Mathematics in Applied Sciences and Engineering
Online First, pp.**1-27**

https://ojs.lib.uwo.ca/mase
https://doi.org/10.5206/mase/14918

GLOBAL STABILITY OF A HCV DYNAMICS MODEL WITH CELLULAR PROLIFERATION AND DELAY

ALEXIS NANGUE, ARMEL WILLY FOKAM TACTEU, AND AYOUBA GUEDLAI

Abstract. In this work, we propose and investigate a delay cell population model of hepatitis C virus (HCV) infection with cellular proliferation, absorption effect, and a non-linear incidence function. First of all, we prove the existence of the local solutions of the model, followed by the existence of the global solutions and the positivity. Moreover, we determine the infection free equilibrium and the basic reproduction rate $\mathcal{R}_0$, which is a threshold number in mathematical epidemiology. Then we prove the existence and uniqueness of the infection persist equilibrium. We also proceed to study the local and global stability of this equilibrium. We show that if $\mathcal{R}_0 < 1$, the infection free equilibrium is globally asymptotically stable, which means that the disease will disappear and if $\mathcal{R}_0 > 1$, we have a unique infection persist equilibrium that is globally asymptotically stable under some conditions. Finally, we perform some numerical simulations to illustrate the obtained theoretical results.

1. Introduction

Hepatitis C is a disease caused by HCV, which is a virus that attacks liver cells, causing them to become inflamed. The World Health Organization (WHO) estimates in [29] that globally, 71 million people are chronic carriers of hepatitis C infection and that in 2016, around 399,000 people died from it, most often as a result of cirrhosis or hepatocellular carcinoma (primary liver cancer). This organization is leading actions to reduce the number of new cases of viral hepatitis by 90% and the number of deaths associated with this disease by 65% by 2030. Due to the severity of hepatitis C infection, it is necessary to develop the tools that help to understand this disease. It is for this reason that several mathematical models have been developed to better understand the dynamics of the hepatitis C virus within the liver itself [1, 2, 7, 18, 20, 19, 17]. Eric Avila Vales et al. in [2] studied an intra-host delay model, which is a pioneer work which inspired the work in the present paper. Indeed, we note that in their model, the loss of pathogens due to the absorption that we can find in [10, 30, 23] in uninfected cells is ignored. When a pathogen enters an uninfected cell, the number of pathogens in the blood decreases by one. This is called the absorption effect (see, for example, [4]). To place the model on a more solid biological basis, we use the saturated infection rate (saturated infection rate found in [25, 30]) and cellular proliferation effect. These three aspects added to the model studied in [2] make the model we are studying a more realistic model in the biological sense. We note that in most intra-host models of virus dynamics, the loss of pathogens due to the absorption into uninfected cells is ignored. In biology, it is natural that, when pathogens are absorbed into susceptible cells, the numbers of pathogens are reduced in the blood volume which : this phenomenon is called absorption effect. Hence, some researchers (see, for example, [4, 16, 30] and the references therein) have included the absorption effect into their models. In several of models with or without delay, the process of cellular infection by free virus particles is typically modelled by the mass action principle, that is to say, the infection rate is assumed to occur at a rate

Received by the editors 30 April 2022; accepted 25 August 2022; published online September 10, 2022.
2020 *Mathematics Subject Classification.* 34A05, 34A06, 34A34, 34D20, 34D23, 37N25.
Key words and phrases. absorption effect, cellular proliferation, delay, global stability, Hepatitis C virus, wellposedness.

proportional to the product of the concentration of virus particles and uninfected target cells. This principle is insufficient to describe the cellular infection process in detail, and some non-linear infection rates have been proposed. Li and Ma [14], Song and Neumann [25] considered a virus dynamics model with Monod functional response $\frac{bxv}{1+\alpha v}$. Regoes et al.[21] and Song and Neumann [26] considered a virus dynamics model with the non-linear infection rates

$$bx\left(\frac{v}{k}\right)^p / \left(1+\left(\frac{v}{k}\right)^p\right) \quad \text{and} \quad \frac{bxv^q}{(1+\alpha v^p)},$$

where p, q, $k>0$ are constants, respectively. Recently, Huang et al. [12] considered a class of models of viral infections with a non-linear infection rate and two discrete intracellular delays, and assumed that the infection rate is given by a general non-linear function of uninfected target cells and free virus particles $F(x,v)$, which satisfies certain conditions.

The rest of this paper is organized as follows. Section 2 gives a description of the newly constructed model. Section 3 deals with the existence, the positivity and boundedness of solutions of our model. In Section 4, the threshold parameter $\mathcal{R}_0(\tau)$ of our DDE model (2.1) is derived and the existence of the equilibria are discussed in relation to the value of $\mathcal{R}_0(\tau)$. Section 5 and section 6 show the local and global stability of the infection free equilibrium and infection persist equilibrium respectively. Additionally, some numerical results are displayed this supports the obtained theoretical results. Finally, a brief discussion and some possible future ideas are presented in Section 7.

2. Model construction

In this section, motivated by what has been said previously, we propose an HCV infection model with time delay, absorption effect and monod functional response, taking into account the proliferation of both exposed cells and HCV infected hepatocytes :

$$\begin{cases} \dfrac{dH(t)}{dt} = \lambda + r_H H(t)\left(1-\dfrac{H(t)+I(t)}{k}\right) - \mu H(t) - \dfrac{\beta H(t)V(t)}{1+aV(t)} \\ \dfrac{dI(t)}{dt} = \dfrac{\beta e^{-\tau m} H(t-\tau)V(t-\tau)}{1+aV(t-\tau)} + r_I I(t)\left(1-\dfrac{H(t)+I(t)}{k}\right) - \alpha I(t) \\ \dfrac{dV(t)}{dt} = \eta I(t) - \gamma V(t) - \dfrac{\beta H(t)V(t)}{1+aV(t)} \end{cases} \tag{2.1}$$

with initial conditions

$$H(\theta)=\varphi_1(\theta)\geq 0,\ I(\theta)=\varphi_2(\theta)\geq 0,\ V(\theta)=\varphi_3(\theta),\ -\tau\leq\theta\leq 0, \tag{2.2}$$

where $\varphi=(\varphi_1,\varphi_2,\varphi_3)\in\mathcal{C}([-\tau,0],\mathbb{R}^3_+)$ which is the Banach space of continuous functions $\varphi:[-\tau,0]\longrightarrow\mathbb{R}^3_+=\left\{(H,I,V)\in\mathbb{R}^3\,|\,H\geq 0,\ I\geq 0,\ V\geq 0\right\}$ with norm $\|\varphi\|=\sup\limits_{-\tau\leq\theta\leq 0}\{|\varphi_1|,|\varphi_2|,|\varphi_3|\}$.

The model (2.1) is a modification of model (2) studied in [2] and later in [1]. The features of the latter is as follows : $H(t)$, $I(t)$ and $V(t)$ denote the concentration of uninfected hepatocytes (or target cells), infected hepatocytes and free virus, respectively. All parameters are assumed to be positive constants. Here, target cells are generated at a constant rate λ and die at a rate μ per uninfected hepatocyte. These hepatocytes are infected at rate β per target cell per virion. Infected cells die at rate α per cell by cytopathic effects. Because of the viral burden on the virus-infected cells, we assume that $\mu\geq\alpha$. In other words, we assume that the average life-time of infected cells $\left(\frac{1}{\alpha}\right)$ is shorter than the average life-time of uninfected cells $\left(\frac{1}{\alpha}\right)$ [5, 24]. The proliferation of infected and uninfected hepatocytes due to mitotic division obeys to a logistic growth. The mitotic proliferation of uninfected hepatocytes is described by $r_H H(t)\left[1-(H(t)+I(t))/k\right]$, and mitotic transmission occurs at a rate $r_I I(t)\left[1-(H(t)+I(t))/k\right]$, which is the mitotic division of infected hepatocytes. It should be mentioned

that the model (2) in [2] has $r_I = r_H$. Uninfected and infected hepatocytes grow at the constant rate r_H and r_I respectively , and k is the maximal number of total hepatocyte population proliferation. Infected cells produce virions at an average rate μ per infected cell, and γ is the clearance rate of virus particles. The population of virions decreases due to the infection at a rate $\beta H(t)V(t)/[1+aV(t)]$: this is absorption phenomenon. It should be noted that according to [20], to have a physiologically realistic model, in an uninfected liver when k is reached, liver size should no longer increase i.e. $\lambda \leq \mu k$. We assume that the contacts between viruses and uninfected target cells are given by an infection rate $\beta H(t)V(t)/[1+aV(t)]$, it is reasonable for us to assume that the infection has a maximal rate of $\frac{\beta}{a}$. The parameter τ accounts for the time between viral entry into a target cell and the production of new virus particles. The recruitment of virus producing cells at time t is given by the number of cells that were newly infected at time $t-\tau$ and are still alive at time t. Here, m is assumed to be a constant death rate for infected but not yet virus-producing hepatocytes. Thus, the probability of surviving the time period from $t-\tau$ to t is $e^{-m\tau}$.

3. Wellposedness

In this section, we show that our model (2.1) is mathematically and biologically well posed.

Theorem 3.1. *All solutions of system (2.1) with initial conditions (2.2), where $H(0) > 0$, $I(0) > 0$, $V(0) > 0$, are positive and under the initial conditions (2.2), the solution (H(t), I(t), V(t)) of model (2.1) is existent and unique. Moreover, for any positive solution (H(t), I(t), V(t)) of system (2.1) we have : $\limsup_{t\to+\infty} H(t) \leq H_0 = \left[(r_H-\mu)+\left((r_H-\mu)^2+4\frac{r_H\lambda}{k}\right)^{1/2}\right]\frac{k}{2r_H}$, the existence of constants $M_I > 0$ and $M_V > 0$ such that $I(t) < M_I$, $V(t) < M_V$.*

Proof. Firstly, we deal with the fact that $\mathbb{R}^3_+$ is positively invariant with respect to the dde model system (2.1). We prove the positivity by contradiction. Suppose $H(t)$ is not always positive. Then, let $t_0 > 0$ be the first time such that $H(t_0) = 0$. From the first equation of system (2.1), $\frac{dH(t_0)}{dt} = \lambda > 0$. By our hypothesis this means that $H(t) < 0$ for $t \in (t-\varepsilon, t_0)$, where ε is an arbitrary small positive constant. Implying that exist $t_0' < t_0$ such that $H(t_0') = 0$: this is a contradiction because we take t_0 as the first value which $H(t_0) = 0$. It follows that $T(t)$ is always positive. We now show that $I(t) > 0$ for all $t > 0$. By considering the second equation of system (2.1), one has :

$$\begin{aligned} I(t) = \quad & I(0)\exp\left(-\alpha t + \int_0^t r_I\left(1-\frac{H(u)+I(u)}{k}\right)du\right) + \exp\left[-\alpha t + \int_0^t r_I\left(1-\frac{H(u)+I(u)}{k}\right)du\right] \\ & \times \int_0^t \left[\frac{\beta e^{-\tau m}H(u-\tau)V(u-\tau)}{1+aV(u-\tau)}\exp\left(-\alpha u + \int_0^u r_I\left(1-\frac{H(\theta)+I(\theta)}{k}\right)d\theta\right)\right]du. \end{aligned} \tag{3.1}$$

$u-\tau \in [-\tau, 0]$ since $u \in [0,\tau]$ and furthermore by assumption for $t \in [-\tau, 0]$ we have : $H(t) > 0$, $I(t) > 0$, $V(t) > 0$, $H(0) > 0$, $I(0) > 0$ and $V(0) > 0$. We deduce that

$$\int_0^t \left[\frac{\beta e^{-\tau m}H(u-\tau)V(u-\tau)}{1+aV(u-\tau)}\exp\left(-\alpha u + \int_0^u r_I\left(1-\frac{H(\theta)+I(\theta)}{k}\right)d\theta\right)\right]du$$

is positive for all $t \in [0,\tau]$ and hence $I(t) > 0$ for all $t \in [0,\tau]$. Let us show by recurrence on n that $I(t) > 0$ for all $t \in [n\tau, (n+1)\tau]$. Let P_n, the proposition : $\forall n \in \mathbb{N}\ I(t) > 0\ \forall t \in [n\tau, (n+1)\tau]$.

a) For $n = 0$, P_0 is verified.
b) Suppose that for $n \in \mathbb{N}$, $I(t) > 0$ for all $t \in [n\tau, (n+1)\tau]$ and show that $I(t) > 0$ for all $t \in [(n+1)\tau, (n+2)\tau]$. According to (3.1), for $u \in [(n+1)\tau, (n+2)\tau]$, we have $u-\tau \in [n\tau, (n+1)\tau]$.

By recurrence assumption, the term

$$\int_0^t \left[\frac{\beta e^{-\tau m} H(u-\tau) V(u-\tau)}{1+aV(u-\tau)} \exp\left(-\alpha u + \int_0^u r_I \left(1 - \frac{H(\theta)+I(\theta)}{k} \right) d\theta \right) \right] du$$

is positive. Therefore I is positive on $[(n+1)\tau, (n+2)\tau]$ and consequently P_{n+1} is true. Hence $I(t) > 0$ for all $t > 0$.

We finally show that $V(t) > 0$ for all $t > 0$. Since $I(t) > 0$ for all $t > 0$ and $\eta > 0$, we have :

$$\frac{dV(t)}{dt} \geq \left(-\gamma - \frac{\beta H(t)}{1+aV(t)} \right) V(t).$$

Integrating the previous expression on $[0, t]$, we obtain :

$$V(t) \geq V_0 \exp\left(\int_0^t \left(-\gamma - \frac{\beta H(u)}{1+aV(u)} \right) du \right),$$

which ensures that $V(t) > 0$ for all $t > 0$. Thus deduce that $\mathbb{R}^3_+$ is positively invariant with respect to model (2.1).

