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

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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 liver 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:

\[
\begin{align*}
\dot{s}(t) &= \beta - \delta s(t) - \alpha_1 s(t) p(t) - \alpha_2 s(t) y(t) + \rho y(t), \\
\dot{y}(t) &= \alpha_1 s(t) p(t) + \alpha_2 s(t) y(t) - \varepsilon y(t) - \rho y(t), \\
\dot{p}(t) &= \gamma p(t) - \gamma p(t) - q z(t) p(t), \\
\dot{z}(t) &= rz(t) p(t) - \mu z(t),
\end{align*}
\]

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 \(\beta\), die at rate \(\delta\), where \(\delta\) is the natural death rate constant. The infection rate due to both virus-to-cell and cell-to-cell transmissions is given by \(\alpha_1 s(t) p(t) + \alpha_2 s(t) y(t)\), where \(\alpha_1\) and \(\alpha_2\) are constants. The infected hepatocytes die at rate \(\varepsilon y(t)\) and cure at rate \(\rho y(t)\), where \(\varepsilon\) and \(\rho\) are constants. Constant \(m\) is the generation rate of the HCV from infected hepatocytes. Antibodies attack the HCV at rate \(q z(t)\), proliferate at rate \(r z(t)\) and die at rate \(\mu z(t)\), where \(q\), \(r\) and \(\mu\) 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:

\[
\begin{align*}
\dot{s}(t) &= \beta - \delta s(t) - \alpha_1 s(t) p(t) - \alpha_2 s(t) y(t) + \rho y(t), \\
\dot{y}(t) &= \alpha_1 s(t) p(t) + \alpha_2 s(t) y(t) - \varepsilon y(t) - \rho y(t),
\end{align*}
\]
\[\dot{y}(t) = m \int_0^h \rho(\tau) e^{-\mu \tau} y(t-\tau) \, d\tau - \gamma p(t) - qz(t) \, p(t), \quad (7)\]

\[\dot{z}(t) = rz(t) \, p(t) - \mu z(t). \quad (8)\]

We assume that, the HCV or infected cell contacts an uninfected hepatocyte at time \(t - \tau\), the cell becomes infected at time \(t\), where \(\tau\) is a distributed parameter over the time interval \([0,h]\). The factors \(e^{-\mu \tau}\) represents the probability of surviving the hepatocyte during the time delay period, where \(\mu\) is a constant. \(\rho(\tau)\) is a probability distribution function satisfying \(\int_0^h \rho(\tau) \, d\tau = 1\) and \(\int_0^h \rho(\tau) e^{\alpha \tau} \, d\tau < \infty\), where \(\zeta\) and \(h\) are positive constants. Let us denote \(\Theta(\tau) = \rho(\tau) e^{-\mu \tau}\) and \(F = \int \Theta(\tau) \, d\tau\), thus \(0 < F \leq 1\). Let the initial conditions for system (5)-(8) be given as:

\[s(\eta) = \zeta_1(\eta), \quad y(\eta) = \zeta_2(\eta), \quad p(\eta) = \zeta_3(\eta), \quad z(\eta) = \zeta_4(\eta), \]

\[\zeta_j(\eta) \geq 0, \quad \eta \in [-h,0], \quad j = 1,\ldots,4, \quad (9)\]

where \(C\) is the Banach space of continuous functions mapping the interval \([-h,0]\) into \(\mathbb{R}_+^4\). 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 \(\frac{d}{dt} \Big|_{t=0} = \beta + \rho y > 0\). Hence, \(s(t) > 0\) for all \(y \geq 0\). Moreover, for all \(t \in [0,h]\) we have

\[y(t) = \zeta_2(0) e^{(\alpha + \rho) t} + \int_0^t e^{(\alpha + \rho)(t-\eta)} \left[ \alpha_s(\eta) p(\eta) + \alpha_z(\eta) y(\eta) \right] \, d\eta \geq 0,\]

\[p(t) = \zeta_3(0) e^{(\gamma + \rho)(t-\eta)} + \int_0^t e^{(\gamma + \rho)(t-\eta)} \Theta(\tau) y(\eta-\tau) \, d\eta \, d\eta \geq 0,\]

\[z(t) = \zeta_4(0) e^{(\rho + \gamma)(t-\eta)} \geq 0.\]

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

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

\[\dot{s}(t) \leq \beta - \delta s(t) + \rho y(t),\]
We let \( Q(t) = s(t) + y(t) \), then
\[
\dot{Q}(t) = \beta - \delta s(t) - \varepsilon y(t) \leq \beta - \sigma_1(s(t) + y(t)) = \beta - \sigma_1 Q(t),
\]
where \( \sigma_1 = \min\{\delta, \varepsilon\} \). Hence \( Q(t) \leq L_1 \), if \( Q(t) \leq L_1 \) where \( L_1 = \frac{\beta}{\sigma_1} \). It follows that \( s(t) \leq L_1 \) and \( y(t) \leq L_1 \) if \( s(0) + y(0) \leq L_1 \). Moreover, let
\[
Q_2(t) = p(t) + \frac{q}{r} z(t),
\]
then
\[
\dot{Q}_2(t) = m \int_{0}^{\frac{h}{q}} \Theta(t) y(t - \tau) d\tau - \gamma p(t) - \frac{q}{r} z(t) \leq mL_1 \gamma - \gamma p(t) - \frac{q}{r} z(t)
\]
\[
\leq mL_1 - \sigma_z \left( p(t) + \frac{q}{r} z(t) \right) = mL_1 - \sigma_1 Q_1(t),
\]
where \( \sigma_z = \min\{\gamma, \mu\} \). It follows that \( \limsup_{t \to \infty} Q_2(t) \leq L_2 \), where \( L_2 = \frac{mL_1}{\sigma_2} \).

