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MODELING THE DYNAMICS OF HEPATITIS C WITH COMBINED TREATMENT

МОДЕЛЮВАННЯ ДИНАМІКИ ГЕПАТИТУ С ІЗ КОМБІНОВАНИМ ЛІКУВАННЯМ

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Abstract. *The problem of mathematical modeling of the immune response to hepatitis C viral infection is considered. The mathematical model of the process is described by a system of nonlinear differential equations. The solution of this system of equations is carried out by an iterative numerical-analytical method using the integral Laplace transform. The obtained results of mathematical modeling provide an opportunity to solve the problems of research and forecasting the development of infectious diseases and to determine the modes of effective treatment of the disease.*

Key words: *hepatitis C, infectious diseases, immune system, iterative schemes, nonlinear differential equations.*

Introduction

Viral infections are a serious problem for human health and prosperity. This is true not only for acute outbreaks, such as Ebola, with high public awareness, but also for chronic infections that have a major impact on health care management.

Hepatitis C virus (HCV) is a relatively common blood-borne disease. It is one of the leading causes of chronic liver disease worldwide and is the fastest growing cause of liver transplantation in developed countries [2]. If liver disease is left untreated, HCV progresses in approximately 7–18% of patients over 20 years, leading to liver failure, cirrhosis, hepatocellular carcinoma, and death [3].

Hepatitis C virus infection [1] causes chronic liver diseases such as liver cirrhosis and liver carcinoma. As chronic HCV infection affects 2–3% of the world's population, HCV is the leading cause of liver transplantation in the West.

There is no vaccine against hepatitis C, but significant progress has been made in the development of direct-acting antiviral agents (DAAs) [5] that specifically target specific genetic proteins encoded by the virus (eg, HCV protease and polymerase). However, there is still considerable room for a deeper "mechanism" understanding of the HCV replication cycle. This includes spatiotemporal analysis of HCV RNA translation, replication and assembly. A deeper understanding of these processes may also have implications for understanding fundamental virus-host interactions of related viruses. The main way of transmission of viruses is among active users of injection drugs (IDU), which is easily transmitted through the sharing of needles and syringes. In the UK, most developed countries and many other developing countries, the iatrogenic risk of HCV is high (eg in South Asia), with

more than 80% of new cases associated with injection drug use, with 15–90% of IDUs testing positive for antibodies to HCV.

Antiviral treatment of hepatitis C (peginterferon-alpha and ribavirin) is recognized as effective and leads to clearance of the virus in approximately 45–80% of cases, depending on the genotype [9].

Mathematical modeling has shown that antiviral treatment can be an effective preventive measure among IDUs, with modest and achievable treatment rates leading to a significant reduction in the prevalence of infection.

Mathematical modeling of the dynamics of hepatitis C serves as the basis for determining the parameters of the model for the purpose of building a system of optimal management of this process and determining optimal modes of antiviral treatment.

In contrast to the existing and widespread approaches to modeling the dynamics of immune processes, which are based on the application of numerical methods of the Runge-Kutta type [4-9] to linearized systems, a numerical analytical approach based on an iterative scheme for solving a system of nonlinear differential equations is proposed.

Mathematical model

A mathematical model for the combined treatment of IFN and ribavirin is considered, consisting of four related equations:

$$\begin{aligned}
\frac{dT}{dt} &= s + rT\left(1-\frac{T+I}{T_{\max}}\right) - dT - \beta T V_I, \\
\frac{dI}{dt} &= \beta T V_I + rI\left(1-\frac{T+I}{T_{\max}}\right) - \delta I, \\
\frac{dV_I}{dt} &= (1-\rho)(1-\varepsilon_p)pI - cV_I, \\
\frac{dV_{NI}}{dt} &= \rho(1-\varepsilon_p)pI - cV_{NI}.
\end{aligned} \tag{1}$$

The initial conditions are chosen as $[4,4\cdot10^6;1,4\cdot10^6;1,3\cdot10^6;0]^T$. (2)

These are the levels of the state variables (approximately) after 25 weeks of infection, starting with $(T^{(0)}\ I^{(0)}\ 10^2)^T$ (Value refers to virion level for HCV patients).

