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Abstract

The study of the functioning of hepatitis B viruses in liver cells using methods of mathematical modeling is considered one of today's pressing issues. In this article, the domains of functional- differential equations in a mathematical model of regulatory mechanisms of hepatocytes interacting with hepatitis B viruses (HBV) are presented. Characteristic molecular genetic systems regulatory mechanisms of the interrelated activities of liver cells and HBV are analyzed. A series of computational experiments show that the "chaos" and "black hole" theories describe two of the more dangerous regimes. As a result of the analysis of the "chaos" regime, small regions with normal behavior, "r-windows" were revealed. These regions allow the system to move from a "chaos" regime to a "regular" or normal regime. The features of the area of the regulatory activities of molecular genetic mechanisms of hepatocytes and HBV under a chaotic regime were characterized by analyzing the dynamics of the Lyapunov exponent. Small regions with regular behavior, "r-windows" in the field of dynamic chaos were defined. The regulatory nature of hepatocytes and HBV can be moved from the region of dynamic chaos to the normal region by using "r-windows". The results of a computational experiment quantitatively analyzing the regulatory mechanisms of liver cells and HBV are presented.

Keywords: regulatory mechanisms, mathematical and computer models, qualitative and quantitative analysis, chaos, black hole

Introduction

Infection with hepatitis B virus (HBV) remains a global public health problem, and chronic infection with HBV can lead to liver cirrhosis and primary hepatocarcinoma. So far, the mechanisms of the onset of liver cirrhosis and liver cancer of viral etiology and methods for their early diagnosis are completely unknown. The development of the infectious process in hepatitis B virus is determined not only by the properties of the HBV virus but also by individual, genetically determined features of the human liver and the interrelated functioning of the molecular genetic systems of HBV and hepatocytes, or liver cells (LC).

Approximately 19.4% of deaths have been caused by infections in recent years, and this figure is gradually increasing. The most deadly virus on the earth is various strains of the hepatitis virus, which kills more than 1.3 million people every year. One of the reasons for this is that people who are positive for the HBV are not aware of their status. According to researchers, only 5% of people in developed and developing countries are aware of their diagnosis and seek treatment in medical institutions [1,2]. Therefore, the study of regulatory mechanisms of hepatitis B in LC using the methods of mathematical and computer modeling is extremely important.

Moneim I.A. and Khalil H.A. [3] studied the global behavior of HBV spread using the SEIR model assuming a constant vaccination rate. Infectivity during the incubation period was considered as the second mode of transmission.

Wiah E.N. et al. [4] constructed a mathematical model 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 parameters that satisfied various conditions was used. The authors hypothesized based on the results obtained that the model could be used to interpret a wide range of clinical manifestations of infection.

Elaiw A.M. et al. [5] considered the dynamics of HBV based on a mathematical model using a system of nonlinear ordinary differential equations. The model included two types of drug therapy, which are used to inhibit the formation of viruses and prevent new infections. The model can be considered as a non-linear control system with control input, defined as a drug with a dose-dependent effect and drug effectiveness. The authors developed treatment regimens for patients with HBV infection by using a multivariate prognostic control model.

Chen X. et al. [6] presented a modified model of the HBV 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 detecting damage to human LC. 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 LC are damaged, ALT is released into the blood, which increases the level of ALT in the serum. Thus, the extent of liver damage can be controlled by ALT levels. Therefore, models including ALT levels can detect immune response activation and liver damage.

Mboya K. et al. [7] formulated and analyzed a nonlinear mathematical model for 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 the spread of disease and to illustrate the analytical results. The authors carried out numerical studies of the model to observe the effect of key parameters on optimal control of HBV infection in the presence of a cytotoxic agent.

Stanca M.C. et al. [8] investigated host defense mechanisms by developing a mathematical model for the antibody response after HBV infection. The model was selected for seven infected adults identified during acute infection and determined the ability of the virus to avoid neutralization at the expense of overproduction of noninfectious subviral particles that have HB proteins on their surface but do not contain a nucleocapsid protein or a viral nucleic acid series. Further, the authors showed that viral clearance can be achieved for low equilibrium levels of anti-HBV antibody, such as in unvaccinated individuals during a strong cellular immune response to controlling early infection.

The work of Laarabi et al. [9] was designed to maximize the number of normal cells (cells of the underlying liver tissue). To date, several studies have been conducted on the mathematical analysis of HBV disease control in the acute and chronic stages. Laarabi et al. studied optimal strategies for antiviral therapy for HBV infection with the growth of logistic hepatocytes without taking into account the effect of cytotoxic cells.

Plaire et al. [10] studied the dynamic behavior of a new model of the HBV with two strains of the virus and CTL immune responses. The authors calculated the base of the reproduction coefficient of the model and showed the dynamic dependences of this threshold. Subsequently, the authors expanded the model constructed by Nowak and Bangham [11] when there is no mutation, including impulse vaccination, and found the conditions for its eradication.

The numerous abovementioned mathematical models describe the dynamics of the HBV in the liver cell, mainly at the cellular level. Following the biological regularity of these processes, the development of an infectious disease occurs in the relationship between the genomes of the HBV and liver cell. Therefore, when 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.

Numerous mathematical models describing the dynamics of HBV in LC have been proposed, including those outlined in [3-11]. In these studies, a mathematical simulation plays an important role in the understanding and quantification of biological mechanisms that govern the dynamics of HBV. Here simulation of the HBV is mainly performed at the cellular level. Following the biological laws of these processes, the development of an infectious disease occurs when a relationship between the genomes of the LC and HBV exists. Therefore, when modeling the functioning of HBV in the liver cell special attention should be given to including the mechanisms of molecular genetic systems of the process. We have developed a new mathematical model of the dynamics of molecular genetic systems LC and HBV.

