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GLOBAL ANALYSIS OF A GENERALIZED VIRAL INFECTION CELLULAR MODEL WITH CELL-TO-CELL TRANSMISSION UNDER THERAPY

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Abstract. In virus dynamics, when a cell is infected, the number of virions outside the cells is reduced by one: this phenomenon is known as absorption effect. Most mathematical in intra-host models neglects this phenomenon. Virus-to-cell infection and direct cell-to-cell transmission are two fundamental modes whereby viruses can be propagated and transmitted. In this work, we propose a new virus dynamics model, which incorporates both modes and takes into account the absorption effect and treatment. First we show mathematically and biologically the well-posedness of our model preceded by the result on the existence and the uniqueness of the solutions. Also, an explicit formula for the basic reproduction number $\mathcal{R}_0$ of the model is determined. By analyzing the characteristic equations we establish the local stability of the uninfected equilibrium and the infected equilibrium in terms of $\mathcal{R}_0$. The global behaviour of the model is investigated by constructing an appropriate Lyapunov functional for uninfected equilibrium and by applying a geometric approach to the study of the infected equilibrium. Numerical simulations are carried out, to confirm the obtained theoretical result in a particular case.

1. Introduction

Mathematical modeling is one of the most coveted areas in which virus infection research is undertaken. It consists of modeling the evolution of the infection using tools, mainly differential equations. The modeling of infectious diseases is a tool that has been used to study the mechanisms by which diseases spread, to predict the future course of an outbreak, and to evaluate strategies to control an epidemic. In recent years, grandiose efforts have been devoted to the mathematical modeling of intra-host viral dynamics. Mathematical models have been developed to describe the process of in vivo infection of many viruses. Many viruses infect humans and cause different infectious diseases such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), Ebola virus, Zika virus, and nowadays new coronavirus (COVID-19 virus). They are often transmitted in the body by two fundamentally distinct modes, either by virus-to-cell infection through the extracellular space or by cell-to-cell transmission involving direct cell-to-cell contact [7, 24, 26, 35, 43]. During both infection modes, a part of infected cells returns to the uninfected state by loss of all covalently closed circular DNA (cccDNA) from their nucleus [13, 20, 10].

To model viral infection dynamics, several mathematical models have been proposed and developed [3, 9]. Most of these models are based on the assumption that healthy cells can only be infected by viruses, and so they consider only the virus-to-cell infection mode [1, 16, 29, 28, 30, 31]. Authors in [23] consider a mathematical model that describes a viral infection of HIV-1 with both virus-to-cell and cell-to-cell transmission with other features. It should be noted that the total infection rate of

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uninfected cells that it has been considered is a particular case from the one we consider in this work. However, there are few virus dynamics models in literature with both modes of transmission [33, 34, 36] and taking into account the cure of infected cells. Motivated by the mentioned biological and mathematical considerations above, [17] propose a virus dynamics model with two transmission modes, i.e., cell-to-cell and virus-to-cell transmission modes. We note that in virus dynamics model proposed by [16], 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 number of pathogens are reduced into the blood volume : this is called absorption effect. Hence, some researchers (see, for example, [2, 27, 42, 14] and the references therein) have included the absorption effect into their models. We also find that the treatment [6] is not taken into account. So, to make this last model a little more realistic, motivated by the works in [16], in the present paper we are concerned with the effect of both virus-to-cell and cell-to-cell transmissions with absorption and antiviral treatments on the global dynamics of a generalized infection viral model.

The rest of this paper is organized as follows. In Section 2, the mathematical model is constructed. Section 3 deals with the existence, the positivity and boundedness of solutions of our model. In addition the threshold parameter $\mathcal{R}_0$ of model (2.2) is determined and the existence of the equilibria is discussed with respect to the value of $\mathcal{R}_0$. In Section 4, local stability of the equilibria are completely discussed. In Section 5, global stability of the equilibria is studied. The global behaviour of the model is investigated by constructing an appropriate Lyapunov functional for uninfected equilibrium and by applying Li-Muldowney global stability-criterion to the infected equilibrium. Numerical simulations are shown in Section 6. Finally, a brief discussion is presented in Section 7.