Since \( p(t) \geq 0 \) and \( z(t) \geq 0 \), then \( \limsup_{t \to \infty} p(t) \leq L_2 \) and \( \limsup_{t \to \infty} z(t) \leq L_3 \), where \( L_3 = \frac{mL_1}{q} \). Therefore, \( s(t), y(t), p(t) \) and \( z(t) \) are ultimately bounded. \( \square \)

According to Proposition 1, we can show that the region
\[
\Delta = \{(s, y, p, z) \in C^4 : \|s\| \leq L_1, \|y\| \leq L_1, \|p\| \leq L_2, \|z\| \leq L_3\},
\]
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 \( R^*_1 > 0 \), such that
1) if \( R_0 \leq 1 \), then there exists only one steady state \( \Pi_0 \),
2) if \( R^*_1 \leq 1 < R_0 \), then there exist only two steady states \( \Pi_0 \) and \( \Pi_1 \),
3) if \( R_0 > 1 \) and \( R^*_1 > 1 \), then there exist three steady states \( \Pi_0 \), \( \Pi_1 \) and \( \Pi_2 \).

**Proof.** Let \( (s, y, p, z) \) be any steady state satisfying
\[
\beta - \delta s - \alpha s p - \alpha_z s y + \rho y = 0, \quad (10)
\]
\[
\alpha s p + \alpha_z s y - \varepsilon y - \rho y = 0, \quad (11)
\]
\[
mF y - \gamma p - qz p = 0, \quad (12)
\]
\[
(rp - \mu) z = 0. \quad (13)
\]
We find that system (10)-(13) admits three steady states.
1) Infection-free steady state \( \Pi_0 = (s_0, 0, 0, 0) \), where \( s_0 = \beta / \delta \).
2) Chronic-infection steady state without immune response \( \Pi_1 = (s_1, y_1, p_1, 0) \), where
\[
s_1 = \frac{(\varepsilon + \rho) y}{Fm\sigma_1 + \gamma\alpha_z},
\]
3) Chronic-infection steady state with immune response \( \Pi_2 = (s_2, y_2, p_2, z_2) \), where
\[
s_2 = \frac{(\varepsilon + \rho) y}{Fm\sigma_1 + \gamma\alpha_z},
\]
and
\[
y_2 = \frac{\gamma p}{\alpha_z},
\]
\[
p_2 = \frac{qz_2}{m},
\]
\[
z_2 = \frac{mF y}{\gamma}. \quad (14)
\]

DOI: 10.4236/jamp.2018.65096
Clearly $\Pi_1$ exists if 

$$\frac{\beta(FmA_i + \gamma z)}{\delta \gamma (\alpha + \rho)} > 1.$$ 

Let us define 

$$R_\alpha = \frac{\beta(FmA_i + \gamma z)}{\delta \gamma (\alpha + \rho)}.$$ 

In terms of $R_\alpha$, we can write the steady state components for $\Pi_1$ as: 

$$s_i = \frac{s_0}{R_\alpha}, \quad y_i = \frac{\delta s_0}{e}(R_\alpha - 1),$$ 

$$p_i = \frac{Fm\delta s_0}{\gamma e}(R_\alpha - 1).$$ 

3) Chronic-infection steady state with humoral immune 

$$\Pi_2 = (s_2, y_2, p_2, z_2),$$ 

where 

$$s_2 = \frac{r y_2 (e + \rho)}{\alpha_i + r y_2 \alpha_2}, \quad y_2 = \frac{-B + \sqrt{B^2 - 4AC}}{2A},$$ 

$$p_2 = \frac{\mu}{r}, \quad z_2 = \frac{z}{q}\left(\frac{rmF_{y_2}}{\mu \gamma} - 1\right).$$ 

where 

$$A = r \alpha_2 e,$$ 

$$B = \mu \alpha_i - r \beta \alpha_2 + r \delta (\alpha + \rho),$$ 

$$C = -\beta \mu \alpha_i.$$ 

We note that $\Pi_2$ exists when $\frac{r F_{y_2} \alpha_2}{\mu \gamma} > 1$. Now we define 

$$R_{\alpha}^i = \frac{r F_{y_2} \alpha_2}{\mu \gamma} = \frac{F_{y_2} \alpha_2}{p_2 \gamma}.$$ 

Then $z_2 = \frac{z}{q}(R_{\alpha}^i - 1)$. 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 $R_{\alpha}^i < 1$, then $R_{Hum}^z < 1$, 

2) if $R_{\alpha}^i > 1$, then $R_{Hum}^z > 1$. 

DOI: 10.4236/jamp.2018.65096
3) if \( R'_c = 1 \) then \( R'_{hum} = 1 \).