Mathematical Model and Analysis

Model of HBV in LC. Studies are carried out on the basis of the method of living systems regulatorics [12], which makes it possible to consider a wide range of phenomena combined with the presence of the regulatory system, the regulatory environment, and combined feedback on, for example, HBV infection of human hepatocytes.

This work is devoted to researching the regulatory mechanisms of LC and HBV based on functional-differential equations. A new mathematical model of the HBV in hepatocytes developed by Hidirov [12-16] can be given as follows [17-21]:

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 LC and HBV, respectively
a, b	constant product formation rates of molecular genetic systems of LC and HBV
c, d	parameters of the degree of inter-repression of molecular genetic systems of hepatocyte and HBV
$\varepsilon_1, \varepsilon_2$	parameters of the regulatory machinery of liver cell and HBV
$\varphi_1(t), \varphi_2(t)$	continuous functions on [0,1]

$$\varepsilon_1 \frac{dX(t)}{dt} = \frac{aX^2(t-1)}{1 + X^2(t-1) + cY^2(t-1)} - X(t);$$
$$\varepsilon_2 \frac{dY(t)}{dt} = \frac{bX(t-1)Y(t-1)}{1 + dX^2(t-1) + Y^2(t-1)} - Y(t);$$
$$X(t) = \varphi_1(t); \; Y(t) = \varphi_2(t) \text{ at } t \in [0,1] \quad (1)$$

The mathematical model was developed on the basis of firmly established biological laws. All parameters are positive and dimensionless.

The parameters are determined from the compliance condition that the developed model corresponds to the biological process under study, based on the experimental data obtained from specialists, thus bringing the mathematical model closer to the real one. This model describes the dynamics of interrelated activity of molecular genetic systems of LC and HBV. The right-hand side of the equation includes activating and suppressing the forces acting on a system of LC and HBV. The qualitative analysis of developed equations to obtain full information about the nature of the molecular and genetic processes in any possible biologically reasonable initial conditions.

We obtain the following equation

$$\varepsilon_1 \frac{dx(t)}{dt} = \frac{a(X_0 + x(t-1))^2}{1 + (X_0 + x(t-1))^2 + c(Y_0 + y(t-1))^2} - (X_0 + x(t));$$
$$\varepsilon_2 \frac{dy(t)}{dt} = \frac{b(X_0 + x(t-1))(Y_0 + y(t-1))}{1 + d(X_0 + x(t-1))^2 + (Y_0 + y(t-1))^2} - (Y_0 + y(t)); \quad (4)$$

Initially, we simplify the first equation from Eq. (4):

$$\varepsilon_1 \frac{dx(t)}{dt} = \frac{a(X_0 + x(t-1))^2}{1 + (X_0 + x(t-1))^2 + c(Y_0 + y(t-1))^2} - (X_0 + x(t)).$$

Model Analysis. This model describes the dynamics of the interrelated activity of hepatocytes and HBV at the molecular genetic level. The system of functional-differential equations (1) is a nonlinear and closed system, and their solution can be constructed by Bellman-Cook's method of sequential integration [22]. Therefore, we qualitatively investigate the equilibrium positions of Eq. (1). To analyze the stability of the equilibrium positions of Eq. (1), it is necessary to study the equilibrium positions of Eq. (1). The equilibrium positions of the system of functional-differential Eq. (1) has the following form:

$$\frac{dX(t)}{dt} = 0; \frac{dY(t)}{dt} = 0;$$
$$X(t-1) = X(t) = X_0; Y(t-1) = Y(t) = Y_0;$$
$$X_0 = const; Y_0 = const;$$
$$X_0 = \frac{aX_0^2}{1 + X_0^2 + cY_0^2};$$
$$Y_0 = \frac{bX_0Y_0}{1 + dX_0^2 + Y_0^2}. \quad (2)$$

The results of a qualitative study show that, for some parameter values, attractors can be type $A(X_0, 0)$ equilibrium positions (dominance of hepatocyte with a positive infection outcome) with positive X_0 and equilibrium positions $B(X_0, Y_0)$ with positive X_0, Y_0 (the presence of symbiotic coexistence of the molecular genetic systems of hepatocyte and hepatitis viruses B leading to chronic hepatitis B).

We linearize around the equilibrium points X_0 and Y_0 a system of functional-differential equations (1). In this case, we enter the small variables $x(t), y(t)$ around the equilibrium points X_0 and Y_0 as follows:

$$X(t) = X_0 + x(t);$$
$$Y(t) = Y_0 + y(t);$$
$$X(t-1) = X_0 + x(t-1);$$
$$Y(t-1) = Y_0 + y(t-1). \quad (3)$$

Where X_0 and Y_0 is equilibrium points for $X(t)$ and $Y(t)$; $x(t)$ and $y(t)$ is a small variable of equilibrium points.

