

Software Development for Quantitative Analyzing of the Regulatory of Liver Cell and Hepatitis B Viruses by Using of Information Technologies

Mahruy Saidalieva, Mohiniso Baxromovna Hidirova^{*}, Abrorjon Maxamatsoliyevich Turgunov

Scientific and Innovation Center of Information and Communication Technologies, Tashkent University of Information Technologies Named After Muhammad Al-Khwarizmi, Tashkent, Uzbekistan

Email address:

regulatorika@yahoo.com (M. Saidalieva), mhidirova@yandex.ru (M. B. Hidirova), abrorjon-2010@inbox.uz (A. M. Turgunov)

^{*}Corresponding author

To cite this article:

Mahruy Saidalieva, Mohiniso Baxromovna Hidirova, Abrorjon Maxamatsoliyevich Turgunov. Software Development for Quantitative Analyzing of the Regulatory of Liver Cell and Hepatitis B Viruses by Using of Information Technologies. *Software Engineering*. Vol. 5, No. 6, 2017, pp. 81-87. doi: 10.11648/j.se.20170506.11

Received: December 5, 2017; **Accepted:** December 15, 2017; **Published:** January 10, 2018

Abstract: In this article, the results on identifying of areas of homogeneous solutions of the functional-differential equations of the mathematical model of regulatory mechanisms of liver cell with hepatitis B viruses by constructing a parametric portrait using of modern information technology were presented. Typical phase trajectories were obtained using the object-oriented programming language Borland Delphi. The features of the area of the chaotic regime regulatory related activities of molecular genetic mechanisms of the liver cell and hepatitis B viruses by analyzing the dynamics of the Lyapunov exponent. Defined small regions with regular behavior ("r-windows") in the field of dynamic chaos. The regulatory of the liver cell and hepatitis B viruses can be moved from the region of dynamic chaos to normal region by using "r-windows".

Keywords: Regulatory Mechanisms, Mathematical and Computer Models, Qualitative and Quantitative Analysis, Parametric Portrait, Symbiosis, Chaos, Black Hole

1. Introduction

Using information technologies in hepatology (for example, in the study of infectious disease by viral hepatitis B) is relevant task of modern hepatology. One of the main goals of using the information technologies in hepatology is to analyze the regulatory mechanisms of the onset and development of infectious disease with hepatitis B virus in the liver cell by using effective means of these technologies, which provides an improvement in the quality of population health protection.

When viruses penetrate the body, complex processes occur this lead, depending on the type of viruses and the response of the cell, either to the development of an acute infectious disease with a pronounced clinical picture, or to the disease that is asymptomatic, or to a long-term chronic disease. Hepatitis B can be the first among human viral hepatitis and the prevalence of the disease, which can subsequently lead to cirrhosis and liver cancer. Around one of third of the world's population is infected with the hepatitis B virus (HBV) and

over 350 million (5-6%) are HBsAg-carriers. One to two million people die each year from complications caused by HBV [1].

At the heart of the formation of a complex infectious process for each type of viral hepatitis are the features of the relationship between viruses and the liver cell. To date, the basic mechanisms of the interrelated activity of the liver cell (hepatocyte) and hepatitis viruses have not been clarified yet.

2. Materials and Methods

One of the main directions of the new millennium is the active introduction of information technologies in all areas of human activity without exception. At present, computer science and information technologies play a significant role in the research activity of living systems, including the interrelated activity of the liver and viral hepatitis B.

Mathematical modeling is widely used in various areas. The mathematical model of a dynamic system is usually a set

of differential equations, ordinary, partial derivatives, or ordinary with delayed arguments.

E. N. Wiah *et al.* [2] considered that the mathematical modeling of the process of interaction of the HBV with the immune system, including the effect of therapy. To describe the interaction between populations of cells and viruses in the body, the authors used a system of nonlinear differential equations. In modeling, a set of various parameters that satisfy different conditions was used. The authors hypothesized on the basis of the results obtained that the model can interpret a wide range of clinical manifestations of infection.

When a virus infects an uninfected cell, various types of infected cells are produced. These include actively infected cells (A), which produce most of the plasma virus, latently infected cells (L) that are expected to produce immediately after infection, persistently infected (P) and defective cells (D).