**Proof.** 1) Let \( R'_c < 1 \), then from Equation (16) we have \( y_s < \frac{\gamma p_s}{mF} \), and then using Equation (14) we get

\[
\frac{-B + \sqrt{B^2 - 4AC}}{2A} < \frac{\gamma p_s}{mF},
\]

that leads to

\[
\left( \frac{2\gamma p_s}{Fm} + B \right)^2 - \left( B^2 - 4AC \right) > 0.
\]

Using Equation (15), we can get

\[
\frac{4\alpha_2 \epsilon \mu \gamma \left(ish\alpha + \gamma\alpha_2 \right)}{m^2 F^2} \left( 1 - R'^c_{hum} \right) > 0
\]

then

\[
R'^c_{hum} = \frac{rFms_i \left( R_0 - 1 \right) \theta}{\mu \epsilon} < 1.
\]

then \( R'^c_{hum} < 1 \). Similarly, one can proof 2) and 3) \( \square \).

### 3. Global Stability

The following theorems investigate the global stability of the steady states of system (5)-(8). Let us define the function \( H : (0, \infty) \rightarrow [0, \infty) \) as

\[
H(t) = t - 1 - \ln t.
\]

Denote \( (s, y, p, z) = (s(t), y(t), p(t), z(t)) \).

**Theorem 1.** Suppose that \( R_0 \leq 1 \), then the infection-free steady state \( \Pi_0 \) is globally asymptotically stable (GAS).

**Proof.** Constructing a Lyapunov functional

\[
L_0(s, y, p, z) = s_0 H\left( s \right) + y + \frac{\alpha s_0}{\gamma} p + \frac{q \alpha s_0}{r \gamma} z
\]

\[
+ \frac{\rho}{2 \left( \delta + \epsilon \right) s_0} \left[ (s - s_0) + y \right]^2
\]

\[
+ \frac{m \alpha s_0}{\gamma} \int_0^\theta \Theta(t) \int_{t-}^\gamma y(\eta) d\eta d\tau.
\]

We calculate \( \frac{dL_0}{dt} \) along the solutions of model (5)-(8) as:

\[
\frac{dL_0}{dt} = \left( 1 - \frac{s_0}{s} \right) \left( \beta - \hat{\delta} s - \alpha s p - \alpha s y + \rho y \right) + \alpha s p + \alpha s y
\]

\[
- \epsilon y - \rho y + \frac{\alpha s_0}{\gamma} \left( \int_0^\theta \Theta(t) y(t - \tau) d\tau - \gamma p - q z \right)
\]

\[
+ \frac{q \alpha s_0}{r \gamma} \left( rz p - \mu z \right) + \frac{\rho}{\delta + \epsilon s_0} \left[ (s - s_0) + y \right] \left( \beta - \hat{\delta} s - \epsilon y \right)
\]

\[
+ \frac{m \alpha s_0}{\gamma} \int_0^\theta \Theta(t) \int_{t-}^\gamma y(t - \tau) d\tau.
\]
Collecting terms of Equation (17) and using $\beta = \hat{\delta} s_0$ we obtain
\[
\frac{dL_{0}}{dt} = \left(1 - \frac{s_{0}}{s}\right)(\hat{\delta} s_{0} - \hat{\delta} s) + \alpha_{s} s_{0} y + \left(1 - \frac{s_{0}}{s}\right) \rho y \nonumber \\
- (\epsilon + \rho) y + \frac{\alpha_{s} s_{0} F y}{y} - \frac{qa \alpha s_{0}}{r \gamma} \mu z - \frac{\rho}{(\delta + \epsilon) s_{0}} \left[(s - s_{0}) + y\right](\hat{\delta} (s - s_{0}) + \epsilon y). 
\]

We note that
\[
\left(1 - \frac{s_{0}}{s}\right) \rho y = -\frac{\rho y}{s_{0}} (s - s_{0})^{2} + \frac{\rho y}{s_{0}} (s - s_{0}).
\]

Therefore
\[
\frac{dL_{0}}{dt} = \hat{\delta} \frac{(s - s_{0})^{2}}{s} + \alpha_{s} s_{0} y - \frac{\rho y}{s_{0}} (s - s_{0})^{2} + \frac{\rho y}{s_{0}} (s - s_{0}) \nonumber \\
- (\epsilon + \rho) y + \frac{\alpha_{s} s_{0} F y}{y} - \frac{qa \alpha s_{0}}{r \gamma} \mu z - \frac{\rho}{(\delta + \epsilon) s_{0}} \left[(s - s_{0}) + y\right] \left(\frac{\hat{\delta} s_{0} - \hat{\delta} s}{(\delta + \epsilon)}\right) 
\]
\[
= \left(\hat{\delta} s_{0} + \rho y + \frac{\rho \hat{\delta} s}{(\delta + \epsilon)}\right) \frac{(s - s_{0})^{2}}{s_{0}} - \frac{\rho \epsilon y^{2}}{(\delta + \epsilon) s_{0}} 
\]
\[
- \frac{qa \alpha s_{0}}{r \gamma} \mu z + (\epsilon + \rho) \left(\frac{ma \alpha F}{\gamma (\epsilon + \rho)} s_{0} - 1\right) y 
\]
\[
= \left(\hat{\delta} s_{0} + \rho y + \frac{\rho \hat{\delta} s}{(\delta + \epsilon)}\right) \frac{(s - s_{0})^{2}}{s_{0}} - \frac{\rho \epsilon y^{2}}{(\delta + \epsilon) s_{0}} 
\]
\[
- \frac{qa \alpha s_{0}}{r \gamma} \mu z + (\epsilon + \rho) (R_{0} - 1) y.
\]

