ISSN: 2350-0328

International Journal of AdvancedResearch in Science, Engineering and Technology

Vol. 6, Issue 4, April 2019

Mathematical modelling of regulatory mechanisms of sudden cardiac death

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ABSTRACT: In following article constructed a mathematical model of regulatorika of the cardiac activity by using functional-differential equations with delay time. Shown the results of qualitative and quantitative analysis of model equation. Various regulatory modes of cardiac activity were revealed such as damping, stationary state, limit cycle, dynamic chaos, "black hole". Developed a computer model for quantitative analyse of regulatory mechanisms of heart activity. Built parametric portrait of cardiac regulatorika based on computational experiment. The condition of transition to "black hole" area is analysed by using the Lamerey diagram.

KEYWORDS: mathematical and computer models, heart regulatorika, dynamic chaos, "black hole" effect, Lamerey diagram, functional-differential equations with delay time, qualitative and quantitative analysis, parametric portrait.

1. INTRODUCTION

The rapid development of modern information and communication technology (ICT) leads to the emergence of new technique and technology. Especially, modern ICTs have a special place in improving the accuracy and early diagnosis in medicine. Modern ITs are widely used in the treatment of various diseases. The use of ICT in cardiology makes it possible to study the regulatory mechanisms of the heart activity (self-management mechanisms), which allows to investigate the occurrence and processes of heart diseases, to apply the obtained knowledge in medical practices.

According to statistics of human mortality from diseases, as reported by the World Health Organizationischaemic heart disease and stroke are the world's biggest killers, accounting for a combined 15.2 million deaths in 2016. These diseases have remained the leading causes of death globally in the last 15 years[1].So we need to continue the investigation ofheart regulatorika because of insufficiently studying the self-organization and self-regulation mechanisms of cardiac functioning.The causes of occurrence and course of heart disease can be explored with the studying of these mechanisms.Mathematical and computer models play an important role in this problem. By using the computer model we can explore the various processeswhich occur in the heart.Computer models are based on mathematical models. In this article was considered the issues of mathematical modeling of cardiac regulatorika and explored the condition of event of sudden cardiac death.

II. RELATED WORKS

Currently, the study of regulatory mechanisms of cardiac activity is one of the main problems. Up today, a number of mathematical models have been developed by scientists from around the world and applied in practice to study patterns of cardiac activity due to the high degree of human mortality in the world from heart diseases.

Computer models are usually based on mathematical models in form of ordinary differential, partial derivatives, functional differential or reaction-diffusion equations. Mathematical modelling of cardiac activity was started about a century agoand is gradually being improved.

O.I.Adebisi et al. [2] have created the mathematical model of cardiac electrical activity with bidomain approach for investigate the excitation wave propagation laws in cardiac tissue. The model was considered in cell level. The model, based on system of two non-linear partial differential equations, is describes the relation of transmembrane potential, the extracellular potential and the ionic currents. The bidomain model was coupled with FitzHughNagumo (FHN) ionic model for describing the ionic current. Author represented the model in discrete form and solved with Euler method

ISSN: 2350-0328

International Journal of AdvancedResearch in Science, Engineering and Technology

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and developed computer application in Java for quantitative analyze. Model can investigate the nature of electrical wave propagation pattern and useful in detection of electrical wave abnormalities in cardiac tissue.

The next work also is dedicated to study of excitation of cardiac fibers based on system of differential equations of reaction-diffusion [3]. This electrophysiological model describes the development process of transmembrane potential of the cardiomyocyte. The presented models can be used in the study of electrophysiological and mechanical activity of the left ventricle of the heart and the asymmetric model given in this work can be used in case of not only normal, but also pathologically changed ventricle.

Next work considered mathematical model of cardiac contraction-relaxing process and consists of 10 ordinary differential equations for conduction and relaxation function, functioning of heart valve, pressure in heart and blood vessels and etc. [4]. The model was constructed in organ level. Simulation was realized in LabVIEW and is used for educational purpose in studying of cardiac functioning in whole body.

Aliev's mathematical model of cardiac electrical activity [5] became famous among scientists because of his simplicity. It consists of following two equations, which first is describes fast change processes of transmembrane potential and the second - slow processes:

$$\frac{\partial u}{\partial t} = \frac{\partial}{\partial x_i} d_{ij} \frac{\partial u}{\partial x_j} - ku(u-a)(u-1) - uv$$
$$\frac{\partial v}{\partial t} = \varepsilon(u,v)(-v - ku(u-a-1)). \qquad (1)$$

There are several works that used and modified mathematical model of Aliev R.R. In work [6] presented the mathematical model for investigation of cardiac electrical activity using simplest two-component model of Aliev R.R. and realized in form of equation for "reaction-diffusion" type. Determined the values of model parameters which best matched to properties of heart muscles. Given an algorithm for modeling the process of propagation of excitation in the heart. Made computer simulation for deducting the necessary information from ECG. Based on the results of simulations performed graphical visualization of propagation of excitation on the surface of the patient's heart.