Active (T_A) and latently (T_L) infected cell populations are considered in the model. It also considers two viral populations - infectious (V_I) and non-infectious (V_{NI}) viruses.

$$\begin{aligned} \frac{dT_{NI}}{dt} &= \lambda - (1 - \eta_R)\gamma T_{NI}V_I - \mu_{NI}T_{NI}; \\ \frac{dT_L}{dt} &= (1 - \pi)(1 - \eta_R)\gamma T_{NI}V_I - \alpha_L T_L - \mu_L T_L; \\ \frac{dT_A}{dt} &= \pi(1 - \eta_R)\gamma T_{NI}V_I + \alpha_L T_L - \mu_A T_A; \\ \frac{dV_{NI}}{dt} &= \eta_p p T_A - \mu_V V_{NI}; \\ \frac{dV_I}{dt} &= (1 - \mu_p) p T_A - \mu_V V_I. \end{aligned} \quad (1)$$

However, the system of equations obtained by the authors does not have an analytical solution, and therefore the analysis of the model is carried out by a numerical method.

A. M. Elaiw *et al.* [3] considered the dynamics of HBV on the basis of a mathematical model using a system of nonlinear ordinary differential equations. The model includes two types of drug therapy, which are used to inhibit to the formation of viruses and prevent new infections. The model can be considered as a non-linear control system with control input, it is defined as dose-dependent drug and drug effectiveness. The authors developed treatment regimens for patients with HBV infection by using a multivariate prognostic control.

C. Xiao *et al.* [4] presented a modified model of the hepatitis B virus with an immune response and alanine aminotransferase (ALT) periods. Most models do not take into account the role of the ALT level. However, ALT plays a major role in the detecting damage to human liver cells. Typically, an increase in ALT levels is associated with the death of uninfected hepatocytes, the natural death of infected hepatocytes, and the death of infected hepatocytes caused by the immune response. When liver cells are damaged, ALT is released into the blood, which increases the level of ALT in the serum. This, the extent of liver damage can be controlled by ALT levels. Therefore, models with ALT levels can detect the activation of the immune response and liver damage.

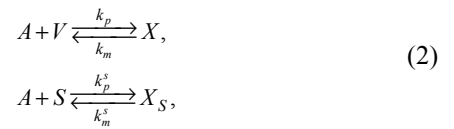
M. Kissa *et al.* [5] formulated and analyzed a nonlinear

mathematical model for studying mathematical modeling of optimal control of HBV infection in the presence of cytotoxic cells. The proposed model describes the interaction between normal cells, HBV and cytotoxic cells. The authors also performed numerical modeling and sensitivity analysis to determine the key parameters contributing to spread of disease, and to illustrate the analytical results. Authors carried out the numerical studies of the model in order to see the effect of key parameters on the optimal control of HBV infection in the presence of a cytotoxic agent.

S. M. Ciupe *et al.* [6] investigated the defense mechanism by developing a mathematical model for the antibody response after hepatitis B virus infection, and the model was selected for these seven infected adults identified during an acute infection and determined the ability of the virus to avoid neutralization at the expense of overproduction of noninfectious subviral particles that have HBs proteins on their surface, but do not contain a nucleocapsid protein and a viral nucleic acid series. Further, the authors showed that viral clearance can be achieved for low equilibrium levels of anti-HBV antibody, as unvaccinated in individuals, when a strong cellular immune response to controlling an early infection.

To include a response to the antibody, S. M. Ciupe *et al.* Summarized the model corresponding to target cells (T) that are predominantly or exclusively uninfected hepatocytes, cells that are productively infected (I), free virus (V), free subviral particles (S), free antibody (A), virus complexes-antibody (X) and a sub-virus particle-antibody complex (X_S).

The authors examined the reversible binding of free anti-HBsAg antibody (A), both with the free virus (V) and with the virus subvirus (S) described by the reaction scheme



where (X) and (X_S) are complexes formed between the antibody and viral and subviral particles, respectively. Based on the scheme (2), the authors constructed the following equations of the virus-host interaction

$$\begin{aligned} \frac{dT}{dt} &= rT\left(1 - \frac{T+I}{T_m}\right) - \beta VT; \\ \frac{dI}{dt} &= \beta VT - \delta I; \\ \frac{dA}{dt} &= p_A(V+S) + r_A A\left(1 - \frac{A}{A_m}\right) + k_m X - k_p AV + k_m^s X_S - k_p^s AS - d_A A; \\ \frac{dX}{dt} &= -k_m X + k_p AV - c_{AV} X; \\ \frac{dX_S}{dt} &= -k_m^s X_S + k_p^s AS - c_{AS} X_S; \\ \frac{dV}{dt} &= \pi I - cV + k_m X - k_p AV; \\ \frac{dS}{dt} &= \pi \theta I - c_S S + k_m^s X_S - k_p^s AS, \end{aligned} \quad (3)$$

where

$$T(0) = T_m > 0, I(0) = 0, A(0) = 0, \\ V(0) = V_0 > 0, S(0) = 0, X(0) = 0, X_S(0) = 0.$$

The total concentration of viral DNA is described by this formula

$$V_T = V + X,$$

and the total concentration of antibodies against to do HBsAg is given by formula

$$A_T = A + X + X_S.$$

The work of H. Laarabi et al. [7] is designed to maximize the number of normal cells (cells of the underlying liver tissue). To date, several studies have been conducted for the mathematical analysis of HBV disease control with acute and chronic stages. H. Laarabi et al. are tested the study of optimal strategies for antiviral therapy of HBV infection with the growth of logistic hepatocytes without taking into account the effect of cytotoxic cells. Therefore, M. Kissa et al. proposed to expand the work [7], including cytotoxic cells and determine optimal control over the disease.