From the above equality

$$\varepsilon_1 \frac{dx(t)}{dt} = \frac{a(X_0^2 + 2X_0x(t-1) + x^2(t-1))}{1 + X_0^2 + 2X_0x(t-1) + x^2(t-1) + cY_0^2 + 2cY_0y(t-1) + cy^2(t-1)} - (X_0 + x(t));$$

$$\varepsilon_1 \frac{dx(t)}{dt} = \frac{a(X_0^2 + 2X_0x(t-1))}{1 + X_0^2 + cY_0^2 + 2(X_0x(t-1) + cY_0y(t-1))} \cdot \frac{1 + X_0^2 + cY_0^2 - 2(X_0x(t-1) + cY_0y(t-1))}{1 + X_0^2 + cY_0^2 - 2(X_0x(t-1) + cY_0y(t-1))} - (X_0 + x(t));$$

$$\varepsilon_1 \frac{dx(t)}{dt} = \frac{a(X_0^2 + 2X_0x(t-1))(1 + X_0^2 + cY_0^2 - 2(X_0x(t-1) + cY_0y(t-1)))}{(1 + X_0^2 + cY_0^2)^2 - (2(X_0x(t-1) + cY_0y(t-1)))^2} - (X_0 + x(t));$$

$$\varepsilon_1 \frac{dx(t)}{dt} = \frac{a(X_0^2 + 2X_0x(t-1))(1 + X_0^2 + cY_0^2)}{(1 + X_0^2 + cY_0^2)^2} -$$

$$- \frac{a(X_0^2 + 2X_0x(t-1))(2X_0x(t-1) + 2cY_0y(t-1))}{(1 + X_0^2 + cY_0^2)^2} - (X_0 + x(t));$$

$$\varepsilon_1 \frac{dx(t)}{dt} = \frac{aX_0^2}{1 + X_0^2 + cY_0^2} + \frac{2aX_0x(t-1)}{1 + X_0^2 + cY_0^2} -$$

$$- \frac{a(2X_0^3x(t-1) + 2cX_0^2Y_0y(t-1) + 4X_0^2x^2(t-1) + 4cX_0x(t-1)Y_0y(t-1))}{(1 + X_0^2 + cY_0^2)^2} - (X_0 + x(t));$$

Based on Eq. (2) and

$$\frac{aX_0}{1 + X_0^2 + cY_0^2} = 1;$$

$$\frac{bX_0}{1 + dX_0^2 + Y_0^2} = 1, \tag{5}$$

according to (5)

$$\varepsilon_1 \frac{dx(t)}{dt} = X_0 + 2x(t-1) - \frac{2aX_0^2(X_0x(t-1) + cY_0y(t-1))}{(1 + X_0^2 + cY_0^2)^2} - (X_0 + x(t));$$

$$\varepsilon_1 \frac{dx(t)}{dt} = X_0 + 2x(t-1) - \frac{2aX_0^2(X_0x(t-1) + cY_0y(t-1))}{1 + X_0^2 + cY_0^2} \cdot \frac{1}{1 + X_0^2 + cY_0^2} - (X_0 + x(t));$$

$$\varepsilon_1 \frac{dx(t)}{dt} = \left(X_0 + 2x(t-1) - \frac{2X_0(X_0x(t-1) + cY_0y(t-1))}{1 + X_0^2 + cY_0^2}\right) \cdot \frac{a}{a} - (X_0 + x(t));$$

$$\varepsilon_1 \frac{dx(t)}{dt} = X_0 + 2x(t-1) - \frac{2}{a}(X_0x(t-1) + cY_0y(t-1)) - (X_0 + x(t));$$

$$\varepsilon_1 \frac{dx(t)}{dt} = X_0 + 2x(t-1) - \frac{2}{a}(X_0x(t-1) + cY_0y(t-1)) - X_0 - x(t);$$

$$\varepsilon_1 \frac{dx(t)}{dt} = 2x(t-1) - \frac{2}{a}X_0x(t-1) - \frac{2c}{a}Y_0y(t-1) - x(t);$$

$$\varepsilon_1 \frac{dX(t)}{dt} = \left(2 - \frac{2}{a}X_0\right)x(t-1) - \frac{2c}{a}Y_0y(t-1) - x(t).$$

From Eq. (4) we simplify the second equation:

$$\varepsilon_2 \frac{dy(t)}{dt} = \frac{b(X_0 + x(t-1))(Y_0 + y(t-1))}{1 + d(X_0 + x(t-1))^2 + (Y_0 + y(t-1))^2} - (Y_0 + y(t));$$

$$\varepsilon_2 \frac{dy(t)}{dt} = \frac{b(X_0Y_0 + X_0y(t-1) + Y_0x(t-1) + x(t-1)y(t-1))}{1 + dX_0^2 + 2dX_0x(t-1) + dx^2(t-1) + Y_0^2 + 2Y_0y(t-1) + y^2(t-1)} - (Y_0 + y(t));$$

$$\varepsilon_2 \frac{dy(t)}{dt} = \frac{b(X_0Y_0 + X_0y(t-1) + Y_0x(t-1))}{1 + dX_0^2 + Y_0^2 + 2dX_0x(t-1) + 2Y_0y(t-1)} \cdot$$

$$\cdot \frac{1 + dX_0^2 + Y_0^2 - (2dX_0x(t-1) + 2Y_0y(t-1))}{1 + dX_0^2 + Y_0^2 - (2dX_0x(t-1) + 2Y_0y(t-1))} - (Y_0 + y(t));$$

$$\varepsilon_2 \frac{dy(t)}{dt} = \frac{b(X_0 Y_0 + X_0 y(t-1) + Y_0 x(t-1)) \cdot (1 + dX_0^2 + Y_0^2 - (2dX_0 x(t-1) + 2Y_0 y(t-1)))}{(1 + dX_0^2 + Y_0^2)^2 - ((2dX_0 x(t-1) + 2Y_0 y(t-1)))^2} - (Y_0 + y(t));$$

$$\varepsilon_2 \frac{dy(t)}{dt} = \frac{b(X_0 Y_0 + X_0 y(t-1) + Y_0 x(t-1)) \cdot (1 + dX_0^2 + Y_0^2)}{(1 + dX_0^2 + Y_0^2)^2 - ((2dX_0 x(t-1) + 2Y_0 y(t-1)))^2} -$$