The assumption in the model is that hepatocytes are produced at a constant rate and have a natural death rate d, while proliferating at a rate, which $T_{\max}$ is the maximum possible level of the hepatocyte population (both uninfected and infected). It is assumed that hepatocytes are infected with virions at a rate of β . It is assumed that the proliferation of infected hepatocytes also occurs at a level r with the level of natural mortality δ. In the absence of any treatment, infected hepatocytes produce infectious virions at a rate of q. The introduction of IFN reduces this production by the factor $(1-\varepsilon)$, where ε is the efficiency of IFN. Finally, the model includes ribavirin efficacy ρ, which reflects the proportion of infectious non-infectious virions with mortality c for both of these populations.

Ribavirin works by converting some ρ of the newly formed virions into non-infectious ones, which divides the virion population into two distinct populations,

namely infectious (V_I) and non-infectious (V_{NI}).

Solving problem

Let's write the system of equations (1) in the following form:

$$\begin{aligned}
\frac{dT}{dt}+(d-r)T &= s-rT\frac{T+I}{T_{\max}}-\beta TV_I = s-T\left(\frac{r}{T_{max}}(T+I)+\beta V_I\right),\\
\frac{dI}{dt}+(\delta-r)I &= \beta TV_I-\frac{r}{T_{max}}I(T+I),\\
\frac{dV_I}{dt}+cV_I &= (1-\rho)(1-\varepsilon_p)pI,\\
\frac{dV_{NI}}{dt}+cV_{NI} &= \rho(1-\varepsilon_p)pI.
\end{aligned} \tag{3}$$

The initial conditions are given as (2).

The parameters of the model (3) are given in table 1.

Tabl. 1. Model Parameters(g/cm^3)

Par.	Value	Dimensionality
s	$2,005\cdot10^3$	cl./(ml.day)
d	$4,7\cdot10^{-3}$	1/day
p	5,4	virion/(cl. day)
β	$0,6\cdot10^{-7}$	ml/(virion day)
c	5,9	1/day
δ	0,3	1/day
r	0,45	1/day
$T_{\max}$	$0,7\cdot10^7$	cl/ml

Given the nonlinearity of the system of equations (3), we will look for its solution using the iterative algorithm [ ], which is based on the application of the integral Laplace transform to this system.

According to the iterative method [14], we first obtain the solution of the linear part of the system of equations (3). Let's apply the integral Laplace transform to the system of equations (3).

$$\begin{aligned}
(p+(d-r))\overline{T}^{(0)}(p) &= T^0+\frac{s}{p}+\mathcal{L}[N_T(t)];\\
(p+(\delta-r))\overline{I}^{(0)}(p) &= I_0+\mathcal{L}[N_I(t)];\\
(p+c)\overline{V}_I^{(0)}(p) &= V_I^0+\mathcal{L}[N_{V_I}(t)];\\
(p+c)\overline{V}_{NI}^{(0)}(p) &= V_{NI}^0+\mathcal{L}[N_{NI}(t)].
\end{aligned}$$

Or:

$$\overline{T}^{(1)}(p)=\frac{s}{d-r}\frac{1}{p}+\left(T^0-\frac{s}{d-r}\right)\frac{1}{p+(d-r)}+\frac{1}{p+(d-r)}\mathcal{L}[N_T^{(0)}(t)];$$

$$\overline{I}^{(1)}(p)=\frac{I^0}{p+(\delta-r)}+\frac{1}{p+(\delta-r)}\mathcal{L}[N_{V_I}^{(0)}(t)];$$

We denote:

$$\alpha_1=d-r,\ \alpha_2=\delta-r,\ \alpha_3=c,\ \alpha_4=\alpha_1+\alpha_2;$$

$$t0_0 = \frac{s}{\alpha_1}, t0_1 = T^0 - \frac{s}{\alpha_1}, r_1 = \frac{r}{T_{\max}}.$$