P. T. Moufo et al. [8] studied the dynamic behavior of a new model of the hepatitis B virus with two strains of the virus and CTL immune responses. The authors calculated the base of reproduction coefficient of the model and showed the dynamic dependences of this threshold. After this, the authors expanded the model constructed by Nowak and Bangham [9], when there is no mutation including impulse vaccination, and found the conditions for its eradication. The results of the study by P. T. Moufo et al. indicate that, if the vaccine is strong enough, both strains lead to extinction, suggesting an excellent adherence.

Above mentioned numerous mathematical models describe the dynamics of the hepatitis B virus in the liver cell, mainly, the cellular level. In accordance with the biological regularity of these processes, the development of an infectious disease occurs in the relationship between the genomes of the hepatitis B viruses and liver cell. Therefore, modeling the functioning of viral hepatitis B in the liver cell, special attention should be paid to the mechanisms of molecular genetic systems of the process under consideration. In the modeling of regulatory of liver cell and hepatitis B viruses, functional-differential equations were used. Equations are built on the basis of firmly established biological facts and the regularities.

3. Results and Discussions

In this paper, the quantitative study of the regulatory mechanisms (regulatorika) of the interrelated activity of molecular genetic systems of hepatocyte and hepatitis B viruses are considered. The recognition of the interrelated activity of the hepatocyte and hepatitis B viruses at the molecular genetic level assumes an analysis of the mechanisms of gene activity in the functioning cell. As a

class of mathematical equations for quantitative analysis of the regulatory of the functioning of genetic systems of hepatocyte and hepatitis B viruses, it is possible to adopt the general equations of the regulatory of molecular genetic systems [10- 12], which have the form:

$$\varepsilon_1 \frac{dX(t)}{dt} = \frac{aX^2(t-1)}{1 + X^2(t-1) + cY^2(t-1)} - X(t); \\ \varepsilon_2 \frac{dY(t)}{dt} = \frac{bX(t-1)Y(t-1)}{1 + dX^2(t-1) + Y^2(t-1)} - Y(t), \tag{4}$$

$$X(t) = \varphi_1(t); Y(t) = \varphi_2(t)$$

$$\text{at } t \in [0, 1],$$

Table 1. Description of variables and model parameters.

Variables and Parameters	Description
$X(t), Y(t)$	the values characterizing the activity of the molecular genetic systems of the liver cell and hepatitis B viruses, respectively
a, b	constant product formation rates of molecular genetic systems of liver cell and hepatitis B viruses
c, d	parameters of the degree of inter-repression of molecular genetic systems of hepatocyte and hepatitis B viruses
$\varepsilon_1, \varepsilon_1 = \tau_x / h$	parameters of the regulatory of liver cell and hepatitis B viruses
$\varepsilon_2, \varepsilon_2 = \tau_y / h$	
τ_x, τ_y	parameters characterizing the "lifespan" of products of molecular genetic systems of hepatocyte and hepatitis B viruses
h	time required for feedback in the system under consideration
$\varphi(t), \varphi(t)$	continuous functions on $[0; 1]$;

All parameters are positive.

The system of ordinary differential equations with retarded argument (4) is nonlinear systems, and a closed system, and their solution can be constructed by Bellman-Cook's method of sequential integration [13].

For certain values of the parameters (4), the activity of the molecular genetic systems of the hepatocyte and the hepatitis B viruses have various regimes (gradual death of molecular-genetic systems of liver cell and hepatitis B viruses, joint activity (symbiosis) of molecular-genetic systems of liver cell and hepatitis B viruses and dominant activity of the molecular-genetic system of the liver cell) (figure 1).

Here, the activity of the molecular genetic systems of the hepatocyte and the hepatitis B viruses are suppressed (figure 1, region A). Besides, activated the molecular genetic system of the hepatocyte is against the background of suppression of hepatitis B viruses activity (figure 1, region C) and together activated the molecular genetic system of the hepatocyte and hepatitis B viruses (figure 1, region D) and activated the molecular genetic system of the hepatitis B viruses is against the background of suppression of hepatocyte activity (figure 1, region B). This describes the symbiotic functioning of the molecular genetic systems of liver cell and hepatitis B viruses. Also, activated of the dominant of the liver cell is against the background of

suppression of hepatitis B viruses' activity (figure 1, region E).