M.MehdiSeyedebrahimi and et.al. [7] simulated software for study transmembrane potential propagation in normal and ischemic tissue of heart on base of Aliev-Panfilov model to describe electrical activity of cardiac tissue. In this work was simulated 3D mapping of transmembrane distribution of ventricle and possible to express ischemic zones and ischemic weight values. For numerical implementation of model equations was used finite difference method.

In work [8] authors modeled the process of electrical activity of heart. On base of mathematical model of Aliev-Panfilov they 3D visualized propagation of excitation wave in heart parts. In simulation was taken into account the space-time organization of the excitation process in the myocardium. The surface of the heart model is projected onto a plane for best design of real surface, and then every point was connected to the grid of solutions of Aliev-Panfilov model for illustration of action potential degree in these points.

We can continue discussion about this topic for a long time. But analyses of existing mathematical models show that attention was not paid enough to factor of spatial- temporal relations of propagation of excitation waves between heart parts in mathematical modelling. Accounting delay time contributes to a more realistic description of heart functioning [9-12]. So it would be purposeful if this factor was taken into account in model equations.

III. MATERIAL AND METHODS

In this article was offered mathematical model of propagation process of excitation waves in cardiac muscles. Let's consider the system of functional-differential equations with a delay argument that simulates the propagation of excitation waves through the layers in the heart regions: from the pacemaker to the left and right atria, through the atrioventricular node, to the left and right ventricles [13]:

$$\frac{1}{h}\frac{dX(t)}{dt} = \frac{AX^6(t-1)(1+BX^6(t-1))^2}{((1+BX^6(t-1))^2 + CX^6(t-1))((1+BX^6(t-1))^2 + DX^6(t-1))} - b_1 X(t), \qquad X(t) = \varphi(t),\ t \in [0,1], \qquad (2)$$

ISSN: 2350-0328
International Journal of AdvancedResearch in Science, Engineering and Technology
Vol. 6, Issue 4, April 2019

$$A=\frac{a_1a_5a_6}{b_5b_6}\cdot\left(\frac{a_2a_3a_4}{b_2b_3b_4}\right)^2,B=\left(\sigma_3\frac{a_2a_3}{b_2b_3}\right)^2,$$

$$C=\left(\sigma_1\frac{a_2a_3a_4a_5}{b_2b_3b_4b_5}\right)^2,D=\left(\sigma_2\frac{a_2a_3a_4a_6}{b_2b_3b_4b_6}\right)^2$$

where $X(t)$ – excitation wave propagation function in the heart muscles (six layers are considered that simulate the right, left atria and ventricles, two excitation nodes); $a_i, b_i\ (i=1,...,6)$ – rates of excitation and decline of activity in the myocardium, respectively; h – delay time; σ_1, σ_2 – inhibition parameters. All parameters are non-negative.

The developed mathematical model (2) is a system of functional-differential equations with delayed arguments, and it is very difficult to obtain the solutions by an analytical method. In this case, it is necessary to analyse the properties of characteristic solutions without defining explicit solutions. So, it is effective to use the methods of qualitative analysis of differential equations.

It was qualitatively analysed equation (2) for defining properties of characteristic solutions. The properties of existence, continuity and uniqueness, limited and non-negativity of characteristic solutions were explored. The existence of critical points has been revealed and the stability of these equilibrium points has been established. A stable trivial (O) and two nontrivial equilibrium points (α and β) are defined and in some condition there are two more equilibrium points (γ and μ) may appeared, which are always unstable (O<α<β<γ<μ). The equilibrium position (α) is stable and the equilibrium position (β) is always unstable according to the condition of the Hayes criterion. The stability of equilibrium points can be checked using condition (3). The stability of point (α) leads to the appearance of a Poincare-type limit cycle, that is, it attracts all solutions onto itself and, with a small circle around itself, repels solutions. At the same time, all unstable equilibrium points always repel solutions. Thus, an oscillating process arises. The qualitative analysis of equation (2) is given in more detail in [13].

$$-\frac{1}{6}<\frac{x_0^6(D+2B(1+Bx_0^6))}{(1+Bx_0^6)^2+Dx_0^6}+\frac{x_0^6(C+2B(1+Bx_0^6))}{(1+Bx_0^6)^2+Cx_0^6}-\frac{1+3Bx_0^6}{1+Bx_0^6}<\frac{1}{6} \quad (3)$$

where x_0 - equilibrium point.

