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Issue Article

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ANALYSIS OF THE MATHEMATICAL MODEL OF REGULATORIKA OF THE LIVER CELLS AND HEPATITIS B VIRUSES

Abstract: *Every year, between 10 and 30 million people worldwide become infected with the hepatitis B virus (HBV). Most of those infected are children and adolescents. The hepatitis B virus uses the cell's resources to begin synthesizing, or replicating, the components needed to build new viruses. DNA polymerase triggers the liver cell to make copies of the hepatitis B virus DNA and thus create more viruses. When the cell finally makes these components, they assemble into a complete virus and these viral copies are released into the blood. After the virus has assembled, so-called waste products remain in the form of surface proteins that are released into the blood. The new hepatitis virus goes on to infect other liver cells and continually repeats this efficient and rapid reproduction process. In fact, thousands of new virus particles can be produced in each liver cell in a single day. The virus easily penetrates the liver, the largest internal organ. If the hepatitis virus manages to evade the body's immune system and encounters a liver cell (hepatocyte), the outer shell of the virus attaches to the surface of the liver cell and the genetic material from the core of the virus is incorporated into the hepatocyte.*

Key words: *hepatitis B virus, hepatocyte, molecular-genetic systems, regulatorika, mathematical model, sequential integration.*
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Introduction

The nature of hepatitis B, the characteristic features of the course of the infection are primarily determined by the genetic, physical, structural and functional organization of the infectious agent - HBV. The infectious virion - the Dane particle - is a DNA-containing virus with a preferential tropism for liver tissue. The structure of the Dane particle is schematically shown in Fig. 1.

Spatio-temporal relationship is very important in living systems. Biological reactions occur in the right place and at the right time. Let's take the cell. Genes are in the nucleus, ribosomes are in the cytoplasm. The information from the genes goes to the cytoplasm and is used there. It will take a long time. Therefore, when modeling gene activity, both the nucleus and the cytoplasm must be taken into account.

The hepatitis B genome controls the replication processes for new viruses. In this process, the functions of **or** are performed by the liver cell nucleus.

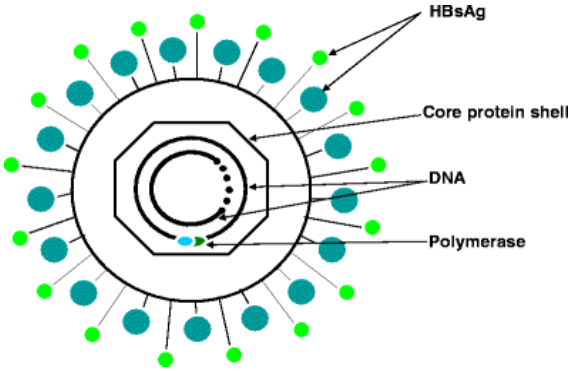

Fig. 1. Structure of the Dane particle and arrangement of antigens [1].

The functions of asta1 are performed by the liver cell cytoplasm environment. **Or** receives information from the external environment and develops specific "signals", and **asta** works on the basis of this "signal" [2]. The functions of **"orasta"** are shown in Fig. 2.

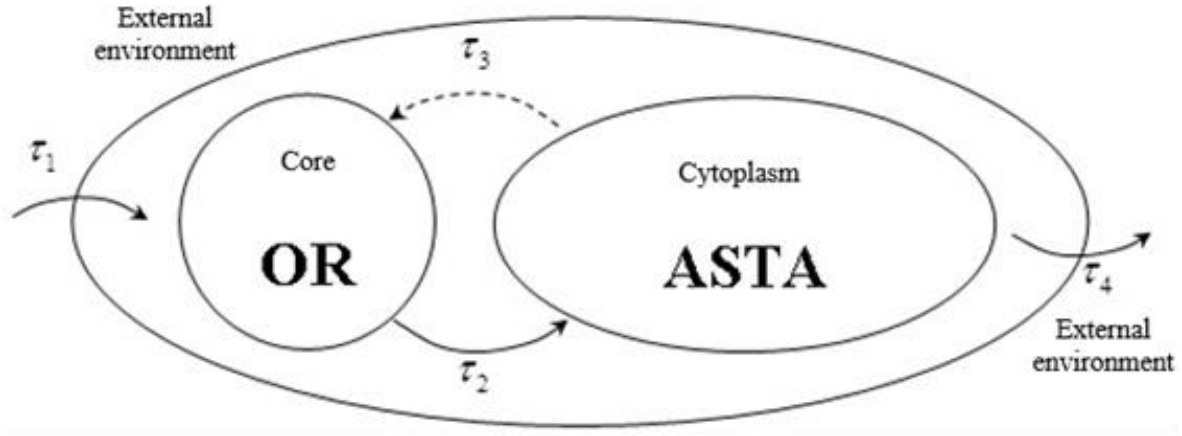

Fig. 2. Scheme or asta of the interconnected activity of the molecular genetic systems of the liver cell and hepatitis B viruses.