Since $R_{0} \leq 1$, then $\frac{dL_{0}}{dt} \leq 0$ for all $s, y, p, z > 0$. Moreover $\frac{dL_{0}}{dt} = 0$ if and only if $s(t) = s(0), y(t) = z(t) = 0$. Let $\Gamma_{0} = \{s, y, p, z\}: \frac{dL_{0}}{dt} = 0$ and $\Gamma_{0}$ be the largest invariant subset of $\Gamma_{0}$. The solution of system (5)-(8) tend to $\Gamma_{0}$. For each element of $\Gamma_{0}$ we have $y(t) = 0$, then $\dot{y}(t)$ and Equation (6) we get
\[
y(t) = 0 = \alpha_{s} s_{0} p(t)
\]

Then $p(t) = 0$. It follows that $\Gamma_{0}$ contains a single point that is $\{\Gamma_{0}\}$. Applying LaSalle’s invariance principle (LIP), we get that $\Pi_{0}$ is GAS.

**Theorem 2.** Suppose that $R_{0}^{+} \leq R_{0} \leq 1 + \frac{P}{\epsilon}$, then $\Pi_{1}$ is GAS.

**Proof.** Let us define a function $L_{i}(s, y, p, z)$ as:
Calculating $\frac{dL_1}{dt}$ along the trajectories of system (5)-(8), we get

\[
\frac{dL_1}{dt} = \left(1 - \frac{s_i}{s}\right) \left(\beta - \hat{\delta}s - \alpha_i s_p - \alpha_i s_y + \rho y\right)
+ \left(1 - \frac{y_i}{y}\right) \left(\alpha_i s_p + \alpha_i s_y - \varepsilon y - \rho y\right)
+ \frac{\alpha_i s_i p_i}{F_{my_i}} \left[1 - \frac{p_i}{P_i}\right] \left[m \Theta(t) y(t - \tau) d\tau - \gamma p - q_p\right] \\
+ \frac{\alpha_i s_i p_i q}{F_{my_i r}} \left[r z p - \mu z + \frac{\rho}{\hat{\delta} + \epsilon} s_i \left[(s - s_i) + (y - y_i)\right] \left(\beta - \hat{\delta}s - \epsilon y\right)\right]
+ \frac{\alpha_i s_i p_i}{F} \int_0^\eta \Theta(t) \left[y - \frac{y(t - \tau)}{y_i} + \ln\left(\frac{y(t - \tau)}{y_i}\right)\right] d\tau.
\]

Collecting terms of Equation (19), we get

\[
\frac{dL_1}{dt} = \left(1 - \frac{s_i}{s}\right) \left(\beta - \hat{\delta}s + \rho y\right) + \alpha_i s_i p + \alpha_i s_i y - \varepsilon y + \rho y\left(1 - \frac{s_i}{s}\right)
+ \frac{\alpha_i s_i p_i}{F_{my_i}} \left[1 - \frac{p_i}{P_i}\right] \left[m \Theta(t) y(t - \tau) d\tau - \gamma p - q_p\right] \\
+ \frac{\alpha_i s_i p_i q}{F_{my_i r}} \left[r z p - \mu z + \frac{\rho}{\hat{\delta} + \epsilon} s_i \left[(s - s_i) + (y - y_i)\right] \left(\beta - \hat{\delta}s - \epsilon y\right)\right]
+ \frac{\alpha_i s_i p_i}{F} \int_0^\eta \Theta(t) \ln\left(\frac{y(t - \tau)}{y_i}\right) d\tau.
\]

Applying condition of equilibrium $\Pi_1$:

\[
\beta = \hat{\delta}s_i + \alpha_i s_i p_i + \alpha_i s_i y_i - \rho y_i = \hat{\delta}s_i + \varepsilon y_i,
\]

\[
p_i = \frac{F_m}{\gamma} y_i, (\varepsilon + \rho) y_i = \alpha_i s_i p_i + \alpha_i s_i y_i,
\]

we get

\[
\frac{dL_1}{dt} = \frac{\hat{\delta}(s - s_i)^2}{s} + \left(\alpha_i s_i p_i + \alpha_i s_i y_i\right) \left[1 - \frac{s_i}{s}\right] + \rho \left(y - y_i\right) \left[1 - \frac{s_i}{s}\right]
+ \frac{\alpha_i s_i p_i}{p_i} + \alpha_i s_i y_i \left(\alpha_i s_i p_i + \alpha_i s_i y_i\right) \frac{y_i}{y_i} - \alpha_i s_i p_i \frac{s_p}{p_i} \frac{y_i}{y_i}
- \alpha_i s_i y_i \frac{s_i}{s_i} + \left(\alpha_i s_i p_i + \alpha_i s_i y_i\right) - \alpha_i s_i p_i \frac{p_i}{p_i}
\]
\[-\frac{\alpha s_{1} p_{1}}{F} \int_{0}^{s} \Theta(\tau) \frac{y(t-\tau)}{y_{1}} \frac{p_{1}}{p} d\tau + \alpha s_{1} p_{1} + \frac{\alpha s_{1} qz p_{1}}{r} - \frac{q z s_{1} \mu}{r y} \]
\[+ \frac{\rho}{(\delta + \epsilon) s_{1}} [(s-s_{1}) + (y-y_{1})] \left[ \delta (s-s_{1}) + y (y-y_{1}) \right] \]
\[+ \alpha s_{1} p_{1} \frac{y}{y_{1}} + \frac{\alpha s_{1} p_{1}}{F} \int_{0}^{s} \Theta(\tau) \ln \left( \frac{y(t-\tau)}{y} \right) d\tau. \]