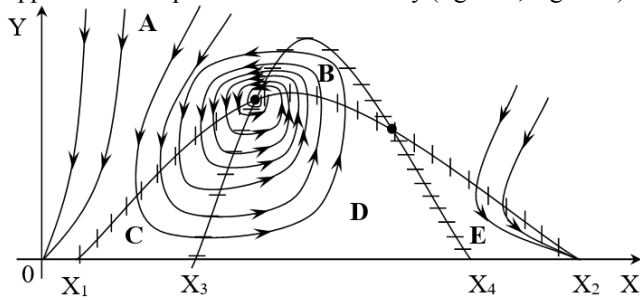


Figure 1. Lethal outcome of the interaction of the "hepatocyte-HBV" system.

For certain values of the parameters of the system of functional-differential equations (4), the regime under consideration qualitatively changes by the Hopf bifurcation-the appearance of oscillatory solutions.

A computer model was developed based on the equations and mathematical model of the regulatory of the interrelated activity of the molecular genetic systems of the hepatocyte and hepatitis B viruses, for the investigation of the regulatory of liver cell and

hepatitis B viruses at the molecular-genetic level in norm and in anomalies, by using the object-oriented programming language Borland Delphi. The developed computer model is designed for carry out computer experiments by computer simulation of the regulatory of hepatocyte and hepatitis B.

The quantitative research of functional-differential equations (4) was accompanied by computer simulation on a PC. The main attention is paid for case of symbiotic coexistence (chronic hepatitis B). The results of computer studies showed the presence of intermittent symbiotic functioning of hepatocyte and hepatitis B viruses (in addition to the regimes observed in quantitative research) irregular oscillations (figure 2) and the "black hole" effect (figure 3). In the latter case, the oscillations are disrupted and the solutions (4) tend to a trivial attractor (figure 3).

$$\varepsilon_1 = 0.1, \quad \varepsilon_2 = 0.03, \quad a = 4.1, \quad b = 2.2, \quad c = 2.6, \quad d = 0.12 \text{ and } X_0 = 5, \quad Y_0 = 6.$$

are values of the parameters of the model (4).

