and organism as a whole. Finally, above-mentioned parameters depend on the functioning muscles by means of which the whole organism is ensured by necessary resources. Then supposing, that excitement nature depends on characteristics of the own excitable medium [9-11] and taking into account the neuro-hormonal influence of organism on sinus node cells we can write:

$$\frac{dx_1(t)}{dt} = F_s(\theta_k(t), \eta_k(t)) F_i(\theta_k(t), \eta_k(t)) - b_0 x_1(t),$$

where F_s is stimulation function; F_i is inhibition function of considered cells.

During study of similar processes, an inhibition function is usually considered as monotonous decreasing function of own arguments [10]. Taking into account the modelling experience of closed regulation systems [10,12] we have

$$\frac{dx_1(t)}{dt} = F_s(\theta_k(t), \eta_k(t)) \exp(-\delta_1 \theta_k(t) - \delta_2 \eta_k(t)) - b_0 x_1(t),$$

where δ_1, δ_2, b_0 are non-negative constants.

Since heart functioning at the norm expects synchronous ventricle activity and activity cessation of one of them leads to stopping heart activity as a whole, the stimulation function can be taken as homogeneous functions of own arguments. Consequently, in the most simplified type, for the excitement value of muscular fibre of sinus node on the initial stage of the heart cycle, we have

$$\frac{dx_1(t)}{dt} = a\theta_k(t)\eta_k(t) \exp(-\delta_1 \theta_k(t) - \delta_2 \eta_k(t)) - b_0 x_1(t), \tag{6}$$

where a is an non-negative constant. Thus, we have obtained the closed system of $n + 2m + 2k + 1$ non-linear differential-delay equations ((1)-(6)). Values n, m, k can be determined based on the biological data. Solutions of the given system of equations can be obtained using the method of consequent integration under given initial conditions on corresponding time segment [6, 8]. For the equations systems (1)-(5) there are zero initial conditions, since muscular fibres of heart are in rest at the moment of new cycle beginning. For the equation (6), which expresses the excitement value of muscular fibre in the sinus node, coefficients and initial conditions of the heart cycle are defined with account of blood pressure values of venous. In this case the first equation of (1) is the heterogeneous differential equation:

$$\frac{dx_2(t)}{dt} = \alpha_1 \varphi(t) - b_1 x_2(t)$$

where $\varphi(t)$ is known function of excitement value of muscular fibres in the sinus node at the initial stage of the heart cycle; $\alpha_1, b_1 - const \geq 0$. Solution of the given equation defines heterogeneous part at the length τ for the second equation (1) and so on.

Solutions of equations (1)-(5) and the right part of equation (6) are defined by means of this technique.

It is necessary to use corresponding reduced systems due to non-linearity and greater amount of considered equations. In work [8] the methods of reduced similar equations are stated in detail and the case of reduced equation for the cardiac tissue excitement by means of this non-linear differential-delay equation is considered

$$\frac{dx(t)}{dt} = ax^2(t-h)\exp(2(1-x(t-h)) - bx(t),$$

where $a, b - const \geq 0$.

This equation can be written in the following non-dimensional form:

$$\frac{1}{bh}\frac{dx(t)}{dt} = \frac{a}{b}x^2(t-1)\exp(2(1-x(t-1)) - x(t), \tag{7}$$

where $x(t)$ is the excitement value of muscular fibres at the moment t; a is the parameter which expresses the average velocity of cardiac fibre excitement; b is the parameter characterizing average velocity of excitement suppression of heart tissue; h is the parameter, characterizing the average time required for realization of feedback in the system of cardiac activity. Values of parameters a and b depend on the level of blood supply in the heart muscles; value of h depends on organism state as a whole. It was shown that equation (7) has stable oscillatory solutions, expresses functional-active regimes of the heart activity and can be used for quantitative and qualitative analysis of the most common regularities of excitement of cardiac tissue as a whole [7,13]. This equations was used (including Navier-Stokes equations for modelling of blood movement in arterial vessels and active and passive diffusion equations for the description of blood transfer in organs and tissues of organism) for creation of minimal closed models for the cardiovascular system and for REGUS software [12]. Using REGUS for an analysis of cardiovascular mechanisms at norm, arrhythmia origin, development and sudden cardiac death, we have shown that software can be used for quantitative analysis of functioning mechanisms for the cardiovascular system. Program REGUS was successfully used for solution of optimization task at surgical treatment of portal hypertension under N 40-96 grant framework (with scientists "Breast surgery" of Institute of MH PUz [14]).