thus
\[\frac{d L}{d t} = -\frac{s}{s_{1}} \left( s_{1} - s \right) + \alpha s_{1} p_{1} \left( \frac{1}{s_{1}} - \frac{s}{s_{1}} \right) + \rho \left( y - y_{1} \right) \left( \frac{1}{s_{1}} - \frac{s}{s_{1}} \right) \]
\[+ \alpha s_{1} y_{1} \left( 2 - \frac{s}{s_{1}} - \frac{s}{s_{1}} \right) - \frac{\alpha s_{1} p_{1}}{s_{1} p_{1}} y \]
\[+ \frac{\alpha s_{1} p_{1}}{F y_{1}} \left( s_{1} - s \right) + \frac{\alpha s_{1} s_{1} s_{1} s_{1}}{s_{1} s_{1} s_{1}} \left( s_{1} - s \right) \frac{y_{1}}{s_{1}} \]
\[+ 2 \alpha s_{1} p_{1} \int_{0}^{s} \Theta(\tau) \left( \frac{y(t-\tau)}{y_{1}} \right) \frac{p_{1}}{p} d\tau + \frac{q z s_{1} \mu}{r} \left( p_{1} - p_{2} \right) z \]
\[+ \frac{\rho}{(\delta + \epsilon) s_{1}} [(s-s_{1}) + (y-y_{1})] \left[ \delta (s-s_{1}) + \epsilon (y-y_{1}) \right] \]
\[+ \alpha s_{1} p_{1} \frac{y}{y_{1}} + \frac{\alpha s_{1} p_{1}}{F} \int_{0}^{s} \Theta(\tau) \ln \left( \frac{y(t-\tau)}{y} \right) d\tau. \]

We note that
\[\rho \left( y - y_{1} \right) \left( \frac{1}{s_{1}} - \frac{s}{s_{1}} \right) = -\frac{\rho (y - y_{1})}{s_{1} s_{1}} (s - s_{1}) + \frac{\rho (y - y_{1})}{s_{1}} (s - s_{1}). \]

Then
\[\frac{d L}{d t} = -\frac{s}{s_{1}} \left( s_{1} - s \right) + \alpha s_{1} p_{1} \left( \frac{1}{s_{1}} - \frac{s}{s_{1}} \right) - \frac{\rho (y - y_{1})}{s_{1} s_{1}} (s - s_{1})^{2} \]
\[+ \frac{\rho (y - y_{1})}{s_{1}} (s - s_{1}) + \alpha s_{1} y_{1} \left( 2 - \frac{s}{s_{1}} - \frac{s}{s_{1}} \right) - \frac{\alpha s_{1} p_{1}}{s_{1} p_{1}} y \]
\[+ 2 \alpha s_{1} p_{1} \int_{0}^{s} \Theta(\tau) \left( \frac{y(t-\tau)}{y_{1}} \right) \frac{p_{1}}{p} d\tau + \frac{q z s_{1} \mu}{r} \left( p_{1} - p_{2} \right) z \]
\[+ \frac{\rho}{(\delta + \epsilon) s_{1}} [(s-s_{1}) + (y-y_{1})] \left[ \delta (s-s_{1}) + \epsilon (y-y_{1}) \right] \]
\[+ \alpha s_{1} p_{1} \frac{y}{y_{1}} + \frac{\alpha s_{1} p_{1}}{F} \int_{0}^{s} \Theta(\tau) \ln \left( \frac{y(t-\tau)}{y} \right) d\tau. \]
Consider the following equalities
\[ \ln \left( \frac{y(t-\tau)}{y} \right) = \ln \left( \frac{p_i y(t-\tau)}{p y_i} \right) + \ln \left( \frac{s_p y_i}{s p y} \right) + \ln \left( \frac{s_i}{s} \right), \quad i = 1, 2. \] (21)

Simplify Equation (20) and let \( i = 1 \), in Equation (21) we get
\[ \frac{dL_i}{dt} = -\left( \hat{\delta} s_i + \rho (y - y_i) + \frac{\rho \hat{\delta} s}{\hat{\delta} + \epsilon} \right) \left( s - s_i \right) - \frac{\rho \epsilon (y - y_i)^2}{(\hat{\delta} + \epsilon) s_i} - \alpha s_i \left( \frac{s_i}{s} - 1 - \ln \left( \frac{s_i}{s} \right) \right) + \alpha s_i \left( 2 - \frac{s_i}{s} - \frac{s}{s_i} \right) \]
\[ - \alpha s_p \left[ \frac{s_p y_i}{s_p y} - 1 - \ln \left( \frac{s_p y_i}{s_p y} \right) \right] \] (22)
\[ - \alpha s_p \frac{1}{F} \int_0^\tau \Theta(\tau) \left[ \frac{p_i y(t-\tau)}{p y_i} - 1 - \ln \left( \frac{p_i y(t-\tau)}{p y_i} \right) \right] d\tau + \frac{q \alpha s_i}{\gamma} (p_i - p_2) z. \]

