Article

Stability Analysis of a Mathematical Model of Hepatitis B Virus with Unbounded Memory Control on the Immune System in the Neighborhood of the Equilibrium Free Point

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Abstract: In the current paper, I research the influence of IL-2 therapy and I introduce the regulation by distributed feedback control with unbounded memory. The results of the stability analysis are presented. The proposed methodology in the article uses the properties of Cauchy matrix $C(t, s)$, especially symmetry property, in order to study the behavior (stability) of the corresponding system of integro-differential equations.

Keywords: functional differential equations; exponential stability; Cauchy matrix; integro-differential systems; hepatitis B; feedback control; immune system

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1. Introduction

Chronic hepatitis B (HBV) occurs in more than 240 millions individuals worldwide [1], causing approximately 350,000 deaths per year [2]. HBV has become one of the major problems faced by the human population and, thus, is a significant reflection of overall human health, primarily due to the increased risk of cirrhosis and carcinoma statuses [3]. With HBV being a member of the Herpesviridae class, a primary feature is DNA integration into the DNA of the host cell. The chronic HBV disease increases the hepatocellular carcinoma disease in at least on 50% of cases [4], and it has a high mortality. Using the vaccines developed leads to a reduction in the number of such cases, but antibody protection decreases with time. Currently used therapeutic methods for chronic HBV are the interferons strategy and the nucleos(t)ide analogous strategy [5]. Interferons (α , β , and γ) are produced from cytokines in the human immune system as a response to infection. They have strong confirmed antiviral reactions, and injections based on interferons (alfa-2a and alfa-2b) can be used for an HBV cure. Five analogues based on interferons have been approved by the USA: lamivudine, adefovir, entecavir, tenofovir disoproxil, and tenofovir alafenamide [1]. Their primary usage is in stopping viral replication. However, in practice, the described methods rarely lead to all of the desired goals. Another possible remedial strategy is based on the usage of interleukin-2 (IL-2) in a combination (NCT02360592 and NCT00451984). The evaluation of combined methods shows great potential for reducing the viral replication rate. The combined method with IL-2 therapy was based on the proposed mathematical model described by the system of integro-differential equations. This approach was proven to be efficient in [6–13]. Previous models predicted the success rate of an antiviral cure but without any relation to the immune response impact [14–16]. As a result, the predictions are not robust and non-realistic due to impact factors such as the lifespan of HBV-infected cells and immune response strength being ignored [17]. Instead of previous models, in the currently proposed model, I relate the two different treatment strategies described above as well as immune system response, and the distributed feedback control function was added in order to obtain better optimization using the added IL-2 treatment.

2. Description of the Model

In [18], a global analysis of hepatitis C was presented. The model was based on the following nonlinear differential system:

$$\begin{cases} X' = r - dX - \beta VX \\ Y' = \beta VX - aY - pYZ \\ V' = kY - uV - qVW \\ W' = -hW + gVW \\ Z' = cYZ - bZ \end{cases} \quad (1)$$

This model presents five equations with five variables that describe the status of the virus–host system on each time. These variables are uninfected cells, infected cells, free virus numbers, antibody response, and CTL response denoted, respectively, by X (cells/mL), Y (cells/mL), V (IU/mL), W (IU/mL), and Z (cells/mL).

I estimate the efficiency of therapy based on two methods: interferon and nucleoside. These are, respectively, denoted by η and ε , and their values are between 0 and 1. Due to their influence on the therapy, they directly affect the growth or the decay of the infected cells. Consider that I obtain the following:

$$\begin{cases} X' = r - dX - (1 - \eta)\beta VX \\ Y' = (1 - \eta)\beta VX - aY - pYZ \\ V' = (1 - \varepsilon)kY - uV - qVW \end{cases} \quad (2)$$

The mathematical models based on systems of differential equations have an important role in the study of viral infections and appropriate cure processes as well as the prediction of patient condition after drug dose treatment and immune system response. In [19], I researched the influence of IL-2 therapy and introduced the distributed control function $U(t)$ in the form $U(t) = \int_0^t e^{-\alpha(t-s)} Z(s) ds$, and the result of exponential stability with this sort of regulation has been obtained in this article. The modified model of HBV is as follows [19]:

$$\begin{cases} X' = r - dX - (1 - \eta)\beta VX \\ Y' = (1 - \eta)\beta VX - aY - pYZ \\ V' = (1 - \varepsilon)kY - uV - qVW \\ W' = -hW + gVW \\ Z' = cYZ - bZ + DU \end{cases} \quad (3)$$

where

$$U(t) = \int_0^t e^{-\alpha(t-s)} Z(s) ds. \quad (4)$$

In the current paper, I study the regulation with delay in the upper and lower bounds of this integral.

