Mathematical modeling regulatory mechanisms of a viral infection caused by hepatitis D virus with taking into account co-infection and super-infection

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Abstract. The purpose of this paper is to develop mathematical and computer models for the regulatory mechanisms of the interconnected activity between liver cells, the hepatitis B virus and hepatitis D virus molecular-genetic systems at hepatitis D infectious process. The paper draws the results made by using methods of quantitative and qualitative analyse of functional-differential equations. The paper concludes that the developed model which has oscillatory mode, chaotic regime and destructive changes that can be identified by chronic hepatitis D with intermittent crisis, with severe hepatitis D and liver cirrhosis. The paper provides a new mathematical and computer models which are able to describe hepatitis D regulatory mechanisms and to diagnose the infectious process course and predict the outcome of disease.

1. Introduction
Due to successful adoption of information technology advances into the various fields of science, the development and application of highly reliable mathematical methods for quantitative investigation of various diseases development regularities, including viral infections, particularly viral hepatitis\[1, 2, 3, 4, 5\] are very actual. In this aspect, mathematical and computer modeling of specific biological processes is becoming increasingly important, recommending itself as a very effective method for studying the dynamics of complex biological systems in normal conditions and under various pathological states. It should be emphasized that, if a clinical experimental research requires weeks and months, and sometimes years, the results of computational experiments conducted on the basis of mathematical and computer models can be obtained in minutes. At the same time, the considered biological process is investigated without using an appliance, a reagents, an experimental animals, that are especially deficient in certain viral infections (viral hepatitis, tuberculosis, HIV / AIDS, etc.), also we can disclosure main regularities in the biosystem functioning with the variables dynamics visualization. Mathematical and computer modeling has a predictive ability regarding occurrence the main modes dynamic characteristics of the considered process. The analysis shows that the study of the infectious processes using mathematical modeling is carried out by applying models to analyze immunological processes \[6, 7, 8\] and to study the mechanisms of epidemiological spread of disease \[9, 10, 11\].
2. Methods and Results

Functional-differential equations with delayed arguments can be used to model the regulatory mechanisms of the liver, taking into account the temporal relationship. The hepatitis B virus (HBV) performs the role as an assistant for hepatitis D virus (HDV) reproduction. Therefore, HDV infection always goes along with HBV infection. HDV infection is developed as a co-infection or superinfection. We use the method for quantitative studies of living systems regulators [12] and we have the following functional differential equations for regulatory mechanisms of the interrelated activity between the molecular-genetic systems of hepatocyte and HBV, HDV [13]:

\[
\frac{dX_i(t)}{dt} = a_i \left( \prod_{m=1}^{P_1} X_m(t-h) \right) e^{-\Omega_1(t)} - \alpha_i X_i(t);
\]

\[
\frac{dY_j(t)}{dt} = b_j \left( \prod_{m=1}^{P_1} X_m(t-h) \right) \left( \prod_{n=1}^{P_2} Y_n(t-q) \right) e^{-\Omega_2(t)} - \beta_j Y_j(t);
\]

\[
\frac{dZ_k(t)}{dt} = c_k \left( \prod_{m=1}^{P_1} X_m(t-h) \right) \left( \prod_{n=1}^{P_2} Y_n(t-q) \right) \left( \prod_{l=1}^{P_3} Z_l(t-q) \right) e^{-\Omega_3(t)} - \gamma_k Z_k(t);
\]

where \(X_i(t), Y_j(t), Z_k(t)\) are the quantities characterizing the activity of the corresponding molecular-genetic systems of the \(i\)-th hepatocyte, \(j\)-th HBV and \(k\)-th HDV at the time moment \(t\); \(\alpha_i, \beta_j, \gamma_k\) are parameters that characterize the decay levels for hepatocyte, HBV, HDV molecular-genetic systems activities accordingly; \(a_i, b_j, c_k\) are parameters characterizing the activity levels the hepatocyte, HBV, HDV molecular-genetic systems activities accordingly; if \(n = 1\), then we have co-infection, and if \(n = 2\), then there is superinfection; all parameters are non-negative.

In many cases, it is useful to construct the corresponding reduced equations (so-called model systems) on the basis of biological, biophysical considerations and mathematical techniques.

We assume that

- for successful developing of the HDV infection process, the HBV genome activity is necessary;
- HDV genome functioning leads to the activity suppression for the HBV genome;
- HDV activity brings to molecular-genetic processes disruption in an infected liver cell;
- HDV RNA conducts autocatalytic ribozyme activity.

