Journal of Applied Mathematics and Physics, 2018, 6, 1120-1138
http://www.scirp.org/journal/jamp
ISSN Online: 2327-4379
ISSN Print: 2327-4352

Effect of Time Delay and Antibodies on HCV Dynamics with Cure Rate and Two Routes of Infection

Ahmed M. Elaiw, Shafeek A. Ghaleb, Aatef Hobiny

Department of Mathematics, Faculty of Science, King Abdulaziz University, Jeddah, KSA
Email: a_m_elaiw@yahoo.com

How to cite this paper: Elaiw, A.M., Ghaleb, S.A. and Hobiny, A. (2018) Effect of Time Delay and Antibodies on HCV Dynamics with Cure Rate and Two Routes of Infection. *Journal of Applied Mathematics and Physics*, **6**, 1120-1138.
https://doi.org/10.4236/jamp.2018.65096

Received: April 22, 2018
Accepted: May 28, 2018
Published: May 31, 2018

Abstract

In this paper we propose and analyze an HCV dynamics model taking into consideration the cure of infected hepatocytes and antibody immune response. We incorporate both virus-to-cell and cell-to-cell transmissions into the model. We incorporate a distributed-time delay to describe the time between the HCV or infected cell contacts an uninfected hepatocyte and the emission of new active HCV. We show that the solutions of the proposed model are nonnegative and ultimately bounded. We derive two threshold parameters which fully determine the existence and stability of the three steady states of the model. Using Lyapunov functionals, we established the global stability of the steady states. The theoretical results are confirmed by numerical simulations.

Keywords

HCV Infection, Distributed Time Delay, Global Stability, Cell-to-Cell Transmission, Lyapunov Function

1. Introduction

Hepatitis C virus is considered one of the dangerous human viruses that infects the liver and causes the lever cirrhosis. Mathematical modeling and analysis of within-host HCV dynamics have been studied by many authors (see e.g. [1]-[12]). These works can help researchers for better understanding the HCV dynamical behavior and providing new suggestions for clinical treatment. Immune response plays an important role in controlling the dynamics of several viruses (see e.g. [13] [14] [15] [16] [17]). Cytotoxic T Lymphocyte (CTL) and antibodies play a central role of immune response. CTL cells attack and kill the infected cells. The B cell produces antibodies to neutralize the viruses. Mathematical models of HCV dynamics with antibody immune response have been proposed in [18] [19] [20]. The models presented in [18] [19] [20] assume that an uninfected hepatocyte becomes infected by contacting with HCV (virus-to-cell transmission). It has been reported in [21] [22] [23] that the HCV can also spread by cell-to-cell transmission.

The "cure" of infected cells has been considered in the virus dynamics models in several works (see e.g. [24]-[39]). In [40], both cure and cell-to-cell transmissions have been considered in the virus dynamics model, but without taking the immune response into account. In a very recent paper, Pan and Chakrabarty [41] have proposed the following mathematical model of HCV dynamics which incorporates 1) both virus-to-cell and cell-to-cell transmissions, 2) cure of infected hepatocytes, and 3) antibody immune response:

$$\dot{s}(t) = \beta - \hat{\delta}s(t) - \alpha_1 s(t)p(t) - \alpha_2 s(t)y(t) + \rho y(t), \tag{1}$$

$$\dot{y}(t) = \alpha_1 s(t)p(t) + \alpha_2 s(t)y(t) - \varepsilon y(t) - \rho y(t), \tag{2}$$

$$\dot{p}(t) = my(t) - \gamma p(t) - qz(t)p(t), \tag{3}$$

$$\dot{z}(t) = rz(t)p(t) - \mu z(t), \tag{4}$$

where, s, y, p and z represent the concentration of uninfected hepatocytes, infected hepatocytes, HCV particles and antibodies, respectively. The uninfected hepatocytes are generated at a constant rate β, die at rate $\hat{\delta}s$, where $\hat{\delta}$ is the natural death rate constant. The infection rate due to both virus-to-cell and cell-to-cell transmissions is given by $\alpha_1 sp + \alpha_2 sy$, where α_1 and α_2 are constants. The infected hepatocytes die at rate εy and cure at rate ρy, where ε and ρ are constants. Constant m is the generation rate of the HCV from infected hepatocytes. Antibodies attack the HCV at rate qzp, proliferate at rate rzp and die at rate μz, where q, r and μ are constants.

It is assumed in model (1)-(4) that, the hepatocytes can produce HCV particles once they are contacted by HCV or infected cells. However, there is a time period from the moment of the uninfected hepatocytes that are contacted by the HCV or infected cells and the moment of producing new active HCV particles [10] [11].

The aim of this paper is to study the qualitative behavior of an HCV dynamics model with antibody immune response. We have incorporated distributed time delay and both virus-to-cell and cell-to-cell transmissions. We derive two threshold parameters and establish the global stability of the three steady states of the model using Lyapunov method.

2. The Model

We propose the following HCV dynamics model with distributed time delay:

$$\dot{s}(t) = \beta - \hat{\delta}s(t) - \alpha_1 s(t)p(t) - \alpha_2 s(t)y(t) + \rho y(t), \tag{5}$$

$$\dot{y}(t) = \alpha_1 s(t)p(t) + \alpha_2 s(t)y(t) - \varepsilon y(t) - \rho y(t), \tag{6}$$

$$\dot{p}(t) = m\int_0^h \rho(\tau) e^{-\mu_1 \tau} y(t-\tau) d\tau - \gamma p(t) - qz(t) p(t), \tag{7}$$

$$\dot{z}(t) = rz(t) p(t) - \mu z(t). \tag{8}$$

We assume that, the HCV or infected cell contacts an uninfected hepatocyte at time $t-\tau$, the cell becomes infected at time t, where τ is a distributed parameter over the time interval $[0,h]$. The factors $e^{-\mu_1 \tau}$ represents the probability of surviving the hepatocyte during the time delay period, where μ_1 is a constant. $\rho(\tau)$ is a probability distribution function satisfying $\rho(\tau) > 0$ and

$$\int_0^h \rho(\tau) d\tau = 1, \quad \int_0^h \rho(\upsilon) e^{\varsigma \upsilon} d\upsilon < \infty,$$

where ς and h are positive constants. Let us denote $\Theta(\tau) = \rho(\tau) e^{-\mu_1 \tau}$ and $F = \int_0^h \Theta(\tau) d\tau$, thus $0 < F \le 1$. Let the initial conditions for system (5)-(8) be given as:

$$\begin{aligned} & s(\eta) = \zeta_1(\eta), \ y(\eta) = \zeta_2(\eta), \\ & p(\eta) = \zeta_3(\eta), \ z(\eta) = \zeta_4(\eta), \\ & \zeta_j(\eta) \ge 0, \eta \in [-h, 0], \\ & \zeta_j \in C([-h,0], \mathbb{R}^4_{\ge 0}), \ j = 1, \cdots, 4, \end{aligned} \tag{9}$$

where C is the Banach space of continuous functions mapping the interval $[-h,0]$ into $\mathbb{R}^4_{\ge 0}$. Then, the uniqueness of the solution for $t > 0$ is guaranteed [42].

2.1. Basic Properties

In this subsection, we investigate the nonnegativity and boundedness of solutions.

Proposition 1. The solutions of system (5)-(8) with the initial states (9) are nonnegative and ultimately bounded.

Proof. From Equation (5) we have $\dot{s}|_{s=0} = \beta + \rho y > 0$. Hence, $s(t) > 0$ for all $y \ge 0$. Moreover, for all $t \in [0,h]$ we have

$$y(t) = \zeta_2(0) e^{-(\varepsilon+\rho)t} + \int_0^t e^{-(\varepsilon+\rho)(t-\eta)} [\alpha_1 s(\eta) p(\eta) + \alpha_2 s(\eta) y(\eta)] d\eta \ge 0,$$

$$p(t) = \zeta_3(0) e^{-\int_0^t (\gamma + qz(\xi)) d\xi} + m\int_0^t e^{-\int_\eta^t (\gamma + qz(\xi)) d\xi} \int_0^h \Theta_2(\tau) y(\eta - \tau) d\tau d\eta \ge 0,$$

$$z(t) = \zeta_4(0) e^{-\int_0^t (\kappa - rp(\xi)) d\xi} \ge 0.$$

By recursive argument we get $y(t) \ge 0$, $p(t) \ge 0$, and $z(t) \ge 0$, for all $t \ge 0$.