Then, for the linear parts of the system of equations, the solutions take the form:

$$T^{(0)}(t) = \frac{s}{\alpha_1} + \left(T^0 - \frac{s}{\alpha_1}\right)e^{-(\alpha_1 t} = t0_0 + t0_1 e^{-\alpha_1 t};$$

$$I^{(0)}(t) = I^0 e^{-(\alpha_2)t}; V_I^{(0)}(t) = V_I^0 e^{-ct}; V_{NI}^{(0)}(t) = V_{NI}^0(t)e^{-ct}.$$

Let's substitute these solutions into the nonlinear parts of the system of equations.

$$N_T^{(0)}(t) = T^{(0)}(t)\left(r_1[T^{(0)}(t) + I^{(0)}(t)] - \beta V_I^{(0)}(t)\right)$$

$$= \left(t0_0 + t0_1 e^{-\alpha_1 t}\right)\left(r_1[t0_0 + t0_1 e^{-\alpha_1 t} + I^0 e^{-\alpha_2 t}(t)] - \beta V_I^0 e^{-ct}\right). \quad (4)$$

Let's apply the Laplace transform and the equivalent simplification algorithm to this expression [15]. The values of the coefficients in this cloud are calculated using the corresponding C program.

$$\mathcal{L}[N_T^{(0)}(t) \approx \frac{b_2^T}{p} + \frac{b_0^T + b_1^T(p + \alpha^T)}{(p + \alpha^T)^2 \pm (\omega^T)^2}.$$

The general scheme of application of the iterative algorithm [14] (write it down for the first equation of the system):

$$\overline{T}^{(k+1)}(p) = \overline{T}^{(0)}(p) + \frac{1}{p + \alpha_1}\mathcal{L}[N_T^{(k)}(t)];$$

or in the space of the originals:

$$N_T^{(k)}(t) = T^{(k)}(t)\left(r_1[T^{(k)}(t) + I^{(k)}(t)] + \beta V_I^{(k)}(t)\right). \quad (5)$$

Substitution of the expressions for the linear parts of the sought functions in (5) with the subsequent application of the Laplace transform and the application of the equivalent simplification algorithm of the obtained expression gives:

$$\overline{T}^{(k+1)}(p) = \overline{T}^{(0)}(p) + \frac{1}{p + \alpha_1}\left[\frac{c_0^T + c_1^T p}{(p + a^T)^2 \pm (\omega^T)^2} + \frac{c_2^T}{p}\right] \quad (6)$$

To obtain the original from this expression, we apply the convolution integral

$$G_1(p)G_2(p) \to \int_0^t g_1(t - \tau)g_2(\tau)s\tau$$

$$= e^{\alpha^T t}\left[b_1 f_1(\omega^T t) + b_2 f_2(\omega^T t)\right] - b_2 e^{\gamma t}$$

In the space of originals, this expression corresponds

$$T^{(1)}(t) = c_0^T + e^{-\alpha^T t}\left[c_1^T f_1(\omega^T t) + c_2^T f_2(\omega^T t)\right] + c_6^T e^{\alpha_1 t}. \quad (7)$$

$$f_1(\omega^T t) = \begin{cases} \sin(\omega^T t), & (\omega^T)^2 > 0, \\ (\omega^T t), & (\omega^T)^2 < 0, \end{cases}; \quad f_2(\omega^T t) = \begin{cases} \cos(\omega^T t), & (\omega^T)^2 > 0, \\ (\omega^T t), & (\omega^T)^2 < 0, \end{cases}. \quad (8)$$

Using a similar algorithm, an expression for .