3. Relation between the Convergence Rate of System (1) and (3)

Using the reduction method, I change the integro-differential system (3) to an ordinary differential system:

$$\begin{cases} X' = r - dX - (1 - \eta)\beta VX \\ Y' = (1 - \eta)\beta VX - aY - pYZ \\ V' = (1 - \varepsilon)kY - uV - qVW \\ W' = -hW + gVW \\ Z' = cYZ - bZ + DU \\ U' = Z - \alpha U \end{cases} \quad (5)$$

Linearizing systems (1) and (5) in the neighborhood of the equilibrium free point

$$P = \{X, Y, V, W, Z, U\} = \left(\frac{r}{d}, 0, 0, 0, 0, 0\right), \quad (6)$$

I obtain the linear systems

$$\begin{cases} x'_1 = r - dx_1 - \frac{\beta r}{d} x_3 \\ x'_2 = -ax_2 + \frac{\beta r}{d} x_3 \\ x'_3 = kx_2 - ux_3 \\ x'_4 = -hx_4 \\ x'_5 = -bx_5 \end{cases}, \quad (7)$$

$$\begin{cases} x'_1 = r - dx_1 - \frac{(1-\eta)\beta r}{d} x_3 \\ x'_2 = -ax_2 + \frac{(1-\eta)\beta r}{d} x_3 \\ x'_3 = (1-\varepsilon)kx_2 - ux_3 \\ x'_4 = -hx_4 \\ x'_5 = Dx_6 - bx_5 \\ x'_6 = x_5 - \alpha x_6 \end{cases} \quad (8)$$

where

$$x_1 = X - \frac{r}{d}, x_2 = Y, x_3 = V, x_4 = W, x_5 = Z, x_6 = U$$

and corresponding homogeneous systems

$$\begin{cases} x'_1 = -dx_1 - \frac{\beta r}{d} x_3 \\ x'_2 = -ax_2 + \frac{\beta r}{d} x_3 \\ x'_3 = kx_2 - ux_3 \\ x'_4 = -hx_4 \\ x'_5 = -bx_5 \end{cases}, \quad (9)$$

$$\begin{cases} x'_1 = -dx_1 - \frac{(1-\eta)\beta r}{d} x_3 \\ x'_2 = -ax_2 + \frac{(1-\eta)\beta r}{d} x_3 \\ x'_3 = (1-\varepsilon)kx_2 - ux_3 \\ x'_4 = -hx_4 \\ x'_5 = Dx_6 - bx_5 \\ x'_6 = x_5 - \alpha x_6 \end{cases} \quad (10)$$

Denote the corresponding matrices of coefficients of system (9) and (10):

$$B = \begin{pmatrix} -d & 0 & -\frac{\beta r}{d} & 0 & 0 \\ 0 & -a & \frac{\beta r}{d} & 0 & 0 \\ 0 & k & -u & 0 & 0 \\ 0 & 0 & 0 & -h & 0 \\ 0 & 0 & 0 & 0 & -b \end{pmatrix}. \quad (11)$$

$$A = \begin{pmatrix} -d & 0 & -\frac{(1-\eta)\beta r}{d} & 0 & 0 & 0 \\ 0 & -a & \frac{(1-\eta)\beta r}{d} & 0 & 0 & 0 \\ 0 & (1-\varepsilon)k & -u & 0 & 0 & 0 \\ 0 & 0 & 0 & -h & 0 & 0 \\ 0 & 0 & 0 & 0 & -b & D \\ 0 & 0 & 0 & 0 & 1 & -\alpha \end{pmatrix}. \quad (12)$$

The characteristic polynomial of system (9) has five roots:

$$\begin{cases} \lambda_1 = -h \\ \lambda_2 = -d \\ \lambda_3 = \frac{-d(a+u) + \sqrt{d^2(a-u)^2 + 4k\beta rd}}{2d} \\ \lambda_4 = \frac{-d(a+u) - \sqrt{d^2(a-u)^2 + 4k\beta rd}}{2d} \\ \lambda_5 = -b \end{cases} \quad (13)$$