Secondly, the existence and uniqueness of the solution $(H(t), I(t), V(t))$ can be easily proved by using the following theorems(Theorem 2.1 and Theorem 2.2 Page 19 in [13]).

Finally, let us show that the solution $(H(t), I(t), V(t))$ is uniformly bounded. For any positive solution of system (2.1), we have

$$\limsup_{t \to +\infty} H(t) \leq H_0 = \left[(r_H - \mu) + \left((r_H - \mu)^2 + 4\frac{r_H \lambda}{k} \right)^{1/2} \right] \frac{k}{2r_H}$$

since the first equation of (2.1) yields

$$\frac{dH(t)}{dt} \leq \lambda - (\mu - r_H) H(t) - \frac{r_H}{k} H^2(t).$$

Then there is a $t_1 > 0$ such that for any sufficiently small $\varepsilon > 0$ one has $H(t) < H_0 + \varepsilon$ for $t > t_1$. Now let for $t \geq 0$, define $U(t)$ as below

$$U(t) = H(t) + I(t) + \beta \int_{t-\tau}^t e^{-m(t-s)} \frac{H(s)V(s)}{1+aV(s)} ds. \tag{3.2}$$

Taking the derivation of the previous expression along the solution, collecting and simplifying some terms, we obtain, for $t \geq 0$,

$$\begin{aligned}
\frac{dU(t)}{dt} &= \lambda + \left((H(t)+I(t)) (r_H + r_I) \right) \left(1 - \frac{H(t)+I(t)}{k} \right) - \mu H(t) - \alpha I(t) \\
&\quad - (r_H I(t) + r_I H(t)) \left(1 - \frac{H(t)+I(t)}{k} \right) - m\beta \int_{t-\tau}^t e^{-m(t-s)} \frac{H(s)V(s)}{1+aV(s)} ds \\
&= \lambda + \left(\frac{r_H + r_I}{4} \right) k - \left(\frac{r_H + r_I}{k} \right) \left(H(t) + I(t) - \frac{k}{2} \right)^2 - \mu H(t) - \alpha I(t) \\
&\quad - (r_H I(t) + r_I H(t)) \left(1 - \frac{H(t)+I(t)}{k} \right) - m\beta \int_{t-\tau}^t e^{-m(t-s)} \frac{H(s)V(s)}{1+aV(s)} ds, \\
&\leq \lambda + \left(\frac{r_H + r_I}{4} \right) k - \mu H(t) - \alpha I(t) - m\beta \int_{t-\tau}^t e^{-m(t-s)} \frac{H(s)V(s)}{1+aV(s)} ds \\
&\leq \lambda + \left(\frac{r_H + r_I}{4} \right) k - bU(t),
\end{aligned}$$

where $b = \min\{\mu, \alpha, m\}$. It follows that

$$\limsup_{t\to+\infty} U(t) \leq \frac{4\lambda + (r_H + r_I)k}{4b},$$

that is, there exist $t_2 > 0$ and $M_1 > 0$ such that $U(t) < M_1$ for $t > t_2$. Then $I(t)$ has an upper bound M_I. It follows from the third equation of system (2.1), that, for $t \geq 0$

$$\frac{dV(t)}{dt} \leq \eta I(t) - \gamma V(t),$$

from which we have that

$$\limsup_{t\longrightarrow+\infty} V(t) \leq \frac{\eta}{\gamma}\frac{4\lambda + (r_H + r_I)k}{4b}.$$

Then there exists $M_V > 0$ such that $V(t) < M_V$ for $t > t_2$. This completes the proof of Theorem 3.1 . □

Remark 3.1. From Theorem 3.1, one has that the solution of initial value problem (2.1), (2.2) enters the region

$$\Gamma = \left\{(H, I, V) \in \mathbb{R}^3_+ | 0 \leq H(t) \leq H_0, 0 \leq I(t) \leq M_I, 0 \leq V(t) \leq M_V\right\}.$$

Hence Γ, of biological interest, positively-invariant under the flow induced by the problem (2.1), (2.2).

Now, we determine the equilibria of model (2.1).

4. Equilibria and basic reproduction number

4.1. **Infection free equilibrium and basic reproduction number.** Model (2.1) always has the uninfected equilibrium $E_0 = (H_0, 0, 0)$.
By using similar techniques in [9] and [27], we obtain the basic reproduction number (spectral radius of next generation matrix) for model (2.1) as

$$\mathcal{R}_0(\tau) = \frac{1}{\alpha}\left[r_I\left(1 - \frac{H_0}{k}\right) + \frac{\eta\beta e^{-\tau m}H_0}{\gamma + \beta H_0}\right].$$

Here, $\mathcal{R}_0(\tau)$ is the average number infected cells produced by one infected hepatocyte after introducing infected hepatocyte into fully susceptible hepatocyte population, that plays a crucial role in the dynamics. Generally, the basic reproduction number $\mathcal{R}_0(\tau)$ helps us to decide whether viruses clean out with time or not. $E_0 = (H_0, 0, 0)$ is the trivial equilibrium of model (2.1).
To find the other equilibrium of (2.1), we solve the following algebraic system :

$$\begin{cases} \lambda + r_H H\left(1 - \dfrac{H+I}{k}\right) - \mu H - \dfrac{\beta HV}{1+aV} = 0, & (4.1)\\ \dfrac{\beta e^{-\tau m}HV}{1+aV} + r_I I\left(1 - \dfrac{H+I}{k}\right) - \alpha I = 0, & (4.2)\\ \eta I - \gamma V - \dfrac{\beta HV}{1+aV} = 0. & (4.3) \end{cases}$$

4.2. **Infection persist equilibrium.**

4.2.1. *Existence of an infection persist equilibrium.*

Proposition 4.1. *The system (2.1) possesses an infection persist equilibrium denoted as* $E_1 = (H_1, I_1, V_1)$ *if* $\mathcal{R}_0(\tau) > 1$.

Proof. From (4.3), one has

$$I_1 = \frac{\gamma}{\eta} V_1 + \frac{\beta H_1 V_1}{\eta(1 + aV_1)}. \tag{4.4}$$

Reporting (4.4) into (4.1) yields the following second degree algebraic equation in H_1 :

$$-\left(\frac{r_H}{k} + \frac{r_H \beta V_1}{k\eta(1 + aV_1)}\right) H_1^2 + \left(r_H - \mu - \frac{r_H}{k}\frac{\gamma}{\eta} V_1 - \frac{\beta V_1}{1 + aV_1}\right) H_1 + \lambda = 0. \tag{4.5}$$

The discriminant of the algebraic equation (4.5) is given by :

$$\Delta = \left(r_H - \mu - \frac{r_H}{k}\frac{\gamma}{\eta} V_1 - \frac{\beta V_1}{1 + aV_1}\right)^2 + 4\lambda\left(\frac{r_H}{k} + \frac{r_H \beta V_1}{k\eta(1 + aV_1)}\right) > 0. \tag{4.6}$$

Thus, equation (4.5) has a unique positive root known as :

$$H_1 = \frac{\left(r_H - \mu - \frac{r_H}{k}\frac{\gamma}{\eta} V_1 - \frac{\beta V_1}{1 + aV_1}\right) + \sqrt{\Delta}}{2\left(\frac{r_H}{k} + \frac{r_H \beta V_1}{k\eta(1 + aV_1)}\right)}.$$

We can once again denote $H_1 = f(V_1)$. Substituting (4.4) into (4.2), one gets:

$$\frac{\beta e^{-\tau m} H_1 V_1}{1 + aV_1} + r_I\left(\frac{\gamma}{\eta} V_1 + \frac{\beta H_1 V_1}{\eta(1 + aV_1)}\right)\left(1 - \frac{H_1 + \frac{\gamma}{\eta} V_1 + \frac{\beta H_1 V_1}{\eta(1+aV_1)}}{k}\right) - \alpha\left(\frac{\gamma}{\eta} V_1 + \frac{\beta H_1 V_1}{\eta(1 + aV_1)}\right) = 0,$$

which is equivalent to

$$\frac{\beta e^{-\tau m} H_1}{1 + aV_1} + r_I\left(\frac{\gamma}{\eta} + \frac{\beta H_1}{\eta(1 + aV_1)}\right)\left(1 - \frac{H_1 + \frac{\gamma}{\eta} V_1 + \frac{\beta H_1 V_1}{\eta(1+aV_1)}}{k}\right) - \alpha\left(\frac{\gamma}{\eta} + \frac{\beta H_1}{\eta(1 + aV_1)}\right) = 0,$$

since $V_1 > 0$. Taking into account the fact that $H_1 = f(V_1)$ one has

$$\frac{\beta e^{-\tau m} f(V_1)}{1 + aV_1} + r_I\left(\frac{\gamma}{\eta} + \frac{\beta f(V_1)}{\eta(1 + aV_1)}\right)\left(1 - \frac{f(V_1) + \frac{\gamma}{\eta} V_1 + \frac{\beta f(V_1) V_1}{\eta(1+aV_1)}}{k}\right) - \alpha\left(\frac{\gamma}{\eta} + \frac{\beta f(V_1)}{\eta(1 + aV_1)}\right) = 0.$$

On the other hand we also have

$$-\left(\frac{r_H}{k} + \frac{r_H \beta V_1}{k\eta(1 + aV_1)}\right) f(V_1)^2 + \left(r_H - \mu - \frac{r_H}{k}\frac{\gamma}{\eta} V_1 - \frac{\beta V_1}{1 + aV_1}\right) f(V_1) + \lambda = 0. \tag{4.7}$$

Let

$$\begin{aligned} F(V_1) \quad = \quad & \frac{\beta e^{-\tau m} f(V_1)}{1 + aV_1} + r_I\left(\frac{\gamma}{\eta} + \frac{\beta f(V_1)}{\eta(1+aV_1)}\right)\left(1 - \frac{f(V_1) + \frac{\gamma}{\eta} V_1 + \frac{\beta f(V_1) V_1}{\eta(1+aV_1)}}{k}\right) \\ & -\alpha\left(\frac{\gamma}{\eta} + \frac{\beta f(V_1)}{\eta(1+aV_1)}\right). \end{aligned} \tag{4.8}$$

Obviously, F is continuous on $[0; +\infty[$. We have, for $V_1 = 0$,

$$F(0) = \beta e^{-\tau m} f(0) + r_I\left(\frac{\gamma}{\eta} + \frac{\beta f(0)}{\eta}\right)\left(1 - \frac{f(0)}{k}\right) - \alpha\left(\frac{\gamma}{\eta} + \frac{\beta f(0)}{\eta}\right),$$

with

$$f(0) = \frac{(r_H - \mu) + \sqrt{(r_H - \mu)^2 + 4\lambda\frac{r_H}{k}}}{2\left(\frac{r_H}{k}\right)} = H_0.$$

We finally obtain

$$F(0) = \alpha\left(\frac{\gamma}{\eta} + \frac{\beta H_0}{\eta}\right)\left[\frac{\eta\beta e^{-\tau m}H_0}{\alpha(\gamma + \beta H_0)} + \frac{r_I}{\alpha}\left(1 - \frac{H_0}{k}\right) - 1\right]$$

which is equivalent to :

$$F(0) = \alpha\left(\frac{\gamma}{\eta} + \frac{\beta H_0}{\eta}\right)(\mathcal{R}_0 - 1). \tag{4.9}$$

$\mathcal{R}_0(\tau) > 1$, implies $F(0) > 0$. From $0 < H_1 = f(V_1) \leq C$, with $C > 0$ according to Theorem 3.1, we have $\lim\limits_{V_1 \to +\infty} \dfrac{\beta e^{-\tau m} f(V_1)}{1 + aV_1} = 0$ since $\lim\limits_{V_1 \to +\infty} \dfrac{\beta e^{-\tau m} C}{1 + aV_1} = 0$ and, consequently

$$\lim_{V_1 \to +\infty} -\alpha\left(\frac{\gamma}{\eta} + \frac{\beta f(V_1)}{\eta(1 + aV_1)}\right) = -\frac{\alpha\gamma}{\eta}$$

and

$$\lim_{V_1 \to +\infty} r_I\left(\frac{\gamma}{\eta} + \frac{\beta f(V_1)}{\eta(1 + aV_1)}\right)\left(1 - \frac{f(V_1) + \frac{\gamma}{\eta}V_1 + \frac{\beta f(V_1)V_1}{\eta(1+aV_1)}}{k}\right) = -\infty.$$

Therefore

$$\lim_{V_1 \to +\infty} F(V_1) = -\infty.$$

The intermediate value theorem ensures the existence of $V_1 > 0$ such that $F(V_1) = 0$. The existence of V_1 also ensures the existence of H_1 and I_1. Therefore the infection persist equilibrium $E_1 = (H_1, I_1, V_1)$ exists. □

Now let's take a look at uniqueness.