2. Formulation and description of the model

The model studied in [16] is described by the following three differential system of equations:

$$\begin{cases} \frac{dT}{dt} = \lambda - dT - f(T,I,V)V - g(T,I)I + \rho I, \\ \frac{dI}{dt} = f(T,I,V)V + g(T,I)I - (a+\rho)I, \\ \frac{dV}{dt} = kI - \mu V, \end{cases} \tag{2.1}$$

where $T(t)$, $I(t)$, and $V(t)$ denote the concentrations of uninfected cells, infected cells, and free viruses at time t, respectively, λ is the recruitment rate of uninfected cells, ρ is the cure rate of infected cells, k is the production rate of free viruses by infected cells, and d, a, and μ are the death rates of uninfected cells, infected cells, and free viruses, respectively. In addition, healthy cells become infected either by free viruses at rate $f(T,I,V)V$ or by direct contact with an infected cell at rate $g(T,I)I$. Hence, the term $f(T,I,V)V + g(T,I)I$ represents the total infection rate of uninfected cells.

As we mentioned above, system (2.1) does not take into account the treatment and the absorption phenomenon. we consider in this paper the following virus dynamics model with therapy and absorption effect,

$$\begin{cases} \frac{dT}{dt} = \lambda - dT - (1-\eta)f(T,I,V)V - g(T,I)I + \rho I, \\ \frac{dI}{dt} = (1-\eta)f(T,I,V)V + g(T,I)I - (a+\rho)I, \\ \frac{dV}{dt} = (1-\varepsilon)kI - \mu V - (1-\eta)f(T,I,V)V, \end{cases} \tag{2.2}$$

where the term $-(1-\eta)f(T,I,V)V$ in the third equation represents the loss of pathogens due to the absorption into uninfected cells. In addition, the therapeutic effect in this model involved blocking virions production (referred to as drug effectiveness) and reducing new infections which, are described in fractions $(1-\varepsilon)$ and $(1-\eta)$, respectively.

System (2.2) is subject to the initial conditions

$$T(0) = T_0,\ I(0) = I_0,\ V(0) = V_0 \text{ with } T_0 \geq 0,\ I_0 \geq 0,\ V_0 \geq 0. \tag{2.3}$$

3. Relevant assumptions and preliminary results

3.1. **Relevant assumptions.** The incidence function g for direct cell-to-cell transmission mode is assumed to be continuously differentiable in the interior of $\mathbb{R}^2_+$ and satisfies the following properties :

(H_{01}): $g(0, I) = 0$ for all $I \geq 0$, $\frac{\partial g}{\partial T}(T, I) \geq 0$ for all $T \geq 0$ and $I \geq 0$(or $g(T, I)$ is a strictly increasing function with respect to T when $f \equiv 0$).
(H_{02}): $\frac{\partial g}{\partial I}(T, I) \leq 0$ for all $T \geq 0$ and $I \geq 0$.

In addition, the incidence function f for virus-to-cell infection mode, which denotes the average number of cells which are infected by each virus in unit time, is assumed to be continuously differentiable in the interior of $\mathbb{R}^3_+$ and has the properties similar to those assumed in [14, 18] :

(H_1): $f(0, I, V) = 0$; for all $I \geq 0$ and $V \geq 0$.
(H_2): $\frac{\partial f}{\partial T}(T, I, V) \geq 0$; for all $T > 0$, $I \geq 0$ and $V \geq 0$.
(H_3): $\frac{\partial f}{\partial I}(T, I, V) \leq 0$ and $\frac{\partial f}{\partial V}(T, I, V) \leq 0$ for all $T \geq 0$, $I \geq 0$ and $V \geq 0$.
(H_4): $f(T, I, V) + V\frac{\partial f}{\partial V}(T, I, V) \geq 0$ for all $T > 0$, $I \geq 0$, and $V \geq 0$.

