Quantitative study of the regulatory mechanisms of cardiac activity and liver function in pathogenesis

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Abstract. The article is devoted to investigate the dynamics of behavior of functional-differential equation with delay of mathematical model of the regulatory mechanisms of cardiac activity and liver function in pathogenesis. Moreover, the results of the computational experiment for the quantitative analysis of the object state are presented. The behavior of the system in the zone of dynamic chaos was analyzed with the use of developed software.

1. Introduction

The study of biological processes in the heart and liver at normal and pathological conditions is very important for the early and accurate diagnosis of myocardial infarction, liver cirrhosis and other diseases. Mathematical models are powerful tools in the study of regulatorika of living systems [1, 2, 3, 4, 5] and, in particular, the heart and liver organs. Therefore, in the following article two important issues were considered: mathematical modeling of cardiac regulatorika and liver regulatorika. Primary researches for studying the cardiac activity has begun about 100 years ago and are still considering as an urgent issue among scientists of the world. Various mathematical models of cardiac activity has been proposed in different researches [6, 7, 8, 9, 10]. Analysis of existing mathematical models shows that only some of them can demonstrate normal functioning of heart activity, some of them demonstrate just dynamic chaos mode. But mathematical model, which is proposed in this article, can show not only the norm and anomaly modes of cardiac activity, but black hole mode too. Black hole mode is the sudden destructive changes of solutions and the pursuit solutions to zero, which means the end of functioning of living systems after non regular oscillation mode. The ability to demonstrate various modes of cardiac activity in mathematical models will allow the study of the regulatory mechanisms of occurrence and progress of cardiac arrhythmia and sudden cardiac death. Second part of this research work is dedicated to the investigation of regulatory mechanisms of interrelated activity of liver cells and hepatitis B viruses. Human viral hepatitis is a traditionally difficult global problem. The basis of the formation of a complex infectious process for each type of viral hepatitis lies in the peculiarities of the relationship between viruses and the liver cells (hepatocytes). According to data of World Health Organization estimates in various countries of the world, millions of people are infected with viral hepatitis. Hepatitis B
is a viral infection that attacks the liver and can cause both acute and chronic disease. The virus is transmitted through contact with the blood or other body fluids of an infected person. About one-third of the world’s population is infected with the hepatitis B virus (HBV) and between one and two million people die each year from complications caused by infection with the hepatitis B virus [11, 12]. So, we need to investigate the regulatory mechanisms of these diseases and mathematical models give us effective research opportunities in this problem.

2. Mathematical modeling of cardiac electrical activity

Excitation wave in heart is generated in sinus node, which is located on the top of right atrium and propagates to both atriums (right and left). The result of propagation of the excitation wave in atriums will cause the contraction of these parts. After that the signal will reach the atrioventricular node. After some delay, it will propagate to both ventricles (right and left). Taking into account the temporal relationship in the propagation of excitation waves in heart parts leads to a functional-differential equation with delay. Let’s try to simulate the propagation stages with the following functional-differential equations:

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

where, \( X(t) \) – excitation wave propagation function in the heart muscles; \( b_1 \) – coefficient expressing the rate of decline the activity in the pacemaker zone; \( h \) – delay time; \( A, B, C, D \) non-negative parameters.

There was developed the software tool in the Delphi 7 environment on the base of the 4th order Runge-Kutte method for quantitative analyze of (1) for investigating the behavior of heart activity in norm and dynamic chaos mode. Figure 2 shows the results, which were obtained in computational experiments, which can identify the different modes of heart functioning.

![Figure 1](image1.png)

**Figure 1.** Results of computational experiments: a stationary state, b regular oscillation, c irregular oscillation, d black hole, sudden cardiac death.
Qualitative and quantitative studies of equation (1) 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 dynamic chaos - the black hole effect (D), it means, a sudden destructive change occurs during irregular behavior and a sudden drop of solutions to zero is observed;
- attenuation mode (E), that is, the gradual programmed tendency of solutions to zero.

As a result of computational experiments, the following parametric portrait of the cardiac activity modes was made:

![Parametric portrait of equations (1): A - stationary state, B1 - oscillatory state, C - dynamic chaos, D - black hole effect, E - attenuation, r-windows - small regions with a stable state, B2 - electromechanical dissociation (agony).](image)

The system located in the stationary region (A) is identified as abnormal regulatorika of the heart activity, that is, it does not respond to getting into different physiological positions of the body, but it has a normal value of parameters. Oscillatory region (B1) characterizes the normal functioning of the heart and has a regular oscillation. The region of dynamic chaos (C) characterizes arrhythmia of the heart (in particular, we can say the fibrillation of the heart ventricles) and borders on one side with the region of normal oscillation, and on the other side with attenuation (programmed death of heart muscles). The result of a computational experiment shows the existence of a small black hole region (D) inside the dynamic chaos region, located near the boundary of the attenuation region, which characterizes the onset of a sudden cardiac death in a state of dynamic chaos. However, the black hole region has such a feature that at the beginning (left side) of this region the period of the system being in a state of irregular fluctuations before the onset of a sharp destructive change takes longer than at the end of this region (right side). Based on this, we can say that it is possible to visualize and predict the degree of death threat and the calculation of time up to this event. Evaluation of this time is an extremely important task in cardiology and is individual for each organism. An algorithm and software for determining the condition of hitting a black hole region have been developed.