ANALYSIS

A mathematical model of a set with a complex non-linear relational function is used to analyze the laws of the quantitative dynamics of the disease of an organism. The introduction of additional variables to determine the degree of the disease of organs allows to predict the course of the disease in the body and evaluate its condition. The equations of this class of viral disease model can be given in the following form:

$$\frac{dV}{dt} = (\beta - \gamma F)V;$$

$$\frac{dC}{dt} = \xi(m)\alpha V(t-\tau)F(t-\tau)\theta(t-\tau) - \mu_C(C - C^*);$$

$$\frac{dF}{dt} = \rho C - \eta\gamma FV - \mu_f F; \qquad (1)$$

$$\frac{dm}{dt} = \sigma V - \mu_m m,$$

where V - the number of viruses; F - number of antibodies; C - number of organ cells; m - relative characteristics of the diseased organ; $\theta(t)$ – Heavyside function,

$$\theta(t) = \begin{cases} 0, & \text{at } t < 0; \\ 1, & \text{at } t \geq 0, \end{cases}$$

β, γ, ρ, η, μ_1, $\xi(m)$,α, μ_0, σ, μ_m, - all parameters are positive [3, 4].

Biostimulation of immunity begins in the body during the chronic period of the disease, that is, the immune system reacts and the development of the viral disease occurs. During the immune system reaction, the cells of the immune system are active.

At the beginning of the last century, Voltaire V. [5], Kostitsyn V.A. [6] and A.N. Kolmogorov [7] made the mathematical methods of these model classes. Mathematical models belonging to this class are called "predator-victim" type models. Models of the "predator-victim" type are based on simple mathematical relations in the class of ordinary differential equations and quantitative indicators of "predators", "victims" and, in some cases, some

characteristics of the habitat of the considered population are taken into account. One of the models of the "predator-victim" type is as follows:

$$\frac{dx}{dt} = (\alpha - \beta y)x; \qquad \frac{dy}{dt} = (-\gamma + \delta x)y, \tag{2}$$

here x - number of victims; y - number of killers; t - time; $\alpha, \beta, \gamma, \delta$ - coefficients reflecting the interdependence between species.

Stephen A. Gourley et al. [8] presented an improved model of the previously widely used viral infection model based on the law of mass motion. The authors used the following system of equations to analyze the biological basis and latent period of viruses:

$$x'(t) = \lambda - dx(t) - \frac{\beta v(t)x(t)}{x(t)+y(t)+e(t)};$$

$$e'(t) = -de(t) + \frac{\beta v(t)x(t)}{x(t)+y(t)+e(t)} - \frac{\beta e^{-d\tau} v(t-\tau)x(t-\tau)}{x(t-\tau)+y(t-\tau)+e(t-\tau)}; \tag{3}$$

$$y'(t) = \frac{\beta e^{-d\tau} v(t-\tau)x(t-\tau)}{x(t-\tau)+y(t-\tau)+e(t-\tau)} - ay(t);$$

$$v'(t) = ky(t) - \mu v(t).$$

In this system $x(t)$ - the number of undamaged cells; $y(t)$ - the number of damaged cells; $e(t)$ - the number of uninfected cells (ie cells occupied by the virus but not producing new virions) and $v(t)$ - the number of free virions.

It is possible to quantitatively describe the laws of the emergence and formation of viral hepatitis B disease of the liver, conduct computer research based on the model of the dynamics of hepatitis B viruses, and model the activity of liver cells and hepatitis B viruses. However, there are still no adequate descriptive study methods of liver cells and the molecular-genetic systems of hepatitis B viruses, which represent the laws of interrelated activity. Therefore, in order to study the biological laws of viral hepatitis B disease that can appear and develop in the liver, it is necessary to mathematically model the regulatory mechanisms of the interrelated activities of liver cells and the molecular-genetic systems of hepatitis B viruses in normal and abnormal conditions.

MATHEMATICAL MODEL OF HBV

It is known that within the framework of the activity of molecular genetic systems, transcription for the synthesis of i-RNA (transferring genetic programs, hereditary information from the genetic apparatus, i.e., DNA in the form of a sequence of nucleotides), translation for the synthesis of polypeptides (the sequence of nucleotides in a chain consisting of amino acids, that is, protein-enzyme elements - sequence translation, i.e. i-RNA reading in cell organoids called ribosomes) and the creation of protein-enzymes (elements that perform the main function of the biosystem and are detailed for the cell) processes.