Then, taking into account above-mentioned formulated features, we have the following model system for functional-differential equations of the HDV molecular-genetic system:

\[
\begin{align*}
\delta_1 \frac{dX(t)}{dt} &= a X^n(t-1) e^{-\omega(t)} - X(t); \\
\delta_2 \frac{dY(t)}{dt} &= b X(t-1) - Y(t); \\
\delta_3 \frac{dZ(t)}{dt} &= c Y(t-1) - Z(t);
\end{align*}
\]

\[
\omega(t) = X(t-1) + Y(t-1) + Z(t-1)
\]

where \(X(t), Y(t), Z(t)\) - values characterizing the activity of corresponding molecular genetic systems of hepatocyte, HBV and HDV in it, at time \(t\); \(\delta_1, \delta_2, \delta_3\) - parameters regulatory system; \(a, b, c\) - parameters characterizing the levels of activities of molecular genetic systems of the
corresponding hepatocyte, HBV and HDV; if \( n = 1 \), we have a co-infection, and at \( n = 2 \), superinfection; all parameters are non-negative. The system of differential-delay equations (1) belongs to the class of functional-differential equations and has an infinite number of basis functions. The Cauchy problem was posed by R. Bellman for these equations (the so-called initial problem) when specifying the initial functions \( X(t) = \varphi_1(t), Y(t) = \varphi_2(t), Z(t) = \varphi_3(t) \), which are continuous on \([0, h]\) with \( t \in [0, h], i = 1, 2, 3 \) and indicated solution by sequential integration method [14].

Assuming the quasistationary process of the functioning the molecular-genetic systems HBV and HDV in hepatocyte, using the methods of reduction and averaging, to quantify the dynamics of the hepatitis D infection process in the liver, we obtain the following functional-differential equation for the hepatocyte molecular-genetic system during HDV infection

\[
\delta \frac{d X(t)}{dt} = a X^n(t - 1) e^{-X(t)} - X(t),
\]

where \( X(t) \) - the value characterizing the state (on average) of the regulatory system of the molecular-genetic system of the liver cell at time \( t \); \( \delta, a \) - parameters of regulatory and the intensity of the molecular-genetic system of the liver cell; \( \delta = \tau/h \) (\( \tau \) - average activity time of products of the hepatocyte genetic system, \( h \) - feedback time of the hepatocyte molecular-genetic system). It should be noted that this infectious process leads to disruption of feedback system of molecular-genetic system of hepatocyte (thereby increasing the value of \( h \)) and reducing the time of products activity for genetic system of the hepatocyte (thereby reducing the value of \( \tau \)). This leads \( \delta \rightarrow 0 \) and (2) can be written as a functional equation

\[
X(t) = a X^n(t - 1) e^{-X(t)}
\]

on the basis of the reduction method of functional-differential equations of living systems [15] and we have its discrete analogue

\[
X_{k+1} = X_k^n e^{-X_k}.
\]

The (1) - (4) realization on PC allows computer simulation of the regulatory mechanisms of hepatocyte molecular-genetic system during HDV infection. The results of model studies, based on targeted computational experiments, showed the presence of the following main modes of regulatorika of the system "hepatocyte - HBV - HDV": oscillatory functioning (figure 1); chaotic functioning of molecular-genetic systems with sharp rises and decreases in activity (figure 2); destructive changes.

![Figure 1](image_url)

Figure 1. Regular oscillations in the "hepatocyte - HBV - HDV" system functioning.
Within the framework of this task, the emergence of self-oscillating solutions is identified as occurrence of chronic hepatitis D. Characteristic indicators of self-oscillations, their amplitude and period determine the severity and frequency of this chronic hepatitis D. Analytical and computational experiments have shown that the model symbiosis of the regulatory hepatocyte - HBV - HDV system at the molecular-genetic level can exist in the following variants:

- periodic alternation of dominance - C1, (for coinfection and superinfection),
- unpredictable behavior (chaos) - C2, (for superinfection),
- a sharp destructive change (black hole effect) - C3 (for superinfection),

which can be identified by chronic hepatitis D with intermittent crisis (C1), with severe hepatitis D (C2), and liver cirrhosis (C3), respectively. To study the behavior of symbiosis of regulatorika hepatocyte - HBV - HDV system (figure 3) in these modes (C1, C2, C3), we developed computer programs that quantitatively analyses the nature of the main dynamic characteristics of each molecular - genetic system under consideration (taking into account the dimension of the deformable space of the mathematical model in the corresponding basin of functional attractors with the construction of Lameray diagrams, calculation of Kolmogorov entropy, Lyapunov exponent, Hausdorff, Information, correlation and higher dimensions on a PC).

Based on the results of computer calculations we can
• determine the mode of conditions (diagnostics);
• predict the onset of regimes C1, C2, C3;
• receive dynamic characteristics of the system behavior

"Hepatocyte - HBV - HDV" in the C1, C2, C3 modes using a sequence of behavior values for mathematical and (or) computer model (quantitative characteristic of the course of the model infectious process).

The developed complex of computer programs is universal, working on the basis of quantitative characteristics of the flow of dynamic process under consideration. It can work with the use of specific clinical data regarding the process under consideration in the body, including the infectious process in the liver with hepatitis viruses. In other words, the model numerical sequence of ”infectious process” can be completely replaced by the numerical sequence of the real infectious process. This means that it is possible to obtain diagnostic and prognostic characteristics of the actual infection process in hepatitis D based on the results of mathematical and computer modeling of the regulatory framework of interrelated activity of the molecular genetic systems of hepatocyte, HBV and HDV.

3. Conclusions
Thus, the existing experimental data and theoretical statements on the patterns of the course of infectious process in hepatitis D allowed us to develop mathematical and computer models of regulatory mechanisms of interconnected activity of liver cells, HBV and HDV at the molecular genetic level. The developed software system using clinical data allows to diagnose the course of the infectious process and predict the onset of its main modes, i.e. the outcome of the disease.

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