Equation (22) can be rewrite as:
\[ \frac{dL_i}{dt} = -\left( \hat{\delta} s_i + \rho (y - y_i) + \frac{\rho \hat{\delta} s}{\hat{\delta} + \epsilon} \right) \left( s - s_i \right) - \frac{\rho \epsilon (y - y_i)^2}{(\hat{\delta} + \epsilon) s_i} - \alpha s_i \left( \frac{s_i}{s} - 1 - \ln \left( \frac{s_i}{s} \right) \right) + \alpha s_i \left( 2 - \frac{s_i}{s} - \frac{s}{s_i} \right) \]
\[ - \alpha s_p \left[ \frac{s_p y_i}{s_p y} - 1 - \ln \left( \frac{s_p y_i}{s_p y} \right) \right] \] (23)
\[ - \alpha s_p \frac{1}{F} \int_0^\tau \Theta(\tau) H \left( \frac{p_i y(t-\tau)}{p y_i} - 1 - \ln \left( \frac{p_i y(t-\tau)}{p y_i} \right) \right) d\tau + \frac{q \alpha s_i}{\gamma} (p_i - p_2) z. \]

We note that
\[ \hat{\delta} s_i - \rho y_i = \frac{\hat{\delta} p s_0}{\epsilon R_0} \left[ \left( 1 + \frac{\rho}{\epsilon} \right) - R_0 \right]. \]

From Lemma 2 we have \( p_i \leq p_2 \), then, \( \frac{dL_i}{dt} \leq 0 \) for all \( s, y_i \) and \( p_i > 0 \), where \( \frac{dL_i}{dt} = 0 \) if and only if \( s = s_i, y = y_i, p = p_i \) and \( z = 0 \). Thus, the global asymptotic stability of \( \Pi_1 \) follows from LIP when \( R_i^* \leq 1 \), and \( 1 < R_0 \leq 1 + \frac{\rho}{\epsilon} \).

Theorem 3. Suppose that \( R_i^* > 1 \) and \( \hat{\delta} s_2 - \rho y_2 \geq 0 \), then \( \Pi_2 \) is GAS.

Proof. Define a function \( L_2(s, y, p, z) \) as:
\[ L_2 = s H \left( \frac{s}{s_2} \right) + y H \left( \frac{y}{y_2} \right) + \frac{\alpha s_2 p_2}{F y_2} H \left( \frac{p}{p_2} \right) + \frac{q \alpha s_i p_2}{F y_2} H \left( \frac{z}{z_2} \right) \]
\[ + \frac{\rho}{2(\hat{\delta} + \epsilon)} \left( s - s_i \right) \left( y - y_i \right) + \frac{\alpha s_2 p_2}{F} \int_0^\tau \Theta(\tau) H \left( \frac{y(\eta)}{y_2} \right) d\eta d\tau. \]
Calculating \( \frac{dL_2}{dt} \) as:

\[
\frac{dL_2}{dt} = \left(1 - \frac{s_2}{s}\right) (\beta - \dot{s}_s - \alpha_s s_p - \alpha_s s_y + \rho y)
+ \left(1 - \frac{y_2}{y}\right) (\alpha_s s_p + \alpha_s s_y - \varepsilon y - \rho y)
+ \frac{\alpha_s s_p F_{my_2}}{F_{my_2}} \left(1 - \frac{\theta}{\theta}ight) \left[ m \left( \frac{\theta}{\theta} \right) y(t) - \gamma p - q z p \right]
+ \frac{q \alpha_s s_p F_{my_2}}{F_{my_2}} \left(1 - \frac{\theta}{\theta}ight) (r z p - \mu z)
+ \frac{\rho}{\delta + \varepsilon} \left[ (s - s_2) + (y - y_2) \right] (\beta - \dot{s}_s - \varepsilon y)
+ \frac{\alpha_s s_p F_{my_2}}{F_{my_2}} \left(1 - \frac{\theta}{\theta}\right) \left[ m \left( \frac{\theta}{\theta} \right) y(t) - \gamma p - q z p \right]
\]