4.2.2. *Uniqueness of the infection persist equilibrium.*

Proposition 4.2. *Let $\Lambda = [4\lambda + (r_H + r_I)k]/4b$. If $e^{-\tau m} > \alpha/\eta$ and $\Lambda/k \leq 1/2$ then the infection persist equilibrium $E_1 = (H_1, I_1, V_1)$ is unique when it exists.*

Proof. From equation (4.8), one has

$$\begin{aligned} F'(V_1) \;=\; & \left(\frac{\beta}{1 + aV_1}\left(e^{-\tau m} - \frac{\alpha}{\eta}\right) + \frac{r_I\beta}{\eta(1 + aV_1)}\left(1 - \frac{f(V_1) + \frac{\gamma}{\eta}V_1 + \frac{\beta f(V_1)V_1}{\eta(1+aV_1)}}{k}\right) + A\right)f'(V_1) \\ & + \frac{a\beta f(V_1)}{(1 + aV_1)^2}\left(\frac{\alpha}{\eta} - e^{-\tau m}\right) - \frac{r_I}{k}\left(\frac{\gamma}{\eta} + \frac{\beta f(V_1)}{\eta(1 + aV_1)}\right)\left(\frac{\gamma}{\eta} + \frac{\beta f(V_1)}{\eta(1 + aV_1)^2}\right) \\ & - \frac{r_I a\beta f(V_1)}{\eta(1 + aV_1)^2}\left(1 - \frac{f(V_1) + \frac{\gamma}{\eta}V_1 + \frac{\beta f(V_1)V_1}{\eta(1+aV_1)^2}}{k}\right), \end{aligned}$$

where

$$A = -\frac{r_I}{k}\left(\frac{\gamma}{\eta} + \frac{\beta f(V_1)}{\eta(1 + aV_1)}\right)\left(1 + \frac{\beta V_1}{\eta(1 + aV_1)}\right).$$

The expression of A can be rewritten in the following form :

$$A \;=\; \frac{r_I\beta}{\eta(1 + aV_1)}\left(1 - \frac{f(V_1) + \frac{\gamma}{\eta}V_1 + \frac{\beta f(V_1)V_1}{\eta(1+aV_1)}}{k}\right) - \frac{r_I\gamma}{\eta k} - \frac{r_I\beta}{\eta(1 + aV_1)}.$$

Thus

$$F'(V_1) = \left[\frac{\beta}{1+aV_1}\left(e^{-\tau m}-\frac{\alpha}{\eta}\right)+\frac{r_I\beta}{\eta(1+aV_1)}\left(1-\frac{2f(V_1)+\frac{2\gamma}{\eta}V_1+\frac{2\beta f(V_1)V_1}{\eta(1+aV_1)}}{k}\right)-\frac{r_I\gamma}{\eta k}\right]f'(V_1)-\frac{r_Ia\beta f(V_1)}{\eta(1+aV_1)^2}\left(1-\frac{f(V_1)+\frac{\gamma}{\eta}V_1+\frac{\beta f(V_1)V_1}{\eta(1+aV_1)}}{k}\right)+\frac{a\beta f(V_1)}{(1+aV_1)^2}\left(\frac{\alpha}{\eta}-e^{-\tau m}\right)-\frac{r_I}{k}\left(\frac{\gamma}{\eta}+\frac{\beta f(V_1)}{\eta(1+aV_1)}\right)\left(\frac{\gamma}{\eta}+\frac{\beta f(V_1)}{\eta(1+aV_1)^2}\right).$$

Dividing equation (4.7) by $f(V_1)$, we obtain

$$-\left(\frac{r_H}{k}+\frac{r_H\beta V_1}{k\eta(1+aV_1)}\right)f(V_1)+\left(r_H-\mu-\frac{r_H}{k}\frac{\gamma}{\eta}V_1-\frac{\beta V_1}{1+aV_1}\right)+\frac{\lambda}{f(V_1)}=0. \tag{4.10}$$

Using the implicit differentiation we get from 4.10 :

$$f'(V_1)=\left(\frac{r_H\gamma}{\eta k}+\frac{\beta}{(1+aV_1)^2}+\frac{r_H\beta f(V_1)}{k\eta(1+aV_1)^2}\right)\left(\frac{r_H}{k}+\frac{\lambda}{f(V_1)^2}+\frac{r_H\beta V_1}{k\eta(1+aV_1)}\right)^{-1}.$$

We deduce from the latter that

$$\begin{aligned}F'(V_1) &= -\frac{\beta}{(1+aV_1)^2}\left(e^{-\tau m}-\frac{\alpha}{\eta}\right)\left(\frac{r_H\gamma}{\eta k}+\frac{\beta}{(1+aV_1)^2}+\frac{r_H\beta f(V_1)}{k\eta(1+aV_1)^2}\right)\left(\frac{r_H}{k}\right.\\ &\left.+\frac{\lambda}{f(V_1)^2}+\frac{r_H\beta V_1}{k\eta(1+aV_1)}\right)^{-1}-\frac{r_I\beta}{\eta(1+aV_1)}\left(1-\frac{2f(V_1)+\frac{2\gamma}{\eta}V_1+\frac{2\beta f(V_1)V_1}{\eta(1+aV_1)}}{k}\right)\\ &\times\left(\frac{r_H\gamma}{\eta k}+\frac{\beta}{(1+aV_1)^2}+\frac{r_H\beta f(V_1)}{k\eta(1+aV_1)^2}\right)\left(\frac{r_H}{k}+\frac{\lambda}{f(V_1)^2}+\frac{r_H\beta V_1}{k\eta(1+aV_1)}\right)^{-1}\\ &+\frac{r_I\gamma}{k\eta}\left(\frac{r_H\gamma}{\eta k}+\frac{\beta}{(1+aV_1)^2}+\frac{r_H\beta f(V_1)}{k\eta(1+aV_1)^2}\right)\left(\frac{r_H}{k}+\frac{\lambda}{f(V_1)^2}+\frac{r_H\beta V_1}{k\eta(1+aV_1)}\right)^{-1}\\ &-\frac{r_Ia\beta f(V_1)}{\eta(1+aV_1)}\left(1-\frac{f(V_1)+\frac{\gamma}{\eta}V_1+\frac{\beta f(V_1)V_1}{\eta(1+aV_1)}}{k}\right)+\frac{a\beta f(V_1)}{(1+aV_1)^2}\left(\frac{\alpha}{\eta}-e^{-\tau m}\right)\\ &-\frac{r_I}{k}\left(\frac{\gamma}{\eta}+\frac{\beta f(V_1)}{\eta(1+aV_1)}\right)\left(\frac{\gamma}{\eta}+\frac{\beta f(V_1)}{\eta(1+aV_1)^2}\right).\end{aligned}$$

The terms

$$\frac{a\beta f(V_1)}{(1+aV_1)^2}\left(\frac{\alpha}{\eta}-e^{-\tau m}\right),$$

$$\frac{-r_I\beta}{\eta(1+aV_1)}\left(1-\frac{2f(V_1)+\frac{2\gamma}{\eta}V_1+\frac{2\beta f(V_1)V_1}{\eta(1+aV_1)}}{k}\right)\left(\frac{r_H\gamma}{\eta k}+\frac{\beta}{(1+aV_1)^2}+\frac{r_H\beta f(V_1)}{k\eta(1+aV_1)^2}\right)\times$$

$$\left(\frac{r_H}{k}+\frac{\lambda}{f(V_1)^2}+\frac{r_H\beta V_1}{k\eta(1+aV_1)}\right)^{-1}$$

and

$$-\frac{\beta}{(1+aV_1)^2}\left(e^{-\tau m}-\frac{\alpha}{\eta}\right)\left(\frac{r_H\gamma}{\eta k}+\frac{\beta}{(1+aV_1)^2}+\frac{r_H\beta f(V_1)}{k\eta(1+aV_1)^2}\right)\left(\frac{r_H}{k}+\frac{\lambda}{f(V_1)^2}+\frac{r_H\beta V_1}{k\eta(1+aV_1)}\right)^{-1}$$

are negative since $\frac{\alpha}{\eta} - e^{-\tau m} \leq 0$ and $\frac{\Lambda}{k} \leq \frac{1}{2}$. Once more we deduce that

$$\begin{aligned} F'(V_1) \leq & \frac{r_I\gamma}{k\eta}\left(\frac{r_H\gamma}{k\eta} + \frac{r_H\beta f(V_1)}{(1+aV_1)^2k\eta} + \frac{r_H\beta f(V_1)}{(1+aV_1)k\eta} + \frac{r_H\beta^2 f^2(V_1)}{(1+aV_1)^3\gamma k\eta}\right)\left(\frac{r_H}{k}\right)^{-1} \\ & -\frac{r_I a\beta f(V_1)}{\eta(1+aV_1)^2}\left(1 - \frac{f(V_1) + \frac{\gamma}{\eta}V_1 + \frac{\beta f(V_1)V_1}{\eta(1+aV_1)}}{k}\right) - \frac{r_I}{k}\left(\frac{\gamma}{\eta} + \frac{\beta f(V_1)}{\eta(1+aV_1)}\right)\times \\ & \left(\frac{\gamma}{\eta} + \frac{\beta f(V_1)}{\eta(1+aV_1)^2}\right), \end{aligned}$$

since

$$\begin{aligned} & \left(\frac{r_H\gamma}{\eta k} + \frac{\beta}{(1+aV_1)^2} + \frac{r_H\beta f(V_1)}{k\eta(1+aV_1)^2}\right)\left(\frac{r_H}{k} + \frac{\lambda}{f(V_1)^2} + \frac{r_H\beta V_1}{k\eta(1+aV_1)}\right)^{-1} \\ & \leq \left(\frac{r_H\gamma}{k\eta} + \frac{r_H\beta f(V_1)}{(1+aV_1)^2k\eta} + \frac{r_H\beta f(V_1)}{(1+aV_1)k\eta} + \frac{r_H\beta^2 f^2(V_1)}{(1+aV_1)^3\gamma k\eta}\right)\left(\frac{r_H}{k}\right)^{-1}. \end{aligned}$$

Thus

$$\begin{aligned} F'(V_1) \leq & \frac{r_I}{k}\left(\frac{\gamma}{\eta} + \frac{\beta f(V_1)}{\eta(1+aV_1)}\right)\left(\frac{\gamma}{\eta} + \frac{\beta f(V_1)}{\eta(1+aV_1)^2}\right) - \frac{r_I}{k}\left(\frac{\gamma}{\eta} + \frac{\beta f(V_1)}{\eta(1+aV_1)}\right)\left(\frac{\gamma}{\eta} + \frac{\beta f(V_1)}{\eta(1+aV_1)^2}\right) \\ & -\frac{r_I a\beta f(V_1)}{\eta(1+aV_1)^2}\left(1 - \frac{f(V_1) + \frac{\gamma}{\eta}V_1 + \frac{\beta f(V_1)V_1}{\eta(1+aV_1)}}{k}\right), \\ F'(V_1) \leq & -\frac{r_I a\beta f(V_1)}{\eta(1+aV_1)^2}\left(1 - \frac{f(V_1) + \frac{\gamma}{\eta}V_1 + \frac{\beta f(V_1)V_1}{\eta(1+aV_1)}}{k}\right). \end{aligned}$$

Therefore

$$F'(V_1) < 0.$$

The fact that F is strictly decreasing function allows us to state that V_1 is unique. Uniqueness of V_1 implies those of H_1 and I_1. Therefore one can concludes that $E_1 = (H_1, I_1, V_1)$ is unique. □

5. Asymptotic stability analysis of the infection free equilibrium

The aim of this section is to study the local and global stability of the infection free equilibrium.

5.1. Local stability analysis of E_0.

The following result gives conditions for equilibrium E_0 to be locally asymptotically stable.

Proposition 5.1. *If $\mathcal{R}_0(\tau) < 1$, then the infection free equilibrium E_0 of system (2.1) is locally asymptotically stable.*

Proof. The characteristic equation associated to the Jacobian matrix at the infection free equilibrium, $E_0 = (H_0, 0, 0)$ is given by the following determinant :

$$\mathcal{P}_{\mathcal{J}(E_0)}(X) = \begin{vmatrix} \left(r_H - \mu - \frac{2r_H}{k}H_0\right) - X & -\frac{r_H}{k}H_0 & -\beta H_0 \\ 0 & \left(r_I - \frac{r_I}{k}H_0 - \alpha\right) - X & \beta e^{-\tau(m+X)}H_0 \\ 0 & \eta & (-\gamma - \beta H_0) - X \end{vmatrix} = 0. \qquad (5.1)$$

Computation of the determinant (5.1) yields :

$$\begin{aligned}\mathcal{P}_{\mathcal{J}(E_0)}(X) &= \left(X-\left(r_H-\mu-2\frac{r_H}{k}H_0\right)\right)\left(X^2+\left(\frac{r_I}{k}H_0+\gamma+\alpha-r_I+\beta H_0\right)X\right)\\ &\quad+\left(-r_I\gamma-r_I\beta H_0+\alpha\gamma+\alpha\beta H_0+\frac{r_I}{k}H_0\gamma+\frac{r_I}{k}H_0^2\beta-\eta\beta e^{(m+X)\tau}H_0\right)=0.\end{aligned}$$

Since

$$r_H\left(1-\frac{H_0}{k}\right)=\mu-\frac{\lambda}{H_0},$$

the first factor of the characteristic equation $\mathcal{P}_{\mathcal{J}(E_0)}(X)=0$ is

$$X=\left(r_H-\mu-2\frac{r_H}{k}H_0\right)-\mu=-\left(\frac{\lambda}{H_0}+\frac{r_HH_0}{k}\right),$$

which have a negative eigenvalue. The other two eigenvalues satisfy the following transcendental polynomial

$$X^2+a_2X+a_3+b_3(\tau)e^{-X\tau}=0, \tag{5.2}$$

where

$$a_2=\frac{r_I}{r_H}\frac{\lambda}{H_0}-\frac{r_I}{r_H}\mu+\lambda+\alpha+\beta H_0,$$

$$a_3=-r_I\gamma\left(1-\frac{H_0}{k}\right)-r_I\beta H_0\left(1-\frac{H_0}{k}\right)+\alpha\left(\gamma+\beta H_0\right)$$

and

$$b_3(\tau)=-\eta\beta e^{-m\tau}H_0.$$

When $\tau=0$, (5.2) yields

$$X^2+a_2X+a_3+b_3(0)=0. \tag{5.3}$$

Note that $a_2>0$ as $-\frac{r_I}{r_H}\mu+\alpha>0$ since $r_I\le r_H$ and $\mu\le\alpha$, and

$$\begin{aligned}a_3+b_3(0) &= -\alpha(\gamma+\beta H_0)\left[\frac{r_I}{\alpha}\left(1-\frac{H_0}{k}\right)+\frac{\eta\beta H_0}{\gamma+\beta H_0}-1\right]\\ &= -\alpha(\gamma+\beta H_0)\left[\mathcal{R}_0(0)-1\right].\end{aligned}$$

If $\mathcal{R}_0(0)<1$ then $a_3+b_3(0)>0$. It follows that for $\tau=0$, according to Routh-Hurwitz criteria [8, 3], infection free equilibrium $E_0=(H_0,0,0)$ is locally asymptotically stable.