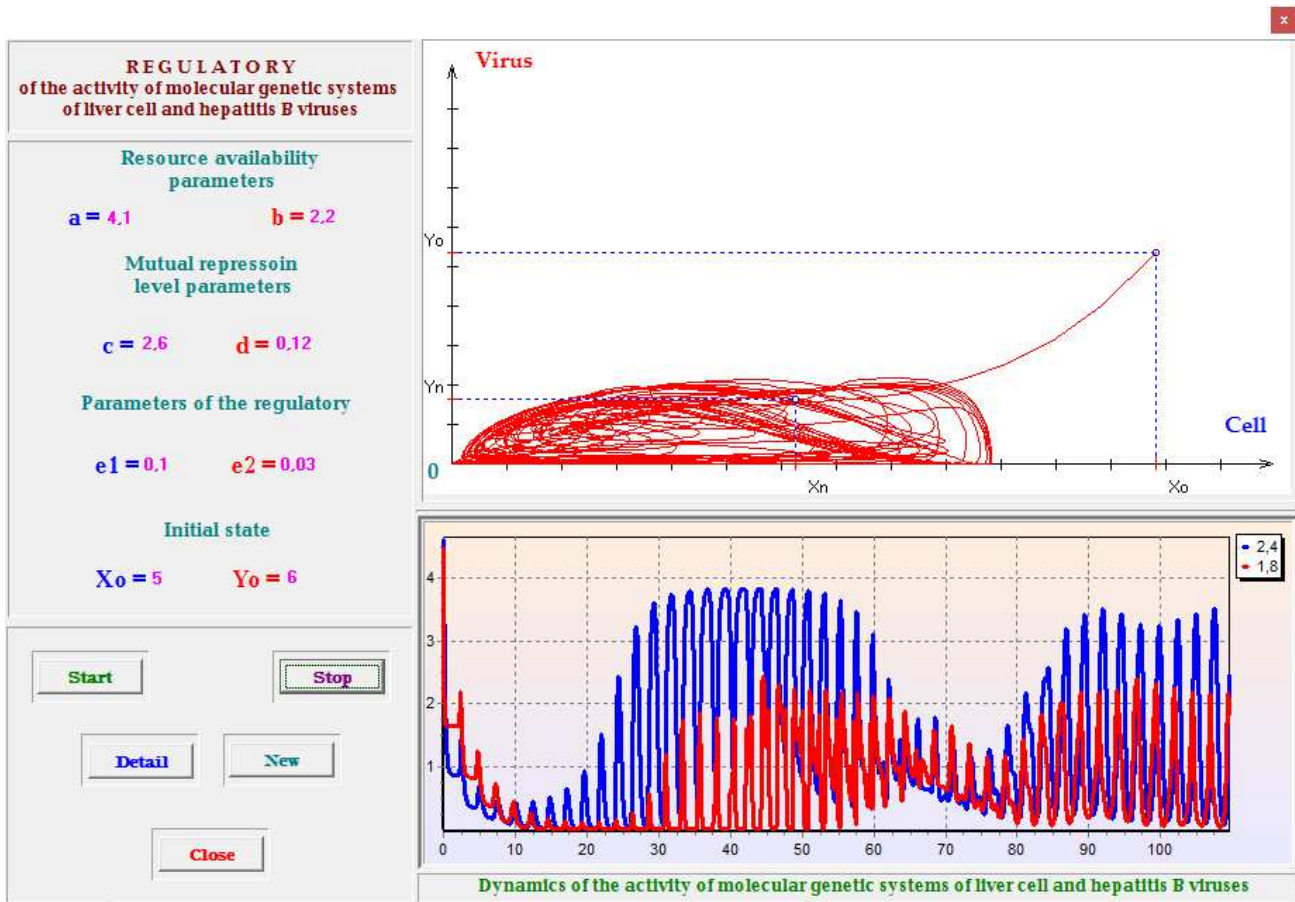


Figure 2. The regime of irregular oscillations of the regulatory of hepatocyte and hepatitis B viruses.

Figure 2 shows the regime of the irregular oscillations of the regulatory of molecular genetic systems of liver cell and hepatitis B viruses. The result in the figure describes the active infectious disease of viral hepatitis B in the liver. In this case, industry specialists must develop operational measures.

Otherwise, death of liver cell can be observed. This leads to loss of the liver organ and death of the human body.

$$\varepsilon_1 = 0.1, \quad \varepsilon_2 = 0.03, \quad a = 4.1, \quad b = 2.22, \quad c = 2.6, \quad d = 0.12 \text{ and } X_0 = 5, \quad Y_0 = 6 \text{ are values of the parameters of the model (4).}$$