Next, we establish the boundedness of the model's solutions. The nonnegativity of the model's solution implies that

$$\dot{s}(t) \le \beta - \hat{\delta} s(t) + \rho y(t),$$

We let $Q_1(t)=s(t)+y(t)$, then

$$\dot{Q}_1(t)=\beta-\hat{\delta}s(t)-\varepsilon y(t)\le\beta-\sigma_1(s(t)+y(t))=\beta-\sigma_1Q_1(t),$$

where $\sigma_1=\min\{\hat{\delta},\varepsilon\}$. Hence $Q_1(t)\le L_1$, if $Q_1(t)\le L_1$ where $L_1=\dfrac{\beta}{\sigma_1}$. It follows that $s(t)\le L_1$ and $y(t)\le L_1$ if $s(0)+y(0)\le L_1$. Moreover, let $Q_2(t)=p(t)+\dfrac{q}{r}z(t)$, then

$$\dot{Q}_2(t)=m\int_0^h\Theta(\tau)y(t-\tau)d\tau-\gamma p(t)-\frac{q\mu}{r}z(t)\le mL_1F-\gamma p(t)-\frac{q\mu}{r}z(t)$$
$$\le mL_1-\sigma_2\left(p(t)+\frac{q}{r}z(t)\right)=mL_1-\sigma_2Q_2(t),$$

where $\sigma_2=\min\{\gamma,\mu\}$. It follows that, $\limsup_{t\to\infty}Q_2(t)\le L_2$, where $L_2=\dfrac{mL_1}{\sigma_2}$. Since $p(t)\ge0$ and $z(t)\ge0$, then $\limsup_{t\to\infty}p(t)\le L_2$ and $\limsup_{t\to\infty}z(t)\le L_3$, where $L_3=\dfrac{r}{q}L_2$. Therefore, $s(t),y(t),p(t)$ and $z(t)$ are ultimately bounded. □

According to Proposition 1, we can show that the region

$$\Delta=\left\{(s,y,p,z)\in C^4:\|s\|\le L_1,\|y\|\le L_1,\|p\|\le L_2,\|z\|\le L_3\right\},$$

is positively invariant with respect to system (5)-(8).

2.2. The Steady States and Threshold Parameters

Lemma 1. For system (5)-(8) there exist two threshold parameters $R_0>0$, and $R_1^z>0$, such that

1) if $R_0\le1$, then there exists only one steady state Π_0,

2) if $R_1^z\le1<R_0$, then there exist only two steady states Π_0 and Π_1,

3) if $R_0>1$ and $R_1^z>1$, then there exist three steady states Π_0, Π_1 and Π_2.

Proof. Let (s,y,p,z) be any steady state satisfying

$$\beta-\hat{\delta}s-\alpha_1sp-\alpha_2sy+\rho y=0, \quad (10)$$

$$\alpha_1sp+\alpha_2sy-\varepsilon y-\rho y=0, \quad (11)$$

$$mFy-\gamma p-qzp=0, \quad (12)$$

$$(rp-\mu)z=0. \quad (13)$$

We find that system (10)-(13) admits three steady states.

1) Infection-free steady state $\Pi_0=(s_0,0,0,0)$, where $s_0=\beta/\hat{\delta}$.

2) Chronic-infection steady state without immune response $\Pi_1=(s_1,y_1,p_1,0)$, where

$$s_1=\frac{(\varepsilon+\rho)\gamma}{Fm\alpha_1+\gamma\alpha_2},$$

$$y_1 = \frac{\hat{\delta} s_1}{\varepsilon}\left(\frac{\beta(Fm\alpha_1 + \gamma\alpha_2)}{\hat{\delta}\gamma(\varepsilon+\rho)} - 1\right),$$

$$p_1 = \frac{Fmy_1}{\gamma}.$$

Clearly Π_1 exists if

$$\frac{\beta(Fm\alpha_1 + \gamma\alpha_2)}{\hat{\delta}\gamma(\varepsilon+\rho)} > 1.$$

Let us define

$$R_0 = \frac{\beta(Fm\alpha_1 + \gamma\alpha_2)}{\hat{\delta}\gamma(\varepsilon+\rho)},$$

In terms of R_0, we can write the steady state components for Π_1 as:

$$s_1 = \frac{s_0}{R_0}, \quad y_1 = \frac{\hat{\delta} s_1}{\varepsilon}(R_0 - 1),$$

$$p_1 = \frac{Fm\hat{\delta} s_1}{\gamma\varepsilon}(R_0 - 1).$$

3) Chronic-infection steady state with humoral immune $\Pi_2 = (s_2, y_2, p_2, z_2)$, where

$$\begin{aligned} s_2 &= \frac{ry_2(\varepsilon+\rho)}{\mu\alpha_1 + ry_2\alpha_2}, \quad y_2 = \frac{-B + \sqrt{B^2 - 4AC}}{2A}, \\ p_2 &= \frac{\mu}{r}, \quad z_2 = \frac{\gamma}{q}\left(\frac{rmFy_2}{\mu\gamma} - 1\right). \end{aligned} \tag{14}$$

where

$$\begin{aligned} A &= r\alpha_2\varepsilon, \\ B &= \mu\varepsilon\alpha_1 - r\beta\alpha_2 + r\hat{\delta}(\varepsilon+\rho), \\ C &= -\beta\mu\alpha_1. \end{aligned} \tag{15}$$

We note that Π_2 exists when $\frac{rF_2my_2}{\mu\gamma} > 1$. Now we define

$$R_1^z = \frac{rFmy_2}{\mu\gamma} = \frac{Fmy_2}{p_2\gamma}. \tag{16}$$

Then $z_2 = \frac{\gamma}{q}(R_1^z - 1)$. We define the basic reproduction number for the humoral immune response R_{Hum} which comes from the limiting (linearized) z-dynamics near $z = 0$ as:

$$R_{Hum}^z = \frac{p_1}{p_2}$$

Lemma 2 1) if $R_1^z < 1$, then $R_{Hum}^z < 1$,
2) if $R_1^z > 1$, then $R_{Hum}^z > 1$,

3) if $R_1^z = 1$ then $R_{Hum}^z = 1$.

Proof. 1) Let $R_1^z < 1$, then from Equation (16) we have $y_2 < \frac{\gamma p_2}{mF}$, and then using Equation (14) we get

$$\frac{-B + \sqrt{B^2 - 4AC}}{2A} < \frac{\gamma p_2}{Fm},$$

that leads to

$$\left(\frac{2A\gamma p_2}{Fm} + B\right)^2 - \left(B^2 - 4AC\right) > 0.$$

Using Equation (15), we can get

$$\frac{4\alpha_2 \varepsilon^2 \mu^2 \gamma \left(Fm\alpha_1 + \gamma\alpha_2\right)}{m^2 F^2}\left(1 - R_{Hum}^z\right) > 0$$

then

$$R_{Hum}^z = \frac{rFms_1\left(R_0 - 1\right)\hat{\delta}}{\mu\varepsilon\gamma} < 1.$$

then $R_{Hum}^z < 1$. Similarly, one can proof 2) and 3) □.

3. Global Stability

The following theorems investigate the global stability of the steady states of system (5)-(8). Let us define the function $H:(0,\infty) \to [0,\infty)$ as $H(\ell) = \ell - 1 - \ln \ell$. Denote $(s, y, p, z) = (s(t), y(t), p(t), z(t))$.

Theorem 1. Suppose that $R_0 \le 1$, then the infection-free steady state Π_0 is globally asymptotically stable (GAS).

Proof. Constructing a Lyapunov functional

$$\begin{aligned} L_0(s,y,p,z) = {} & s_0 H\left(\frac{s}{s_0}\right) + y + \frac{\alpha_1 s_0}{\gamma} p + \frac{q\alpha_1 s_0}{r\gamma} z \\ & + \frac{\rho}{2\left(\hat{\delta} + \varepsilon\right)s_0}\left[\left(s - s_0\right) + y\right]^2 \\ & + \frac{m\alpha_1 s_0}{\gamma}\int_0^h \Theta(\tau)\int_{t-\tau}^t y(\eta)\,\mathrm{d}\eta\,\mathrm{d}\tau. \end{aligned}$$

We calculate $\frac{\mathrm{d}L_0}{\mathrm{d}t}$ along the solutions of model (5)-(8) as:

$$\begin{aligned} \frac{\mathrm{d}L_0}{\mathrm{d}t} = {} & \left(1 - \frac{s_0}{s}\right)\left(\beta - \hat{\delta}s - \alpha_1 sp - \alpha_2 sy + \rho y\right) + \alpha_1 sp + \alpha_2 sy \\ & - \varepsilon y - \rho y + \frac{\alpha_1 s_0}{\gamma}\left(m\int_0^h \Theta(\tau) y(t-\tau)\,\mathrm{d}\tau - \gamma p - qzp\right) \\ & + \frac{q\alpha_1 s_0}{r\gamma}\left(rzp - \mu z\right) + \frac{\rho}{\left(\hat{\delta}+\varepsilon\right)s_0}\left[\left(s - s_0\right) + y\right]\left(\beta - \hat{\delta}s - \varepsilon y\right) \\ & + \frac{m\alpha_1 s_0}{\gamma}\int_0^h \Theta(\tau)\left[y - y(t-\tau)\right]\mathrm{d}\tau. \end{aligned} \tag{17}$$

Collecting terms of Equation (17) and using $\beta = \hat{\delta} s_0$ we obtain

$$\begin{aligned}\frac{\mathrm{d}L_0}{\mathrm{d}t} &= \left(1-\frac{s_0}{s}\right)\left(\hat{\delta}s_0-\hat{\delta}s\right)+\alpha_2 s_0 y+\left(1-\frac{s_0}{s}\right)\rho y \\ &\quad -\left(\varepsilon+\rho\right)y+\frac{\alpha_1 s_0 F}{\gamma}my-\frac{q\alpha_1 s_0}{r\gamma}\mu z \\ &\quad -\frac{\rho}{\left(\hat{\delta}+\varepsilon\right)s_0}\left[\left(s-s_0\right)+y\right]\left(\hat{\delta}\left(s-s_0\right)+\varepsilon y\right).\end{aligned} \tag{18}$$