It is necessary to note that the reduced system of equations (the reduced system is derived from equations (1)-(6)) for a description of the cardiac tissue excitement with account of average values of excitable cells in pacemaker, auricles and ventricles can be used for analysis of possible anomalies in auricles, ventricles and pacemaker

$$\begin{aligned}
\frac{dx(t)}{dt} &= a_1\theta(t-\tau_0)\eta(t-\tau_0)e^{(-\delta_1\theta(t-\tau_0)-\delta_2\eta(t-\tau_0))} - b_1x(t);\\
\frac{dy(t)}{dt} &= a_2x(t-\tau_1) - b_2y(t);\\
\frac{dz(t)}{dt} &= a_3x(t-\tau_2) - b_3z(t);\\
\frac{d\theta(t)}{dt} &= a_4y(t-\tau_3) - b_4\theta(t);\\
\frac{d\eta(t)}{dt} &= a_5z(t-\tau_4) - b_5\eta(t);
\end{aligned} \tag{8}$$

where $x(t), y(t), z(t), \theta(t), \eta(t)$ are variables, expressing levels of pacemaker, auricles and ventricles excitement accordingly; a, b, δ, τ are positive constants.

Results of qualitative analysis (8) show the existence of the trivial stable state. Existence of non-trivial equilibrium state depends on the solution of the equation

$$A\xi e^{-\delta\xi} = 1, \tag{9}$$

$$A = \frac{a_1a_2...a_5}{b_1b_2...b_5}, \qquad \delta = \delta_1\frac{a_2a_4}{b_2b_4} + \delta_2\frac{a_3a_5}{b_3b_5}.$$

Analysis of (9) shows presence of two positive roots when

$$A > \delta e.$$

Qualitative and quantitative analysis of stability of non-trivial equilibrium (8) using PC have shown the presence of unstable equilibrium and area of oscillatory solutions. There are Pouncare type limit cycles (normal cardiac activity) and irregular fluctuations (various forms of arrhythmia). In some cases, during computer experiments based on the modified REGUS, there is the break-down of oscillations (effect of "black hole"), that denotes the sudden cardiac death and sharp failure in blood pressure in the circulation system. Qualitative analysis (8) in detail with the determination of common regularities of solution behaviour in the phase space and construction of parametric portrait are subject of further researches

Thus depending on considered problems in the field of the quantitative analysis of cardiac activity there are: the differential-delay equation (7) and the system of differential-delay equations (8). Considered preliminary results of their qualitative analysis shows the existence of stationary stabile state, periodic solutions, irregular oscillations and effect of "black hole" under certain conditions. If the state of their existence can be identified with concrete values of parameters of cardiac activity in clinic conditions then we can realize modelling of concrete diseases of cardiovascular system [14] and offer recommendations for the choice treatment tactics.

This research was partially supported by the 40-96 grant of Fund of support of fundamental research AS RUz and the 41/2000 grant of Fund of fundamental research of GC RUz.

References

[1] Goldberger A.L. Cardiac chaos //Science. 243 (4987). 1419. 1989.
[2] Winfree A.T. Electrical turbulence in three-dimensional heart muscle //Science, 266. 1003-1006. 1994.
[3] Efimov I.R., Cheng Y., Wollenzier B., Tchou P.J., Mechanism of external defibrillation failure and success: virtual-electrode induced phase singularity and re-excitation, Circulation. 100(18): I-839. 1999.
[4] Gray A.R., Jalife J. Spiral waves and the heart //International Journal of Bifurcation and Chaos, Vol.6, No. 3. 415-435. 1996.
[5] Samie F.H., Mandapati R., Gray R.A., Watanabe Y., Zuur C., Beaumont J., Jalife J. A mechanism of transition from ventricular fibrillation to tachycardia: Effect of calcium channel blockade on the dynamics of rotating waves. Circulation Research. 86. 684-691. 2000.
[6] Hidirova M.B. Cybernetic simulation of "heart-vessels" systems. In proceedings, 10-th International Congress on Cybernetics and Systems. August, 26-31, Buharest. T. 2. 77. 1996.
[7] Hidirova M.B. Mathematical of regulation mechanisms of cardiovascular systems. "Innovation - 2001". 163-164. Tashkent. 2001.
[8] Hidirova M.B. On one closed model of cardiovascular system: main equations and results of computing experiments. Problemy mechaniki, , N5. 26-30. 1998.
[9] Krinsky B.I., Mikhailov F.S. Autowaves. M.: Znanie. 64. 1984.
[10] Hidirov B.N. On method for research of regulatorika of living systems // Voprosy Kibernetiki. N 128, 41-46. Tashkent. 1984.
[11] Hidirova M.B. On one closed model of cardiovascular system: norm and anomalies of cardiac activity . Problemy mechaniki. 3. 29-33. 1998.
[12] Hidirova M.B. The program for hybrid modelling of cardiovascular system (REGUS). The certificate No 83. It is registered in the State register of the computer programs. 1997.
[13] Hidirova M.B. On one closed model of cardiovascular system: Mechanics of cardiac activity. Problemy mechaniki. 2. 39-43. 1998.
[14] Hidirova M.B., Adylova F.T. Mathematical Modeling of Portal Hypertension //Proceedings, Ninth World Congress on Medical Informatics, August 18-22, Korea, Seoul. Edited by B.Cesnik, A.T.McGray. Press. Amsterdam-Berlin-Oxford-Tokyo-Washington. DS. 399. 1998.

Faculty of mechanics and mathematics, Moscow State University, Russia and National University of Uzbekistan, Tashkent, 700174, Uzbekistan

E-mail address: bahrom@cyber.uzsci.net,hidirova@yahoo.com