Taking into account that the molecular-genetic systems of viruses are active together with the molecular-genetic systems of liver cells, which can only be autonomously active, using the methods of modeling the regulatory dynamics of living systems [2], the regulatory mechanisms of the interrelated activity of the molecular-genetic systems of liver cells and hepatitis viruses are described by the following Goodwin led to the appearance of a system of functional-differential equations with delayed arguments of the type [9, 10, 11]:

$$\frac{dX_i(t)}{dt} = \frac{\alpha_i \prod_{l=1}^{n} X_l(t-h)}{1+\sum_{l=1}^{n} c_{1il} X_l^{n+m}(t-h) + \sum_{l=1}^{m} c_{2il} Y_l^{n+m}(t-h)} - \frac{1}{\tau_{X_i}} X_i(t);$$

$$\frac{dY_j(t)}{dt} = \frac{\beta_j \left(\prod_{l=1}^{m} Y_l(t-h)\right)\left(\prod_{k=1}^{n} X_k(t-h)\right)}{1+\sum_{p=1}^{n} d_{1jp} X_p^{n+m}(t-h) + \sum_{p=1}^{m} d_{2jp} Y_p^{n+m}(t-h)} - \frac{1}{\tau_{Y_j}} Y_j(t); \tag{4}$$

where $X_i(t)$, $Y_j(t)$ - values characterizing the activity of molecular-genetic systems of liver cells and hepatitis viruses at the moment of time t; h - the temporal radius of the cell (the time required for feedback in molecular-genetic systems); $\{\alpha, \beta\}$ and $\{c, d\}$ - positive parameters representing the levels of resource supply and inhibition of the gene system in question; $\{\tau\}$ - "living time" of gene activity products; n, m - the number of genetic systems of liver cells and

hepatitis viruses under consideration, respectively; $i = 1, 2, ..., n, \quad j = 1, 2, ..., m.$

The system of equations (4) is complex in nature, and the use of this system of equations for the qualitative and quantitative analysis of regulatory mechanisms of the interrelated activity of liver cells and the molecular genetic systems of hepatitis B viruses requires the development of a model system of the system of equations (4) [12, 13, 14]. In many cases, it allows to analyze the characteristic solutions and to determine the main modes of the state of the mathematical models under consideration.

In the interaction between the genomes of hepatitis B viruses and the genomes of liver cells, the implementation of infectious processes in liver cells causes the genetic systems of liver cells to accept "self-dependence" (not less than two). In addition, it is necessary to take into account the obligatory participation of both genomes (in accordance with the two-fold "interdependence") in the modeling of the activity of genetic systems of hepatitis B viruses [15, 16]. Taking into account the above, the system of minimal model equations of regulatory interaction of molecular-genetic systems of liver cells and hepatitis B viruses can be adopted in the following form:

$$\begin{aligned} \frac{dX(t)}{dt} &= \frac{\alpha X^2(t-h)}{1+c_1X^2(t-h)+c_2Y^2(t-h)} - \frac{1}{\tau_X}X(t); \\ \frac{dY(t)}{dt} &= \frac{\beta X(t-h)Y(t-h)}{1+d_1X^2(t-h)+d_2Y^2(t-h)} - \frac{1}{\tau_Y}Y(t), \end{aligned} \tag{5}$$

where $X(t)$, $Y(t)$ are values characterizing the activity of molecular genetic systems of liver cells and hepatitis B viruses, respectively; α, β - constant rate of appearance of products of the system under consideration; c_1, c_2, d_1, d_2 - parameters of level of repression of liver cells and molecular-genetic systems of hepatitis B viruses; h - the time required for feedback in the considered system; τ_X, τ_Y - "living time" of products of molecular genetic systems of liver cells and hepatitis B viruses.

If we introduce the following notations into this system of equations (5),

$$\varepsilon_1 = \frac{\tau_X}{h}, \ \varepsilon_2 = \frac{\tau_Y}{h}, \ a = \frac{\alpha\tau_X}{c_1}, \ b = \frac{\beta\tau_Y}{c_1},$$

$$c = \frac{c_2}{d_2}, \ d = \frac{d_1}{c_1} \text{ and } t = \theta h$$

we have a system of functional-differential equations with a delayed argument representing regulatory mechanisms of the interaction of the molecular-genetic systems of liver cells and hepatitis B viruses [17, 18, 19]:

$$\begin{aligned} \varepsilon_1 \frac{dX(\theta)}{d\theta} &= \frac{aX^2(\theta-1)}{1+X^2(\theta-1)+cY^2(\theta-1)} - X(\theta); \\ \varepsilon_2 \frac{dY(\theta)}{d\theta} &= \frac{bX(\theta-1)Y(\theta-1)}{1+dX^2(\theta-1)+Y^2(\theta-1)} - Y(\theta); \end{aligned} \tag{6}$$

$$\theta > 1;$$

here $\varepsilon_1, \varepsilon_2$ - regulatory parameters; a, b - the constant rate of product formation and c, d - parameters of the degree of mutual repression of liver cells and molecular-genetic systems of hepatitis B viruses; all parameters are positive.