$$\overline{I}^{(1)}(p) = \overline{I}^{(0)}(p) + \frac{1}{p + \alpha_2}\frac{c_0^I + c_1^I p}{(p + a^I)^2 \pm (d^I)^2}$$

$$I^{(1)}(t) = c_0^I + e^{-\alpha^I t}\left[c_1^I f_1(\omega^I t) + c_2^I f_2(\omega^I t)\right] + c^I 6e^{\alpha_2 t}.$$

$$V_I^{(1)}(t) = c_0^{V_I} + e^{-\alpha^{V_I} t}\left[c_1^{V_I} f_1(\omega^{V_I} t) + c_2^{V_I} f_2(\omega^{V_I} t)\right] + c_6^{V_I} e^{\alpha_3} 2t.$$

$$V_{NI}^{(1)}(t) = c_0^{V_{NI}} + e^{-\alpha^{V_{NI}} t}\left[c_1^{V_{NI}} f_1(\omega^{V_{NI}} t) + c_2^{V_{NI}} f_2(\omega^{V_{NI}} t)\right] + c_6^{V_{NI}} e^{\alpha_4 t}.$$

The following iterations lead, thanks to the application of the algorithm of equivalent simplification of fractional-rational expressions with the use of continued fractions, to the solutions of the system of nonlinear equations (3), similar in form to the given solutions. At subsequent iterations, expressions of the form *(4)* instead of exponents contain expressions of the form (8). The above algorithms are implemented in an algorithmic language

Simulation results

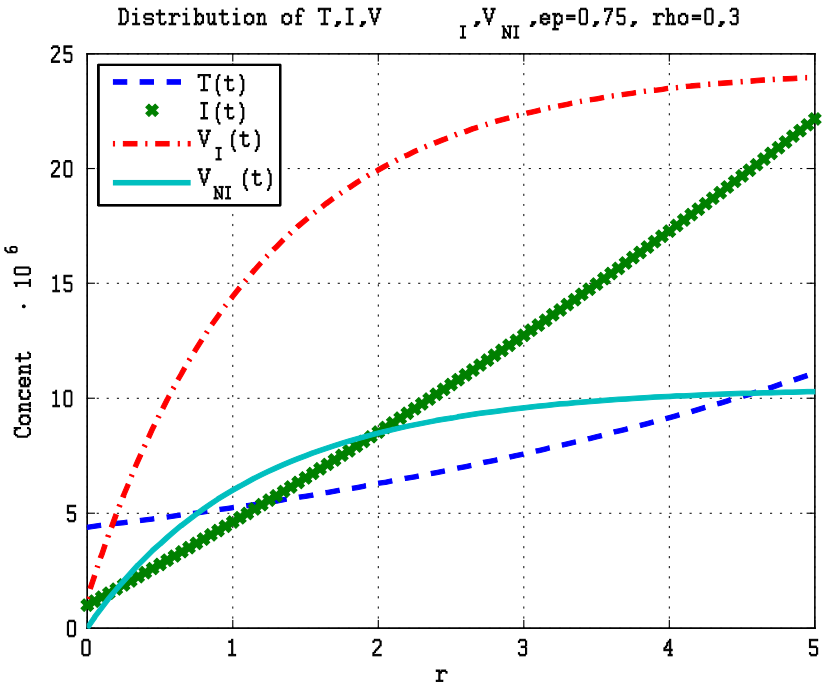

Рис.1 Розподіл концентрації компонентів за ep=0,75, rho=0,3.