Qualitative and quantitative studies of equation (2) show the presence of the following modes of characteristic solutions: stationary mode reflecting a certain type of arrhythmia (A); self-oscillating solution showing normal functioning (B1 and B2); dynamic chaos mode (C); the mode of sudden breakdown of decisions corresponding to sudden cardiac death during the dynamic chaos - the “black hole” effect (D), that is, a sudden destructive change occurs in irregular behavior and sudden drop the solutions to zero; attenuation mode (E), that is, gradual programmed pursuit of solutions to zero.

In the equilibrium position of the object under consideration we can have the following functional (4) and discrete (5) equations:

$$x(t)=\frac{Ax^6(t-1)(1+Bx^6(t-1))^2}{b_1((1+Bx^6(t-1))^2+Cx^6(t-1))((1+Bx^6(t-1))^2+Dx^6(t-1))} \quad (4)$$

$$x_{i+1}=\frac{Ax_i^6(1+Bx_i^6)^2}{b_1((1+Bx_i^6)^2+Cx_i^6)((1+Bx_i^6)^2+Dx_i^6)} \quad (5)$$

To identify the characteristic solutions (2), a software tool was developed based on Lamerey diagram for equations (5) and different modes of functioning of the regulatory mechanisms of the cardiac activity were obtained (Fig. 1).

ISSN: 2350-0328
International Journal of AdvancedResearch in Science, Engineering and Technology
Vol. 6, Issue 4, April 2019

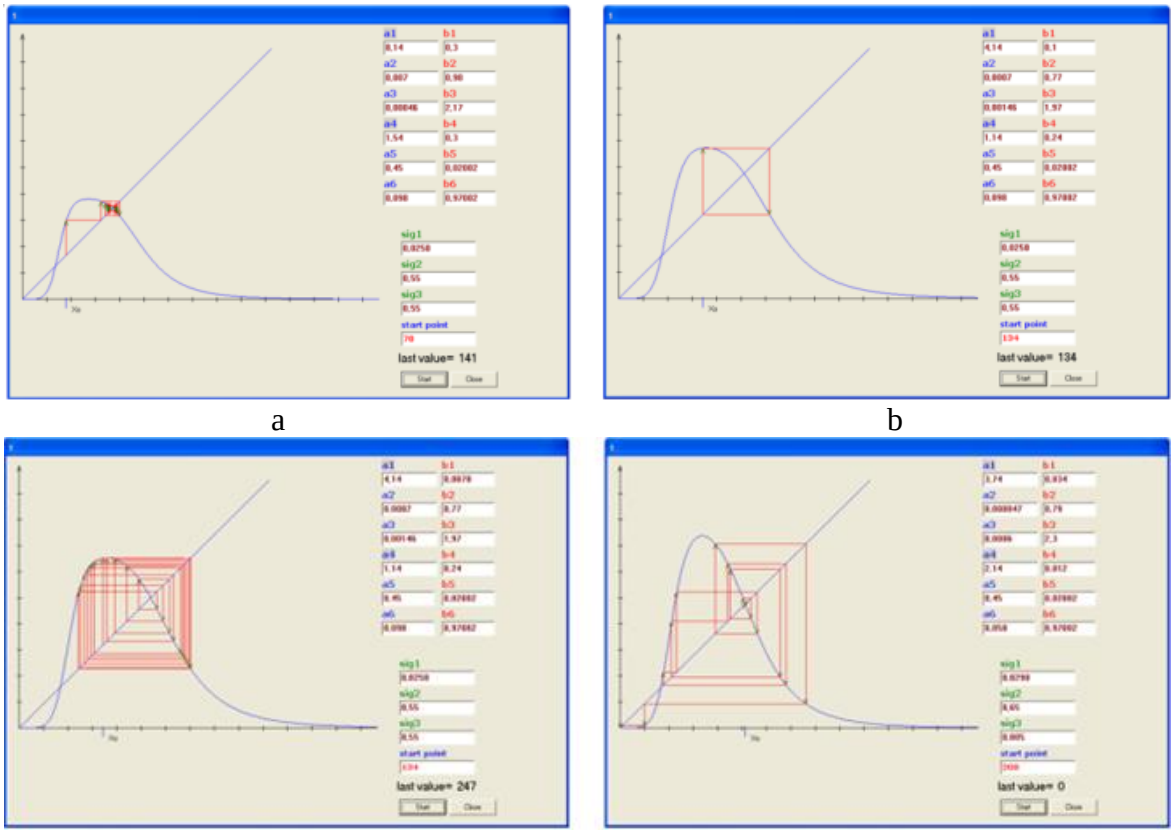

Figure 1. Lamerey diagram of equation (5) and obtained modes: a – stationary state, b – self-oscillation, c – dynamic chaos, d – "black hole" effect.