Now, let us consider the distribution of the roots of (5.2) when $\tau>0$.

Assume that, $X=\omega i$, $(\omega>0)$ is a solution of (5.2). The substitution of $X=\omega i$, $(\omega>0)$ into (5.2) yields :

$$-\omega^2+i\omega a_2+a_3+b_3(\tau)\cos\omega\tau-ib_3(\tau)\sin\omega\tau=0,$$

then separating in real and imaginary parts the previous equation, we obtain

$$\begin{cases}a_3-\omega^2 &= -b_3(\tau)\cos\omega\tau\\ a_2\omega &= b_3(\tau)\sin\omega\tau.\end{cases}$$

Squaring and adding the last two equations, we get

$$\begin{cases}(a_3-\omega^2)^2 &= b_3^2(\tau)\cos^2\omega\tau,\\ a_2^2\omega^2 &= b_3^2(\tau)\sin^2\omega\tau,\end{cases}$$

and simplifications yields

$$\omega^4+(a_2^2-2a_3)\omega^2+(a_3^2-b_3^2(\tau))=0.$$

Furthermore, if

$$\omega^2=Z;\quad A=a_2^2-2a_3;\quad B(\tau)=a_3^2-b_3^2(\tau),$$

we obtain equation

$$F(Z) = Z^2 + AZ + B(\tau) = 0, \tag{5.4}$$

where

$$A = (\gamma + \beta H_0)^2 + \left(\frac{r_I\lambda}{r_H H_0} - \frac{r_I\mu}{r_H} + \alpha\right)^2 > 0$$

and

$$B(\tau) = a_3^2 - b_3^2(\tau) = (a_3 - b_3(\tau))\,(a_3 + b_3(\tau))\,.$$

We know that

$$a_3 + b_3(\tau) = -\alpha(\gamma + \beta H_0)(\mathcal{R}_0(\tau) - 1).$$

Thus,

$$B(\tau) = \alpha(\gamma + \beta H_0)^2(1 - \mathcal{R}_0(\tau))\left(\tfrac{r_I\lambda}{r_H H_0} - \tfrac{r_I\mu}{r_H} + \alpha + \tfrac{\mu\beta e^{-\tau m} H_0}{\gamma + \beta H_0}\right).$$

Since

$$-\frac{r_I H}{r_H} + \alpha > 0,$$

if $\mathcal{R}_0(\tau) < 1$, then $B(\tau) > 0$. Now as $A > 0$, $B(\tau) > 0$ and $\omega > 0$, then $F(Z) > 0$ for any $Z > 0$ which contradicts $F(Z) = 0$. This show that characteristic equation (5.4) does not have pure imaginary roots when $\mathcal{R}_0(\tau) < 1$.

Now, let us show that equation (5.2) has all its roots with real negative part when $\mathcal{R}_0(\tau) < 1$. Let

$$P(X) = X^2 + a_2 X + a_3 \quad \text{et} \quad q(X) = b_3(\tau).$$

and

$$a = -r_I\left(1 - \frac{H_0}{k}\right) + \alpha \quad \text{et} \quad p = \gamma + \beta H_0,$$

thus :

$$a_2 = a + p \quad \text{et} \quad a_3 = ap,$$

and

$$P(X) = X + (a + p)X + ap.$$

Let us verify if the four conditions of Theorem 1 p.187 [6] are satisfied.

1) Using the Routh-Hurwitz criteria [8, 3], if $P(X) = 0$, it follows that if $a + p = a_2 > 0$ and

$$ap = a_3(\gamma + \beta H_0)\left(-r_I\left(1 - \frac{H_0}{k}\right) + \alpha\right) > 0,$$

then the real part of X 2: $\mathcal{R}_e(X) < 0$. Here the first condition holds.

2) For $0 \le y < +\infty$, we have:

$$\begin{aligned} p(-iy) &= -y^2 - i(a + p)y + ap \\ \overline{p(-iy)} &= -y^2 + i(a + p)y + ap \\ &= p(iy) \\ \overline{q(-iy)} &= \eta\beta H_0 e^{-m\tau} \\ &= q(iy). \end{aligned}$$

And the second condition is satisfied.

3) For $0 \leq y < +\infty$

$$\begin{aligned} p(iy) &= -y^2 + (a+p)iy + ap \\ |p(iy)|^2 &= (ap-y)^2 + y(a+p)^2 \\ &= (a^2+y^2)(p^2+y^2), \end{aligned}$$

thus $|p(iy)| \geq ap$. Note that for $\mathcal{R}_0(\tau) < 1$,

$$\begin{aligned} ap - \eta\beta H_0 e^{m\tau} &= (\gamma+\beta H_0)\left(-r_I\left(1-\frac{H_0}{k}\right) + \alpha - \frac{\eta\beta H_0 e^{-m\tau}}{\gamma+\beta H_0}\right) \\ &= \frac{(\gamma+\beta H_0)}{\alpha}(1-\mathcal{R}_0(\tau)) > 0. \end{aligned}$$

Thus

$$ap > \eta\beta H_0 e^{-m\tau}.$$

Therefore

$$ap > |q(iy)|,$$

and it follows that

$$|p(iy)| > |q(iy)|.$$

4) The last condition holds since:

$$\frac{|q(X)|}{|p(X)|} = \frac{\eta\beta H_0 e^{-m\tau}}{X^2 + (a+p)X + ap}$$

and

$$\lim_{|X|\to+\infty}\left|\frac{q(X)}{p(X)}\right| = 0.$$

Finally, if $\mathcal{R}_0(\tau) < 1$, the infection free equilibrium E_0 of system (2.1) is locally asymptotically stable. This completes the proof. □

5.2. **Global stability analysis of E_0.** For biological models and virus dynamics models in particular, it is interesting to study the stability of positive equilibria. All hepatocytes populations must persist. It is also necessary for all hepatocyte population to be present initially. Therefore, a genuine concept of global stability for positive equilibrium points in biological models is that every model solution that starts in the positive orthant $\mathbb{R}^3_+$ must remain there for all finite values of t and converge to the equilibrium when t tends to ∞.

In this section, applying Lyapunov functionals as in Vargas-De-Leon [28], we consider the global stability of the infection free equilibrium E_0.

Theorem 5.2. *Assume that the condition $r_H = (\gamma+\beta H_0)r_I e^{\tau m}/\gamma$ holds. If $\mathcal{R}_0(\tau) < 1$, then the infection free equilibrium $E_0 = (H_0, 0, 0)$ of system (2.1) is globally asymptotically stable in $\mathbb{R}^3_+$.*

Proof. Define the Lyapunov functional

$$\begin{aligned} U(t) &= e^{m\tau} r_I \int_{H_0}^{H(t)} \frac{\eta - H_0}{\eta} d\eta + e^{m\tau} r_H I(t) + \frac{r_H \beta H_0 V(t)}{\gamma+\beta H_0} \\ &\quad + r_H \beta \int_0^\tau \frac{H(t-\omega)V(t-\omega)}{1+cV(t-\omega)} d\omega. \end{aligned} \tag{5.5}$$

U is defined and continuous for any positive solution $(H(t), I(t), V(t))$ of system (2.1). Let us calculate the derivative of $U(t)$ along a positive solution of (2.1). We have:

$$\begin{aligned}\frac{dU(t)}{dt} &= e^{m\tau}r_I\frac{(H-H_0)}{H}\dot{H}(t) + r_H e^{\tau m}\dot{I}(t) + \frac{r_I\beta H_0}{\gamma+\beta H_0}\dot{V}(t)\\ &\quad +\beta r_H\frac{d}{dt}\int_0^\tau \frac{H(t-\omega)V(t-\omega)}{1+aV(t-\omega)}d\omega.\end{aligned}$$

Since $u = t-\omega$ and

$$\beta r_H\frac{d}{dt}\int_0^\tau \frac{H(t-\omega)V(t-\omega)}{1+aV(t-\omega)}d\omega = -\beta r_H\frac{d}{du}\int_t^{t-\tau}\frac{H(u)V(u)}{1+aV(u)}du,$$

it follows that

$$\begin{aligned}\frac{dU(t)}{dt} &= e^{m\tau}r_I\frac{(H-H_0)}{H}\left(\lambda + r_H\left(1-\frac{H+I}{k}\right) - \mu H - \frac{\beta HV}{1+aV}\right)\\ &\quad +\frac{r_H\beta H(t-\tau)V(t-\tau)}{1+aV(t-\tau)} + r_H e^{m\tau}r_I I\left(1-\frac{H+I}{k}\right) - r_H\alpha e^{m\tau}I\\ &\quad +\frac{r_H\beta H_0\eta I}{\gamma+\beta H_0} - \frac{r_H\beta H_0\gamma V}{\gamma+\beta H_0} - \frac{r_H\beta^2 H_0 HV}{(\gamma+\beta H_0)(1+aV)} - \frac{r_H\beta H(t-\tau)V(t-\tau)}{1+aV(t-\tau)}\\ &\quad +\frac{r_H\beta HV}{1+aV}.\end{aligned}$$

Using the fact that

$$r_H - \mu = \frac{r_H H_0}{k} - \frac{\lambda}{H_0},$$

we get

$$\begin{aligned}\frac{dU(t)}{dt} &= e^{m\tau}r_I\frac{(H-H_0)}{H}\left(\lambda + \frac{r_H}{k}H_0 H - \frac{\lambda}{H_0}H - \frac{r_H}{k}IH - \frac{\beta HV}{1+aV}\right)\\ &\quad +e^{m\tau}Ir_H r_I\left(1-\frac{H_0}{k}\right) - e^{m\tau}Ir_H r_I\left(\frac{H-H_0}{k}\right) - r_H e^{m\tau}r_I\frac{I^2}{k} - r_H\gamma\alpha e^{m\tau}I\\ &\quad +\frac{r_H\beta H_0\eta I}{\gamma+\beta H_0} - \frac{r_H\beta H_0\gamma V}{\gamma+\beta H_0} - \frac{r_H\beta^2 H_0 HV}{(\gamma+\beta H_0)(1+aV)} + \frac{r_H\beta HV}{1+aV};\\ &= -\frac{r_H r_I}{H_0}e^{m\tau}\left((H-H_0)+I\right)^2 + e^{m\tau}r_H\alpha I(\mathcal{R}_0(\tau)-1)\\ &\quad -\lambda e^{m\tau}\frac{r_I(H-H_0)^2}{HH_0} + \beta H_0 V\left(\frac{r_I e^{m\tau}}{1+aV} - \frac{r_H\gamma}{\gamma+\beta H_0}\right)\\ &\quad +\frac{\beta HV}{1+aV}\left(-r_I e^{m\tau} + \frac{r_H\gamma}{\gamma+\beta H_0}\right).\end{aligned}$$

Therefore,

$$\frac{dU(t)}{dt} \leq e^{m\tau}r_I\frac{(H-H_0)^2}{HH_0} - \frac{r_H}{k}r_I e^{m\tau}\left((H-H_0)+I\right)^2 + e^{m\tau}r_H\alpha I(\mathcal{R}_0(\tau)-1) \tag{5.6}$$

since

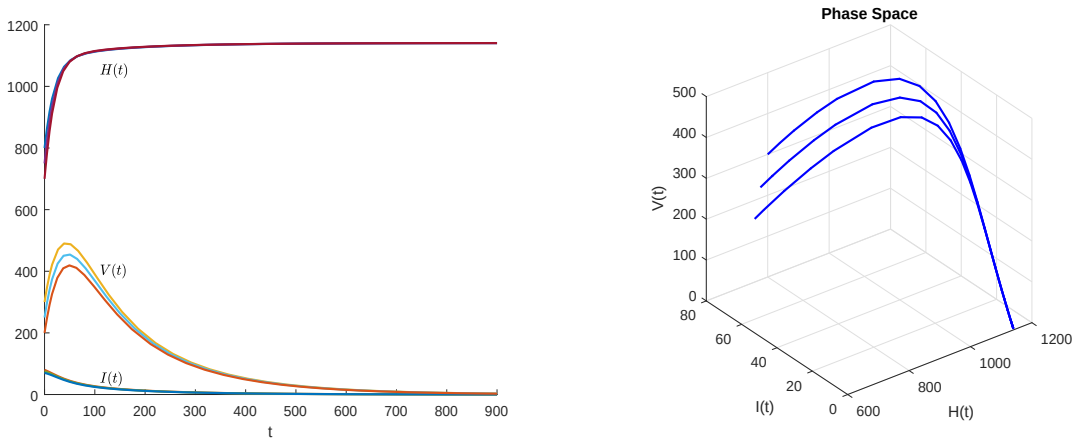
$$\frac{r_H\gamma}{\gamma+\beta H_0} = r_I e^{m\tau}.$$

Thus $\frac{dU(t)}{dt} \leq 0$ since $\mathcal{R}_0(\tau) < 1$.Furthermore, $\frac{dU(t)}{dt} = 0$ if and only if $H(t) = H_0$, $I(t) = 0$ and $V(t) = 0$. Therefore, the largest compact invariant set in $\left\{(H(t), I(t), V(t)) \,/\, \frac{dU(t)}{dt} = 0\right\}$ when $\mathcal{R}_0(\tau) \leq 1$ is $E_0 = (H_0, 0, 0)$, where E_0 is the infection free equilibrium. This shows that $\lim_{t\longrightarrow\infty}(H(t), I(t), V(t)) = (H_0, 0, 0)$. By the Lyapunov-LaSalle invariance theorem for delay differential systems (Theorem 2.5.3 in [13]), this implies that E_0 is globally asymptotically stable in the interior of $\mathbb{R}^3_+$. □

5.3. **Numerical results.** In this section, we present some numerical simulations which validate our theoretical results. To explore system (2.1) and illustrate the stability of infection free equilibrium solution, we consider the set of following parameters value :

$$\begin{array}{c} \tau = 5;\ r_H = 0,05;\ r_I = 0.0428;\ m = 0,021;\ k = 1200\ ; \\ a = 0,001;\ \beta = 9,2419.10^{-7};\ \mu = 0,02;\ \gamma = 0,02; \\ \alpha = 0,021;\ \lambda = 20;\ \eta = 0,2\ . \end{array} \tag{5.7}$$

We obtain Figure 1.