In the system of functional-differential equations with delayed arguments (6), we introduce the following continuous function in the interval $\theta \in [0,1]$ as an initial condition:

$$\begin{aligned} X(\theta) &= \varphi_1(\theta), \\ Y(\theta) &= \varphi_2(\theta). \end{aligned} \tag{7}$$

It is known that dynamic models used in biology and medicine often take into account that the future development of the process depends not only on the current state, but also on the history of the process development [20]. In this case, it is not enough to give the initial condition value at the point for dynamic models. Because it is necessary to include the initial function representing the development history of the process, and this should be given not at the current time, but at the previous time. Therefore, the initial condition $\varphi_1(\theta)$, $\varphi_2(\theta)$ of this mathematical model (6) must be given in section $[0,1]$.

Thus, we call the system of functional-differential equations with delayed arguments (6) given by the initial conditions (7) a mathematical model representing the activity of regulatory mechanisms of liver cells and hepatitis B viruses. It is possible to qualitatively analyze

the properties of the solutions of the developed mathematical model equations without reaching explicit solutions.

SEQUENTIAL INTEGRATION

The analysis of the mathematical model of the regulatorika of liver cells and hepatitis B viruses leads to the understanding of the general laws of the formation of infectious viral hepatitis B disease, which occurs as a result of the effects of hepatitis B viruses on the liver cells at the molecular-genetic level, and to the identification of dynamic types of their behavior [21, 22]. The considered system of functional-differential equations with delayed arguments is a nonlinear system, and it is difficult to find its analytical solutions. Therefore, a qualitative analysis of the system of equations (6) is required. The mathematical model of regulatorika of liver cells and hepatitis B viruses can be presented in the following form [23, 24, 25, 26]:

$$\varepsilon_1 \frac{dX(t)}{dt} = \frac{aX^2(t-1)}{1+X^2(t-1)+cY^2(t-1)} - X(t);$$

$$\varepsilon_2 \frac{dY(t)}{dt} = \frac{bX(t-1)Y(t-1)}{1+dX^2(t-1)+Y^2(t-1)} - Y(t); \qquad (8)$$

$$t > 1;$$

$$X(t) = \varphi_1(t),\ Y(t) = \varphi_2(t),\ \ t \in [0,1].$$

The regulatory mathematical model of liver cells and hepatitis B viruses is found by successive integration for $t > 1$ solutions of the system of equations $\varphi_1(t), \varphi_2(t)$ satisfying initial conditions given in $[0, 1]$ intervals [27, 28, 29, 30].

We check the presence of continuous solutions of the system of functional-differential equations (8) with delayed arguments of the Goodwin type, a mathematical model of the regulatorika of liver cells and hepatitis B viruses. We are looking for solutions in the first quarter in order to ensure that the available solutions satisfy the biological laws of regulatory mechanisms of liver cells and hepatitis B viruses.

We find the solutions of equation (8) in the interval $[0, 1]$ for $t > 1$ of the continuous initial conditions $\varphi_1(t)$ and $\varphi_2(t)$ given in the interval $(1, 2]$. In the interval $[0, 1]$, $X(t)$ and $Y(t)$ are equal to the continuous functions $\varphi_1(t)$ and $\varphi_2(t)$, respectively. $X(t-1) = \varphi_1(t-1),\ Y(t-1) = \varphi_2(t-1)$ follows from this. We put these conditions in (8) and get the following equations:

$$\varepsilon_1 \frac{dX(t)}{dt} = \frac{a\varphi_1^2(t-1)}{1+\varphi_1^2(t-1)+c\varphi_2^2(t-1)} - X(t);$$
$$\varepsilon_2 \frac{dY(t)}{dt} = \frac{b\varphi_1(t-1)\varphi_2(t-1)}{1+d\varphi_1^2(t-1)+\varphi_2^2(t-1)} - Y(t). \qquad (9)$$