We analysed the transition condition of object to the "black hole" effect with the use of Lamerey diagram (Fig. 2).

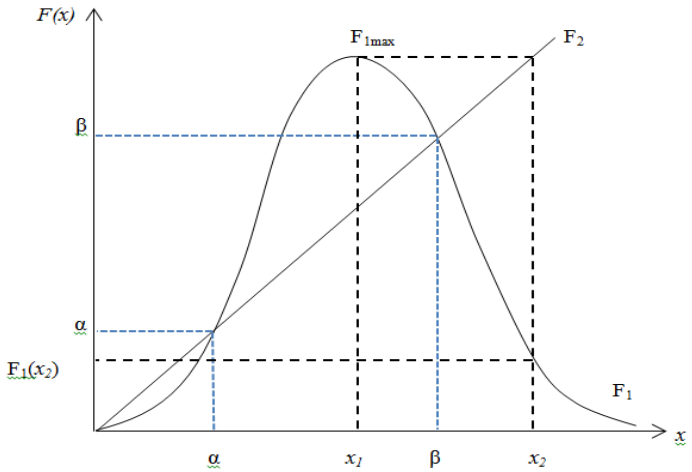

Fig. 2. Transition to the "black hole" mode

$$F_1(x_2) < \alpha \quad (6)$$

ISSN: 2350-0328
International Journal of AdvancedResearch in Science, Engineering and Technology
Vol. 6, Issue 4, April 2019

In fig. 2, the sudden cardiac death effect may be occurred when condition (6) is fulfilled. Here, α and β are non-trivial equilibrium points of equation (2). The value of the function F1 and x2 can be calculated as follow:

$$x_2 = \frac{4AB}{b_1(4B+C)(4B+D)}$$

$$F_1(x_2) = \frac{A}{D-C}\left(\frac{1}{1+\frac{Cx_2^{\,6}}{(Bx_2^{\,6}+1)^2}} - \frac{1}{1+\frac{Dx_2^{\,6}}{(Bx_2^{\,6}+1)^2}}\right) \quad (7)$$

When condition (6) is satisfied, a “black hole” effect will be occurring, that is, a sudden cardiac death is observed. Calculating the value of α in condition (6) with analytical way is very complex, so we can use numerical methods. A software tool has been developed for quantitative analysis the equation (2) and fig. 3 shows the interface of the program with the "black hole" effect.

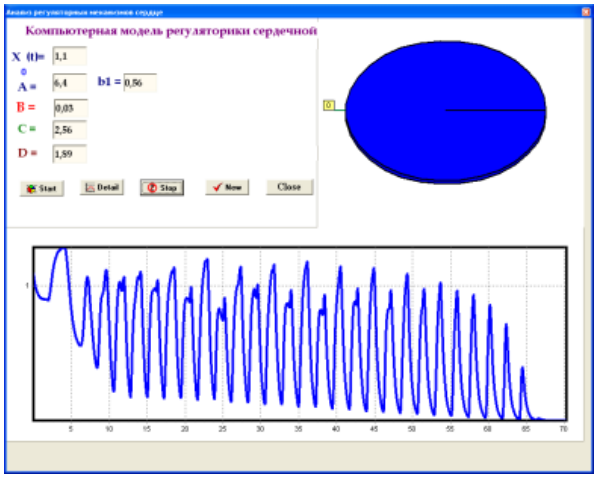

Fig. 3. “Black hole” mode

IV. CONCLUSION

Mathematical and computer models on base of a functional-differential equation with a delay argument (2) allow investigate specific type of arrhythmia which may attack sudden cardiac death. The definition of the transition condition of the “black hole” effect is possible with condition (6).Computational experiments were carried out for the quantitative analysis of functional-differential equation (2) and the following cardiac modes were revealed:

- extinction of cardiac activity;
- stationary state;
- regularoscillationbehaviour;
- irregular oscillation - dynamic chaos;
- the“black hole” effect - sudden cardiac death.

Due to the fact that the proposed mathematical model can reflect different modes, it can be used to study cardiac activity in normal and abnormal conditions.

ISSN: 2350-0328

International Journal of AdvancedResearch in Science, Engineering and Technology

Vol. 6, Issue 4, April 2019

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