Collecting terms of Equation (24) and applying the equilibrium conditions for \( \Pi_2 \):

\[
\beta = \dot{s}_s + \alpha_s s_p s_2 + \alpha_s s_y y_2 - \rho y_2 = \dot{s}_s + \varepsilon y_2,
\]

\[
p_z = \frac{\mu}{r}, \quad (\varepsilon + \rho) y_2 = \alpha_s s_p s_2 + \alpha_s s_y y_2
\]

we get

\[
\frac{dL_2}{dt} = -\delta \left( s - s_2 \right)^2 + \left( \alpha_s s_p + \alpha_s s_y y_2 + \rho (y - y_2) \right) \left(1 - \frac{s_2}{s}\right) + \alpha_s s_p + \alpha_s s_y y
- \left( \alpha_s s_p + \alpha_s s_y y_2 \right) \frac{y}{y_2} - \alpha_s s_p \frac{y_2}{s_2 y} - \alpha_s s_y \frac{s}{s_2} + \left( \alpha_s s_p + \alpha_s s_y y_2 \right)
- \frac{\alpha_s s_p F_{my_2}}{F_{my_2}} \left(1 - \frac{\theta}{\theta}\right) \left[ m \left( \frac{\theta}{\theta} \right) y(t) - \gamma p - q z p \right]
+ \frac{q \alpha_s s_p F_{my_2}}{F_{my_2}} \left(1 - \frac{\theta}{\theta}\right) (r z p - \mu z)
+ \frac{\rho}{\delta + \varepsilon} \left[ (s - s_2) + (y - y_2) \right] (\beta - \dot{s}_s - \varepsilon y)
+ \frac{\alpha_s s_p F_{my_2}}{F_{my_2}} \left(1 - \frac{\theta}{\theta}\right) \left[ m \left( \frac{\theta}{\theta} \right) y(t) - \gamma p - q z p \right]
- \left( \alpha_s s_p + \alpha_s s_y y_2 \right) \frac{y}{y_2} - \alpha_s s_p \frac{y_2}{s_2 y} - \alpha_s s_y \frac{s}{s_2}
+ \left( \alpha_s s_p + \alpha_s s_y y_2 \right) \frac{p}{p_2} + \frac{q \alpha_s s_p F_{my_2}}{F_{my_2}} \left(1 - \frac{\theta}{\theta}\right) \left[ m \left( \frac{\theta}{\theta} \right) y(t) - \gamma p - q z p \right]
\]
\[ + \frac{\alpha_s s_y p_y y}{y^2} y - \frac{\rho}{(\delta + \epsilon)} s_y \left[(s - s_y) + (y - y_y)\right] \left(\hat{\delta}(s - s_y) + \epsilon(y - y_y)\right) \]

\[ + \frac{\alpha_s s_y p_y}{F} \int_0^\delta \Theta(\tau) \ln \left(\frac{y(t - \tau)}{y}\right) d\tau. \]

We note that

\[ \rho(y - y_y) \left(1 - \frac{s_y}{s}\right) = -\frac{\rho(y - y_y)}{s s_y} (s - s_y)^2 + \frac{\rho(y - y_y)}{s_y} (s - s_y) \]

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

\[ \frac{dL_2}{dt} = -\left(\hat{\delta} s_y + \rho(y - y_y) + \frac{\rho \hat{s}_y}{\delta + \epsilon} \right)\frac{(s - s_y)^2}{s s_y} - \frac{\rho \epsilon(y - y_y)^2}{(\delta + \epsilon) s} \]

\[ - \alpha_s s_y p_y \left(\frac{s_y}{s} - 1 - \ln \left(\frac{s_y}{s}\right)\right) + \alpha_s s_y y_y \left(2 - \frac{s}{s_y} - \frac{s}{s_y}\right) \]

\[ - \alpha_s s_y p_y \left(\frac{s s_y y_y}{s_y s_y} - 1 - \ln \left(\frac{s s_y y_y}{s_y s_y}\right)\right) \]

\[ - \frac{\alpha_s s_y p_y}{F} \int_0^\delta \Theta(\tau) \left[p_{2 y}(t - \tau) - 1 - \ln(p_{2 y}(t - \tau) )\right] d\tau. \]

Equation (25) can be simplified as:

\[ \frac{dL_2}{dt} = -\left(\hat{\delta} s_y + \rho(y - y_y) + \frac{\rho \hat{s}_y}{\delta + \epsilon} \right)\frac{(s - s_y)^2}{s s_y} - \frac{\rho \epsilon(y - y_y)^2}{(\delta + \epsilon) s} \]

\[ - \alpha_s s_y p_y H \left(\frac{s}{s_y}\right) + \alpha_s s_y y_y \left(2 - \frac{s}{s_y} - \frac{s}{s_y}\right) \]

\[ - \frac{\alpha_s s_y p_y}{F} H \left(\frac{s s_y y_y}{s_y s_y}\right) - \frac{\alpha_s s_y p_y}{F} \int_0^\delta \Theta(\tau) H \left(p_{2 y}(t - \tau)\right) d\tau. \]

We note that, \( \frac{dL_2}{dt} \leq 0 \) when \( \hat{\delta} s_y - \rho y_y \geq 0 \), where \( \frac{dL_2}{dt} = 0 \) occurs at \( \Pi_2 \).