Furthermore, there is a narrow region (B2) with regular oscillation between the regions of dynamic chaos and attenuation, which is consistent with the position of electromechanical dissociation in which briefly observed normal ECG data in the absence of heart contractions. The attenuation region (E) is characterized by a gradual decrease of the vital resources of the
heart and the desire of solutions to the trivial attractor, which corresponds with the end of the heart function.

The analysis of the behavior of biosystem with the use of the Lyapunov’s exponent method gives the predominant result of assessing the stability of the state in normal and dynamic chaos. The essence of the method is that the sign of the Lyapunov’s exponent is determined, which means the rate of convergence or divergence of the two trajectories of the function at a certain initial point with an initial small perturbation. The indicator is determined in one-dimensional phase space. If the sign of the indicator is negative, then the system is in a steady state, otherwise is in an unstable state.

The algorithm for calculating the Lyapunov’s exponent on a computer requires a discrete form of equation (1) and its derivation. We obtain the following discrete equation (2) in the equilibrium position of the object under consideration from equation (1).

\[ x_{i+1} = \frac{Ax_i(1+Bx_i)^2}{b_1((1+Bx_i)^2+Cx_i(1+Bx_i)^2+Dx_i^2)} \quad (2) \]

Lyapunov’s exponent is calculated as follows:

\[ \lambda(x) = \lim_{n \to \infty} \frac{1}{n} \sum_{i=0}^{n} \ln \left| \frac{df(x_i)}{dt} \right| \quad (3) \]

Using the flowchart below to calculate the Lyapunov’s exponent (3), a software tool has been developed to illustrate the state and evaluate the behavior of the functioning of the cardiac activity.

![Figure 3. Screen view of the Lyapunov’s exponent calculation program.](image)

In figure 3 we can see that the graph is not monotonous, in small changes of parameters the graph can drastically change its direction and cross the horizontal axis. This means the existence of the so-called r-windows (small regions with stable behavior) in the field of dynamic chaos. Developed program shows the calculated Lyapunov’s exponent and the number of r-windows regions in a certain narrow parameter range. Being in these regions, although the system is considered sustainable, it is in a wide region of dynamic chaos. This means with minor external influences the system will be in an unstable and unpredictable state. By adjusting the parameters, it is possible to lead systems from the region of dynamic chaos to the region of normal behavior, forming a chain using r-windows.

3. Mathematical modeling of regulatory mechanisms of interrelated activity of liver cells and hepatitis B viruses

The knowledge of the interrelated activity of the hepatocytes and hepatitis viruses at the molecular genetic level involves the analysis of the mechanisms of gene activity in a functioning
Regulation of gene activity is achieved through genetic regulatory systems based on interactions between cellular and viral DNA, RNA, and enzyme proteins. In the past century, powerful mathematical methods were developed for modeling intracellular processes by means of velocity equations [13]. Temporal parameters, consisting of the times of transcription, translation, the action of genetic products and feedback, can be taken into account using the equations:

\[
\frac{dx_i}{dt} = a_i r_i (x_1(t-h_{i1}), x_2(t-h_{i2}), \ldots, x_n(t-h_{in})) - \gamma_i x_i; \quad i = 1, 2, \ldots, n.
\]  

(4)

Where \(h_{i1}, \ldots, h_{in} > 0\) denote the discrete times necessary for the implementation of the chain of genetic regulation in general. Parameters \(\{a\} > 0\) are synthesis constants and \(\{\gamma\} > 0\) are decay constants. The velocity equations (4) express the balance between the number synthesized and decomposing of molecules per unit of time. Using these methods, models of genetic regulatory mechanisms can be created by defining a specific form of the functions \(r_i\) (\(i = 1, \ldots, n\)).