The characteristic polynomial of system (10) has six roots:

$$\begin{cases} \lambda_1^* = -h \\ \lambda_2^* = -d \\ \lambda_3^* = \frac{-d(a+u) + \sqrt{d^2(a-u)^2 + 4k\beta rd(\varepsilon-1)(\eta-1)}}{2d} \\ \lambda_4^* = \frac{-d(a+u) - \sqrt{d^2(a-u)^2 + 4k\beta rd(\varepsilon-1)(\eta-1)}}{2d} \\ \lambda_5^* = -\left(\frac{\alpha+b}{2}\right) + \frac{\sqrt{(\alpha-b)^2 + 4D}}{2} \\ \lambda_6^* = -\left(\frac{\alpha+b}{2}\right) - \frac{\sqrt{(\alpha-b)^2 + 4D}}{2} \end{cases} \quad (14)$$

Theorem 1. *If all of the coefficients of system (1) are positive, then system (1) is exponentially stable.*

Proof. It is clear that, in (13), eigenvalues $\lambda_1, \lambda_2, \lambda_4, \lambda_5$ are real and negative. Eigenvalue λ_3 is real and negative if $d^2(a-u)^2 + 4k\beta rd < d^2(a+u)^2$, i.e., $4k\beta rd < 4d^2au$. However, the following inequality is always true: $0 < \frac{dau}{k\beta r}$. $\square$

Let us denote the following:

$$(\varepsilon-1)(\eta-1) < \frac{aud}{\beta kr}, \quad (15)$$

$$D < \alpha b. \quad (16)$$

Theorem 2. [19] *If all of the coefficients of system (5) are positive, η and ε are parameters defined between 0 to 1, and inequalities (15) and (16) are fulfilled, then system (5) is exponentially stable.*

Let us denote the corresponding spectral radius of systems (9) and (10) by

$$\rho = \max_{1 \leq i \leq 5} |\lambda_i|, \quad \rho^* = \max_{1 \leq j \leq 6} |\lambda_j^*|.$$

Theorem 3. *If all of the coefficients of system (5) are positive, η and ε are parameters defined between 0 to 1, and inequalities (15) and (16) are fulfilled, then system (5) is exponentially stable and $\rho \leq \rho^*$.*

Proof. It is clear from (13) and (14) that $\lambda_1 = \lambda_1^* = -h < 0, \lambda_2 = \lambda_2^* = -d < 0$.

I have to show that $|\lambda_4^*| > |\lambda_4|$ because $|\lambda_4| > |\lambda_3|$ and $|\lambda_4^*| > |\lambda_3^*|$.

$$\frac{d(a+u) + \sqrt{d^2(a-u)^2 + 4k\beta rd(\varepsilon-1)(\eta-1)}}{2d} > \frac{d(a+u) + \sqrt{d^2(a-u)^2 + 4k\beta rd}}{2d}.$$

I obtain the following true inequality: $(\varepsilon-1)(\eta-1) > 0$.

Now I have to show that $|\lambda_6^*| > |\lambda_5|$ because $|\lambda_6^*| > |\lambda_5^*|$.

$$\left(\frac{\alpha+b}{2}\right) + \frac{\sqrt{(\alpha-b)^2 + 4D}}{2} > b.$$

Therefore,

$$\sqrt{(\alpha-b)^2 + 4D} > b - \alpha.$$

If $b - \alpha \leq 0$, this inequality is true, and if $b - \alpha > 0$, I also obtain a true inequality: $D > 0$. $\square$

4. Exponential Stability of System (3) with Unbounded Memory Control Function

Consider system (3), where

$$U(t) = \int_{t-\tau(t)}^t e^{-\alpha(t-s)} Z(s) ds. \quad (17)$$

Denote

$$\tilde{U}(t) = \int_0^t e^{-\alpha(t-s)} Z(s) ds. \quad (18)$$

Let us write (17) in the following form:

$$\begin{aligned} U(t) &= \int_0^t e^{-\alpha(t-s)} Z(s) ds - e^{-\alpha\tau(t)} \int_0^{t-\tau(t)} e^{-\alpha((t-\tau(t))-s)} Z(s) ds \\ &= \tilde{U}(t) - e^{-\alpha\tau(t)} \tilde{U}(t - \tau(t)). \end{aligned} \quad (19)$$