$$- \frac{b(X_0 Y_0 + X_0 y(t-1) + Y_0 x(t-1)) \cdot (2dX_0 x(t-1) + 2Y_0 y(t-1))}{(1 + dX_0^2 + Y_0^2)^2 - ((2dX_0 x(t-1) + 2Y_0 y(t-1)))^2} - (Y_0 + y(t));$$

$$\varepsilon_2 \frac{dy(t)}{dt} = \frac{bX_0 Y_0}{1 + dX_0^2 + Y_0^2} + \frac{bX_0 y(t-1)}{1 + dX_0^2 + Y_0^2} + \frac{bY_0 x(t-1)}{1 + dX_0^2 + Y_0^2} -$$

$$- \frac{b(X_0 Y_0 + X_0 y(t-1) + Y_0 x(t-1)) \cdot (2dX_0 x(t-1) + 2Y_0 y(t-1))}{(1 + dX_0^2 + Y_0^2)^2} - (Y_0 + y(t)).$$

According to (2) and (5)

$$\varepsilon_2 \frac{dy(t)}{dt} = Y_0 + y(t-1) + \frac{bY_0 x(t-1)}{1 + dX_0^2 + Y_0^2} - \frac{2bdX_0^2 Y_0 x(t-1) + 2bX_0 Y_0^2 y(t-1)}{(1 + dX_0^2 + Y_0^2)^2} +$$

$$+ \frac{2bdX_0^2 x(t-1)y(t-1) + 2bX_0 Y_0 x(t-1)y(t-1) + 2bdX_0 Y_0 x^2(t-1) + 2bY_0^2 y^2(t-1)}{(1 + dX_0^2 + Y_0^2)^2} - (Y_0 + y(t));$$

$$\varepsilon_2 \frac{dy(t)}{dt} = Y_0 + y(t-1) + \frac{bY_0 x(t-1)}{1 + dX_0^2 + Y_0^2} - \frac{2bdX_0^2 Y_0 x(t-1) + 2bX_0 Y_0^2 y(t-1)}{(1 + dX_0^2 + Y_0^2)^2} - (Y_0 + y(t));$$

$$\varepsilon_2 \frac{dy(t)}{dt} = Y_0 + y(t-1) + \frac{bY_0 x(t-1)}{1 + dX_0^2 + Y_0^2} - \frac{2bX_0 Y_0 (dX_0 x(t-1) + Y_0 y(t-1))}{(1 + dX_0^2 + Y_0^2)^2} - (Y_0 + y(t));$$

$$\varepsilon_2 \frac{dy(t)}{dt} = \left(Y_0 + y(t-1) + \frac{bY_0 x(t-1)}{1 + dX_0^2 + Y_0^2} - \frac{2Y_0 (dX_0 x(t-1) + Y_0 y(t-1))}{1 + dX_0^2 + Y_0^2} \right) \cdot \frac{bX_0}{bX_0} - (Y_0 + y(t));$$

$$\varepsilon_2 \frac{dy(t)}{dt} = Y_0 + y(t-1) + \frac{Y_0}{X_0} x(t-1) - \frac{2}{b} \frac{Y_0}{X_0} (dX_0 x(t-1) + Y_0 y(t-1)) - (Y_0 + y(t));$$

$$\varepsilon_2 \frac{dy(t)}{dt} = Y_0 + y(t-1) + \frac{Y_0}{X_0} x(t-1) - \frac{2d}{b} Y_0 x(t-1) - \frac{2 Y_0^2}{b X_0} y(t-1) - Y_0 - y(t);$$

$$\varepsilon_2 \frac{dy(t)}{dt} = y(t-1) + \frac{Y_0}{X_0} x(t-1) - \frac{2d}{b} Y_0 x(t-1) - \frac{2 Y_0^2}{b X_0} y(t-1) - y(t);$$

$$\varepsilon_2 \frac{dY(t)}{dt} = \left(\frac{Y_0}{X_0} - \frac{2d}{b} Y_0 \right) x(t-1) + \left(1 - \frac{2 Y_0^2}{b X_0} \right) y(t-1) - y(t).$$

Thus, we obtain the following linear equation around equilibrium points X_0 and Y_0 of Eq. (1):

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

$$\varepsilon_2 \frac{dy(t)}{dt} = \left(\frac{Y_0}{X_0} - \frac{2d}{b} Y_0 \right) x(t-1) + \left(1 - \frac{2}{b} \frac{Y_0^2}{X_0} \right) y(t-1) - y(t). \tag{6}$$

We construct a characteristic equation for Eq. (6). The solutions of the characteristic equation are as follows:

$$x(t) = e^{\lambda t}; y(t) = e^{\lambda t}$$

and we use the following equality:

$$\frac{dx(t)}{dt} = \lambda e^{\lambda t}; \frac{dy(t)}{dt} = \lambda e^{\lambda t};$$
$$x(t-1) = e^{\lambda(t-1)}; y(t-1) = e^{\lambda(t-1)}.$$

We have a system of Eq. (7).

$$\lambda \varepsilon_1 e^{\lambda t} = \left(2 - \frac{2}{a} X_0\right) e^{\lambda(t-1)} - \frac{2c}{a} Y_0 e^{\lambda(t-1)} - e^{\lambda t};$$
$$\lambda \varepsilon_2 e^{\lambda t} = \left(\frac{Y_0}{X_0} - \frac{2}{bc} Y_0\right) e^{\lambda(t-1)} + \left(1 - \frac{2}{b} \frac{Y_0^2}{X_0}\right) e^{\lambda(t-1)} - e^{\lambda t}. \tag{7}$$