We note that

$$\left(1-\frac{s_0}{s}\right)\rho y = -\frac{\rho y}{s s_0}\left(s-s_0\right)^2+\frac{\rho y}{s_0}\left(s-s_0\right).$$

Therefore

$$\begin{aligned}\frac{\mathrm{d}L_0}{\mathrm{d}t} &= -\hat{\delta}\frac{\left(s-s_0\right)^2}{s}+\alpha_2 s_0 y-\frac{\rho y}{s s_0}\left(s-s_0\right)^2+\frac{\rho y}{s_0}\left(s-s_0\right) \\ &\quad -\left(\varepsilon+\rho\right)y+\frac{\alpha_1 s_0 F}{\gamma}my-\frac{q\alpha_1 s_0}{r\gamma}\mu z-\frac{\rho\hat{\delta}\left(s-s_0\right)^2}{\left(\hat{\delta}+\varepsilon\right)s_0} \\ &\quad -\frac{\rho\varepsilon\left(s-s_0\right)y}{\left(\hat{\delta}+\varepsilon\right)s_0}-\frac{\rho\hat{\delta}\left(s-s_0\right)y}{\left(\hat{\delta}+\varepsilon\right)s_0}-\frac{\rho\varepsilon y^2}{\left(\hat{\delta}+\varepsilon\right)s_0} \\ &= -\left(\hat{\delta}s_0+\rho y+\frac{\rho\hat{\delta}s}{\hat{\delta}+\varepsilon}\right)\frac{\left(s-s_0\right)^2}{s s_0}-\frac{\rho\varepsilon y^2}{\left(\hat{\delta}+\varepsilon\right)s_0} \\ &\quad -\frac{q\alpha_1 s_0}{r\gamma}\mu z+\left(\varepsilon+\rho\right)\left(\frac{\left(m\alpha_1 F+\gamma\alpha_2\right)s_0}{\gamma\left(\varepsilon+\rho\right)}-1\right)y \\ &= -\left(\hat{\delta}s_0+\rho y+\frac{\rho\hat{\delta}s}{\hat{\delta}+\varepsilon}\right)\frac{\left(s-s_0\right)^2}{s s_0}-\frac{\rho\varepsilon y^2}{\left(\hat{\delta}+\varepsilon\right)s_0} \\ &\quad -\frac{q\alpha_1 s_0}{r\gamma}\mu z+\left(\varepsilon+\rho\right)\left(R_0-1\right)y.\end{aligned}$$

Since $R_0 \le 1$, then $\frac{\mathrm{d}L_0}{\mathrm{d}t} \le 0$ for all $s,y,p,z>0$. Moreover $\frac{\mathrm{d}L_0}{\mathrm{d}t}=0$ if and only if $s(t)=s(0), y(t)=z(t)=0$. Let $\Gamma_0=\left\{(s,y,p,z):\frac{\mathrm{d}L_0}{\mathrm{d}t}=0\right\}$ and Γ_0 be the largest invariant subset of Γ_0. The solution of system (5)-(8) tend to Γ_0. For each element of Γ_0 we have $y(t)=0$, then $\dot{y}(t)$ and Equation (6) we get

$$y(t)=0=\alpha_1 s_0 p(t)$$

Then $p(t)=0$. It follows that Γ_0 contains a single point that is $\{\Gamma_0\}$. Appling LaSalle's invariance principle (LIP), we get that Π_0 is GAS.

Theorem 2. Suppose that $R_1^z \le 1 < R_0 \le 1+\frac{\rho}{\varepsilon}$, then Π_1 is GAS.

Proof. Let us define a function $L_1(s,y,p,z)$ as:

$$L_1 = s_1 H\left(\frac{s}{s_1}\right) + y_1 H\left(\frac{y}{y_1}\right) + \frac{\alpha_1 s_1 p_1}{Fmy_1} p_1 H\left(\frac{p}{p_1}\right) + \frac{\alpha_1 s_1 p_1 q}{Fmy_1 r} z + \frac{\rho}{2\left(\hat{\delta}+\varepsilon\right)s_1}\left[\left(s-s_1\right)+\left(y-y_1\right)\right]^2 + \frac{\alpha_1 s_1 p_1}{F}\int_0^h \Theta(\tau)\int_{t-\tau}^{t} H\left(\frac{y(\eta)}{y_1}\right)\mathrm{d}\eta\mathrm{d}\tau.$$

Calculating $\frac{\mathrm{d}L_1}{\mathrm{d}t}$ along the trajectories of system (5)-(8), we get

$$\begin{aligned}\frac{\mathrm{d}L_1}{\mathrm{d}t} &= \left(1-\frac{s_1}{s}\right)\left(\beta - \hat{\delta}s - \alpha_1 sp - \alpha_2 sy + \rho y\right) \\ &+ \left(1-\frac{y_1}{y}\right)\left(\alpha_1 sp + \alpha_2 sy - \varepsilon y - \rho y\right) \\ &+ \frac{\alpha_1 s_1 p_1}{Fmy_1}\left(1-\frac{p_1}{p}\right)\left(m\int_0^h \Theta(\tau) y(t-\tau)\mathrm{d}\tau - \gamma p - qzp\right) \\ &+ \frac{\alpha_1 s_1 p_1 q}{Fmy_1 r}\left(rzp - \mu z\right) + \frac{\rho}{\left(\hat{\delta}+\varepsilon\right)s_1}\left[\left(s-s_1\right)+\left(y-y_1\right)\right]\left(\beta - \hat{\delta}s - \varepsilon y\right). \\ &+ \frac{\alpha_1 s_1 p_1}{F}\int_0^h \Theta(\tau)\left[\frac{y}{y_1} - \frac{y(t-\tau)}{y_1} + \ln\left(\frac{y(t-\tau)}{y}\right)\right]\mathrm{d}\tau.\end{aligned} \tag{19}$$

Collecting terms of Equation (19), we get

$$\begin{aligned}\frac{\mathrm{d}L_1}{\mathrm{d}t} &= \left(1-\frac{s_1}{s}\right)\left(\beta - \hat{\delta}s + \rho y\right) + \alpha_1 s_1 p + \alpha_2 s_1 y - \left(\varepsilon+\rho\right) y_1 \frac{y}{y_1} \\ &- \left(\alpha_1 sp + \alpha_2 sy\right)\frac{y_1}{y} + \left(\varepsilon+\rho\right) y_1 - \frac{\alpha_1 s_1 p_1}{Fmy_1}\gamma p_1 \frac{p}{p_1} \\ &- \frac{\alpha_1 s_1 p_1}{Fy_1}\int_0^h \Theta(\tau) y(t-\tau)\frac{p_1}{p}\mathrm{d}\tau + \frac{\alpha_1 s_1 p_1}{Fmy_1}\gamma p_1 + \frac{\alpha_1 s_1 p_1}{Fmy_1} qzp_1 \\ &- \frac{\alpha_1 s_1 p_1 q}{Fmy_1 r}\mu z + \frac{\rho}{\left(\hat{\delta}+\varepsilon\right)s_1}\left[\left(s-s_1\right)+\left(y-y_1\right)\right]\left(\beta - \hat{\delta}s - \varepsilon y\right) \\ &+ \frac{\alpha_1 s_1 p_1}{y_1} y + \frac{\alpha_1 s_1 p_1}{F}\int_0^h \Theta(\tau)\ln\left(\frac{y(t-\tau)}{y}\right)\mathrm{d}\tau.\end{aligned}$$

Applying condition of equilibrum Π_1:

$$\beta = \hat{\delta}s_1 + \alpha_1 s_1 p_1 + \alpha_2 s_1 y_1 - \rho y_1 = \hat{\delta}s_1 + \varepsilon y_1,$$

$$p_1 = \frac{Fm}{\gamma} y_1, \left(\varepsilon+\rho\right) y_1 = \alpha_1 s_1 p_1 + \alpha_2 s_1 y_1$$

we get

$$\begin{aligned}\frac{\mathrm{d}L_1}{\mathrm{d}t} &= -\hat{\delta}\frac{(s-s_1)^2}{s} + \left(\alpha_1 s_1 p_1 + \alpha_2 s_1 y_1\right)\left(1-\frac{s_1}{s}\right) + \rho\left(y-y_1\right)\left(1-\frac{s_1}{s}\right) \\ &+ \alpha_1 s_1 p_1 \frac{p}{p_1} + \alpha_2 s_1 y_1 \frac{y}{y_1} - \left(\alpha_1 s_1 p_1 + \alpha_2 s_1 y_1\right)\frac{y}{y_1} - \alpha_1 s_1 p_1 \frac{sp}{s_1 p_1}\frac{y_1}{y} \\ &- \alpha_2 s_1 y_1 \frac{s}{s_1} + \left(\alpha_1 s_1 p_1 + \alpha_2 s_1 y_1\right) - \alpha_1 s_1 p_1 \frac{p}{p_1}\end{aligned}$$