Reducing the integro-differential system (3), where $U(t)$ is defined by (17) to an ordinary differential system, I obtain the following:

$$\begin{cases} X' = r - dX - (1-\eta)\beta VX \\ Y' = (1-\eta)\beta VX - aY - pYZ \\ V' = (1-\varepsilon)kY - uV - qVW \\ W' = -hW + gVW \\ Z' = cYZ - bZ + D\tilde{U} - De^{-\alpha\tau(t)}\tilde{U}(t - \tau(t)) \\ \tilde{U}' = Z - \alpha\tilde{U} \end{cases}. \quad (20)$$

Linearizing system (20) in the neighborhood of the equilibrium free point (6), I obtain the corresponding homogeneous linear systems:

$$\begin{cases} x_1'(t) = r - dx_1(t) - \frac{(1-\eta)\beta r}{d} x_3(t) \\ x_2'(t) = -ax_2(t) + \frac{(1-\eta)\beta r}{d} x_3(t) \\ x_3'(t) = (1-\varepsilon)kx_2(t) - ux_3(t) \\ x_4'(t) = -hx_4(t) \\ x_5'(t) = Dx_6(t) - bx_5(t) - De^{-\alpha\tau(t)}x_6(t - \tau(t)) \\ x_6'(t) = x_5(t) - \alpha x_6(t) \end{cases} \quad (21)$$

where

$$x_1(t) = X - \frac{r}{d}, x_2(t) = Y, x_3(t) = V, x_4(t) = W, x_5(t) = Z, x_6(t) = \tilde{U}$$

Let us denote the following:

$$\begin{aligned} c_{11} &= \frac{d(a+u)}{2d}, c_{12} = \frac{\sqrt{4k\beta rd(\varepsilon-1)(\eta-1)+d^2(a-u)^2}}{2d}, c_{13} = \frac{\alpha+b}{2}, c_{14} = \frac{\sqrt{(\alpha-b)^2+4D}}{2}, \\ c_{15} &= \frac{\beta r(\eta-1)}{d(-c_{11}+c_{12}+d)}, c_{16} = \frac{\beta r(\eta-1)}{d(-c_{11}+c_{12}+a)}, c_{17} = \frac{\beta r(\eta-1)}{d(-c_{11}-c_{12}+d)}, c_{18} = \frac{\beta r(\eta-1)}{d(-c_{11}-c_{12}+a)}, \\ c_{19} &= \frac{D}{-\frac{\alpha}{2}+\frac{b}{2}+c_{14}}, c_{21} = \frac{D}{-\frac{\alpha}{2}+\frac{b}{2}-c_{14}}, c_{22} = \frac{c_{15}-c_{17}}{c_{16}-c_{18}}, c_{23} = \frac{1}{c_{16}-c_{18}}, c_{25} = \frac{c_{15} \cdot c_{18}-c_{16} \cdot c_{17}}{c_{16}-c_{18}}, \\ c_{26} &= \frac{c_{18}}{c_{16}-c_{18}}, c_{27} = \frac{c_{16}}{c_{16}-c_{18}}, c_{28} = \frac{1}{c_{19}-c_{21}}, c_{31} = \frac{c_{21}}{c_{19}-c_{21}}, c_{32} = \frac{c_{19}}{c_{19}-c_{21}}. \end{aligned} \quad (22)$$

I assume that the denominators are not zero.

The Cauchy matrix of system (10) is the following (see [19]):

$$\begin{aligned} C_1(t,s) &= \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} e^{-d(t-s)}, \\ C_2(t,s) &= \begin{pmatrix} c_{22} \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} e^{-d(t-s)} + \begin{pmatrix} -c_{15} \cdot c_{23} \\ c_{16} \cdot c_{23} \\ -c_{23} \\ 0 \\ 0 \\ 0 \end{pmatrix} e^{(-c_{11}+c_{12})(t-s)} + \begin{pmatrix} c_{17} \cdot c_{23} \\ -c_{18} \cdot c_{23} \\ c_{23} \\ 0 \\ 0 \\ 0 \end{pmatrix} e^{(-c_{11}-c_{12})(t-s)}, \\ C_3(t,s) &= \begin{pmatrix} c_{25} \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} e^{-d(t-s)} + \begin{pmatrix} -c_{15} \cdot c_{26} \\ c_{16} \cdot c_{26} \\ -c_{26} \\ 0 \\ 0 \\ 0 \end{pmatrix} e^{(-c_{11}+c_{12})(t-s)} + \begin{pmatrix} c_{17} \cdot c_{27} \\ -c_{18} \cdot c_{27} \\ c_{27} \\ 0 \\ 0 \\ 0 \end{pmatrix} e^{(-c_{11}-c_{12})(t-s)}, \\ C_4(t,s) &= \begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \end{pmatrix} e^{-h(t-s)}, \\ C_5(t,s) &= \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ c_{19} \cdot c_{28} \\ c_{28} \end{pmatrix} e^{(-c_{13}+c_{14})(t-s)} + \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ -c_{21} \cdot c_{28} \\ -c_{28} \end{pmatrix} e^{(-c_{13}-c_{14})(t-s)}, \end{aligned}$$