From (7) we obtain:

$$\left(2 - \frac{2}{a} X_0\right) e^{-\lambda} - 1 - \lambda \varepsilon_1 - \frac{2c}{a} Y_0 e^{-\lambda} = 0;$$
$$\left(\frac{Y_0}{X_0} - \frac{2}{bc} Y_0\right) e^{-\lambda} + \left(1 - \frac{2}{b} \frac{Y_0^2}{X_0}\right) e^{-\lambda} - 1 - \lambda \varepsilon_2 = 0. \tag{8}$$

This Eq. (8) is a characteristic equation of Eq. (6) and can be written in determinant form.

$$\begin{vmatrix} \left(2 - \frac{2}{a} X_0\right) e^{-\lambda} - 1 - \lambda \varepsilon_1 & -\frac{2c}{a} Y_0 e^{-\lambda} \\ \left(\left(\frac{1}{X_0} - \frac{2d}{b}\right) Y_0\right) e^{-\lambda} & \left(1 - \frac{2}{b} \frac{Y_0^2}{X_0}\right) e^{-\lambda} - 1 - \lambda \varepsilon_2 \end{vmatrix} = 0. \tag{9}$$

If $\frac{1}{X_0} = \frac{2d}{b}$, then Eq. (9) can be written by dividing into two equations:

$$\left(2 - \frac{2}{a} X_0\right) e^{-\lambda} - 1 - \lambda \varepsilon_1 = 0. \tag{10}$$

$$\left(1 - \frac{2}{b} \frac{Y_0^2}{X_0}\right) e^{-\lambda} - 1 - \lambda \varepsilon_2 = 0. \tag{11}$$

First, for the analysis of Eq. (1), using the conditions of the Hayes criterion [23], it is necessary to arrive at the transcendental equation. This is an example of an equation: $(\lambda + a)e^{\lambda} + b = 0$.

For this, we write the equation in the form $e^{-\lambda} = \frac{1}{e^{\lambda}}$.

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

We multiply the resulting equation by e^{λ}

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

We multiply this equation to $\frac{1}{\varepsilon_1}$ and describe it as follows.

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

The resulting equation is the transcendent equation. We can apply the Hayes criteria to this equation. Using these steps for the second equation of Eq. (11), we obtain the following:

$$\left(\lambda + \frac{1}{\varepsilon_2}\right) e^{\lambda} + \left(\frac{2}{b} \frac{Y_0^2}{X_0} - 1\right) \frac{1}{\varepsilon_2} = 0.$$

Therefore, transcendent equations for equations system (1) are as follows:

$$\left(\lambda + \frac{1}{\varepsilon_1}\right) e^{\lambda} + \left(\frac{2}{a} X_0 - 2\right) \frac{1}{\varepsilon_1} = 0. \tag{12}$$

$$\left(\lambda + \frac{1}{\varepsilon_2}\right) e^{\lambda} + \left(\frac{2}{b} \frac{Y_0^2}{X_0} - 1\right) \frac{1}{\varepsilon_2} = 0. \tag{13}$$

Conditions of the Hayes criterion following conditions:

$$a > -1;$$
$$a + b > 0;$$
$$b < \xi \sin \xi - a \cos \xi.$$

Where ξ - root of equation $\xi = -tg\xi$.
For (12) we apply the condition of the Hayes criterion:

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

Given the positive value of the general parameters (1), then $\frac{1}{\varepsilon_1} > -1$ discharged.

2) $\frac{1}{\varepsilon_1} + \left(\frac{2}{a} X_0 - 2\right) \frac{1}{\varepsilon_1} > 0$. In this case we obtain $X_0 > \frac{1}{2} a$.

3) $\left(\frac{2}{a} X_0 - 2\right) \frac{1}{\varepsilon_1} < \xi \sin \xi - \frac{1}{\varepsilon_1} \cos \xi$.

Where ξ - root of the equation $\xi = -\frac{1}{\varepsilon_1} tg\xi$ for $\frac{1}{\varepsilon_1} \neq 0$, $0 < \xi < \pi$. According to condition $\varepsilon_1 \xi = -tg\xi$, $y_1 = \varepsilon_1 \xi, y_2 = -tg\xi$.

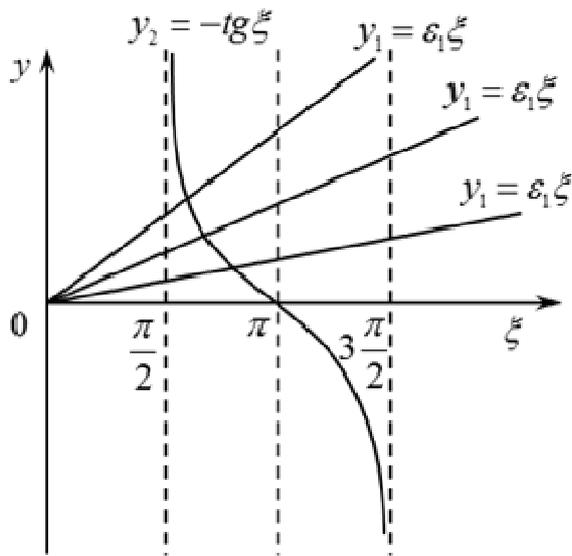**Figure 1. Fulfillment of the Third Condition of the Hayes Criterion**

3.1) $\varepsilon_1 \to \infty$, $\xi \to \frac{\pi}{2}$, $\left(\frac{2}{a}X_0 - 2\right)\frac{1}{\varepsilon_1} < \frac{\pi}{2}$.