$$-\frac{\alpha_1 s_1 p_1}{F}\int_0^h \Theta(\tau)\frac{y(t-\tau)}{y_1}\frac{p_1}{p}\mathrm{d}\tau+\alpha_1 s_1 p_1+\frac{\alpha_1 s_1}{\gamma}qzp_1-\frac{q\alpha_1 s_1\mu}{r\gamma}z$$
$$+\frac{\rho}{(\hat{\delta}+\varepsilon)s_1}\left[(s-s_1)+(y-y_1)\right]\left(\hat{\delta}(s_1-s)+\alpha_1 s_1 p_1+\alpha_2 s_1 y_1-\rho y_1-\varepsilon y\right)$$
$$+\alpha_1 s_1 p_1\frac{y}{y_1}+\frac{\alpha_1 s_1 p_1}{F}\int_0^h \Theta(\tau)\ln\left(\frac{y(t-\tau)}{y}\right)\mathrm{d}\tau.$$

thus

$$\frac{\mathrm{d}L_1}{\mathrm{d}t}=-\hat{\delta}\frac{(s-s_1)^2}{s}+\alpha_1 s_1 p_1\left(1-\frac{s_1}{s}\right)+\rho(y-y_1)\left(1-\frac{s_1}{s}\right)$$
$$+\alpha_2 s_1 y_1\left(2-\frac{s_1}{s}-\frac{s}{s_1}\right)-\alpha_1 s_1 p_1\frac{sp}{s_1 p_1}\frac{y_1}{y}+2\alpha_1 s_1 p_1$$
$$-\frac{\alpha_1 s_1 p_1}{Fy_1}\int_0^h \Theta(\tau)y(t-\tau)\frac{p_1}{p}\mathrm{d}\tau+\frac{\alpha_1 s_1}{\gamma}qzp_1-\frac{q\alpha_1 s_1\mu}{r\gamma}z$$
$$-\frac{\rho}{(\hat{\delta}+\varepsilon)s_1}\left[(s-s_1)+(y-y_1)\right]\left(\hat{\delta}(s-s_1)+\varepsilon(y-y_1)\right)$$
$$+\frac{\alpha_1 s_1 p_1}{F}\int_0^h \Theta(\tau)\ln\left(\frac{y(t-\tau)}{y}\right)\mathrm{d}\tau.$$

We note that

$$\rho(y-y_1)\left(1-\frac{s_1}{s}\right)=-\frac{\rho(y-y_1)}{ss_1}(s-s_1)^2+\frac{\rho(y-y_1)}{s_1}(s-s_1).$$

Then

$$\begin{aligned}\frac{\mathrm{d}L_1}{\mathrm{d}t}&=-\hat{\delta}\frac{(s-s_1)^2}{s}+\alpha_1 s_1 p_1\left(1-\frac{s_1}{s}\right)-\frac{\rho(y-y_1)}{ss_1}(s-s_1)^2\\
&\quad+\frac{\rho(y-y_1)}{s_1}(s-s_1)+\alpha_2 s_1 y_1\left(2-\frac{s_1}{s}-\frac{s}{s_1}\right)-\alpha_1 s_1 p_1\frac{sp}{s_1 p_1}\frac{y_1}{y}\\
&\quad+2\alpha_1 s_1 p_1-\frac{\alpha_1 s_1 p_1}{F}\int_0^h \Theta(\tau)\frac{y(t-\tau)}{y_1}\frac{p_1}{p}\mathrm{d}\tau+\frac{q\alpha_1 s_1}{\gamma}(p_1-p_2)z\\
&\quad-\frac{\rho}{(\hat{\delta}+\varepsilon)s_1}\left[(s-s_1)+(y-y_1)\right]\left(\hat{\delta}(s-s_1)+\varepsilon(y-y_1)\right)\\
&\quad+\frac{\alpha_1 s_1 p_1}{F}\int_0^h \Theta(\tau)\ln\left(\frac{y(t-\tau)}{y}\right)\mathrm{d}\tau\\
&=-\left(\hat{\delta}s_1+\rho(y-y_1)+\frac{\rho\hat{\delta}s}{\hat{\delta}+\varepsilon}\right)\frac{(s-s_1)^2}{ss_1}-\frac{\rho\varepsilon(y-y_1)^2}{(\hat{\delta}+\varepsilon)s_1}+\alpha_1 s_1 p_1\left(1-\frac{s_1}{s}\right)\\
&\quad+\frac{\rho(y-y_1)}{s_1}(s-s_1)+\alpha_2 s_1 y_1\left(2-\frac{s_1}{s}-\frac{s}{s_1}\right)-\alpha_1 s_1 p_1\frac{sp}{s_1 p_1}\frac{y_1}{y}+2\alpha_1 s_1 p_1\\
&\quad-\frac{\alpha_1 s_1 p_1}{F}\int_0^h \Theta(\tau)\frac{y(t-\tau)}{y_1}\frac{p_1}{p}\mathrm{d}\tau+\frac{q\alpha_1 s_1}{\gamma}(p_1-p_2)z-\frac{\rho\hat{\delta}(s-s_1)(y-y_1)}{(\hat{\delta}+\varepsilon)s_1}\\
&\quad-\frac{\rho\varepsilon(s-s_1)(y-y_1)}{(\hat{\delta}+\varepsilon)s_1}+\frac{\alpha_1 s_1 p_1}{F}\int_0^h \Theta(\tau)\ln\left(\frac{y(t-\tau)}{y}\right)\mathrm{d}\tau.\end{aligned}\tag{20}$$

Consider the following equalities

$$\ln\left(\frac{y(t-\tau)}{y}\right)=\ln\left(\frac{p_i y(t-\tau)}{p y_i}\right)+\ln\left(\frac{s p y_i}{s_i p_i y}\right)+\ln\left(\frac{s_i}{s}\right),\quad i=1,2. \tag{21}$$

Simplify Equation (20) and let $i=1$, in Equation(21) we get

$$\begin{aligned}\frac{\mathrm{d}L_1}{\mathrm{d}t}=&-\left(\hat{\delta}s_1+\rho(y-y_1)+\frac{\rho\hat{\delta}s}{\hat{\delta}+\varepsilon}\right)\frac{(s-s_1)^2}{ss_1}-\frac{\rho\varepsilon(y-y_1)^2}{(\hat{\delta}+\varepsilon)s_1}\\&-\alpha_1 s_1 p_1\left(\frac{s_1}{s}-1-\ln\left(\frac{s_1}{s}\right)\right)+\alpha_2 s_1 y_1\left(2-\frac{s_1}{s}-\frac{s}{s_1}\right)\\&-\alpha_1 s_1 p_1\left[\frac{s p y_1}{s_1 p_1 y}-1-\ln\left(\frac{s p y_1}{s_1 p_1 y}\right)\right]\\&-\frac{\alpha_1 s_1 p_1}{F}\int_0^h\Theta(\tau)\left[\frac{p_1 y(t-\tau)}{p y_1}-1-\ln\left(\frac{p_1 y(t-\tau)}{p y_1}\right)\right]\mathrm{d}\tau\\&+\frac{q\alpha_1 s_1}{\gamma}(p_1-p_2)z.\end{aligned} \tag{22}$$

Equation (22) can be rewrite as:

$$\begin{aligned}\frac{\mathrm{d}L_1}{\mathrm{d}t}=&-\left(\hat{\delta}s_1+\rho(y-y_1)+\frac{\rho\hat{\delta}s}{\hat{\delta}+\varepsilon}\right)\frac{(s-s_1)^2}{ss_1}-\frac{\rho\varepsilon(y-y_1)^2}{(\hat{\delta}+\varepsilon)s_1}\\&-\alpha_1 s_1 p_1 H\left(\frac{s}{s_1}\right)+\alpha_2 s_1 y_1\left(2-\frac{s_1}{s}-\frac{s}{s_1}\right)-\alpha_1 s_1 p_1 H\left(\frac{s p y_1}{s_1 p_1 y}\right)\\&-\frac{\alpha_1 s_1 p_1}{F}\int_0^h\Theta(\tau)H\left(\frac{p_1 y(t-\tau)}{p y_1}\right)\mathrm{d}\tau+\frac{q\alpha_1 s_1}{\gamma}(p_1-p_2)z.\end{aligned} \tag{23}$$

We note that

$$\hat{\delta}s_1-\rho y_1=\frac{\hat{\delta}\rho s_0}{\varepsilon R_0}\left[\left(1+\frac{\rho}{\varepsilon}\right)-R_0\right].$$

From Lemma 2 we have $p_1\le p_2$, then, $\frac{\mathrm{d}L_1}{\mathrm{d}t}\le 0$ for all s_1, y_1 and $p_1>0$, where $\frac{\mathrm{d}L_1}{\mathrm{d}t}=0$ if and only if $s=s_1, y=y_1, p=p_1$ and $z=0$. Thus, the global asymptotic stability of Π_1 follows from LIP when $R_1^z\le 1$, and $1<R_0\le 1+\frac{\rho}{\varepsilon}$.

□

Theorem 3. Suppose that $R_1^z>1$ and $\hat{\delta}s_2-\rho y_2\ge 0$, then Π_2 is GAS.