$$C_6(t, s) = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ -c_{19} \cdot c_{31} \\ -c_{31} \end{pmatrix} e^{(-c_{13}+c_{14})(t-s)} + \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ c_{21} \cdot c_{32} \\ c_{32} \end{pmatrix} e^{(-c_{13}-c_{14})(t-s)}. \quad (23)$$

Let us denote $\tau_* = \text{ess inf}_{t \geq 0} |\tau(t)|$ and

$$Q_1 = De^{\alpha\tau_*} \left(\left| \frac{c_{28}}{c_{14} - c_{13}} \right| + \left| \frac{c_{28}}{c_{13} + c_{14}} \right| + \left| \frac{c_{31}}{c_{14} - c_{13}} \right| + \left| \frac{c_{32}}{c_{13} + c_{14}} \right| \right)$$

Theorem 4. If all of the coefficients of system (5) are positive; η and ε are parameters defined between 0 to 1; $D < \alpha b$; and inequalities (15), (16), and $Q_1 < 1$ are fulfilled, then system (20) is exponentially stable.

Proof. I can write system (10) in the following form:

$$X'(t) = AX(t), \quad (24)$$

where

$$X(t) = \text{col}\{x_1(t), x_2(t), x_3(t), x_4(t), x_5(t), x_6(t)\},$$

and A is defined by (12).

It is known that the general solution of the system

$$X'(t) - AX(t) = K_1(t) \quad (25)$$

can be represented in the following form:

$$X(t) = \int_0^t C(t, \gamma) K_1(\gamma) d\gamma + C(t, 0) X(0) \quad (26)$$

where $C(t, s)$ is a Cauchy matrix (23) of system (10). I can rewrite system (21) in the following form:

$$\begin{cases} x_1'(t) + dx_1(t) + \frac{(1-\eta)\beta r}{d} x_3(t) = r \\ x_2'(t) + ax_2(t) - \frac{(1-\eta)\beta r}{d} x_3(t) = 0 \\ x_3'(t) - (1-\varepsilon)kx_2(t) + ux_3(t) = 0 \\ x_4'(t) + hx_4(t) = 0 \\ x_5'(t) - Dx_6(t) + bx_5(t) = -De^{-\alpha\tau(t)} x_6(t - \tau(t)) \\ x_6'(t) - x_5(t) + \alpha x_6(t) = 0 \end{cases} \quad (27)$$

Without loss of generality, I assume that $X(0) = 0$.

Substituting $X(t) = \int_0^t C(t, \gamma) K_1(\gamma) d\gamma$ into system (27), I have

$$x_6(t - \tau(t)) = \sum_{i=1}^6 \int_0^{t-\tau(t)} c_{6i}((t - \tau(t)), \gamma) k_{1i}(\gamma) d\gamma$$

and the following system for $K_1(t)$:

$$K_1(t) = (\Omega_1 K_1)(t) + F_1(t),$$

where

$$K_1(t) = \begin{pmatrix} k_{1_1}(t) \\ k_{1_2}(t) \\ k_{1_3}(t) \\ k_{1_4}(t) \\ k_{1_5}(t) \\ k_{1_6}(t) \end{pmatrix}, F_1(t) = \begin{pmatrix} r \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

and the operator $\Omega_1 : L_\infty \rightarrow L_\infty$ is defined by

$$(\Omega_1 K_1)(t) = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ \omega_1 K_1(t) \\ 0 \end{pmatrix}$$