3.2) $\varepsilon_1 \to 0$, $\xi \to \pi$, $\left(\frac{2}{a}X_0 - 2\right)\frac{1}{\varepsilon_1} < \frac{1}{\varepsilon_1}$.

3.1) $\left(\frac{2}{a}X_0 - 2\right)\frac{1}{\varepsilon_1} < \frac{\pi}{2}$. Due to $\varepsilon_1 \to \infty$ is $\frac{1}{\varepsilon_1} \approx 0$.

Herewith

$$\frac{\pi}{2} > 0.$$

3.2) By simplifying $\left(\frac{2}{a}X_0 - 2\right)\frac{1}{\varepsilon_1} < \frac{1}{\varepsilon_1}$, we obtain $X_0 < 1\frac{1}{2}a$.

Reducing the conditions of the Hayes criteria

1) $\frac{1}{\varepsilon_1} > -1$;

2) $X_0 > \frac{1}{2}a$;

3.1) $\frac{\pi}{2} > 0$;

3.2) $X_0 < 1\frac{1}{2}a$.

To analyze the condition of the Hayes criterion, we have the following general conditions:

$$\frac{1}{2}a < X_0 < 1\frac{1}{2}a.$$
(14)

We continue the analysis of (11) using the conditions of the Hayes criterion, as in (10), and it is necessary to arrive at the transcendental equation $(\lambda + a)e^\lambda + b = 0$.

$$\left(\lambda + \frac{1}{\varepsilon_2}\right)e^\lambda + \left(\frac{2}{b}\frac{Y_0^2}{X_0} - 1\right)\frac{1}{\varepsilon_2} = 0.$$
(15)

For the (15) we apply the condition of the Hayes criterion:

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

Given the positive value of the general parameters (1), then $\frac{1}{\varepsilon_2} > -1$ is satisfied.

2) $\frac{1}{\varepsilon_2} + \left(\frac{2}{b}\frac{Y_0^2}{X_0} - 1\right)\frac{1}{\varepsilon_2} > 0$. Wherein $\frac{Y_0^2}{X_0} > 0$.

3) $\left(\frac{2}{b}\frac{Y_0^2}{X_0} - 1\right)\frac{1}{\varepsilon_2} < \xi \sin\xi - \frac{1}{\varepsilon_2}\cos\xi$.

Where ξ - root of the equation $\xi = -\frac{1}{\varepsilon_2}tg\xi$ at $0 < \xi < \pi$, if $\frac{1}{\varepsilon_2} \neq 0$. According to condition $\varepsilon_2\xi = -tg\xi$, $y_1 = \varepsilon_2\xi$, $y_2 = -tg\xi$.

3.1) $\varepsilon_2 \to 0$, $\xi \to \frac{\pi}{2}$, $\left(\frac{2}{b}\frac{Y_0^2}{X_0} - 1\right)\frac{1}{\varepsilon_2} < \frac{\pi}{2}$.

3.2) $\varepsilon_2 \to \infty$, $\xi \to \pi$, $\left(\frac{2}{b}\frac{Y_0^2}{X_0} - 1\right)\frac{1}{\varepsilon_2} < \frac{1}{\varepsilon_2}$.

3.1) $\left(\frac{2}{b}\frac{Y_0^2}{X_0} - 1\right)\frac{1}{\varepsilon_2} < \frac{\pi}{2}$. Due to $\varepsilon_2 \to \infty$ is $\frac{1}{\varepsilon_2} \approx 0$.
Herewith

$$\frac{\pi}{2} > 0.$$

3.2) By simplifying $\left(\frac{2}{b}\frac{Y_0^2}{X_0} - 1\right)\frac{1}{\varepsilon_2} < \frac{1}{\varepsilon_2}$, we obtain

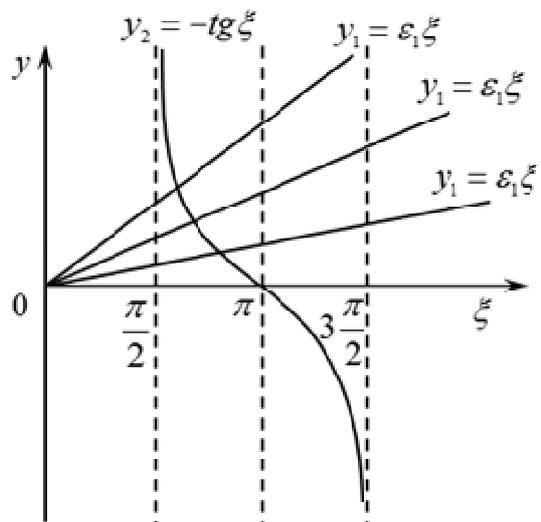$$\frac{Y_0^2}{X_0} < b.$$

Figure 2. Fulfillment of the Third Condition of the Hayes Criterion

Thus, we give the condition of the Hayes criterion:

1) $\frac{1}{\varepsilon_2} > -1$;

2) $\frac{Y_0^2}{X_0} > 0$;

3.1) $\frac{\pi}{2} > 0$;

3.2) $\frac{Y_0^2}{X_0} < b$.

To analyze the condition of the Hayes criterion, we have the following general conditions:

$$0 < \frac{Y_0^2}{X_0} < b. \tag{16}$$

So, by summarizing the terms of the Hayes criterion, we obtain the following conditions:

$$\frac{1}{2}a < X_0 < 1\frac{1}{2}a;$$

$$0 < \frac{Y_0^2}{X_0} < b. \tag{17}$$

Therefore, when the general conditions of the Hayes criterion (17) are met, the equilibrium positions $A(X_0, 0)$ and $B(X_0, Y_0)$ of Eq. (1) are stable. The results of qualitative analysis have shown that in some values of model parameters of HBV in the hepatocyte, the equilibrium positions $A(X_0, 0)$ and $B(X_0, Y_0)$ may be stable, and in some values, their stability may be impaired. Therefore, we can observe the following regimes of the 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".