Proof. Define a function $L_2(s,y,p,z)$ as:

$$\begin{aligned}L_2=&s_2 H\left(\frac{s}{s_2}\right)+y_2 H\left(\frac{y}{y_2}\right)+\frac{\alpha_1 s_2 p_2}{Fmy_2}p_2 H\left(\frac{p}{p_2}\right)+\frac{q\alpha_1 s_2 p_2}{Frmy_2}z_2 H\left(\frac{z}{z_2}\right)\\&+\frac{\rho}{2(\hat{\delta}+\varepsilon)s_2}\left[(s-s_2)+(y-y_2)\right]^2+\frac{\alpha_1 s_2 p_2}{F}\int_0^h\Theta(\tau)\int_{t-\tau}^{t}H\left(\frac{y(\eta)}{y_2}\right)\mathrm{d}\eta\,\mathrm{d}\tau.\end{aligned}$$

Calculating $\frac{\mathrm{d}L_2}{\mathrm{d}t}$ as:

$$\begin{aligned}\frac{\mathrm{d}L_2}{\mathrm{d}t}=&\left(1-\frac{s_2}{s}\right)\left(\beta-\hat{\delta}s-\alpha_1 sp-\alpha_2 sy+\rho y\right)\\&+\left(1-\frac{y_2}{y}\right)\left(\alpha_1 sp+\alpha_2 sy-\varepsilon y-\rho y\right)\\&+\frac{\alpha_1 s_2 p_2}{Fmy_2}\left(1-\frac{p_2}{p}\right)\left(m\int_0^h\Theta(\tau)y(t-\tau)\mathrm{d}\tau-\gamma p-qzp\right)\\&+\frac{q\alpha_1 s_2 p_2}{Frmy_2}\left(1-\frac{z_2}{z}\right)\left(rzp-\mu z\right)\\&+\frac{\rho}{\left(\hat{\delta}+\varepsilon\right)s_2}\left[\left(s-s_2\right)+\left(y-y_2\right)\right]\left(\beta-\hat{\delta}s-\varepsilon y\right)\\&+\frac{\alpha_1 s_2 p_2}{F}\int_0^h\Theta(\tau)\left[\frac{y}{y_2}-\frac{y(t-\tau)}{y_2}+\ln\left(\frac{y(t-\tau)}{y}\right)\right]\mathrm{d}\tau.\end{aligned}\tag{24}$$

Collecting terms of Equation (24) and applying the equilibrium conditions for Π_2:

$$\beta=\hat{\delta}s_2+\alpha_1 s_2 p_2+\alpha_2 s_2 y_2-\rho y_2=\hat{\delta}s_2+\varepsilon y_2,$$

$$p_2=\frac{\mu}{r},\ \left(\varepsilon+\rho\right)y_2=\alpha_1 s_2 p_2+\alpha_2 s_2 y_2$$

$$\varepsilon y_2=\frac{\varepsilon}{mF}\left(\gamma p_2+qp_2 z_2\right).$$

we get

$$\begin{aligned}\frac{\mathrm{d}L_2}{\mathrm{d}t}=&-\hat{\delta}\frac{\left(s-s_2\right)^2}{s}+\left(\alpha_1 s_2 p_2+\alpha_2 s_2 y_2+\rho\left(y-y_2\right)\right)\left(1-\frac{s_2}{s}\right)+\alpha_1 s_2 p+\alpha_2 s_2 y\\&-\left(\alpha_1 s_2 p_2+\alpha_2 s_2 y_2\right)\frac{y}{y_2}-\alpha_1 s_2 p_2\frac{sp}{s_2 p_2}\frac{y_2}{y}-\alpha_2 s_2 y_2\frac{s}{s_2}+\left(\alpha_1 s_2 p_2+\alpha_2 s_2 y_2\right)\\&-\frac{\alpha_1 s_2 p_2}{Fmy_2}\left(Fmy_2-qp_2 z_2\right)\frac{p}{p_2}-\frac{\alpha_1 s_2 p_2}{F}\int_0^h\Theta(\tau)\frac{y(t-\tau)}{y_2}\frac{p_2}{p}\mathrm{d}\tau\\&+\frac{\alpha_1 s_2 p_2}{Fmy_2}\left(Fmy_2-qp_2 z_2\right)-\frac{q\alpha_1 s_2 p_2}{Fmy_2}z_2 p+\frac{q\alpha_1 s_2 p_2}{Frmy_2}\mu z_2\\&+\frac{\rho}{\left(\hat{\delta}+\varepsilon\right)s_2}\left[\left(s-s_2\right)+\left(y-y_2\right)\right]\left(\hat{\delta}\left(s_2-s\right)+\alpha_1 s_2 p_2+\alpha_2 s_2 y_2-\rho y_2-\varepsilon y\right)\\&+\frac{\alpha_1 s_2 p_2}{y_2}y+\frac{\alpha_1 s_2 p_2}{F}\int_0^h\Theta(\tau)\ln\left(\frac{y(t-\tau)}{y}\right)\mathrm{d}\tau\\=&-\hat{\delta}\frac{\left(s-s_2\right)^2}{s}+\left(\alpha_1 s_2 p_2+\alpha_2 s_2 y_2\right)\left(1-\frac{s_2}{s}\right)+\rho\left(y-y_2\right)\left(1-\frac{s_2}{s}\right)+\alpha_1 s_2 p_2\frac{p}{p_2}\\&+\alpha_2 s_2 y_2\frac{y}{y_2}-\left(\alpha_1 s_2 p_2+\alpha_2 s_2 y_2\right)\frac{y}{y_2}-\alpha_1 s_2 p_2\frac{sp}{s_2 p_2}\frac{y_2}{y}-\alpha_2 s_2 y_2\frac{s}{s_2}\\&+\left(\alpha_1 s_2 p_2+\alpha_2 s_2 y_2\right)-\alpha_1 s_2 p_2\frac{p}{p_2}-\frac{\alpha_1 s_2 p_2}{F}\int_0^h\Theta(\tau)\frac{y(t-\tau)}{y_2}\frac{p_2}{p}\mathrm{d}\tau+\alpha_1 s_2 p_2\end{aligned}$$

$$+\frac{\alpha_1 s_2 p_2}{y_2}y-\frac{\rho}{\left(\hat{\delta}+\varepsilon\right)s_1}\left[\left(s-s_2\right)+\left(y-y_2\right)\right]\left(\hat{\delta}\left(s-s_2\right)+\varepsilon\left(y-y_2\right)\right)$$

$$+\frac{\alpha_1 s_2 p_2}{F}\int_0^h\Theta(\tau)\ln\left(\frac{y(t-\tau)}{y}\right)\mathrm{d}\tau.$$

We note that

$$\rho\left(y-y_2\right)\left(1-\frac{s_2}{s}\right)=-\frac{\rho\left(y-y_2\right)}{ss_2}\left(s-s_2\right)^2+\frac{\rho\left(y-y_2\right)}{s_2}\left(s-s_2\right)$$

Using equalities (21) in case $i=2$, we get

$$\begin{aligned}\frac{\mathrm{d}L_2}{\mathrm{d}t}=&-\left(\hat{\delta}s_2+\rho\left(y-y_2\right)+\frac{\rho\hat{\delta}s}{\hat{\delta}+\varepsilon}\right)\frac{\left(s-s_2\right)^2}{ss_2}-\frac{\rho\varepsilon\left(y-y_2\right)^2}{\left(\hat{\delta}+\varepsilon\right)s_2}\\&-\alpha_1 s_2 p_2\left(\frac{s_2}{s}-1-\ln\left(\frac{s_2}{s}\right)\right)+\alpha_2 s_2 y_2\left(2-\frac{s_2}{s}-\frac{s}{s_2}\right)\\&-\alpha_1 s_2 p_2\left[\frac{spy_2}{s_2p_2y}-1-\ln\left(\frac{spy_2}{s_2p_2y}\right)\right]\\&-\frac{\alpha_1 s_2 p_2}{F}\int_0^h\Theta(\tau)\left[\frac{p_2y(t-\tau)}{py_2}-1-\ln\left(\frac{p_2y(t-\tau)}{py_2}\right)\right]\mathrm{d}\tau.\end{aligned}\tag{25}$$

Equation (25) can be simplified as:

$$\begin{aligned}\frac{\mathrm{d}L_2}{\mathrm{d}t}=&-\left(\hat{\delta}s_2+\rho\left(y-y_2\right)+\frac{\rho\hat{\delta}s}{\hat{\delta}+\varepsilon}\right)\frac{\left(s-s_2\right)^2}{ss_2}-\frac{\rho\varepsilon\left(y-y_2\right)^2}{\left(\hat{\delta}+\varepsilon\right)s_2}\\&-\alpha_1 s_2 p_2 H\left(\frac{s}{s_2}\right)+\alpha_2 s_2 y_2\left(2-\frac{s_2}{s}-\frac{s}{s_2}\right)\\&-\frac{\alpha_1 s_2 p_2}{F}H\left(\frac{spy_2}{s_2p_2y}\right)-\frac{\alpha_1 s_2 p_2}{F}\int_0^h\Theta(\tau)H\left(\frac{p_2y(t-\tau)}{py_2}\right)\mathrm{d}\tau.\end{aligned}$$