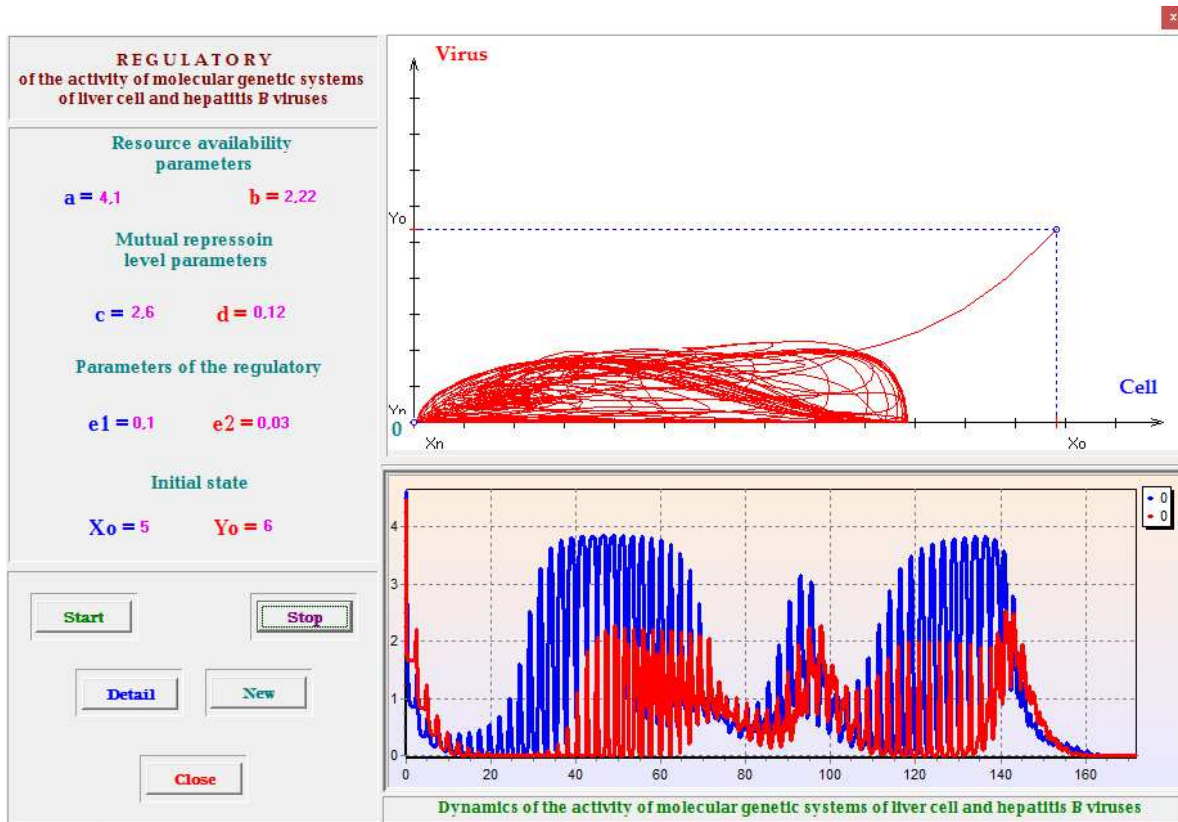


Figure 3. The regime of the black hole"of the regulatory of hepatocyte and hepatitis B viruses.

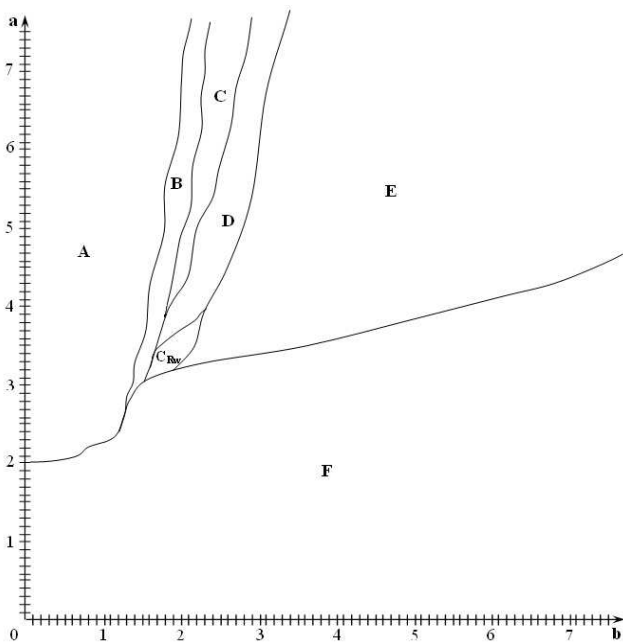


Figure 4. Parametric portrait of the equations of the mathematical model of the molecular genetic mechanisms of the interrelated activity of the genetic systems of hepatocyte and hepatitis B viruses for certain values of the parameters (A is the region of the active hepatocyte regime, B is the stable mode region, C is the region of limit cycles (normal region), D is the dynamic chaos region, C_{Rw} is the "r-windows" area ("l-windows" is small normal region (C) in the dynamic chaos region (D)), E is the black hole" area, F is the fading mode region).

In the figure 3 shows the regime of the "black hole" regulatory of molecular genetic systems of liver cell and hepatitis B viruses. The result in this figure describes the functioning of the molecular genetic systems of the liver cell and HBV tends to zero and deaths of the human body.

Let's consider the presence of the main modes of the regulatory of the interrelated activity of molecular genetic systems of liver cell and hepatitis B viruses. The result of constructing the parametric portrait of the model (4) is shown in the figure 5 with the following values of the parameters and the initial conditions [14-18]:

$X_0=1.5, Y_0=1, c=3, d= 0.333, \epsilon_1 = 0.2, \epsilon_2 = 0.01$ are values of the parameters of the model (4).

The mode of irregular oscillations is characterized by a violation of the hepatocyte regulation system with a consequent deterioration of its functional activity. A quantitative study of the structural organization of the region of irregular oscillations, and the region of dynamic chaos, shows the strong inhomogeneity with sharp spasmodic changes in randomness-the Lyapunov exponent.

As shown by calculations on the PC, in the regime of dynamic chaos, small regions are observed-r-windows, within which the behavior of solutions (4) has a regular character. This indicates the possibility of temporary improvement of the hepatocyte state during infection with the hepatitis B virus. However, this improvement is temporary and small perturbations are again lead molecular

genetic systems of the hepatocyte into a regime of dynamic chaos.

The entry into the region of irregular oscillations can be predicted: it is preceded by the series of bursts of values of the Lyapunov exponent-Hopf bifurcation in the Feigenbaum scenario. The outbursts can be fixed by analyzing solutions on the PC. This allows predicting the onset of destructive changes in the hepatocyte under the influence of HBV.