The global asymptotic stability of \( \Pi_2 \) follows from LIP. □

4. Numerical Simulations

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

\[ \rho(\tau) = \hat{\delta}(\tau - \tau_1), \]

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

\[ \int_0^\delta \rho(\tau) d\tau = 1, \quad F = \int_0^\delta \hat{\delta}(\tau - \tau_1) e^{-\mu} d\tau = e^{-\mu h}. \]

Moreover,

\[ \int_0^\delta \hat{\delta}(\tau - \tau_1) e^{-\mu} y(t - \tau) d\tau = e^{-\mu h} y(t - \tau_1). \]
Hence, model (5)-(8), becomes
\begin{align*}
\dot{s}(t) &= \beta - \delta s(t) - \alpha s(t) p(t) - \alpha z(t) y(t) + \rho y(t), \quad (26) \\
\dot{y}(t) &= \alpha s(t) p(t) + \alpha z(t) y(t) - \varepsilon y(t) - \rho y(t), \quad (27) \\
\dot{p}(t) &= me^{-\rho t} y(t - \tau_1) - \gamma p(t) - qz(t) p(t), \quad (28) \\
\dot{z}(t) &= rz(t) p(t) - \mu z(t). \quad (29)
\end{align*}

For model (26)-(29), the threshold parameters are given by:
\begin{align*}
R_0 &= \frac{s_0 \left(e^{-\rho t_1} m a_1 + \gamma a_2\right)}{(\varepsilon + \rho) \gamma}, \\
R_t^x &= \frac{re^{-\rho t_1} m y_2}{\mu y}, \\
R_{\text{Hum}}^x &= \frac{re^{-\rho t_1} m s_0 \delta}{\mu c y R_0 - 1}, \quad (30)
\end{align*}

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 $a$, $\mu$ and $\beta$ 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:** \((\xi_1(\eta), \xi_2(\eta), \xi_3(\eta), \xi_4(\eta)) = (600, 1, 1, 10), \) (Solid lines in the figures)
- **Initial-2:** \((\xi_1(\eta), \xi_2(\eta), \xi_3(\eta), \xi_4(\eta)) = (200, 1.5, 3, 5), \) (Dashed lines in the figures)
- **Initial-3:** \((\xi_1(\eta), \xi_2(\eta), \xi_3(\eta), \xi_4(\eta)) = (90, 4, 9, 12), \) \(\eta \in (-\infty, 0]. \) (Dotted lines in the figures)

Further, we fix the value of $\tau_1 = 0.2$ and we use three sets of parameters $a_1$ and $r$ to investigate the following five scenarios.

- **Scenario 1:** \(a_1 = 0.0001\) and $r = 0.008$. For this set of parameters, we have $R_0 = 0.7934 < 1$ and $R_t^x = 0.6276 < 1$. 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 $\Pi_0$ 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).

<table>
<thead>
<tr>
<th>Notation</th>
<th>Value</th>
<th>Notation</th>
<th>Value</th>
<th>Notation</th>
<th>Value</th>
<th>Notation</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$</td>
<td>10</td>
<td>$\rho$</td>
<td>0.01</td>
<td>$q$</td>
<td>0.1</td>
<td>$\mu_i$</td>
<td>0.1</td>
</tr>
<tr>
<td>$\delta$</td>
<td>0.01</td>
<td>$\epsilon$</td>
<td>0.5</td>
<td>$r$</td>
<td>Varied</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$a_1$</td>
<td>Varied</td>
<td>$m$</td>
<td>10</td>
<td>$\mu$</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.0001</td>
<td>$\gamma$</td>
<td>3</td>
<td>$\tau_1$</td>
<td>Varied</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Scenario 2: \( \alpha_i = 0.001 \) and \( r = 0.001 \). With such choice we get, \( R^i_0 = 0.5538 < 1 < R_0 = 6.1695 < 1 + \frac{\varepsilon}{\rho} = 51 \) and \( \Pi_i \) exists with \( \Pi_i = (162.09, 16.76, 51.03, 0) \). This result confirms Lemma 1. Theorem 2 states that, \( \Pi_i \) 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 \( R^i_0 = 0.5538 < 1 < R_0 \). (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:** $\alpha_i = 0.001$ and $r = 0.01$. Then, we calculate $R_0 = 6.1695 > 1$, $R_i^* = 3.1669 > 1$ and $\delta_1 \sigma_1 - \rho y_2 = 4.6948 > 0$. Lemma 1 and Theorem 3 establish that, $\Pi_1$ 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 $\Pi_1 = (480.24,10.4,10.83,74.74)$. 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 $\alpha_i = 0.001$ and $r = 0.01$. we assume that $\tau^* = \tau_i$. **Table 2** contains the values of all threshold parameters and equilibria of system (26)-(29) with different values of $\tau^*$.

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

![Figure 3](image-url)

**Figure 3.** The simulation of trajectories of system (26)-(29) in case of $R_i^* > 1$. (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 $\tau^*$.

<table>
<thead>
<tr>
<th>$\tau^*$</th>
<th>$R_0$</th>
<th>$R_i^*$</th>
<th>The steady states</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>6.73</td>
<td>3.47</td>
<td>$E_i = (480.24,10.4,10,74)$</td>
</tr>
<tr>
<td>8</td>
<td>3.13</td>
<td>1.57</td>
<td>$E_i = (479.88,10.42,10.01,16.8)$</td>
</tr>
<tr>
<td>15</td>
<td>1.65</td>
<td>0.77</td>
<td>$E_i = (603.61,7.73,5.76,0)$</td>
</tr>
<tr>
<td>23</td>
<td>0.85</td>
<td>0.35</td>
<td>$E_i = (1000,0,0,0,0,0)$</td>
</tr>
</tbody>
</table>
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 $\Pi_0$.

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