(A) (B)

FIGURE 1. Dynamical behaviour of system (2.1) with the set of parameter values (5.7)

We have $\mathcal{R}_0(5) = 0.5513 < 1$ and the infection free equilibrium $E_0 = (1140.8; 0; 0)$ is globally asymptotically stable. The graph in **(a)** shows the time series of the solutions with constant initial conditions. The graph in **(b)** shows the trajectory in the phase diagram of system 2.1, which illustrates the stability of the uninfected E_0 with the history functions $\varphi_1(\theta) = 800$, $\varphi_2(\theta) = 80$, $\varphi_3(\theta) = 300$ (first trajectory); $\varphi_1(\theta) = 750$, $\varphi_2(\theta) = 75$, $\varphi_3(\theta) = 250$ (second trajectory); $\varphi_1(\theta) = 700$, $\varphi 2(\theta) = 70$, $\varphi_3(\theta) = 200$ (third trajectory).

6. Asymptotic stability analysis of the infection persist equilibrium

The aim of this section is to study the local and global stability of the infection persist equilibrium for system (2.1).

6.1. **Local stability analysis of E_1.** We now study the local stability behaviour of the infection persist equilibrium E_1 when $\mathcal{R}_0(\tau) > 1$ for system (2.1). Thus, linearizing system (2.1) at the infection persist equilibrium $E_1 = (H_1, I_1, V_1)$, we obtain that the associated transcendental characteristic equation is given by

$$\begin{vmatrix} -\frac{\lambda}{H_1} - \frac{r_H}{k}H_1 - X & -\frac{r_H}{k}H_1 & -\frac{\beta H_1}{(1+aV_1)^2} \\ \frac{\beta e^{-(m+X)\tau}}{1+aV_1} - \frac{r_I}{k}I_1 & -\frac{\beta e^{-\tau m}H_1V_1}{(1+aV_1)I_1} - \frac{r_I}{k}I_1 - X & \frac{\beta e^{-(m+X)\tau}H_1}{(1+aV_1)^2} \\ -\frac{\beta V_1}{1+aV_1} & \eta & -\gamma - \frac{\beta H_1}{(1+aV_1)^2} - X \end{vmatrix} = 0.$$

When we take into account the identities

$$r_H - \mu = -\frac{\lambda}{H_1} + \frac{r_H}{k}H_1 + \frac{r_H}{k}I_1 + \frac{\beta V_1}{1+aV_1},$$

$$r_I - \alpha = -\frac{\beta e^{-\tau m}H_1V_1}{(1+aV_1)I_1} + \frac{r_I}{k}H_1 + \frac{r_I}{k}I_1,$$

the characteristic equation reduces to

$$X^3 + a_2(\tau)X^2 + a_1(\tau)X + \big[b_1(\tau)X + b_2(\tau)\big]e^{-X\tau} + a_0(\tau) = 0. \tag{6.1}$$

where

$$a_2(\tau) = \frac{\lambda}{H_1} + \frac{r_H}{k}H_1 + \frac{\beta e^{-m\tau}H_1V_1}{(1+aV_1)I_1} + \frac{r_I}{k}I_1 + \gamma + \frac{\beta H_1}{(1+aV_1)^2},$$

$$a_1(\tau) = \frac{\beta e^{-\tau m}H_1V_1}{(1+aV_1)I_1}\gamma + \frac{r_I}{k}\gamma I_1 + \frac{r_I\beta H_1I_1}{(1+aV_1)^2} + \frac{\beta^2 e^{-\tau m}H_1^2V_1}{(1+aV_1)^3I_1} + \left(\frac{\lambda}{H_1} + \frac{r_H}{k}H_1\right)\times$$

$$\left(\frac{\beta e^{-\tau m}H_1V_1}{(1+aV_1)I_1} + \frac{r_H}{k}I_1 + \frac{\beta H_1}{(1+aV_1)^2} + \gamma\right) - \frac{r_H}{k}H_1I_1 - \frac{\beta^2 H_1V_1}{(1+aV_1)^3},$$

$$a_0(\tau) = \left(\frac{\lambda}{H_1} + \frac{r_H}{k}H_1\right)\left(\frac{\beta e^{-m\tau}H_1V_1}{(1+aV_1)I_1}\gamma + \frac{r_I}{k}\gamma I_1 + \frac{r_I\beta H_1I_1}{k(1+aV_1)^2}\right.$$

$$\left. + \frac{\beta^2 e^{-\tau m}H_1^2V_1}{(1+aV_1)^3I_1}\right) + \frac{r_H}{k}H_1\left(-\frac{r_I}{k}\gamma I_1 - \frac{r_I\beta H_1I_1}{k(1+aV_1)^2}\right) + \frac{\beta H_1}{(1+aV_1)^2}\times$$

$$\left(-\frac{r_I\eta I_1}{k} - \frac{r_I\beta V_1I_1}{k(1+aV_1)} - \frac{\beta^2 e^{-\tau m}H_1V_1^2}{(1+aV_1)^2I_1}\right),$$

$$b_1(\tau) = -\frac{\eta\beta e^{-(m+X)\tau}H_1}{(1+aV_1)^2} + \frac{r_H}{k}H_1\frac{\beta e^{-(m+X)\tau}V_1}{(1+aV_1)},$$

$$b_2(\tau) = -\left(\frac{\lambda}{H_1} + \frac{r_H}{k}H_1 + \frac{r_H}{k}I_1\right)\frac{\eta\beta e^{-(m+X)\tau}H_1}{(1+aV_1)^2} + \frac{r_H\beta e^{-(m+X)\tau}H_1V_1}{k(1+aV_1)}\gamma$$

$$- \frac{\beta H_1}{(1+aV_1)^2}\frac{\eta\beta e^{-(m+X)\tau}V_1}{(1+aV_1)}.$$

Define

$$P(\lambda,\tau) = X^3 + a_2(\tau)X^2 + a_1(\tau)X + a_0(\tau)$$

and

$$Q(\lambda,\tau) = b_1(\tau)X + b_2(\tau).$$

When $\tau = 0$, we have from (6.1) that

$$P(\lambda, 0) + Q(\lambda, 0) = X^3 + a_2(0)X^2 + (a_1(0) + b_1(0))X + b_2(0) + a_0(0) = 0. \tag{6.2}$$

By the Routh-Hurwitz criterion the conditions for the real part of X to be negative are $a_2(0) > 0$, $a_0(0) + b_2(0) > 0$ and $Q = a_2(0)(a_1(0) + b_1(0)) - (a_0(0) + b_1(0)) > 0$. In our case $a_2(0) > 0$. In other hand, we have

$$\begin{aligned}
a_1(0) + b_1(0) = {} & \frac{\beta H_1 V_1}{(1+aV_1)I_1}\gamma\frac{aV_1}{1+aV_1} + \frac{r_I}{k}\gamma I_1 + \frac{r_I\beta H_1 I_1}{(1+aV_1)^2} + \frac{r_H}{k}H_1^2\frac{\beta}{(1+aV_1)^2} \\
& + \left(\frac{\lambda}{H_1} + \frac{r_H}{k}H_1\right)\left(\frac{\beta H_1 V_1}{(1+aV_1)I_1} + \gamma\right) + \frac{\lambda}{H_1}\frac{r_I}{k}I_1 + \frac{r_H H_1 I_1}{k}(r_H - r_I) \\
& - r_H H_1\left(1 - \frac{H_1 + I_1}{k}\right)\frac{\beta}{(1+aV_1)^2} + \frac{\beta H_1}{(1+aV_1)^2}\mu \\
= {} & \frac{a\beta H_1 V_1^2\gamma}{(1+aV_1)^2 I_1} + \frac{\beta H_1}{(1+aV_1)^2}\left(\mu + r_I I_1 - r_H\left(1 - \frac{2H_1 + I_1}{k}\right)\right) \\
& + \left(\frac{\lambda}{H_1} + \frac{r_H}{k}H_1\right)\left(\frac{\beta H_1 V_1}{(1+aV_1)I_1} + \gamma\right) + \frac{\lambda}{H_1}\frac{r_I}{k}I_1 \\
& + \frac{r_H H_1 I_1}{k}(r_H - r_I) + \frac{r_I\gamma I_1}{k},
\end{aligned}$$

since

$$\frac{\eta\beta H_1}{(1+aV_1)^3 I_1} = \frac{\beta H_1 V_1\gamma}{(1+aV_1)^2 I_1} + \frac{\beta^2 H_1^2 V_1}{(1+aV_1)^3 I_1}$$

and

$$-\frac{\beta^2 H_1 V_1}{(1+aV_1)^3} = -\frac{\beta\lambda}{(1+aV_1)^2} - r_H H_1\left(1 - \frac{H_1 + I_1}{k}\right)\frac{\beta}{(1+aV_1)^2} + \frac{\beta H_1}{(1+aV_1)^2}\mu.$$

It follows that if

$$\mu + r_I I_1 - r_H\left(1 - \frac{2H_1 + I_1}{k}\right) > 0, \tag{6.3}$$

then

$$a_1(0) + b_1(0) > 0. \tag{6.4}$$

Furthermore, using (4.3) we obtain

$$\begin{aligned}
a_0(0)+b_2(0) &= \left(\frac{\lambda}{H_1}+\frac{r_H}{k}H_1\right)\left(1-\frac{1}{1+aV_1}\right)\frac{\beta H_1V_1}{(1+aV_1)I_1}\gamma \\
&\quad + \frac{\lambda}{H_1}\left(\frac{r_I}{k}\gamma I_1+\frac{r_I\beta H_1I_1}{k(1+aV_1)^2}\right)+\frac{r_H\beta H_1V_1}{k(1+aV_1)}\gamma+\frac{\eta\beta^2H_1V_1}{(1+aV_1)^3} \\
&\quad - \frac{r_I\beta H_1I_1}{k(1+aV_1)^2}\left(\frac{\gamma}{I_1}V_1+\frac{\beta H_1V_1}{1+aV_1I_1}\right)-\frac{r_I\beta^2H_1V_1I_1}{k(1+aV_1)^3}-\frac{\beta^3H_1^2V_1^2}{(1+aV_1)^4I_1}, \\
&= \left(\frac{\lambda}{H_1}+\frac{r_H}{k}H_1\right)\left(1-\frac{1}{1+aV_1}\right)\frac{\beta H_1V_1}{(1+aV_1)I_1}\gamma \\
&\quad + \frac{\lambda}{H_1}\left(\frac{r_I}{k}\gamma I_1+\frac{r_I\beta H_1I_1}{k(1+aV_1)^2}\right)+\frac{\beta H_1V_1\gamma}{k(1+aV_1)}\times \\
&\quad \left(r_H-\frac{r_I}{1+aV_1}\right)-\frac{r_I\beta^2H_1^2V_1}{k(1+aV_1)^3}-\frac{r_I\beta^2H_1V_1I_1}{k(1+aV_1)^3}-\frac{\beta^3H_1^2V_1^2}{(1+aV_1)^4I_1} \\
&\quad + \frac{\beta^2H_1V_1}{(1+aV_1)^3}\left(\frac{\gamma}{I_1}V_1+\frac{\beta H_1V_1}{(1+aV_1)I_1}\right) \\
&= \left(\frac{\lambda}{H_1}+\frac{r_H}{k}H_1\right)\left(1-\frac{1}{1+aV_1}\right)\frac{\beta H_1V_1}{(1+aV_1)I_1}\gamma \\
&\quad + \frac{\lambda}{H_1}\left(\frac{r_I}{k}\gamma I_1+\frac{r_I\beta H_1I_1}{k(1+aV_1)^2}\right)+\frac{\beta H_1V_1}{k(1+aV_1)}\gamma\times \\
&\quad \left(r_H-\frac{r_I}{1+aV_1}\right)-\frac{r_I\beta^2H_1^2V_1}{k(1+aV_1)^3}-\frac{r_I\beta^2H_1V_1I_1}{k(1+aV_1)^3}+\frac{\beta^2H_1V_1^2}{(1+aV_1)^3I_1}\gamma, \\
&= \left(\frac{\lambda}{H_1}+\frac{r_H}{k}H_1\right)\frac{a\beta H_1V_1^2}{(1+aV_1)^2I_1}\gamma+\frac{\beta H_1V_1}{k(1+aV_1)}\gamma\left(r_H-\frac{r_I}{1+aV_1}\right) \\
&\quad + \frac{\lambda}{H_1}\left(\frac{r_I}{k}\gamma I_1+\frac{r_I\beta H_1I_1}{k(1+aV_1)^2}\right)+\frac{r_I\beta^2H_1V_1}{(1+aV_1)^3}\left(1-\frac{H_1+I_1}{k}\right) \\
&\quad + \frac{\beta^2H_1V_1}{(1+aV_1)^3}\left(\frac{V_1}{I_1}-r_I\right).
\end{aligned}$$