We note that, $\frac{\mathrm{d}L_2}{\mathrm{d}t}\le 0$ when $\hat{\delta}s_2-\rho y_2\ge 0$, where $\frac{\mathrm{d}L_2}{\mathrm{d}t}=0$ occurs at Π_2. The global asymptotic stability of Π_2 follows from LIP. □

4. Numerical Simulations

This section is devoted to performing some numerical simulations for model (5)-(8). Let us choose

$$\rho(\tau)=\tilde{\delta}\left(\tau-\tau_1\right),$$

where $\tilde{\delta}(.)$ is the Dirac delta function and $\tau_1\in[0,h]$ is constant. Let $h\to\infty$, then we obtain

$$\int_0^\infty\rho_1(\tau)\mathrm{d}\tau=1,\quad F=\int_0^\infty\tilde{\delta}\left(\tau-\tau_1\right)\mathrm{e}^{-\mu\tau}\mathrm{d}\tau=\mathrm{e}^{-\mu_1\tau_1}.$$

Moreover,

$$\int_0^\infty\tilde{\delta}\left(\tau-\tau_1\right)\mathrm{e}^{-\mu_1\tau}y(t-\tau)\mathrm{d}\tau=\mathrm{e}^{-\mu_1\tau_1}y\left(t-\tau_1\right).$$

Hence, model (5)-(8), becomes

$$\dot{s}(t)=\beta-\hat{\delta}s(t)-\alpha_1 s(t)p(t)-\alpha_2 s(t)y(t)+\rho y(t), \tag{26}$$

$$\dot{y}(t)=\alpha_1 s(t)p(t)+\alpha_2 s(t)y(t)-\varepsilon y(t)-\rho y(t), \tag{27}$$

$$\dot{p}(t)=m\mathrm{e}^{-\mu_1\tau_1}y(t-\tau_1)-\gamma p(t)-qz(t)p(t), \tag{28}$$

$$\dot{z}(t)=rz(t)p(t)-\mu z(t). \tag{29}$$

For model (26)-(29), the threshold parameters are given by:

$$\begin{aligned} R_0&=\frac{s_0\left(\mathrm{e}^{-\mu_1\tau_1}m\alpha_1+\gamma\alpha_2\right)}{(\varepsilon+\rho)\gamma},\\ R_1^z&=\frac{r\mathrm{e}^{-\mu_1\tau_1}my_2}{\mu\gamma},\\ R_{Hum}^z&=\frac{r\mathrm{e}^{-\mu_1\tau_1}ms_0\hat{\delta}}{\mu\varepsilon\gamma R_0}(R_0-1), \end{aligned} \tag{30}$$

where y_2 is given by Equation (14). Model (26)-(29) will be solved using the values of the parameters listed in Table 1.

Now we investigate our theoretical results given in **Theorem 1-3**. We consider the following two cases:

Case I: Effect of *α*, *μ* and *h* on the asymptotic behaviors of steady states:

In this case, we have chosen three different initial conditions for model (26)-(29) as follows:

Initial-1: $(\zeta_1(\eta),\zeta_2(\eta),\zeta_3(\eta),\zeta_4(\eta))=(600,1,1,10)$, (Solid lines in the figures)

Initial-2: $(\zeta_1(\eta),\zeta_2(\eta),\zeta_3(\eta),\zeta_4(\eta))=(200,1.5,3,5)$, (Dashed lines in the figures)

Initial-3: $(\zeta_1(\eta),\zeta_2(\eta),\zeta_3(\eta),\zeta_4(\eta))=(90,4,9,12)$, $\eta\in(-\infty,0]$. (Dotted lines in the figures)

Further, we fix the value of $\tau_1=0.2$ and we use three sets of parameters α_1 and r to investigate the following five scenarios.

Scenario 1: $\alpha_1=0.0001$ and $r=0.008$. For this set of parameters, we have $R_0=0.7934<1$ and $R_1^z=0.6276<1$. From Figure 1 it can be seen that the solutions with all initial conditions converge to $\Pi_0=(1000,0,0,0)$. This means that according to Theorem 1 Π_0 is GAS. In this case the healthy state will be reached and the HCV particles will be removed.

Table 1. Some parameters and their values of model (26)-(29).

Notation	Value	Notation	Value	Notation	Value	Notation	Value
β	10	ρ	0.01	q	0.1	μ_1	0.1
$\hat{\delta}$	0.01	ε	0.5	r	Varied		
α_1	Varied	m	10	μ	0.1		
α_2	0.0001	γ	3	τ_1	Varied		

Scenario 2: $\alpha_1 = 0.001$ and $r = 0.001$. With such choice we get, $R_1^z = 0.5538 < 1 < R_0 = 6.1695 < 1 + \frac{\varepsilon}{\rho} = 51$ and Π_1 exists with $\Pi_1 = (162.09, 16.76, 51.03, 0)$. This result confirms Lemma 1. Theorem 2 states that, Π_1 is GAS and this is shown in Figure 2. This case represents the

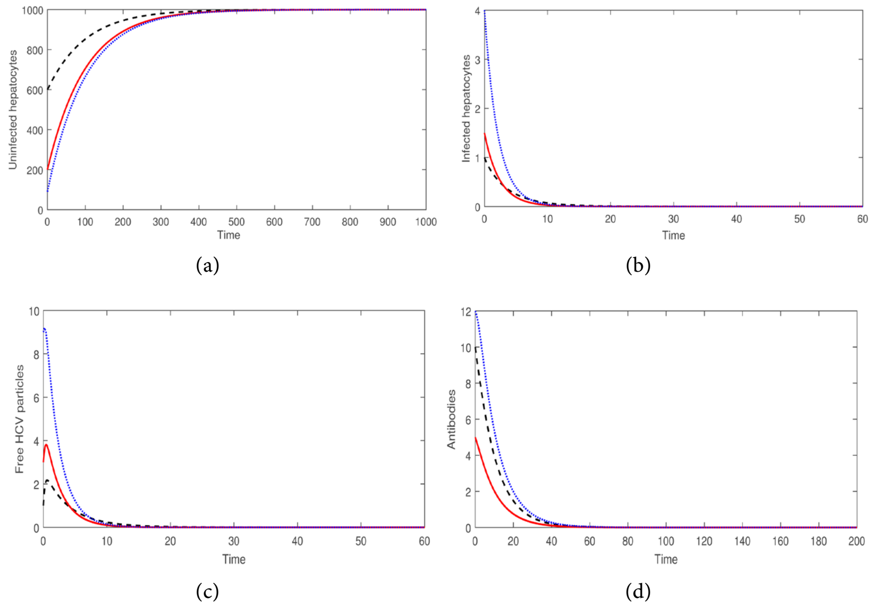

Figure 1. The simulation of trajectories of system (26)-(29) in case of $R_0 \leq 1$. (a) The concentration of uninfected hepatocytes; (b) The concentration of infected hepatocytes; (c) The concentration of free HCV particles; (d) The concentration of antibodies.

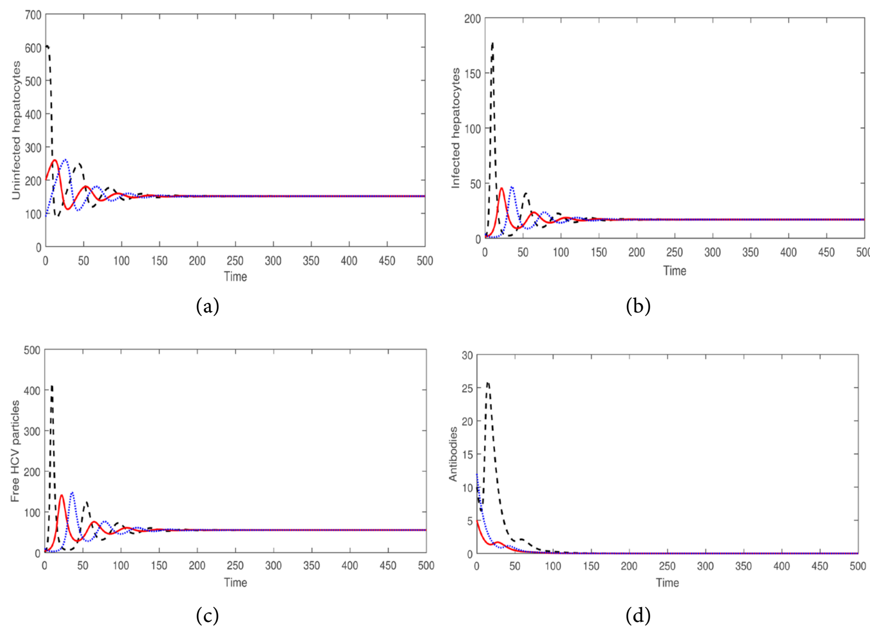

Figure 2. The simulation of trajectories of system (26)-(29) in case of $R_1^z = 0.5538 < 1 < R_0$. (a) The concentration of uninfected hepatocytes; (b) The concentration of infected hepatocytes; (c) The concentration of free HCV particles; (d) The concentration of antibodies.

persistence of the HCV particles but with inactive antibody immune response.