The application of the method of modeling the regulatory mechanisms of living systems [7], leads to the following mathematical model of the regulatory mechanisms of the interrelated activity of the molecular genetic systems of the hepatocytes and hepatitis B viruses [14, 15]

\[
\begin{align*}
\varepsilon_1 \frac{dX(t)}{dt} &= \frac{aX^2(t-1)}{1+X^2(t-1)+Y^2(t-1)} - X(t); \\
\varepsilon_2 \frac{dY(t)}{dt} &= \frac{bX(t-1)Y(t-1)}{1+dX^2(t-1)+Y^2(t-1)} - Y(t); \\
X(t) &= \varphi_1(t), \quad Y(t) = \varphi_2(t), \quad t \in [0, 1],
\end{align*}
\]

(5)

where \(X(t), Y(t)\) - the values characterizing the activity of the molecular genetic systems of the hepatocytes and HBV; \(a, b\) - constant product formation rates of molecular genetic systems of hepatocytes and HBV; \(c, d\) - parameters of the degree of interrepression of molecular genetic systems of hepatocytes and hepatitis B viruses; \(\varepsilon_1, \varepsilon_2\) - parameters of the regulatory of hepatocytes and HBV; \(\varphi_1(t), \varphi_2(t)\) - continuous functions on interval \([0, 1]\). All parameters are positive.

Conditions for the non-negativity of the genetic elements of the hepatocytes and viruses, as well as the limited resources of the cell, lead to the requirements of finding solutions in the first quadrant and the limited solutions. The results of a qualitative study show the feasibility of these requirements for equation (5). To find equilibrium positions \((X_0 = const; \ Y_0 = const)\) of functional-differential equations (5), according to the reasoning in sources [16, 17], we have:

\[
\frac{aX_0^2}{1+X_0^2+Y_0^2} = X_0; \\
\frac{bX_0Y_0}{1+dX_0^2+Y_0^2} = Y_0.
\]

The trivial equilibrium position (5) is an attractor. For some values of parameters, the attractors can be equilibrium positions of type \(A(X_0, 0)\) with positive \(X_0\) and a nontrivial equilibrium position \(B(X_0, Y_0)\) with positive \(X_0, Y_0\).

To analyze the stability of the equilibrium position, it is necessary to look at around the equilibrium point of equation (5). By introducing small variable changes, as:

\[
\begin{align*}
X(t) &= X_0 + x(t); \quad Y(t) = Y_0 + y(t); \\
X(t-1) &= X_0 + x(t-1); \quad Y(t-1) = Y_0 + y(t-1).
\end{align*}
\]

(6)
We have the following equation:

\[
\varepsilon_1 \frac{dx(t)}{dt} = \left(2 - \frac{2}{a} X_0\right) x(t-1) - \frac{2c}{a} Y_0 y(t-1) - x(t);
\]

\[
\varepsilon_2 \frac{dy(t)}{dt} = \left(\frac{Y_0}{X_0} - \frac{2d}{b} Y_0\right) x(t-1) + \left(1 - \frac{2}{b} Y^2_0\right) y(t-1) - y(t),
\]

which is a linearized equation for small around of equilibrium point of equation (5). Let us find the characteristic equations for the linearized equation (6).

\[
\begin{vmatrix}
\left(2 - \frac{2}{a} X_0\right) e^{-\lambda} - 1 - \lambda \varepsilon_1 & -\frac{2c}{a} Y_0 e^{-\lambda} \\
\left(\frac{1}{X_0} - \frac{2d}{b} Y_0\right) e^{-\lambda} & \left(1 - \frac{2}{b} Y^2_0\right) e^{-\lambda} - 1 - \lambda \varepsilon_2
\end{vmatrix} = 0;
\]

and we have the characteristic equations (7). If \(\frac{Y_0}{X_0} = \frac{2bc}{Y_0}\), then we obtain equations (8) and (9)

\[
\left(2 - \frac{2}{a} X_0\right) e^{-\lambda} - 1 - \lambda \varepsilon_1 = 0;
\]

\[
\left(1 - \frac{2}{b} Y^2_0\right) e^{-\lambda} - 1 - \lambda \varepsilon_2 = 0.
\]

To analyze equations (8) and (9), with the use of Hayes’s criterion [18], it is necessary to transfer these equations into the form of transcendental equation \((\lambda + a) e^\lambda + b = 0\):

\[
\left(\lambda + \frac{1}{\varepsilon_1}\right) e^\lambda + \left(\frac{2}{a} X_0 - 2\right) \frac{1}{\varepsilon_1} = 0.
\]

\[
\left(\lambda + \frac{1}{\varepsilon_2}\right) e^\lambda + \left(\frac{2 Y^2_0}{b} - 1\right) \frac{1}{\varepsilon_2} = 0.
\]

There were obtained the following conditions after applying Hayes’s criterion for equation (10).

1) \(\frac{1}{\varepsilon_1} > -1\).

2) \(X_0 > \frac{1}{2} a\).

3) \(X_0 < \frac{1}{2} a\).

There were obtained the following conditions after applying Hayes’s criterion for equation (11).