where

$$\begin{aligned} (\Omega_1 K_1)(t) = & -De^{-\alpha\tau(t)} \int_0^{t-\tau(t)} \left(c_{28}e^{(-c_{13}+c_{14})(t-\tau(t)-\gamma)} - c_{28}e^{(-c_{13}-c_{14})(t-\tau(t)-\gamma)} \right) k_{1_5}(\gamma) d\gamma \\ & -De^{-\alpha\tau(t)} \int_0^{t-\tau(t)} \left(-c_{31}e^{(-c_{13}+c_{14})(t-\tau(t)-\gamma)} + c_{32}e^{(-c_{13}-c_{14})(t-\tau(t)-\gamma)} \right) k_{1_6}(\gamma) d\gamma, \end{aligned}$$

according to (23). Estimating the norm of the operator Ω_1 , I obtain the assertion of this theorem. $\square$

5. Exponential Stability of System (3) with Delay in Upper Limit of Control Function

Consider system (3), where

$$U(t) = \int_0^{t-\tau(t)} e^{-\alpha(t-s)} Z(s) ds. \quad (28)$$

Denote

$$\tilde{U}(t) = \int_0^t e^{-\alpha(t-s)} Z(s) ds. \quad (29)$$

Let us write (28) in the following form:

$$U(t) = e^{-\alpha\tau(t)} \int_0^{t-\tau(t)} e^{-\alpha((t-\tau(t))-s)} Z(s) ds = e^{-\alpha\tau(t)} \tilde{U}(t - \tau(t)). \quad (30)$$

Reducing integro-differential system (3), where $U(t)$ is defined by (28), to an ordinary differential system, I obtain

$$\begin{cases} X' = r - dX - (1 - \eta)\beta VX \\ Y' = (1 - \eta)\beta VX - aY - pYZ \\ V' = (1 - \varepsilon)kY - uV - qVW \\ W' = -hW + gVW \\ Z' = cYZ - bZ + D\tilde{U} + De^{-\alpha\tau(t)}\tilde{U}(t - \tau(t)) - D\tilde{U} \\ \tilde{U}' = Z - \alpha\tilde{U} \end{cases}. \quad (31)$$

Linearizing systems (31) in the neighborhood of the equilibrium free point (6), I obtain the corresponding homogeneous linear systems:

$$\begin{cases} x_1'(t) = r - dx_1(t) - \frac{(1-\eta)\beta r}{d} x_3(t) \\ x_2'(t) = -ax_2(t) + \frac{(1-\eta)\beta r}{d} x_3(t) \\ x_3'(t) = (1-\varepsilon)kx_2(t) - ux_3(t) \\ x_4'(t) = -hx_4(t) \\ x_5'(t) = Dx_6(t) - bx_5(t) + De^{-\alpha\tau(t)}x_6(t - \tau(t)) - Dx_6(t) \\ x_6'(t) = x_5(t) - \alpha x_6(t), \end{cases} \quad (32)$$

where

$$x_1(t) = X - \frac{r}{d}, x_2(t) = Y, x_3(t) = V, x_4(t) = W, x_5(t) = Z, x_6(t) = \tilde{U}$$

Let us denote $\tau_* = \text{ess inf}_{t \geq 0} |\tau(t)|$ and

$$\begin{aligned} (\Omega_2 K_2)(t) &= De^{-\alpha\tau(t)} \int_0^{t-\tau(t)} \left(c_{28} e^{(-c_{13}+c_{14})(t-\tau(t)-\gamma)} - c_{28} e^{(-c_{13}-c_{14})(t-\tau(t)-\gamma)} \right) k_{25}(\gamma) d\gamma \\ &\quad De^{-\alpha\tau(t)} \int_0^{t-\tau(t)} \left(-c_{31} e^{(-c_{13}+c_{14})(t-\tau(t)-\gamma)} + c_{32} e^{(-c_{13}-c_{14})(t-\tau(t)-\gamma)} \right) k_{26}(\gamma) d\gamma \\ &\quad - D \int_0^t \left(c_{28} e^{(-c_{13}+c_{14})(t-\gamma)} - c_{28} e^{(-c_{13}-c_{14})(t-\gamma)} \right) k_{25}(\gamma) d\gamma \\ &\quad - D \int_0^t \left(-c_{31} e^{(-c_{13}+c_{14})(t-\gamma)} + c_{32} e^{(-c_{13}-c_{14})(t-\gamma)} \right) k_{26}(\gamma) d\gamma. \\ Q_2 &= De^{\alpha\tau_*} \left(\left| \frac{c_{28}}{c_{14}-c_{13}} \right| + \left| \frac{c_{28}}{c_{13}+c_{14}} \right| + \left| \frac{c_{31}}{c_{14}-c_{13}} \right| + \left| \frac{c_{32}}{c_{13}+c_{14}} \right| \right) \\ &\quad + D(2|c_{28}| + |c_{31}| + |c_{32}|) \end{aligned}$$