Finally, if

$$r_I < \frac{V_1}{I_1},$$

then

$$a_0(0)+b_2(0) > 0.$$

Thus, if $\tau = 0$, by the Routh-Hurwitz criterion, we have the following theorem :

Theorem 6.1. *Assume $\mathcal{R}_0(0) > 1$, if $Q > 0$ and $r_I < \frac{V_1}{I_1}$ then the unique infection persist equilibrium $E_1 = (H_1, I_1, V_1)$ is locally asymptotically stable as $\tau = 0$.*

Now we are going to check if it is possible to have a complex root with a positive real part for $\tau > 0$, assuming

$$H(1) : a_0 + b_0 > 0, \quad a_2(a_1 + b_1) - (a_0 + b_0) > 0.$$

Note that $X = 0$ is not root of the equation because $a_0 + b_2 > 0$. Suppose then that $X = i\omega$, $(\omega > 0)$, is a root of equation given by:

$$P(X, \tau) + Q(X, \tau)e^{-X\tau} = 0 \tag{6.5}$$

with

$$\begin{aligned} P(X, \tau) &= X^3 + a_2(\tau)X^2 + a_1(\tau) + a_0(\tau), \\ Q(X, \tau) &= b_1(\tau)X + b_2(\tau) \end{aligned}$$

As $X = i\omega$ is a root of equation (6.5), we have

$$P(i\omega, \tau) + Q(i\omega, \tau)e^{-i\omega\tau} = 0$$

and

$$-i\omega^3 - a_2(\tau)\omega^2 + ia_1(\tau)\omega + a_0(\tau) + (b_1(\tau)i\omega + b_2(\tau))\, e^{-i\omega\tau} = 0.$$

And it follows that

$$-i\omega^3 - a_2(\tau)\omega^2 + ia_1(\tau)\omega + a_0(\tau) + (ib_1(\tau)\omega + b_2(\tau))\,(\cos\omega\tau - i\sin\omega\tau) = 0$$

We obtain : $-i\omega^3 - a_2(\tau)\omega^2 + ia_1(\tau)\omega + a_0(\tau) + ib_1(\tau)\omega\cos\omega\tau + b_2(\tau)\cos\omega\tau + b_1(\tau)\omega\cos\omega\tau - ib_2(\tau)\sin\omega\tau = 0$. Consequently, we have the following relation :

$$\begin{cases} a_0(\tau) - a_2(\tau)\omega^2 = -b_2(\tau)\cos\omega\tau - b_1(\tau)\omega\sin\omega\tau & (6.6) \\ a_1(\tau)\omega - \omega^3 = -b_1(\tau)\omega\cos\omega\tau + b_2(\tau)\sin\omega\tau. & (6.7) \end{cases}$$

Multiplying (6.6) by $-b_1(\tau)\omega$ and (6.7) by $b_2(\tau)$, we get :

$$\frac{(-a_0(\tau) + a_2(\tau)\omega^2)b_1(\tau)\omega + (a_1(\tau)\omega - \omega^3)b_2(\tau)}{b_2^2(\tau) + b_1^2(\tau)\omega^2} = \sin\omega\tau.$$

Therefore

$$\sin\omega\tau = \frac{(a_2(\tau)b_1(\tau) - b_2(\tau))\omega^3 + (a_1(\tau)b_2(\tau) - a_0(\tau)b_1(\tau))\omega}{b_2^2(\tau) + b_1^2(\tau)\omega^2}.$$

Similarly, multiplying (6.6) by $b_2(\tau)$ and (6.7) by $b_1(\tau)\omega$, we obtain:

$$\cos\omega\tau = \frac{b_1(\tau)\omega^4 + [a_2(\tau)b_2(\tau) - a_1(\tau)b_1(\tau)]\omega^2 - a_0(\tau)b_2(\tau)}{b_2^2(\tau) + b_1^2(\tau)\omega^2}.$$

Moreover for $X = i\omega$, we get :

$$P(i\omega, \tau) = -i\omega^3 - a_2(\tau)\omega^2 + ia_1(\tau)\omega + a_0(\tau),$$

and

$$Q(i\omega, \tau) = ib_1(\tau)\omega + b_2(\tau).$$

Therefore one has :

$$\begin{aligned} \frac{P(i\omega, \tau)}{Q(i\omega, \tau)} &= \frac{i(a_2(\tau)b_1(\tau) - b_2(\tau))\omega^3 + (a_1(\tau)b_2(\tau) - a_0(\tau)b_1(\tau)\omega)}{b_2^2(\tau) + b_1^2(\tau)\omega^2} \\ &\quad - \frac{\Big(b_1(\tau)\omega^4 + \Big(a_2(\tau)b_2(\tau) - a_1(\tau)b_1(\tau)\Big)\omega^2 - a_0(\tau)b_2(\tau)\Big)}{b_2^2(\tau) + b_1^2(\tau)\omega^2}. \end{aligned}$$

It follows that :

$$\sin(\omega\tau) = \mathcal{I}_m\left(\frac{Q(i\omega, \tau)}{P(i\omega, \tau)}\right)$$

and

$$\cos(\omega\tau) = -\mathcal{R}_e\left(\frac{Q(i\omega,\tau)}{P(i\omega,\tau)}\right).$$

Thus from the fact that $\sin^2(\omega\tau)+\cos^2(\omega\tau)=1$ we have

$$\frac{|Q(i\omega,\tau)|^2}{|P(i\omega,\tau)|^2}=1 \quad \text{and} \quad |Q(i\omega,\tau)|^2=|Q(i\omega,\tau)|^2.$$

We conclude that ω is a positive root of the equation $|P(i\omega,\tau)|^2-|Q(i\omega,\tau)|^2=0$. Furthermore

$$|P(X,\tau)|^2=\omega^6+a_2^2(\tau)-2a_1(\tau)\omega^4+a_1^2(\tau)-2a_0(\tau)a_2(\tau)\omega^2+a_0^2(\tau)$$

and

$$|Q(X,\tau)|^2=b_2^2(\tau)+b_1^2(\tau)\omega^2.$$

We get

$$\omega^6-A\omega^4+B\omega^2+C=0 \tag{6.8}$$

where

$$\begin{aligned} A=&\quad a_2(\tau)-2a_1(\tau),\\ B=&\quad a_1^2(\tau)-2a_0(\tau)a_2(\tau)-b_1^2(\tau),\\ C=&\quad a_0^2(\tau)-b_2^2(\tau). \end{aligned}$$

Let $z=\omega^2$, we obtain

$$z^3+Az^2+Bz+C=0 \tag{6.9}$$

Suppose that (6.9) has at least one positive root. Let z_0 be the smallest value of its roots. Then (6.8) has the root $\omega_0=\sqrt{z_0}$ and from (6.7) we get the value of τ associated with ω_0 such that $X=\omega i$ is a pure imaginary root of (6.5). This value of τ is given by:

$$\tau_0=\frac{1}{\omega_0}\arccos\left[\frac{b_2(a_2\omega_0^2-a_0)+b_1\omega_0(\omega_0^3-a_1\omega_0)}{b_2^2+b_1^2\omega_0^2}\right].$$

Ultimately we can summarize what precedes in the following result. Thus according to Theorem 2.4 p.48 [22], we have :

Theorem 6.2. *Suppose $(H(1))$ is verified,*

1. *If $C\geq 0$ and $\Lambda=A^2-3B<0$, then the roots of (6.5) have a negative real part for all $\tau\geq 0$, therefore the infection persist equilibrium $E_1(H_1,I_1,V_1)$ is locally asymptotically stable.*
2. *If $C<0$ or $C\geq 0$, $z_1>0$ and $z_1^3+Az_1^2+Bz_1+C\leq 0$, then all the roots of the equation (6.5) have a negative real part when $\tau\in[0,\tau_0]$, and therefore the infection persist equilibrium $E_1(H_1,I_1,V_1)$ is locally asymptotic stable in $[0,\tau_0]$.*

6.2. **Global stability analysis of E_1.**

Theorem 6.3. *Denote*

$$\varepsilon=\mu-r_H+\frac{r_H}{k}(H_1+I_1),\quad \Lambda=\frac{4\lambda+(r_H+r_I)k}{4b},\quad et\quad \Omega=\frac{\eta\Lambda}{\gamma}.$$

Assume

$$r_H=r_Ie^{m\tau},\quad \varepsilon>0\quad and\quad k>\frac{\beta^3H_1V_1^2\Lambda(1+a\Omega)}{4\varepsilon\eta^2(1+aV_1)^4}+\frac{a\beta\Lambda V_1}{\eta I_1(1+aV_1)},$$

then the unique infection persist equilibrium$E_1=(H_1,I_1,V_1)$ for system (2.1) is globally asymptotically stable for any $\tau\geq 0$.

Proof. Define a Lyapunov functional for E_1

$$L(t) = \tilde{L}(t) + \frac{\beta H_1 V_1}{1+aV_1} L_+(t), \tag{6.10}$$

where

$$\tilde{L}(t) = r_I e^{m\tau} \int_{H_1}^{H} \frac{\eta - H_1}{\eta} d\eta + r_H e^{m\tau} \int_{I_1}^{I} \frac{\eta - I_1}{\eta} d\eta + r_I \frac{e^{m\tau}\beta H_1 V_1}{\eta I_1(1+aV_1)} \int_{V_1}^{V} \left(1 - \frac{V_1(1+\eta)}{\eta(1+aV_1)}\right) d\eta$$

and

$$L_+(t) = r_H \int_0^\tau \left(\frac{H(t-\tau)V(t-\tau)(1+aV_1)}{H_1V_1(1+aV(t-\tau))} - 1 - \ln \frac{H(t-\omega)V(t-\tau)(1+aV)}{H_1V_1(1+aV(t-\tau))} \right) d\omega.$$

We have :

$$\frac{dL_+(t)}{dt} = \frac{d}{dt} r_H \int_0^\tau \left(\frac{H(t-\omega)V(t-\omega)(1+aV_1)}{H_1V_1(1+aV(t-\omega))} - 1 - \ln \frac{H(t-\omega)V(t-\omega)(1+aV)}{H_1V_1(1+aV(t-\omega))} \right) d\omega.$$

Denote

$$u = t - \omega,$$

we obtain :

$$\begin{aligned}
\frac{dL_+(t)}{dt} &= -r_H \frac{du}{dt}\frac{d}{du} \int_t^{t-\tau} \left(\frac{H(u)V(u)(1+aV_1)}{H_1V_1(1+aV(u))} - 1 - \ln \frac{H(u)V(u)(1+aV)}{H_1V_1(1+aV(u))} \right) d\omega \\
&= -r_H \left[\frac{H(u)V(u)(1+aV_1)}{H_1V_1(1+aV(u))} - 1 - \ln \frac{H(u)V(u)(1+aV)}{H_1V_1(1+aV(u))} \right]_{\omega=t}^{t-\tau}, \\
&= -\frac{r_H H(t-\tau)V(t-\tau)(1+aV_1)}{H_1V_1(1+aV(t-\tau))} + r_H \ln \frac{H(t-\tau)V(t-\tau)(1+aV)}{H_1V_1(1+aV(t-\tau))} \\
&\quad + \frac{r_H HV(1+aV_1)}{H_1V_1(1+aV)} - r_H \ln \frac{HV(1+aV_1)}{H_1V_1(1+aV)}, \\
&= -\frac{r_H H(t-\tau)V(t-\tau)(1+aV_1)}{H_1V_1(1+aV(t-\tau))} + r_H \ln \frac{I_1 H(t-\tau)V(t-\tau)(1+aV)}{IH_1V_1(1+aV(t-\tau))}, \\
&\quad + \frac{r_H HV(1+aV_1)}{H_1V_1(1+aV)} + r_H \ln \frac{H_1}{H} + r_H \ln \frac{IV_1(1+aV)}{I_1V(1+aV_1)}.
\end{aligned}$$

Besides, a direct calculation yields :

$$\begin{aligned}
\frac{d\tilde{L}(t)}{dt} &= r_I e^{m\tau} \frac{(H-H_1)}{H} \dot{H} + r_H e^{m\tau} \frac{(I-I_1)}{I} \dot{I} + r_I e^{m\tau} \frac{\beta H_1 V_1}{\eta I_1(1+aV_1)} \left(1 - \frac{V_1(1+aV)}{V(1+aV_1)}\right) \dot{V}, \\
&= (H-H_1) r_I e^{m\tau} \left(\frac{\lambda}{H} - \frac{r_H}{k}(H+I) - \frac{\beta V}{1+aV} + r_H - \mu \right) \\
&\quad + r_H e^{m\tau} (I-I_1) \left(\frac{\beta e^{-\tau} H(t-\tau)V(t-\tau)}{I(1+aV(t-\tau))} - \frac{r_I}{k}(H+I) + r_I - \alpha \right) \\
&\quad + r_I e^{m\tau} \frac{\beta H_1 V_1}{\eta I_1(1+aV_1)} \left(1 - \frac{V_1(1+aV)}{V(1+aV_1)}\right) \left(\eta I - \gamma V - \frac{\beta HV}{1+aV} \right).
\end{aligned}$$