The significance of these assumptions is as follows :

- (H_{01}) means that the incidence rate by cell-to-cell transmission is equal to zero if there are no susceptible cells. This incidence rate is increasing when the numbers of infected cells are constant and the number of susceptible cells increases. Biologically speaking, the greater the amount of susceptible cells, the greater the average number of cells infected by direct contact with an infected cell in the unit time.
- (H_{02}) means that the greater the amount of infected cells, the lower the average number of cells infected by direct contact in the unit time.
- (H_1) means that the incidence rate for virus-to-cell infection mode is equal to zero if there are no susceptible cells.
- (H_2) signifies that the incidence rate is increasing when the numbers of infected cells and viruses are constant and the number of susceptible cells increases. Hence, the second hypothesis means; the more the amount of susceptible cells, the more the average number of cells which are infected by each virus in the unit time will occur.
- The first assumption of (H_3) means the more the amount of infected cells, the less the average number of cells which are infected by each virus in the unit time will be and the second assumption of (H_3) means the more the amount of infected virus, the less the average number of cells which are infected by each virus in the unit time will be.
- (H_4) means that if the total number of cells is constant, the more the amount of virus is, then the more the number of cells which are infected in the unit time will be.

Therefore, the hypotheses summarized in assumptions (H_{01}) - (H_4) are reasonable and consistent with the reality. For more informations concerning the biological significance of hypotheses (H_{01}), (H_{02}), (H_1), (H_2) and (H_3) , we refer the readers to [15, 41]. Furthermore, the five assumptions (H_{01}), (H_{02}), (H_1), (H_2) and (H_3) are satisfied by most incidence rates existing in the literature.

3.2. **Positivity and boundedness.** First of all we show that the solutions of system 2.2 with non-negative initial conditions remain nonnegative and bounded for all $t \geq 0$. Let $\mathbb{R}^3_+ = \{(T, I, V) \in \mathbb{R}^3 : T \geq 0,\ I \geq 0,\ V \geq 0\}$.

It is well known by the fundamental theory of ordinary differential equations (uniqueness of solutions

of Cauchy problem), that system (2.2) has a unique local solution $(T(t), I(t), V(t))$ satisfying the initial conditions (2.3). We have the following results.

Theorem 3.1. *Let (T, I, V) be a solution of the initial value problem (2.2), (2.3) on an interval $[t_0, t_1)$ with $t_1 > t_0 \geq 0$. Assume that the initial data of the initial value problem (2.2), (2.3) satisfy $T_0 \geq 0$, $I_0 > 0$, and $V_0 > 0$. Then T, I and V remain positive for all $t \in [t_0, t_1)$.*

Proof. We first prove that $T(t)$ is positive for all $t > 0$. Suppose $T(t)$ is not always positive. Let $\tau > 0$ be the first time such that $T(\tau) = 0$. By the first equation of (2.2) we have $\frac{dT}{dt}(\tau) = \lambda + \rho I(\tau) > 0$, provided $T(\tau) > 0$, which implies $T(t) < 0$ for $t \in (\tau - \epsilon, \tau)$, for sufficiently small $\epsilon > 0$. A contradiction. Therefore $T(t)$ is positive for all $t > 0$. Now let us show that $I(t)$ and $V(t)$ are positive. Call the variables x_i. If there is an index i and a time t $(t_0 \leq t < t_1)$ for which $x_i(t) = 0$, we consider t_* be the infimum of all such t for any i. Then the restriction of the solution to the interval $[t_0, t_*)$ is positive and $x_i(t_*) = 0$ for a certain value of i. The second and third equation of system (2.2) can be written in the form:

$$\frac{dx_i(t)}{dt} = -x_i F_i(x_1, x_2, x_3) + G_i(x_1, x_2, x_3),\ i \in \{2, 3\}$$

where

$$\begin{aligned}
F_2(x_1, x_2, x_3) &= a + \rho, \\
F_3(x_1, x_2, x_3) &= \mu + (1 - \eta) f(x_1, x_2, x_3), \\
G_2(x_1, x_2, x_3) &= (1 - \eta) f(x_1, x_2, x_3) x_3 + g(x_1, x_2), \\
G_3(x_1, x_2, x_3) &= (1 - \eta) k x_2
\end{aligned}$$

are. non-negative. As a consequence $\frac{dx_i(t)}{dt} \geq -x_i F_i(x_1, x_2, x_3)$ and $\frac{d}{dt}(\log x_i) \geq -F_i(x_1, x_2, x_3) \geq -C$, $i \in 2, 3$, for a positive constant C. To show this, we use the fact that the solution remains in a compact set. It follows that $x_i(t_*) \geq x_i(t_0) e^{-C(t_* - t_0)} > 0$, which is a contradiction and the Theorem 3.1 is proven. □

This means that the first quadrant $\mathbb{R}^3_+$ is positively invariant with respect to system (2.2). The boundedness of the solutions is guaranteed by the following theorem.