Scenario 3: $\alpha_1 = 0.001$ and $r = 0.01$. Then, we calculate $R_0 = 6.1695 > 1$, $R_1^z = 3.1669 > 1$ and $\hat{\delta} s_2 - \rho y_2 = 4.6948 > 0$. Lemma 1 and Theorem 3 establish that, Π_2 exists and it is globally asymptotically stable. From **Figure 3**, we find that the numerical results agree with the theoretical one presented in Theorem 3. For all initial conditions the states reach the steady state $\Pi_2 = (480.24, 10.4, 10, 83.74)$. This case corresponds to a chronic HCV infection with active antibody immune response.

Case II: Effect of the time delays on the free HCV particles dynamics:

Let us take the initial conditions (**Initial-2).** We choose the values $\alpha_1 = 0.001$ and $r = 0.01$. we assume that $\tau^* = \tau_1$. **Table 2** contains the values of all threshold parameters and equilibria of system (26)-(29) with different values of τ^*.

From **Table 2** we can see that, the values of R_0, and R_1^z are decreased as τ^* is increased. Moreover, τ^* has a significant effect on the stability of steady states of the system. **Table 2** and **Figure 4** show that a high value of τ^*

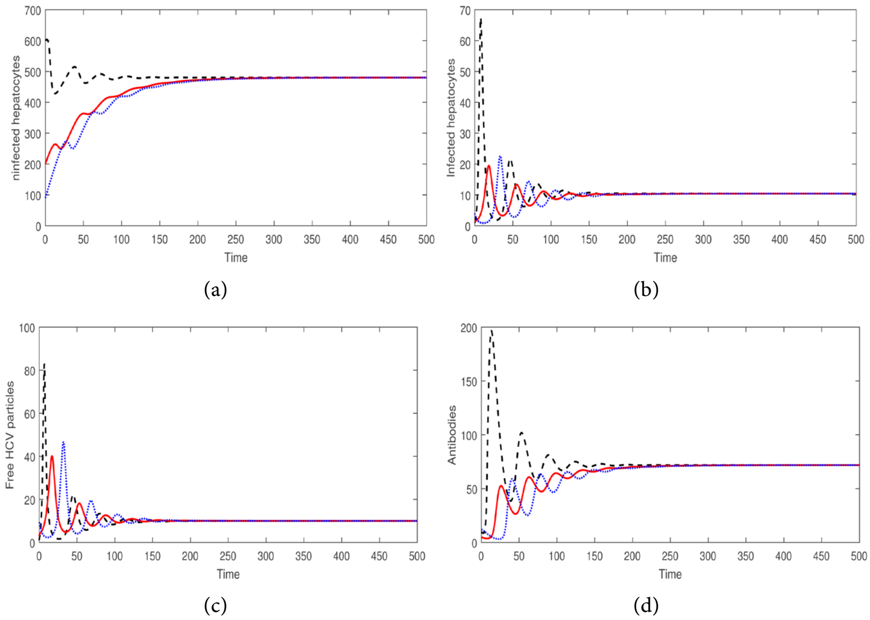

Figure 3. The simulation of trajectories of system (26)-(29) in case of $R_1^z > 1$. (a) The concentration of uninfected hepatocytes; (b) The concentration of infected hepatocytes; (c) The concentration of free HCV particles; (d) The concentration of antibodies.

Table 2. The values of the threshold parameters and the equilibria of system (26)-(29) with different values of τ^*.

τ^*	R_0	R_1^z	The steady states
0.0	6.73	3.47	$E_2 = (480.24, 10.4, 10, 74)$
8	3.13	1.57	$E_2 = (479.88, 10.42, 10.01, 16.8)$
15	1.65	0.77	$E_1 = (603.61, 7.73, 5.76, 0)$
23	0.85	0.35	$E_0 = (1000, 0, 0, 0, 0, 0)$

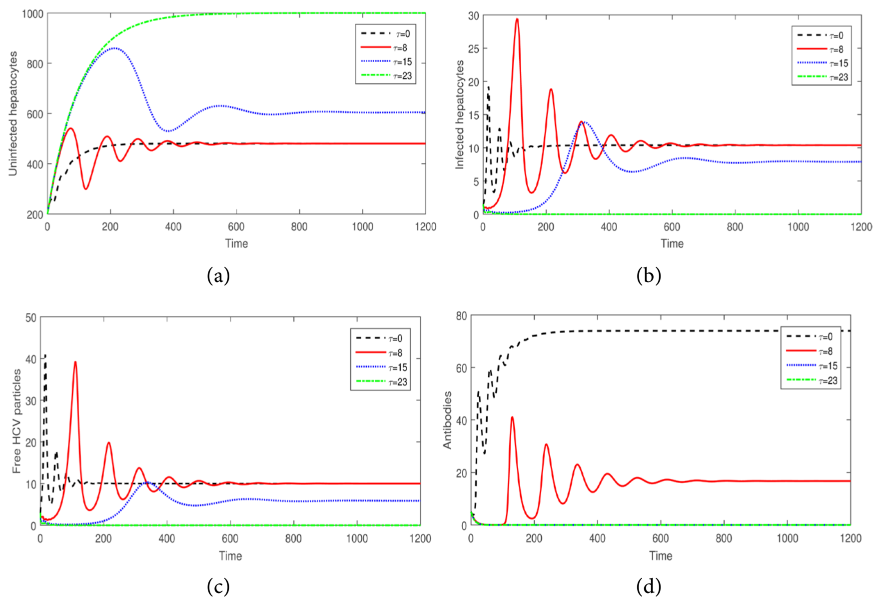

Figure 4. The effect of delays on the behaviour of all trajectories of system (26)-(29). (a) The concentration of uninfected hepatocytes; (b) The concentration of infected hepatocytes; (c) The concentration of free HCV particles; (d) The concentration of antibodies.

decreases the concentration of infected hepatocytes, free HCV particles, antibodies, and increases the population of uninfected hepatocytes. Therefore, the steady states of the system will eventually stabilized around the healthy state Π_0.

References

[1] Banerjee, S., Keval, R. and Gakkhar, S. (2013) Modeling the Dynamics of Hepatitisc Virus with Combined Antiviral Drug Therapy: Interferonand Rivavirin. *Mathematical Biosciences*, **245**, 235-248. https://doi.org/10.1016/j.mbs.2013.07.005

[2] Crotty, S., Cameron, C.E. and Andino, R. (2001) RNA Virus Error Catastrophe: Direct Molecular Test by Using Ribavirin. *Proceedings of the National Academy of Sciences of the United States of America*, **98**, 6895-6900. https://doi.org/10.1073/pnas.111085598

[3] Dahari, H., Lo, A., Ribeiro, R.M. and Perelson, A.S. (2007) Modeling Hepatitis C Virus Dynamics: Liver Regeneration and Critical Drug Efficacy. *Journal of Theoretical Biology*, **247**, 371-381. https://doi.org/10.1016/j.jtbi.2007.03.006

[4] Dahari, H., Ribeiro, R.M. and Perelson, A.S. (2007) Triphasic Decline of Hepatitis C Virus RNA during Antiviral Therapy. *Hepatology*, **46**, 16-21. https://doi.org/10.1002/hep.21657

[5] Dixit, N.M., Layden-Almer, J.E., Layden, T.J. and Perelson, A.S. (2004) Modelling How Ribavirin Improves Interferon Response Rates in Hepatitis C Virus Infection. *Nature*, **432**, 922-924. https://doi.org/10.1038/nature03153

[6] Keval, R., Banerjee, S. and Gakkhar, S. (2012) Dynamics of Hepatitis C Virus (HCV) Infection with Gompertzian Proliferation. *Procedia Engineering*, **38**, 2453-2462. https://doi.org/10.1016/j.proeng.2012.06.290

[7] Li, J., Men, K., Yang, Y. and Li, D. (2015) Dynamical Analysis on a Chronic Hepatitis C Virus Infection Model with Immune Response. *Journal of Theoretical Biology*,

365, 337-346. https://doi.org/10.1016/j.jtbi.2014.10.039

[8] Reluga, T.C., Dahari, H. and Perelson, A.S. (2009) Analysis of Hepatitis C Virus Infection Models with Hepatocyte Homeostasis. *SIAM Journal of Applied Mathematics*, **69**, 999-1023. https://doi.org/10.1137/080714579

[9] Wang, Y., Zhou, Y., Brauer, F. and Heffernan, J.M. (2013) Viral Dynamics Model with CTL Immune Response Incorporating Antiretroviral Therapy. *Journal of Mathematical Biology*, **67**, 901-934. https://doi.org/10.1007/s00285-012-0580-3

[10] Zhang, F., Li, J., Zheng, C.W. and Wang, L. (2017) Dynamics of an HBV/HCV Infection Model with Intracellular Delay and Cell Proliferation. *Communications in Nonlinear Science and Numerical Simulation*, **42**, 464-476. https://doi.org/10.1016/j.cnsns.2016.06.009

[11] Zhao, Y. and Xu, Z. (2014) Global Dynamics for a Delayed Hepatitis C Virus Infection Model. *Electronic Journal of Differential Equations*, **132**, 1-18.