Hence using (4.1), (4.2) and (4.3) we get :

$$\begin{aligned}\frac{d\tilde{L}(t)}{dt} &= r_I e^{m\tau}(H-H_1)\left(\frac{\lambda}{H}-\frac{r_H}{k}(H+I)-\frac{\beta V}{1+aV_1}-\frac{\lambda}{H_1}+\frac{r_H}{k}(H_1+I_1)\right.\\ &\left.+\frac{\beta V_1}{1+aV_1}\right)+r_H e^{m\tau}(I-I_1)\left(\frac{\beta e^{-m\tau}H(t-\tau)V(t-\tau)}{I(1+aV(t-\tau))}-\frac{r_I}{k}(H+I)\right.\\ &\left.+\frac{r_I}{k}(H_1+I_1)-\frac{\beta e^{-m\tau}H_1(t-\tau)V_1(t-\tau)}{I_1(1+aV_1)}\right)+\frac{r_I e^{m\tau}\beta H_1 V_1}{\eta I_1(1+aV_1)}\times\\ &\left(1-\frac{V_1(1+aV)}{V(1+aV_1)}\right)\left(\frac{(\eta IV_1-I_1V)}{V_1}+\frac{\beta V H_1}{(1+aV_1)}-\frac{\beta VH}{(1+aV)}\right).\end{aligned}$$

Cancelling identical terms with opposite signs and collecting terms yields consecutively

$$\begin{aligned}\frac{d\tilde{L}(t)}{dt} &= r_I e^{m\tau}(H-H_1)\left(\frac{-\lambda(H-H_1)^2}{HH_1}-\frac{r_H}{k}[(H-H_1)+(I-I_1)]\right.\\ &\left.-\beta\left(\frac{V}{1+aV}-\frac{V_1}{1+aV}\right)\right)+r_H(I-I_1)\left(\frac{\beta H(t-\tau)V(t-\tau)}{I(1+aV(t-\tau))}\right.\\ &\left.-\frac{\beta H_1V_1}{I_1(1+aV_1)}-\frac{r_I}{k}e^{m\tau}\left((H-H_1)+(I-I_1)\right)\right)+\frac{r_1e^{m\tau}\beta H_1V_1}{\eta I_1(1+aV_1)}\times\\ &\left(1-\frac{V_1(1+aV)}{V(1+aV_1)}\right)\left(\frac{\eta(IV_1-I_1V)}{V_1}+\frac{\beta VH_1}{(1+aV_1)}-\frac{\beta VH}{(1+aV)}\right)\\ &= -\lambda r_I e^{m\tau}\frac{(H-H_1)^2}{HH_1}+\Big(-\frac{r_H}{k}r_I e^{m\tau}(H-H_1)^2\\ &-\frac{r_H}{k}r_I e^{m\tau}(H-H_1)(I-I_1)-\frac{r_I r_H}{k}e^{m\tau}(H-H_1)(I-I_1)\\ &-\frac{r_I r_H}{k}e^{m\tau}(I-I_1)^2\Big)+\frac{\beta H_I V_I}{1+aV_1}\left(-e^{m\tau}\frac{r_H HV(1+aV_1)}{H_1V_1(1+aV)}+\frac{r_H H(t-\tau)V(t-\tau)(1+aV_1)}{H_1V_1(1+aV(t-\tau))}\right)\\ &+\frac{\beta H_1V_1}{1+aV_1}\left(\frac{-r_He^{m\tau}IV_1(1+aV)}{I_1V(1+aV)}-\frac{r_HI_1H(t-\tau)V(t-\tau)(1+aV_1)}{H_1IV_1(1+aV(t-\tau))}\right)\\ &+\frac{\beta H_1V_1}{1+aV_1}\left(r_Ie^{m\tau}\frac{H}{H_1}+r_Ie^{m\tau}\frac{V(1+aV_1)}{V_1(1+aV)}-r_Ie^{m\tau}\frac{V}{V_1}+r_Ie^{m\tau}\frac{(1+aV)}{1+aV_1}\right)\\ &-\frac{r_Ie^{m\tau}\beta^2H_1V_1}{\eta(1+aV_1)^3}(V-V_1)(H-H_1)+\frac{r_Ie^{m\tau}a\beta^2H_1HV_1(V-V_1)^2}{\eta I_1(1+aV_1)^3(1+aV)}.\end{aligned}$$

$$
\begin{aligned}
&= -\lambda r_I e^{m\tau}\frac{(H-H_1)^2}{HH_1} - \frac{r_H r_I}{k}e^{m\tau}\bigg((H-H_1)+(I-I_1)\bigg)^2\\
&+ \frac{\beta H_1 V_1}{1+aV_1}\left(-e^{m\tau}\frac{r_I HV(1+aV_1)}{H_1V_1(1+aV)} + \frac{r_H H(t-\tau)V(t-\tau)(1+aV_1)}{H_1V_1(1+aV(t-\tau))}\right)\\
&+ \frac{\beta H_1 V_1}{1+aV_1}\left(\frac{e^{m\tau}r_I V(1+aV_1)}{V_1(1+aV)} - e^{m\tau}r_I\frac{V}{V_1} + \frac{e^{m\tau}r_I(1+aV)}{1+aV_1} - e^{m\tau}r_I\right)\\
&+ \frac{\beta H_1 V_1}{1+aV_1}\bigg(3r_I e^{m\tau} - r_I e^{m\tau}\frac{H_1}{H} - \frac{e^{m\tau}r_I V_1(1+aV)I}{I_1V(1+aV_1)}\\
&- \frac{r_H I_1 H(t-\tau)V(t-\tau)(1+aV_1)}{H_1IV_1(1+aV(t-\tau))}\bigg) - \frac{r_I e^{m\tau}\beta^2 H_1V_1}{\eta(1+aV_1)^3}(V-V_1)(H-H_1)\\
&+ \frac{r_I e^{m\tau}a\beta^2 H_1HV_1(V-V_1)^2}{\eta I_1(1+aV_1)^3(1+aV)} + \frac{r_I e^{m\tau}\beta H_1V_1}{1+aV_1}\left(\frac{H_1}{H}+\frac{H}{H_1}-2\right).
\end{aligned}
$$

Additionally,

$$\frac{H_1}{H}+\frac{H}{H_1}-2 = \frac{(H-H_1)^2}{HH_1},$$

thus,

$$
\begin{aligned}
\frac{d\tilde{L}(t)}{dt} &= r_I e^{m\tau}\left(-\lambda+\frac{\beta H_1V_1}{1+aV_1}\right)\frac{(H-H_1)^2}{HH_1} - \frac{r_H r_I}{k}e^{m\tau}\bigg((H-H_1)+(I-I_1)\bigg)^2\\
&+ \frac{\beta H_1V_1}{1+aV_1}\left(-\frac{e^{m\tau}r_I HV(1+aV_1)}{H_1V_1(1+aV)} + \frac{r_H H(t-\tau)V(t-\tau)(1+aV_1)}{H_1V_1(1+aV(t-\tau))}\right)\\
&+ \frac{\beta H_1V_1}{1+aV_1}\bigg(-\frac{r_I e^{m\tau}V(1+aV_1)I}{I_1V_1(1+aV)} - \frac{r_H I_1 H(t-\tau)V(t-\tau)(1+aV_1)I}{H_1IV_1(1+aV(t-\tau))}\\
&+ 3r_I e^{m\tau} - r_I e^{m\tau}\frac{H}{H_1}\bigg) + r_I e^{m\tau}\frac{\beta H_1V_1}{1+aV_1}\left(1-\frac{V_1(1+aV)}{V(1+aV_1)}\right)\left(\frac{V(1+aV_1)}{V_1(1+aV)}-\frac{V}{V_1}\right)\\
&- \frac{r_1 e^{m\tau}\beta^2 H_1V_1}{\eta(1+aV_1)^3}(V-V_1)(H-H_1) + \frac{r_1 e^{m\tau}a\beta^2 H_1HV_1(V-V_1)^2}{\eta I_1(1+aV_1)^3(1+aV)}.
\end{aligned}
$$

The fact that

$$\lambda - \frac{\beta H_1V_1}{1+aV_1} = (\mu-r_H)H_1 + \frac{r_H H_1}{k}(H_1+I_1)$$

yields

$$
\begin{aligned}
\frac{d\tilde{L}(t)}{dt} &= -r_I e^{m\tau}\frac{\varepsilon}{H}(H-H_1)^2 - \frac{r_H r_I}{k}e^{m\tau}\left((H-H_1)+(I-I_1)\right)^2\\
&+ \frac{\beta H_1V_1}{1+aV_1}\bigg(-e^{m\tau}\frac{r_1 HV(1+aV_1)}{H_1V_1(1+aV)} + \frac{r_H H(t-\tau)V(t-\tau)(1+aV_1)}{H_1V_1(1+aV(t-\tau))}\bigg)
\end{aligned}
$$

$$+\frac{\beta H_1V_1}{1+aV_1}\bigg(3e^{m\tau}r_I-e^{m\tau}r_I\frac{H_1}{H}-\frac{e^{m\tau}r_1IV_1(1+aV)}{I_1V(1+aV_1)}$$

$$-\frac{r_HI_1H(t-\tau)V(t-\tau)(1+aV_1)}{H_1IV_1(1+aV(t-\tau))}\bigg)-\frac{kr_Ie^{m\tau}\beta H_1}{(1+aV)(1+aV_1)^2}(V-V_1)^2$$

$$-r_I\frac{e^{m\tau}\beta^2H_1V_1}{\eta(1+aV_1)^3}(V-V_1)(H-H_1)+\frac{r_Ie^{m\tau}a\beta^2H_1HV_1(V-V_1)^2}{\eta I_1(1+aV_1)^3(1+aV)}.$$

It follows that

$$\begin{aligned}\frac{d\tilde{L}(t)}{dt}\leq\ & -r_Ie^{m\tau}\frac{\varepsilon}{H}\bigg((H-H_1)+\frac{\beta^2HH_1V_1}{2\eta(1+aV_1)^3}(V-V_1)\bigg)^2\\ &+\frac{r_Ie^{m\tau}\beta H_1}{(1+aV)(1+aV_1)^2}\bigg(-k+\frac{\beta^3H_1V_1^2\Lambda(1+a\Omega)}{4\varepsilon\eta^2(1+aV_1)^4}+\frac{a\beta\Lambda V_1}{\eta I_1(1+aV_1)}\bigg)(V-V_1)^2\\ &+\frac{\beta H_1V_1}{1+aV_1}\bigg(-e^{m\tau}\frac{r_IHV(1+aV_1)}{H_1V_1(1+aV)}+\frac{r_HH(t-\tau)V(t-\tau)(1+aV_1)}{H_1IV_1(1+aV(t-\tau))}\bigg)\\ &+\frac{\beta H_1V_1}{1+aV_1}\bigg(3e^{m\tau}r_I-e^{m\tau}r_I\frac{H_1}{H}-\frac{e^{m\tau}r_1IV_1(1+aV)}{I_1V(1+aV_1)}\\ &-\frac{r_HI_1H(t-\tau)V(t-\tau)(1+aV_1)}{H_1IV_1(1+aV(t-\tau))}\bigg)-\frac{r_Ir_H}{k}e^{m\tau}\Big((H-H_1)+(I-I_1)\Big)^2.\end{aligned}$$

According to (6.10), we have:

$$\frac{dL}{dt}=\frac{d\tilde{L}}{dt}+\frac{\beta H_1V_1}{1+aV_1}\frac{dL_+}{dt}.$$

Thus,

$$\begin{aligned}\frac{dL(t)}{dt}\leq & -\frac{r_Hr_I}{k}e^{m\tau}\left((H-H_1)+(I-I_1)\right)^2--\frac{r_Ir_H}{k}e^{m\tau}\Big((H-H_1)+(I-I_1)\Big)^2\\ &-r_Ie^{m\tau}\frac{\varepsilon}{H}\bigg((H-H_1)+\frac{\beta^2HH_1V_1}{2\eta(1+aV_1)^3}(V-V_1)\bigg)^2+\frac{r_Ie^{m\tau}\beta H_1}{(1+aV)(1+aV_1)^2}\times\end{aligned}$$

$$\bigg(-k+\frac{\beta^3H_1V_1^2\Lambda(1+a\Omega)}{4\varepsilon\eta^2(1+aV_1)^4}+\frac{a\beta\Lambda V_1}{\eta I_1(1+aV_1)}\bigg)(V-V_1)^2$$

$$-\frac{r_Ie^{m\tau}\beta H_1V_1}{(1+aV_1)}\left(\frac{H_1}{H}-1-\ln\frac{H_1}{H}\right)-\frac{r_Ie^{m\tau}\beta H_1V_1}{(1+aV_1)}\bigg(\frac{IV_1(1+aV)}{I_1V(1+aV_1)}-1$$

$$-\ln\frac{IV_1(1+aV)}{I_1V(1+aV_1)}\bigg)-r_Ie^{m\tau}\frac{\beta H_1V_1}{1+aV_1}\bigg(\frac{H(t-\tau)V(t-\tau)(1+aV_1)}{H_1IV_1(1+aV(t-\tau))}-1$$

$$-\ln\frac{H(t-\tau)V(t-\tau)(1+aV)}{H_1IV_1(1+aV(t-\tau))}\bigg).$$

The function $x \mapsto x - 1 - \ln x$ is positive on $]0; +\infty[$, therefore, since

$$-k + \frac{\beta^3 H_1 V_1^2 \Lambda(1+a\Omega)}{4\varepsilon\eta^2(1+aV_1)^4} + \frac{a\beta\Lambda V_1}{\eta I_1(1+aV_1)} \leq 0 \quad and \quad \varepsilon > 0$$

we deduce that

$$\frac{dL(t)}{dt} \leq 0.$$

Furthermore, $\frac{dL(t)}{dt} = 0$ if and only if $H(t) = H(t-\tau) = H_1$, $V(t) = V(t-\tau) = V_1$ and $I(t) = I_1$. Therefore, the largest compact invariant set $\mathcal{M}$ is the singleton $\{E_1\}$, where E_1 is the infection persist equilibrium. This shows that $\lim_{t\longrightarrow\infty}(H, I, V) = (H_1, I_1, V_1)$. By the Lyapunov-LaSalle invariance theorem for delay differential systems (Theorem 2.5.3 in [13]), this implies that E_1 is globally asymptotically stable in the interior of $\mathbb{R}^3_+$. □