Results and Discussion

To carry out computational experiments, we created a computer model based on Eq. (1) using the Runge-Kutta method [24, 25]. We obtain some results by performing computational experiments.

Figure 3 shows the dominant function model of the genetic system of a hepatocyte with the following parameter values ($\varepsilon_1 = 0.2$; $\varepsilon_2 = 0.04$; $a = 12.2$; $b = 10.6$; $c = 4.1$; $d = 5.8$ and $X_0 = 3.9$; $Y_0 = 6$), thus the activation of only the molecular genetic system of a hepatocyte with loss of HBV activity is described, and the liver will be healthy.

Figure 4 shows the dynamic chaos regulatory model of the molecular genetic systems of a LC and HBV with the following parameter values ($\varepsilon_1 = 0.069$; $\varepsilon_2 = 0.019$; $a = 9.3$; $b = 13.4$; $c = 4.16$; $d = 7.8$ and $X_0 = 5.3$; $Y_0 = 8$). The results in the figure show that the irregular functioning of the molecular genetic systems of the LC and HBV, and this describes the

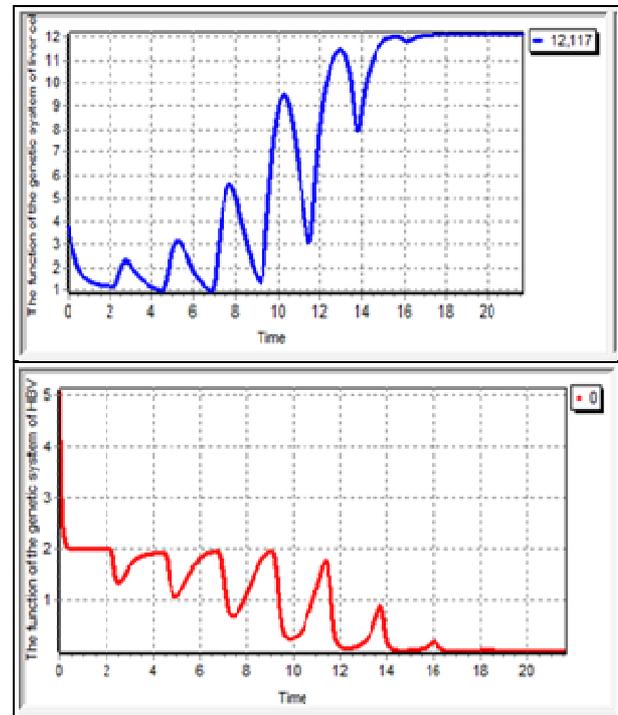active infectious disease phase of viral hepatitis B in the liver.

Figure 3. The Dominant Functioning Model of the Regulatory Mechanism of a Hepatocyte
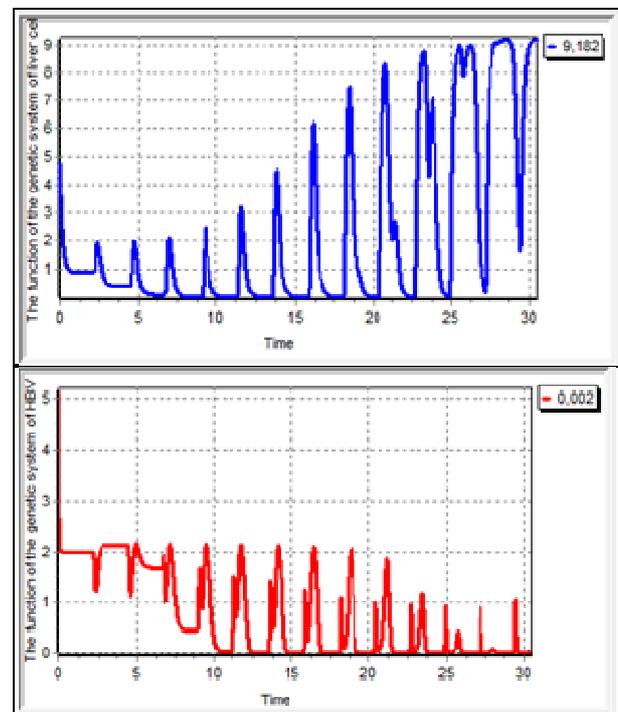

Figure 4. The Dynamic Chaos Model of the Regulatory Mechanism of a Hepatocyte and HBV

Figure 5 shows the "black hole" regulatory model of the molecular genetic system of hepatocytes and the HBV with the following parameter values ($\varepsilon_1 = 0.2$; $\varepsilon_2 = 0.04$; $a = 12.2$; $b = 8.6$; $c = 4.1$; $d = 1.8$ and $X_0 = 4.9$; $Y_0 = 4$). The results in the figure show that the functioning of the molecular genetic system of the LC and HBV tends to zero and destroys the body.