Theorem 5. If all of the coefficients of system (5) are positive; η and ε are parameters defined between 0 to 1; and inequalities (15), (16), and $Q_2 < 1$ are fulfilled, then system (31) is exponentially stable.

Proof. I can write system (10) in the following form:

$$X'(t) = AX(t), \quad (33)$$

where

$$X(t) = \text{col}\{x_1(t), x_2(t), x_3(t), x_4(t), x_5(t), x_6(t)\},$$

and A defined by (12).

It is known that the general solution of the system

$$X'(t) - AX(t) = K_2(t) \quad (34)$$

can be represented in the following form:

$$X(t) = \int_0^t C(t, \gamma) K_2(\gamma) d\gamma + C(t, 0) X(0) \quad (35)$$

where $C(t, s)$ is a Cauchy matrix (23) of system (10). I can rewrite system (32) in the following form:

$$\begin{cases} x_1'(t) + dx_1(t) + \frac{(1-\eta)\beta r}{d} x_3(t) = r \\ x_2'(t) + ax_2(t) - \frac{(1-\eta)\beta r}{d} x_3(t) = 0 \\ x_3'(t) - (1-\varepsilon)kx_2(t) + ux_3(t) = 0 \\ x_4'(t) + hx_4(t) = 0 \\ x_5'(t) - Dx_6(t) + bx_5(t) = De^{-\alpha\tau(t)}x_6(t-\tau(t)) - Dx_6(t) \\ x_6'(t) - x_5(t) + \alpha x_6(t) = 0 \end{cases} \quad (36)$$

Without loss of generality, I assume that $X(0) = 0$.

Substituting $X(t) = \int_0^t C(t, \gamma)K_2(\gamma)d\gamma$ into system (36), I have

$$x_6(t - \tau(t)) = \sum_{i=1}^6 \int_0^{t-\tau(t)} c_{6i}((t - \tau(t)), \gamma)k_{2i}(\gamma)d\gamma$$

and the following system for $K_2(t)$:

$$K_2(t) = (\Omega_2 K_2)(t) + F_2(t),$$

where

$$K_2(t) = \begin{pmatrix} k_{21}(t) \\ k_{22}(t) \\ k_{23}(t) \\ k_{24}(t) \\ k_{25}(t) \\ k_{26}(t) \end{pmatrix}, F_2(t) = \begin{pmatrix} r \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

and the operator $\Omega_2 : L_\infty \longrightarrow L_\infty$ is defined by

$$(\Omega_2 K_2)(t) = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ \omega_2 K_2(t) \\ 0, \end{pmatrix}$$

where

$$\begin{aligned} (\Omega_2 K_2)(t) &= De^{-\alpha\tau(t)} \int_0^{t-\tau(t)} \left(c_{28}e^{(-c_{13}+c_{14})(t-\tau(t)-\gamma)} - c_{28}e^{(-c_{13}-c_{14})(t-\tau(t)-\gamma)} \right) k_{25}(\gamma)d\gamma \\ &\quad De^{-\alpha\tau(t)} \int_0^{t-\tau(t)} \left(-c_{31}e^{(-c_{13}+c_{14})(t-\tau(t)-\gamma)} + c_{32}e^{(-c_{13}-c_{14})(t-\tau(t)-\gamma)} \right) k_{26}(\gamma)d\gamma \\ &\quad -D \int_0^t \left(c_{28}e^{(-c_{13}+c_{14})(t-\gamma)} - c_{28}e^{(-c_{13}-c_{14})(t-\gamma)} \right) k_{25}(\gamma)d\gamma \\ &\quad -D \int_0^t \left(-c_{31}e^{(-c_{13}+c_{14})(t-\gamma)} + c_{32}e^{(-c_{13}-c_{14})(t-\gamma)} \right) k_{26}(\gamma)d\gamma. \end{aligned}$$

according to (23). Estimating the norm of the operator Ω_2 , I obtain the assertion of this theorem. $\square$

6. Simulations

In order to validate the proposed model (3), I chose a validation set defined by the initial conditions and dose of the drugs.