1) \(\frac{1}{\varepsilon_2} > -1\).

2) \(\frac{Y^2_0}{X_0} > 0\).

3) \(\frac{Y^2_0}{X_0} < b\).

Thus, if the conditions of the Hayes’s criterion are satisfied, then the equilibrium point of equation (5) is stable. Otherwise, it is unstable. It describes that we can observe the following regimes of functioning of the interrelated activity of the molecular genetic systems of hepatocytes and HBV: limit cycles of the Poincar type, dynamic chaos, and the effects of the black hole.
Developed mathematical model of functional differential equations of the regulatory mechanisms of the interrelated activity of the molecular genetic systems of the hepatocytes and hepatitis B viruses allow to quantitatively investigate the basic patterns of the infectious process in the hepatocytes in diseases of viral hepatitis B. The possibility of predicting the onset of the listed modes and their main characteristics allow, with computer support of laboratory and clinical studies of the infection process in hepatitis B, realize to diagnose and predict the characteristic stages of hepatitis B. To carry out computational experiments, we created a computer model based on equation (5) with use of method of the Runge-Kutta [19, 20].

Computational experiments on the quantitative analysis of regulatory of hepatocytes and HBV show the presence of some regimes.

Figure 4. The regime of the dynamic chaos of the regulatory of hepatocytes and hepatitis B viruses.

Figure 5. The regime of the "black hole" of the regulatory of hepatocytes and hepatitis B viruses.

Figure 4 shows the regime of the dynamic chaos regulatory of molecular genetic systems of hepatocytes and HBV with the following values of parameters $\varepsilon_1 = 0.069; \varepsilon_2 = 0.019; a = 9.3; b = 13.4; c = 4.16; d = 7.8$ and $X_0 = 5.3; Y_0 = 8$. The results in figure 5 show that the irregular functioning of the molecular genetic systems of hepatocytes and HBV, which describes the active infectious disease of viral hepatitis B in the liver.

Figure 5 shows the regime of the "black hole" regulatory of molecular genetic systems of hepatocytes and hepatitis B viruses with the following values of parameters $\varepsilon_1 = 0.2; \varepsilon_2 = 0.04; a = 12.2; b = 8.6; c = 4.1; d = 1.8$ and $X_0 = 4.9; Y_0 = 4$. The obtained results in the figure 6 show that the functioning of the molecular genetic systems of the liver cells and HBV tends to zero and destroys the body.

Based on the results of computational experiments, it is possible to develop a parametric portrait of functioning the regulatory mechanisms of interrelated activity of hepatocytes and hepatitis B viruses. The result of constructing the parametric portrait of the mathematical model (5) is shown in figure 6 with the following values of the parameters and the initial conditions $X_0 = 1.5, Y_0 = 1, c = 3, d = 0.333, \varepsilon_1 = 0.2, \varepsilon_2 = 0.01$:

Figure 6. Parametric portrait of the equation (5).
According to figure 6,
- \( A \) is the region of the active hepatocytes mode;
- \( B \) is the stable mode region;
- \( C \) is the region of limit cycles (normal region);
- \( D \) is the dynamic chaos region;
- \( C_{Rw} \) is the \( r \)-windows region (\( r \)-windows is a small normal region, which located in the dynamic chaos region \( D \));
- \( E \) is the black hole region;
- \( F \) is the fading mode region.

The parametric portrait includes all the modes of the regulatory of liver cells and hepatitis B viruses. The parametric portrait allows to analyze the regimes of the interrelated activity of liver cells and hepatitis B viruses at the molecular genetic level.

4. Conclusions

Thus, the results of a qualitative and quantitative analyses of equation (1) show the existence of various modes of functioning, which is quite consistent with normal heart activity and anomalies, and argue that the methods of mathematical modeling can be successfully applied in practical medicine to study heart regulatorika and the method of behavior correction for improving functioning of the heart. The developed mathematical and computer models make it possible to carry out computational experiments for the quantitative analysis of the behavior of considered object, which ensures the specialists to improve the quality of early computer diagnostics and treatment tactics.

The developed mathematical and computer models for the study of functioning hepatocytes and HBV regulatory mechanisms allow to assess the state of the interrelated activity of the molecular genetic systems of the liver cells and HBV; establish the molecular genetic basis of pathogenesis; to assess and predict the occurrence of characteristic stages of the clinical course with viral hepatitis B.

Aknowledgments

The authors express deep gratitude to candidate of physical and mathematical sciences B.N. Hidirov for the formulation of tasks and assistance at all stages of the study. This work was supported by grant from the Scientific and Innovation Center of Information and Communication Technologies at Tashkent University of Information Technologies named after Muhammad Al-Khwarizmi (A-5-005).

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