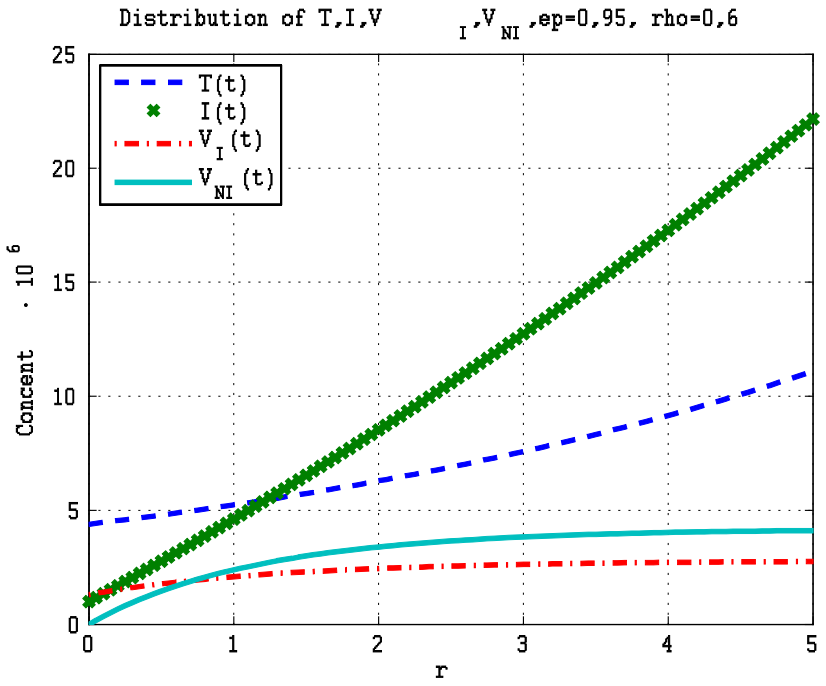

Рис.2 Розподіл концентрації компонентів за ep=0,95, rho=0,3.

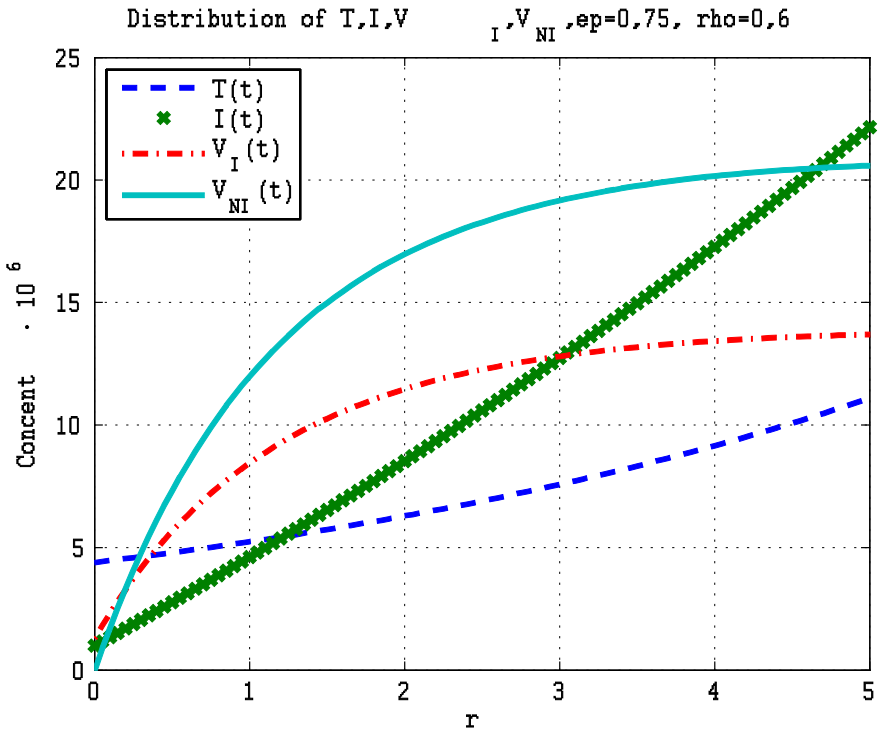

Рис.3 Розподіл концентрації компонентів за ep=0,75, rho=0,6.

In fig. 1-3 the results of modeling the problem for different values of parameters and efficiency of ribavirin use are presented.

Conclusions

Mathematical modeling of the system of nonlinear differential equations describing the dynamics of a common infectious disease, hepatitis C, was performed. The use of a numerical-analytical method of solving a system of nonlinear differential equations to obtain the solution of this system of equations made it possible to determine the ranges of changes in the parameters of the model, which provide the possibility of effective use of combined means of treatment of viral hepatitis C.

The conducted research provides an opportunity to build a system of optimal regulation of the process of combined treatment and is the goal of further research by the authors.