In the case of model studies of general regulatory mechanisms, the functioning of the molecular genetic system of the liver cell for hepatitis B viruses can be used for small values of ϵ_1, ϵ_2 , the functional equation [19-20].

$$\begin{aligned} X(t) &= \frac{aX^2(t-1)}{1+X^2(t-1)+cY^2(t-1)}; \\ Y(t) &= \frac{bX(t-1)Y(t-1)}{1+dX^2(t-1)+Y^2(t-1)}, \end{aligned} \tag{5}$$

and its discrete analogue

$$\begin{aligned} X_{k+1} &= \frac{aX_k^2}{1+X_k^2+cY_k^2}; \\ Y_{k+1} &= \frac{bX_kY_k}{1+dX_k^2+Y_k^2}. \end{aligned} \tag{6}$$

For the analysis of chaotic regimes of the molecular genetic system of the liver cell in case of viral load, a computer program Lap was developed (Figures 5, 6).

$a=9.4, b=10.6, c=3.15, d=0.1$ and $X_0=1$ are values of the parameters of the (6).

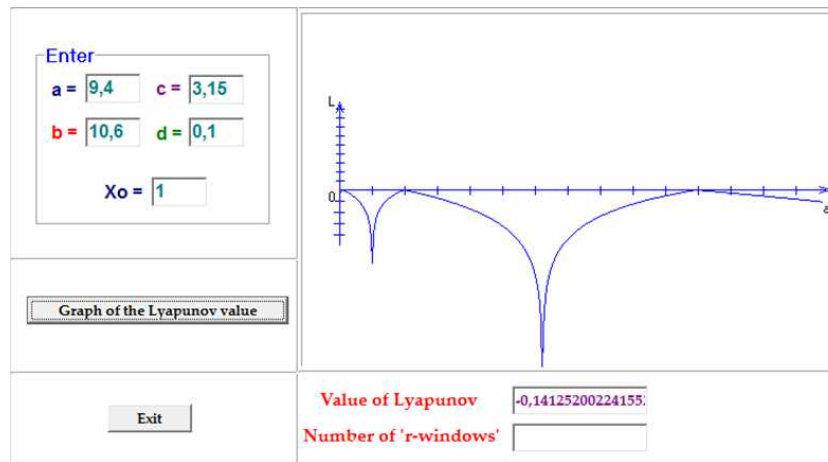


Figure 5. The graph of Lyapunov value and Lyapunov exponent for the discrete equation (6).

According to the results shown in Figure 5, the molecular genetic system of liver cell can be in the "r-windows". Because, the value of Lyapunov is negative and graph of Lyapunov value didn't cross the 'a' axis.

$a=8.4, b=10.6, c=3.15, d=0.1$ and $X_0=1$ are values of the parameters of the (6).

In Figure 6, the Lyapunov value is positive and the

Lyapunov graph has crossed the 'a' axis and also number of "r-windows" are 4. This means, molecular genetic systems of liver cell and HBV is in zone of dynamic chaos that has 4 small normal regions. The system of "Hepatocyte-HBV" can be moved from the region of dynamic chaos (D) to normal region (C) by using "r-windows".

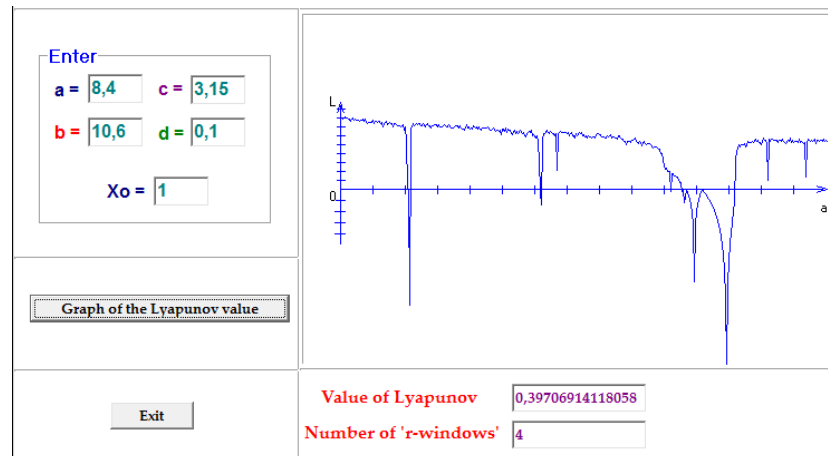


Figure 6. The graph of Lyapunov value and Lyapunov exponent for the discrete equation (6).

4. Conclusions

Thus, the existing experimental data and theoretical rules regarding regularities of infection with hepatitis B enabled us to develop mathematical and computer models of regulatory mechanisms related to the activities of liver cell and hepatitis B virus at the molecular genetic level. The developed software system for the quantitative study of functioning of hepatitis B at the hepatocyte makes it possible to diagnose the course of infectious process and to predict one of its basic modes, i.e. cause of decease, by using the clinical data.