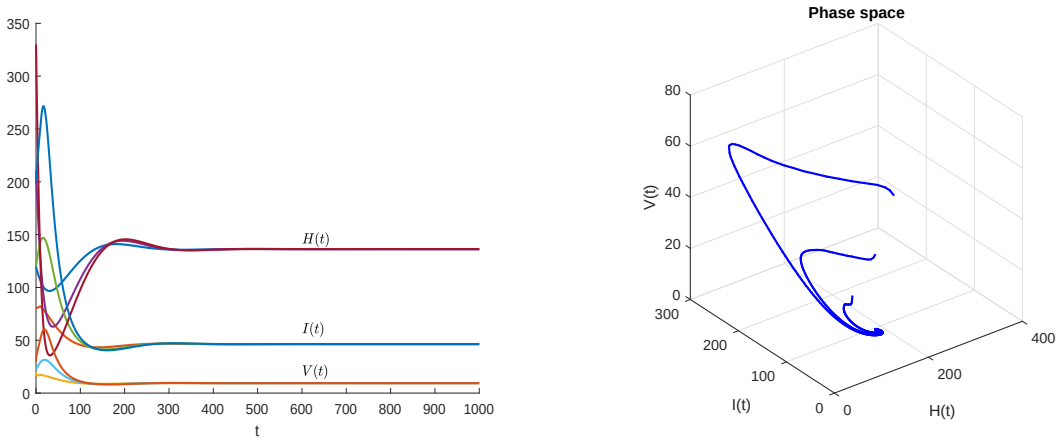
6.3. **Numerical results.** In this section, we present some numerical simulations which validate our theoretical results. To explore system (2.1) and illustrate the stability of infection persist equilibrium solution, we consider the set of following parameter value :

$$\begin{array}{c} \tau = 10;\ \beta = 0.0027;\ r_H = 0.01;\ m = 0.02;\ r_I = 0.0061;\ \lambda = 5; \\ \mu = 0.02;\ a = 0.001;\ \eta = 0.5\ ;\ \gamma = 2.1;\ \alpha = 0.05\ ;\ \varepsilon = 0.0116 > 0; \\ \Lambda = 550;\ E_0(379.7959; 0; 0);\ E_1 = (156.9218; 38.0708; 7.5522) \\ k = 1200 > \frac{\beta^3 H_1 V_1^2 \Lambda(1+a\Omega)}{4\varepsilon\eta^2(1+aV_1)^4} + \frac{a\beta\Lambda V_1}{\eta I_1(1+aV_1)} = 8.0643. \end{array} \tag{6.11}$$

For these parameter values, calculation by the formula of basic reproduction number leads to $\mathcal{R}_0 = 2.0729 > 1$; and thus, the infection persist equilibrium $E_1 = (156.9218; 38.0708; 7.5522)$ is globally asymptotically stable. This conclusion is demonstrated in Figure 2). The graph in **(a)** shows the time series of the solutions with constant initial conditions. The graph in **(b)** shows the trajectory in the phase diagram of system 2.1, which illustrates the stability of the infected E_1 with the history functions $\varphi_1(\theta) = 120$, $\varphi_2(\theta) = 80$, $\varphi_3(\theta) = 20$ (first trajectory); $\varphi_1(\theta) = 210$, $\varphi_2(\theta) = 120$, $\varphi_3(\theta) = 25$ (second trajectory); $\varphi_1(\theta) = 330$, $\varphi_2(\theta) = 200$, $\varphi_3(\theta) = 30$ (third trajectory).

7. Conclusion

In order to better understand the dynamics of HCV viral infection, this paper presents a mathematical study on the global dynamics of improved intra-host HCV models based on models in [2] and [1]. In this work we have established results about the local and global stability of equilibria known as infection free equilibrium and infection persist equilibrium. We can conclude that the stability of infection free equilibrium is completely determined by the value of the basic reproductive number $\mathcal{R}_0(\tau)$. If $\mathcal{R}_0(\tau) < 1$, then the infection free equilibrium will be asymptomatically stable and unstable if $\mathcal{R}_0(\tau) > 1$. For the infection persist equilibrium, we established conditions to ensure the local stability. We have needed another conditions to ensure the global stability for this equilibrium. Most of the results obtained in the present work generalize, in the same framework, those obtained by Eric Avila Vales et al. in [1] in the sense that in [1] the proliferation rates of infected and uninfected hepatocytes are identical and the



(A) (B)

FIGURE 2. Dynamical behaviour of system (2.1) with the set of parameter values (6.11)

absorption phenomenon was absent.

This work can be developed in many ways as follows:

(i) By taking into consideration the effect of several time discrete delays that may occur during the infection process, diffusion of cells and virions or other biological processes. For example, the following model can be study:

$$\begin{cases} \dfrac{\partial H(x,t)}{\partial t} = D_H \Delta H(x,t) + \lambda + r_H H(x,t)\left(1 - \dfrac{H(x,t)+I(x,t)}{k}\right) \\ \qquad\qquad -\mu H(x,t) - \dfrac{\beta H(x,t) V(x,t)}{1+aV(x,t)}, \\ \dfrac{\partial I(x,t)}{\partial t} = D_I \Delta I(x,t) + \dfrac{\beta e^{-\tau_1 m_1} H(x,t-\tau_1) V(x,t-\tau_1)}{1+aV(x,t-\tau_1)} \\ \qquad\qquad +r_I I(x,t)\left(1 - \dfrac{H(x,t)+I(x,t)}{k}\right) - \alpha I(x,t) v, \\ \dfrac{\partial V(x,t)}{\partial t} = D_V \Delta V(x,t) + \eta e^{-\tau_2 m_2} I(x,t-\tau_2) - \gamma V(x,t) - \dfrac{\beta H(x,t) V(x,t)}{1+aV(x,t)}, \end{cases}$$

where the parameter τ_1 accounts for the time between viral entry into a target cell and the production of new virus particles, after which the cells produce virus at per capita rate $\eta e^{-\tau_2 m_2}$ with a delay of τ_2. The constant m_1 is assumed to be the death rate for cells that are infected but not yet producing virus, so that $e^{-\tau_1 m_1}$ is the probability of surviving from time $t-\tau_2$ to time t. Likewise the constant m_2 is assumed to be the birth rate of the virions so that $e^{-\tau_2 m_2}$ is the probability of producing a fraction of η virions from time $t-\tau_2$ to time t. And D_H, D_I and D_V give the rates at which the target cells, the infected cells and the virus particles diffuse respectively;

(ii) By fitting the model with real data and finding a better estimation for the values of parameters.

(iii) Using a more general incidence rate as a function with certain desired properties, as considered in [11] or considering distributed delays in the equations for the infected cells and the virus particles, as is discussed in [15].

(iv) By investigating HCV co-infections with other viruses.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] E. Avila-Vales, A. Canul-Pech, G. E. García-Almeida, and A. G. C. Pérez, *Global stability of a delay virus dynamics model with mitotic transmission and cure rate*, Mathematical Modelling and Analysis of Infectious Diseases (K Hattaf and H Dutta, eds.), vol. 302, (2020) Springer, pp. 93–136.

[2] E. Avila-Vales, N. Chan-Chi, G. E .García-Almeida, and C. V. Leon, *Stability and hopf bifurcation in a delayed viral infection model with mitosis transmission*, Applied Mathematics and Computation **259** (2015), 293–312.

[3] L. J. S. Allen, *An introduction to mathematical biology*, Upper Saddle River, New Jersey, 2007.

[4] R. M. Anderson, R. M. May, and S. Gupta, *Non-linear phenomena in host-parasite interactions*, Parasitology **99** (1989), 59–79.

[5] R. Avedano, L. Esteva, J. A. Flores, J. L .Allen, G. Gomes, and J. E. Estrada, *A mathematical model for the dynamics of hepatitis C*, Comput. Math. Methods Med **4** (2002), no. 2, 109–118.

[6] F. Brauer, *Absolute stability in delay equations*, Journal of Differential Equa- tions **69** (1987), no. 2, 185–191.

[7] M. S. F. Chong, S. Masitah, L. Crossley, and A. Madzvamuse, *The stability analyses of the mathematical models of hepatitis C virus infection*, Modern Applied Science **9** (2015), no. 3, 250–271, ISSN 1913-1844.

[8] W. A. Coppel, *Stability and asymptotic behaviour of differential equation*, Boston Health, 1965.

[9] O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz, *On the definition and the computation of the basic reproduction ratio r0 in models for infectious diseases in heterogeneous populations*, J. Math. Biol **28** (1990), 365–382.

[10] K. Hattaf and N. Yousfi, *Global stability of a virus dynamics model with cure rate and absorption*, Journal of the Egyptian Mathematical Society **22** (2014), 386–389.

[11] K. Hattaf, N. Yousfi, and A. Tridane, *Mathematical analysis of a virus dynamics model with general incidence rate and cure rate*, Nonlinear Anal. RWA **13** (2012), 1866–1872.

[12] G. Huang, Y. Takeuchi, and W. Ma, *Lyapunov functionals for delay differential equations model of viral infections*, SIAM J. Appl. Math. **70** (2010), no. 7, 2693–2708.

[13] Y. Kuang, *Delay differential equations with applications in population dynamics*, Academic Press, San Diego, 1993.

[14] D. Li and W. Ma, *Asymptotic properties of an HIV-1 infection model with time delay*, J. Math. Anal. Appl. **332** (2007), 683–691.

[15] M. Y. Li, H. Shu, and A. Tridane, *Impact of intracellular delays and target-cell dynamics on in vivo viral infections*, SIAM J. Appl. Math. **70** (2010), no. 7, 2434–2448.

[16] A. Murase, T. Sasaki, and T. Kajiwara, *Stability analysis of pathogen-immune interaction dynamics*, J. Math. Biol. **51** (2005), 247–267.

[17] A. Nangue, *Global stability analysis of the original cellular model of hepatitis C virus infection under therapy*, American Journal of Mathematical and Computer Modelling **4** (2019), no. 3, 58–65.

[18] ———, *A delay-differential equation model of HCV infection with absorption under therapy*, Far East Journal of Applied Mathematics **108** (2020), no. 2, 151–178.

[19] A. Nangue, T. Donfack, and D. A. N. Yafago, *Global dynamics of an hepatitis C virus mathematical cellular model with a logistic term*, European Journal Of Pure And Applied Mathematics **12** (2019), no. 3, 944–959.

[20] A. Nangue, C. Fokoue, and R. Poumeni, *The global stability analysis of a mathematical cellular model of hepatitis C virus infection with non-cytolytic process*, journal of Applied Mathematics and Physics **7** (2019), 1531–1546.

[21] R. R.Regoes, D. Ebert, and S. Bonhoeffer, *Dose-dependent infection rates of parasites produce the allee effect in epidemiology*, Proc. R. Soc. Lond. Ser. B **269** (2002), 271–279.

[22] S. Ruan and S. Wei, *On the zeros of a third degree exponential polynomial with applications to a delayed model for the control of testosterone secretion*, IMA J. Math. Appl. Med. Biol. **18** (2001), 41–52.

[23] B. G. Sampath Aruna Pradeep and W Ma, *Stability properties of a delayed hiv dynamics model with beddington-deangelis functional response and absorption effect*, Mathematical Analysis **21** (2014), 421–434.

[24] L. Song, C. Ma, Q. Li, A. 1Fan, and K. Wang, *Global dynamics of a viral infection model with full ligistic terms and antivirus treatments*, Int. J. Biomath. **10** (2017), no. 01, 1750012.

[25] X. Song and A. U. Neumann, *Global stability and periodic solution of the viral dynamics*, J. Math. Anal. Appl. **329** (2007), 281–297.

[26] ———, *Global stability and periodic solution of the viral dynamics.*, J. Math. Anal. Appl. **329** (2007), 281–297.

[27] P. van den Driessche and J. Watmough, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission*, Mathematical Biosciences **180** (2002), 29–48.

[28] C. Vargas-De-Leon, *Global properties for virus dynamics model with mitotic transmission and intracellular delay*, J. Math. Ana. Appl **381** (2011), 884–890.
[29] WHO, *World health organization, global hepatitis report 2017*, ISBN:978-92-4-156545-5 (2018).
[30] R. Xu, *Global dynamics of a delayed HIV-1 infection model with absorption and saturation infection*, Int. J. Biomath. **5** (2012), no. 3, ID 1260012 (13 pages).

Corresponding author, Higher Teachers' Training College , University of Maroua, Cameroon, P.O.Box 55 Maroua
Current address: same
Email address: alexnanga02@gmail.com

Higher Teachers' Training College , University of Maroua, Cameroon, P.O.Box 55 Maroua
Current address: University of Maroua, Faculty of Sciences, Department of Mathematics and Computer Science, Cameroon, P.O. Box 814 Maroua
Email address: tacteufokam@gmail.com

Higher Teachers' Training College , University of Maroua, Cameroon, P.O.Box 55 Maroua
Current address: University of Maroua, Faculty of Sciences, Department of Mathematics and Computer Science, Cameroon, P.O. Box 814 Maroua
Email address: guedlaiayoubagg@gmail.com