Set 1: initial conditions $X(0) = 0.5$, $Y(0) = 0.1$, $V(0) = 0.1$, $W(0) = 0.1$, $Z(0) = 0.1$, and $U(0) = 0.1$ and dose of the drugs $\epsilon = 0.5$, $\eta = 0.5$, $\alpha = 2$, and $D = 0.1$.

Set 2: initial conditions $X(0) = 0.1$, $Y(0) = 0.5$, $V(0) = 0.5$, $W(0) = 0.1$, $Z(0) = 0.1$, and $U(0) = 0$ and dose of the drugs $\epsilon = 0.1$, $\eta = 0.1$, $\alpha = 10$, and $D = 0.2$.

Set 3: initial conditions $X(0) = 0.01$, $Y(0) = 0.9$, $V(0) = 0.2$, $W(0) = 0.01$, $Z(0) = 0.1$, and $U(0) = 0.2$ and dose of the drugs $\epsilon = 0.01$, $\eta = 0.02$, $\alpha = 5$, and $D = 0.01$.

Set 4: initial conditions $X(0) = 0.01$, $Y(0) = 1$, $V(0) = 0.5$, $W(0) = 0.1$, $Z(0) = 0.2$, $U(0) = 0.5$ and dose of the drugs $\epsilon = 0.001$, $\eta = 0.1$, $\alpha = 1$, $D = 0.05$.

Set 5: initial conditions $X(0) = 1$, $Y(0) = 1$, $V(0) = 0.1$, $W(0) = 0.001$, $Z(0) = 0.0002$, and $U(0) = 0.0001$ and dose of the drugs $\epsilon = 0.25$, $\eta = 0.1$, $\alpha = 2$, and $D = 0.01$.

Set 6: initial conditions $X(0) = 2$, $Y(0) = 10$, $V(0) = 5$, $W(0) = 0.0001$, $Z(0) = 0.0001$, and $U(0) = 0.0001$ and dose of the drugs $\epsilon = 0.01$, $\eta = 0.9$, $\alpha = 7$, and $D = 0.5$.

Set 7: initial conditions $X(0) = 0.1$, $Y(0) = 10$, $V(0) = 5$, $W(0) = 0.1$, $Z(0) = 0.01$, and $U(0) = 1$ and dose of the drugs $\epsilon = 0.9$, $\eta = 0.1$, $\alpha = 0.1$, and $D = 0.001$.

Set 8: initial conditions $X(0) = 1$, $Y(0) = 2$, $V(0) = 0.1$, $W(0) = 0.1$, $Z(0) = 0.2$, and $U(0) = 0.1$ and dose of the drugs $\epsilon = 0.2$, $\eta = 0.8$, $\alpha = 0.5$, and $D = 0.005$.

Remark 1. From [20], I used the following values of the parameters in system (1):

$$d = 0.00333, g = q = 5, b = 0.112, \beta = 7, h = 2, a = 0.56, u = 0.67, p = c = 5.14,$$

$$k = 20, r = 6.17 \times 10^{-4}.$$

The results of the simulations are presented in Figures 1–8 accordingly.

Figure 1. Set 1.

Figure 2. Set 2.

Figure 3. Set 3.

Figure 4. Set 4.

Figure 5. Set 5.

Figure 6. Set 6.

Figure 7. Set 7.

Figure 8. Set 8.

7. Conclusions

In this paper, I presented a mathematical model for HBV infection, considering a possible co-treatment with the standard of care and IL-2 and using distributed control with unbounded memory.

In Section 2, I obtained the relation between the convergence rate of system (1) and modified system (3). I obtained a faster stability convergence for system (3) in the stability state; thus, patients can achieve faster improvements in their health conditions.

In Sections 3 and 4, I obtained the exponential stability of system (3) using the proposed distributed control with unbounded memory. A delay in the upper or lower limits of the integral can show the start and end periods of patient treatment. I showed estimates of this delay such that a patient achieves stabilization in their health condition and improvements.

In Section 5, I presented the simulations, where the chosen parameters of system (3) satisfy the conditions of Theorem 2. The results of the simulations on the validation set show that the chosen treatment stabilizes a patient's health condition.

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