Based on the results of computational experiments, a parametric portrait of the regulatory of the interrelated activity of molecular genetic systems of hepatocyte and hepatitis B viruses was developed. On the basis of parametric portraits, it is possible to analyze all modes of functioning of regulatory mechanisms of liver cell and hepatitis B viruses at the molecular-genetic level.

References

- [1] World Health Organization. (2014). News bulletin. <http://www.who.int/topics/hepatitis/en/>
- [2] Wiah E. N., Adetunde I. A., Brew L. (2012). Mathematical Modeling of the Interaction of Hepatitis B Virus with the Immune System Including the Effect of Therapy // International Journal of Modern Mathematical Sciences. 1 (2): 53-72.
- [3] Elaiw A. M., Alghamdi M. A., Aly Sh. (2013). Hepatitis B Virus Dynamics: Modeling, Analysis, and Optimal Treatment Scheduling // Discrete Dynamics in Nature and Society. 9.
- [4] Chen X., Sun K., Qiu J., Chen X., Yang Ch., Zhang A. (2014). Dynamics analysis of an amended HBV infection model with a simulation for anti-HBV infection therapy // Proceedings of the 33rd Chinese Control Conference. Nanjing, China. 2829-2834.
- [5] Mboya K., Makinde D. O., Massawe E. S. (2015). Cytotoxic Cells and Control Strategies are Effective in Reducing the HBV Infection through a Mathematical Modelling // International Journal of Prevention and Treatment. 4 (3): 48-57.
- [6] Stanca M. C., Ruy M. R., Alan S. P. (2014). Antibody Responses during Hepatitis B Viral Infection // PLoS Comput Biol. 10 (7): 1-16.
- [7] Laarabi H., Abta A., Rachik M. and Rouyaghroumni J. (2013). Optimal antiviral treatment strategies of HBV infection model with logistic hepatocytes growth. ISRN Biomathematics.
- [8] Plaire T. M., Jean J. T., Boulchard M., Bowong S. (2015). Mathematical analysis of the effect of a pulse vaccination to an HBV mutation // ARIMA Journal. 21: 3-19.
- [9] Nowak M. A., Bangham C. R. M. (1996). Population dynamics of immune responses to persistent viruses. Science 272: 74-79.
- [10] Hidirov B. N. (2014). Selected works on mathematical modeling of the regulatory of living systems. Moscow: Izhevsk. 304.
- [11] Hidirov B. N., Turgunov A. M. (2010). Mathematical modeling of regulatory mechanisms for the development of viral hepatitis B // Questions of computational and applied mathematics. Tashkent. 125: 153-160.
- [12] Hidirov B. N., Turgunov A. M. (2012). Modeling of molecular genetics mechanisms of control of viral hepatitis B. Uzbek journal of the Problems of Informatics and Energetics. 2-3: 13-18.
- [13] Bellman R., Cooke K. (1963). Differential Difference Equations. Academic Press. 548.
- [14] Saidaliev M., Hidirova M. B., Turgunov A. M. (2014). Areas of homogeneous solutions of the equations of the mathematical model of the regulatory of liver in hepatitis B. Uzbek journal of the Problems of Informatics and Energetics. 6: 3-8.
- [15] Saidaliev M., Hidirova M. B., Turgunov A. M. (2015). Modeling of the regulatory of the liver cell in the quasi-stationary state of the hepatitis B virus. Scientific - technical and information-analytical journal TUIT - TUIT BULLETIN. 3 (35)/2015: 160-165.
- [16] Hidirova M. B., Turgunov A. M. (2015). Computer modeling of infectious disease with viral hepatitis B using information technologies. Materials of the XV International Scientific and Methodical Conference "Informatics: Problems, Methodology, Technologies". 1: 478-481.
- [17] Turgunov A. (2017). Analysis of the regulatory of the liver cell and hepatitis B viruses using a computer model. Collection of reports of the republican scientific and technical conference "The importance of information and communication technologies in the innovative development of real sectors of the economy". 1: 263-265.
- [18] Turgunov A. M. (2017). On the modeling of regulatory of the liver cell and hepatitis B viruses. Scientific journal "Problems of computational and applied mathematics". 4 (10): 53-62.
- [19] Hidirova M. B. (2014). On the solutions of the functional differential equation of the regulatory of living systems // Bulletin of the Moscow University series 1. Mathematics. Mechanics. 1: 50-52.
- [20] Turgunov A. M. (2017). Characteristic regimes of the behavior of solutions of the regulator equations of the "Hepatocyte-HBV" system. Materials of the XVII International Scientific and Methodical Conference "Informatics: Problems, Methodology, Technologies". 2: 446-450.