[12] Neumann, A.U., Lam, N.P., Dahari, H., Gretch, D.R., Wiley, T.E., Layden, T.J. and Perelson, A.S. (1998) Hepatitis C viral Dynamics *In Vivo* and the Antiviral Efficacy of Interferon-Alpha Therapy. *Science*, **282**, 103-107. https://doi.org/10.1126/science.282.5386.103

[13] Elaiw, A.M., AlShamrani, N.H. and Hattaf, K. (2017) Dynamical Behaviors of a General Humoral Immunity Viral Infection Model with Distributed Invasion and Production. *International Journal of Biomathematics*, **10**, Article ID: 1750035. https://doi.org/10.1142/S1793524517500358

[14] Elaiw, A.M., Raezah, A.A. and Hattaf, K. (2017) Stability of HIV-1 Infection with Saturated Virus-Target and Infected-Target Incidences and CTL Immune Response, *International Journal of Biomathematics*, **10**, Article ID: 1750070. https://doi.org/10.1142/S179352451750070X

[15] Wang, X., Elaiw, A.M. and Song, X. (2012) Global Properties of a Delayed HIV Infection Model with CTL Immune Response. *Applied Mathematics and Computation*, **218**, 9405-9414. https://doi.org/10.1016/j.amc.2012.03.024

[16] Elaiw, A.M. and Al Shamrani, N.H. (2015) Global Stability of Humoral Immunity Virus Dynamics Models with Nonlinear Infection Rate and Removal. *Nonlinear Analysis: Real World Applications*, **26**, 161-190. https://doi.org/10.1016/j.nonrwa.2015.05.007

[17] Elaiw, A.M. and AlShamrani, N.H. (2017) Stability of a General Delay-Distributed Virus Dynamics Model with Multi-Staged Infected Progression and Immune Response. *Mathematical Methods in the Applied Sciences*, **40**, 699-719. https://doi.org/10.1002/mma.4002

[18] Wodarz, D. (2003) Hepatitis C Virus Dynamics and Pathology: The Role of CTL and Antibody Responses. *Journal of General Virology*, **84**, 1743-1750. https://doi.org/10.1099/vir.0.19118-0

[19] Yousfi, N., Hattaf, K. and Rachik, M. (2009) Analysis of a HCV Model with CTL and Antibody Responses. *Applied Mathematical Sciences*, **3**, 2835-2845.

[20] Meskaf, A., Tabit, Y. and Allali, K. (2015) Global Analysis of a HCV Model with CTL, Antibody Responses and Therapy. *Applied Mathematical Sciences*, **9**, 3997-4008. https://doi.org/10.12988/ams.2015.54334

[21] Timpe, J.M., Stamataki, Z., Jennings, A., Hu, K., Farquhar, M.J., Harris, H.J., Schwarz, A., Desombere, I., Roels, G.L., Balfe, P. and McKeating, J.A. (2008) Hepatitis C Virus Cell-Cell Transmission in Hepatoma Cells in the Presence of Neutralizing Antibodies. *Hepatology*, **47**, 17-24. https://doi.org/10.1002/hep.21959

[22] Xiao, F., Fofana, I., Heydmann, L., Barth, H., Soulier, E., Habersetzer, F., Doffoel, M., Bukh, J., Patel, A.H., Zeisel, M.B. and Baumert, T.F. (2014) Hepatitis C Virus Cell-Cell Transmission and Resistance to Direct-Acting Antiviral Agents. *PLOS Pathogens*, **10**, e1004128. https://doi.org/10.1371/journal.ppat.1004128

[23] Mojaver, A. and Kheiri, H. (2016) Dynamical Analysis of a Class of Hepatitis C Virus Infection Models with Application of Optimal Control. *International Journal of Biomathematics*, **9**, Article ID: 1650038. https://doi.org/10.1142/S1793524516500388

[24] Dahari, H., Major, M., Zhang, X., Mihalik, K., Rice, C.M., Perelson, A.S., Feinstone, S.M. and Neumann, A.U. (2005) Mathematical Modeling of Primary Hepatitis C Infection: Noncytolytic Clearance and Early Blockage of Virion Production. *Gastroenterology*, **128**, 1056-1066. https://doi.org/10.1053/j.gastro.2005.01.049

[25] Dubey, B., Dubey, P. and Dubey, U.S. (2016) Modeling the Intracellular Pathogen-Immune Interaction with Cure Rate. *Communications in Nonlinear Science and Numerical Simulation*, **38**, 72-90. https://doi.org/10.1016/j.cnsns.2016.02.007

[26] Maziane, M., El Lotfi, M., Mahrouf, M., Hattaf, K. and Yousfi, N. (2016) A Delayed HIV Infection Model with Specific Nonlinear Incidence Rate and Cure of Infected Cells in Eclipse Stage. *Applied Mathematical Sciences*, **10**, 2121-2130. https://doi.org/10.12988/ams.2016.63128

[27] Hattaf, K. and Yousfi, N. (2014) Global Stability of a Virus Dynamics Model, with Cure Rate and Absorption. *Journal of the Egyptian Mathematical Society*, **22**, 386-389. https://doi.org/10.1016/j.joems.2013.12.010

[28] Zhou, X.Y., Song, X.Y. and Shi, X.Y. (2008) A Differential Equation Model of HIV Infection of CD4+ T-Cells with Cure Rate. *Journal of Mathematical Analysis and Applications*, **342**, 1342-1355. https://doi.org/10.1016/j.jmaa.2008.01.008

[29] Liu, X., Wang, H., Hu, Z. and Ma, W. (2011) Global Stability of an HIV Pathogenesis Model with Cure Rate. *Nonlinear Analysis: Real World Applications*, **12**, 2947-2961. https://doi.org/10.1016/j.nonrwa.2011.04.016

[30] Wang, K., Fan, A. and Torres, A. (2010) Global Properties of an Improved Hepatitis B Virus Model. *Nonlinear Analysis: Real World Applications*, **11**, 3131-3138. https://doi.org/10.1016/j.nonrwa.2009.11.008

[31] Hattaf, K. and Yousfi, N. (2011) Hepatitis B Virus Infection Model with Logistic Hepatocyte Growth and Cure Rate. *Applied Mathematical Sciences*, **5**, 2327-2335.

[32] Hattaf, K. and Yousfi, N. (2011) Dynamics of HIV Infection Model with Therapy and Cure Rate. *International Journal of Tomography and Statistics*, **16**, 74-80.

[33] Hattaf, K. and Yousfi, N. (2012) Two Optimal Treatments of HIV Infection Model. *World Journal of Modelling and Simulation*, **8**, 27-35.

[34] Vargas-De-Leon, C. (2012) Analysis of a Model for the Dynamics of Hepatitis B with Noncytolytic Loss of Infected Cells. *World Journal of Modelling and Simulation*, **8**, 243-259.

[35] Hattaf, K., Yousfi, N. and Tridane, A. (2012) Mathematical Analysis of a Virus Dynamics Model with General Incidence Rate and Cure Rate. *Nonlinear Analysis: Real World Applications*, **13**, 1866-1872. https://doi.org/10.1016/j.nonrwa.2011.12.015

[36] Tian, Y.N. and Liu, X.N. (2014) Global Dynamics of a Virus Dynamical Model with General Incidence Rate and Cure Rate. *Nonlinear Analysis: Real World Applications*, **16**, 17-26. https://doi.org/10.1016/j.nonrwa.2013.09.002

[37] Jia, J. and Sh, X. (2016) Analysis of a Viral Infection Model with Immune Impairment and Cure Rate. *Journal of Nonlinear Sciences and Applications*, **9**, 3287-3298.

https://doi.org/10.22436/jnsa.009.05.115

[38] Wang, J., Lang, J. and Liu, X. (2015) Global Dynamics for Viral Infection Model with Beddington-Deangelis Functional Response and an Eclipse Stage of Infected Cells, Discrete and Continuous. *Dynamical Systems Series B*, **20**, 3215-3233. https://doi.org/10.3934/dcdsb.2015.20.3215

[39] Wang, Y. and Liu, X. (2015) Dynamical Behaviors of a Delayed HBV Infection Model with Logistic Hepatocyte Growth, Cure Rate and CTL Immune Response. *Japan Journal of Industrial and Applied Mathematics*, **32**, 575-593. https://doi.org/10.1007/s13160-015-0184-6

[40] Hattaf, K. and Yousfi, N. (2016) A Generalized Virus Dynamics Model with Cell-to-Cell Transmission and Cure Rate. *Advances in Difference Equations*, **2016**, 174. https://doi.org/10.1186/s13662-016-0906-3

[41] Pan, S. and Chakrabarty, S.P. (2018) Threshold Dynamics of HCV Model with Cell-to-Cell Transmission and a Non-Cytolytic Cure in the Presence of Humoral Immunity. *Communications in Nonlinear Science and Numerical Simulation*, **61**, 180-197. https://doi.org/10.1016/j.cnsns.2018.02.010

[42] Hale, J.K. and Verduyn Lunel, S. (1993) Introduction to Functional Differential Equations. Springer-Verlag, New York. https://doi.org/10.1007/978-1-4612-4342-7