References

[1] Pachpute G., Chakrabarty S. Dynamics of hepatitis C under optimal therapy and sampling based analysis. *Commun Nonlinear Sci Numer Simulat*, 18, 2013, pp. 2202–2212.

[2] Martin N., Pitcher A., Vickerman P. Optimal Control of Hepatitis C Antiviral Treatment. Programme Delivery for Prevention amongst a Population of Injecting Drug Users. *PLoS One*, 2011, V.6, No 8, e23309, 17 p.

[3] Knodel M., Targett-Adams P., Grillo A. Advanced Hepatitis C Virus Replication PDE Models within a Realistic Intracellular Geometric Environment. *International Journal of Environmental Research and Public Health*, 2019, 16, 53 p.

[4] Knodel M., Reiter S., Targett-Adams P. 3D Spatially Resolved Models of

the Intracellular Dynamics of the Hepatitis C Genome Replication Cycle. *Viruses*, 2017, 9, 282.

[5] Knodel M., Nagel A., Reiter S., Rupp M. Quantitative analysis of Hepatitis C NS5A viral protein dynamics on the ER surface. *Viruses*, 2018, 10, 28.

[6] Kohli A., Shaffer, A., Sherman, A. Treatment of hepatitis C: A systematic review. *JAMA*, 2014, 312, p. 631–640.

[7] Dahari H., Ribeiro R., Rice C., Perelson A. Mathematical Modeling of Subgenomic Hepatitis C Virus Replication in Huh-7 Cells. *J. Virol.*, 2007, 81, p. 750–760.

[8] Dahari H., Guedj J., Perelson A. Hepatitis C Viral Kinetics in the Era of Direct Acting Antiviral Agents and IL28B. *Curr. Hepat. Rep.*, 2011, 10, p. 214–227.

[9] Rong L., Guedj J., Dahari H. Analysis of hepatitis C virus decline during treatment with the protease inhibitor danoprevir using a multiscale model. *PLoS Comput. Biol.*, 2013, 9, e1002959.

[10] Chukkapalli V., Berger, K., Kelly S. Daclatasvir inhibits hepatitis C virus NS5A motility and hyper-accumulation of phosphoinositides. *Virology*, 2015, 476, p. 168–179.

[11] Lindenbach, B., Rice C. The ins and outs of hepatitis C virus entry and assembly. *Nat. Rev. Microbiol.*, 2013, 11, p. 688–700.

[12] Asselah T., Boyer N., Saadoun D. Direct-acting antivirals for the treatment of hepatitis C virus infection: optimizing current IFN-free treatment and future perspectives. Liver Int. 36, 2016, pp. 47–57.

[13] Braciale T., Hahn Y., Burton D. (2013). Adaptive immune response to viral infections, in Fields Virology, eds B. N. Fields, D. M. Knipe, and P. M. Howley (Philadelphia, PA: Wolters Kluwer Health; Lippincott Williams, Wilkins), 214–285.

[14] Zelenskaya N., Zelensky K.. Approximation of Bessel functions by rational functions. *Electronics and control systems*, N 2 (44). p. 123--129. 2015.

[15] Zelensky K. Iterative method for solving nonlinear boundary value problems. *Scientific Notes of Lutsk National University*, vol. 26, t, 2, P. 49—55, 2010.

[16] Zelensky K. Mathemanical modeling of polimer media in extruders. Thesis of Doctor of technical sciences, 2021, Kyiv, 45 p.

Анотація. *Розглядається задача математичного моделювання імунної відповіді на вірусні інфекцію гепатиту С. Математична модель процесу описується системою нелінійних диференційних рівнянь. Розв'язання цієї системи рівнянь здійснюється ітераційним числово -аналітичним методом із застосуванням інтегрального перетворення Лапласа. Отримані результати математичного моделювання надають можливість вирішувати задачі дослідження і прогнозування розвитку інфекційних захворювань та визначити режими ефективного лікування хвороби.*

Ключові слова*: гепатит С, інфекційні захворювання, імунна система, ітераційні схеми, нелінійні диференційні рівняння.*