The solution you are looking for should look like this:

$$X(t) = g(t)e^{-\frac{t}{\varepsilon_1}},\quad Y(t) = q(t)e^{-\frac{t}{\varepsilon_2}}. \qquad (10)$$

From this

$$\frac{dX(t)}{dt} = \frac{dg(t)}{dt}e^{-\frac{t}{\varepsilon_1}} - \frac{1}{\varepsilon_1}g(t)e^{-\frac{t}{\varepsilon_1}};$$
$$\frac{dY(t)}{dt} = \frac{dq(t)}{dt}e^{-\frac{t}{\varepsilon_2}} - \frac{1}{\varepsilon_2}q(t)e^{-\frac{t}{\varepsilon_2}}$$

we find expressions and we can write equation (9) in the following form:

$$\varepsilon_1 \frac{dg(t)}{dt}e^{-\frac{t}{\varepsilon_1}} - g(t)e^{-\frac{t}{\varepsilon_1}} = \frac{a\varphi_1^2(t-1)}{1+\varphi_1^2(t-1)+c\varphi_2^2(t-1)} - g(t)e^{-\frac{t}{\varepsilon_1}};$$
$$\varepsilon_2 \frac{dq(t)}{dt}e^{-\frac{t}{\varepsilon_2}} - q(t)e^{-\frac{t}{\varepsilon_2}} = \frac{b\varphi_1(t-1)\varphi_2(t-1)}{1+d\varphi_1^2(t-1)+\varphi_2^2(t-1)} - q(t)e^{-\frac{t}{\varepsilon_2}}. \qquad (11)$$

After simplifying these resulting equations (11)

$$\frac{dg(t)}{dt} = \frac{a}{\varepsilon_1}e^{\frac{t}{\varepsilon_1}}\frac{\varphi_1^2(t-1)}{1+\varphi_1^2(t-1)+c\varphi_2^2(t-1)};$$
$$\frac{dq(t)}{dt} = \frac{b}{\varepsilon_2}e^{\frac{t}{\varepsilon_2}}\frac{\varphi_1(t-1)\varphi_2(t-1)}{1+d\varphi_1^2(t-1)+\varphi_2^2(t-1)} \qquad (12)$$

we get the equations. Then, by integrating the resulting equations (12), we get (13).

$$g(t) = g(1) + \frac{a}{\varepsilon_1}e^{\frac{\tau}{\varepsilon_1}}\int_1^t \frac{\varphi_1^2(\tau-1)}{1+\varphi_1^2(\tau-1)+c\varphi_2^2(\tau-1)}d\tau;$$
$$q(t) = q(1) + \frac{b}{\varepsilon_2}e^{\frac{\tau}{\varepsilon_2}}\int_1^t \frac{\varphi_1(\tau-1)\varphi_2(\tau-1)}{1+d\varphi_1^2(\tau-1)+\varphi_2^2(\tau-1)}d\tau, \qquad (13)$$

We replace the found $g(t)$ and $q(t)$ with the sought $X(t)$ and $Y(t)$, that is, based on (8) the following

$$X(t) = X(1)e^{\frac{1-t}{\varepsilon_1}} + \frac{a}{\varepsilon_1}\int_1^t \frac{\varphi_1^2(\tau-1)}{1+\varphi_1^2(\tau-1)+c\varphi_2^2(\tau-1)} e^{\frac{\tau-t}{\varepsilon_1}} d\tau;$$
$$Y(t) = Y(1)e^{\frac{1-t}{\varepsilon_2}} + \frac{b}{\varepsilon_2}\int_1^t \frac{\varphi_1(\tau-1)\varphi_2(\tau-1)}{1+d\varphi_1^2(\tau-1)+\varphi_2^2(\tau-1)} e^{\frac{\tau-t}{\varepsilon_2}} d\tau \quad (14)$$

we get the solution (14).

The found equality (14) is the solution of the equation (8) in the interval $(1, 2]$ satisfying the initial conditions given in the interval $[0, 1]$ and, in turn, is the initial condition for the interval $(2, 3]$.

This process of successive integration allows us to find continuous solutions of (8) for $t > 1$, and if this process is continued, the existence and continuity of the solutions can be assured.

CONCLUSION

Considering spatio-temporal relations in modeling gives an opportunity to obtain realistic results: normal and anomalous states of living systems can be expressed (self-control is lost and system destruction is a "black hole"). Thus, computational analysis of the interaction of hepatitis B viruses and liver cell genomes by applying mathematical modeling methods allows for computational research of the main laws of their interaction during infection on the basis of qualitative and computer analysis at the molecular-genetic level. The results of the computational studies, in turn, show that various clinical forms of viral hepatitis B infection can occur and develop.

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