The blue graphic image shown in Figures 3-5 describes the activity of the genetic system of the hepatocyte and the red graphic image describes that of the HBV. The model describes irregular oscillations 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 strong inhomogeneity with sharp spasmodic changes in randomness: the Lyapunov graph. Entry into the region of irregular oscillations can be predicted: it is preceded by a series of bursts of values of the Lyapunov graph. The outbursts can be fix by analyzing solutions on the PC. This allows prediction of 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 LC for HBV can be used for small values of ε_1 and ε_2, according to the functional equation [26]

$$X(t) = \frac{aX^2(t-1)}{1 + X^2(t-1) + cY^2(t-1)};$$
$$Y(t) = \frac{bX(t-1)Y(t-1)}{1 + dX^2(t-1) + Y^2(t-1)}; \qquad (18)$$

and its discrete analogue

$$X_{k+1} = \frac{aX_k^2}{1 + X_k^2 + cY_k^2};$$

$$Y_{k+1} = \frac{bX_kY_k}{1 + dX_k^2 + Y_k^2}. \qquad (19)$$

For the analysis of the chaotic regime of the molecular genetic system of LC in case of a viral load, a computer program called Lap was developed (Figure 5). $a = 8.1$; $b = 10.2$; $c = 3.15$; $d = 0.1$ and $X_0 = 1$, $Y_0 = 1$ are values of the parameters of Eq. (1).
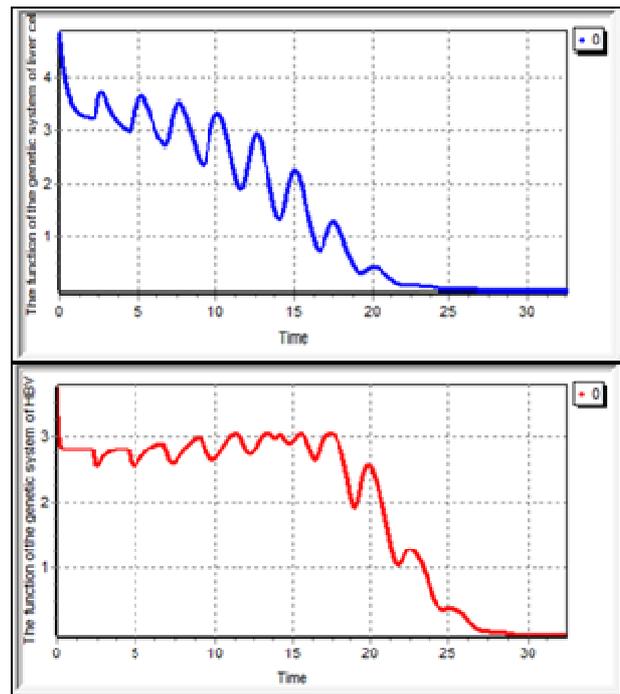

Figure 5. The "Black Hole" Model of the Regulatory Mechanism of a Hepatocyte and HBV

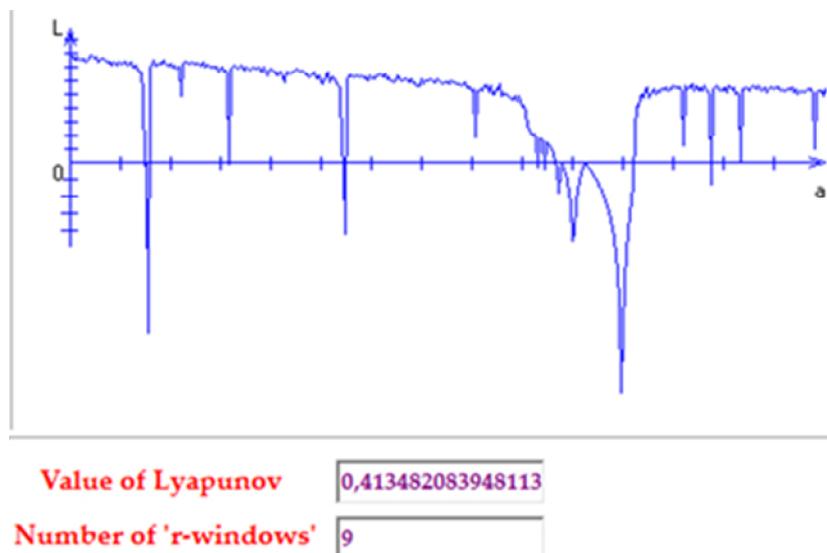| Value of Lyapunov | 0,413482083948113 |
| Number of 'r-windows' | 9 |

Figure 6. The Lyapunov Value and Lyapunov Graph for Eq. (1) [27]

In Figure 6, the values on the Lyapunov graph lie above the axis a, thus one can see the functioning of the interrelated activity of the molecular genetic systems of the LC and HBV under the dynamic chaos model. However, some values lie below the axis a. In these places, the values of Lyapunov are negative. This means that at these points the equilibrium positions are stable. It can be seen from the figure that there are 9 such stable areas, called "r-windows". The molecular genetic systems of the LC and HBV can be moved from a region of dynamic chaos to a normal region by using "r-windows".

Conclusion

The functional-differential equations developed to model regulation of the interconnected activity of the molecular genetic systems of hepatocytes and HBV allow us to study quantitatively the main patterns of the infectious process in hepatocyte with hepatitis B. In the course of quantitative studies, the following regimes of the process under consideration were obtained: purification, symbiosis, regular and irregular fluctuations, and sharp destructive changes that determine the various forms of the clinical disease.

Calculations performed on the PC showed, in the dynamic chaos regime, small regions called "r-windows", inside which the behavior of the solution (1) was regular. This indicates the possibility of a temporary improvement in the state of the hepatocyte during infection with the HBV. However, this improvement is temporary, and small disturbances again bring the molecular genetic system of hepatocytes into a dynamic chaos regime. The ability to predict the onset of these regimes and their main characteristics allows, with computer support for laboratory and clinical studies of the infection process in hepatitis B, diagnosis and prediction of the characteristic stages of the course of the disease with hepatitis B.

Acknowledgments

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