Theorem 3.2. *All solutions of (2.2) are uniformly bounded in the compact subset*

$$\Omega = \left\{ (T, I, V) \in \mathbb{R}^3_+ : T \leq \frac{\lambda}{\delta},\ I \leq \frac{\lambda}{\delta},\ V \leq \frac{(1 - \varepsilon) k \lambda}{\delta} \right\},$$

where $\delta = \min\{a, d\}$.

Proof. Let $(T(t), I(t), V(t))$ be any solution with nonnegative initial condition (T_0, I_0, V_0). Adding the first two equations of system (2.2), we obtain

$$\begin{aligned}
\frac{d}{dt}(T + I) &= \lambda - dT - aI, \\
&\leq \lambda - \delta(T + I).
\end{aligned}$$

Hence

$$\limsup_{t \to +\infty} (T(t) + I(t)) \leq \frac{\lambda}{\delta}.$$

Similarly, from the third equation of system (2.2) one has :

$$\begin{aligned}
\frac{dV}{dt} &\leq (1 - \varepsilon) k \frac{\lambda}{\delta} - \mu V - f(T, I, V) V, \\
&\leq (1 - \varepsilon) k \frac{\lambda}{\delta} - \mu V.
\end{aligned}$$

Hence,

$$\limsup_{t\to\infty}(V(t)) \leq \frac{(1-\varepsilon)k\lambda}{\delta}.$$

Hence, all solutions of system (2.2) starting in $\mathbb{R}^3_+$ are eventually confined in the region Ω. This completes the proof. □

Remark 3.1. We would like to make the following remarks.

(i) These two previous theorems show mathematically and biologically the well-posedness [22] of our model (2.2).

(ii) From these two results, if the initial data satisfy the inequalities $T_0 + I_0 \leq \frac{\lambda}{\delta}$ and $V_0 \leq \frac{(1-\varepsilon)k\lambda}{\delta}$ then the whole solution most satisfy these inequalities. This means that we have identified an invariant subset and for biological considerations, we will study system (2.2) in the subset Ω.

3.3. **Equilibra.**

3.3.1. *Basic reproduction numbers and disease-free equilibrium.* Now, we discuss the existence of equilibria. By simple computation system (2.2) always has one uninfected equilibrium of the form $E^0 = (T^0, 0, 0)$ with $T^0 = \dfrac{\lambda}{d}$. This will allow us to determine a threshold parameter to discuss the dynamic behaviour of the epidemic model. This later will be decisive for the rest of the work. This parameter is called the basic reproduction number and it measures the expected average number of new infected cells generated by a single virion in a completely healthy cell.
According to the concept of next generation matrix in [8] and the computation of the basic reproduction number presented in [39], we can compute the basic reproduction number of system (2.2). We have the following result :

Proposition 3.3. *The basic reproduction number of the model (2.2) is given as :*

$$\mathcal{R}_0 = \frac{(1-\varepsilon)(1-\eta)kf(\frac{\lambda}{d},0,0) + (\mu+(1-\eta)f(\frac{\lambda}{d},0,0))g(\frac{\lambda}{d},0)}{(a+\rho)(\mu+(1-\eta)f(\frac{\lambda}{d},0,0))}$$

which can be rewritten as

$$\mathcal{R}_0 = \mathcal{R}_{01} + \mathcal{R}_{02}$$

where

$$\mathcal{R}_{01} = \frac{(1-\varepsilon)k(1-\eta)f(\frac{\lambda}{d},0,0)}{(a+\rho)(\mu+(1-\eta)f(\frac{\lambda}{d},0,0))} \text{ and } \mathcal{R}_{02} = \frac{g(\frac{\lambda}{d},0)}{a+\rho}.$$

Proof. Based on notations in [39], the nonnegative matrix F and the non-singular M-matrix V are given by :

$$F = \begin{pmatrix} g(T^0,0) & (1-\eta)f(\frac{\lambda}{d},0,0) \\ 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} -(a+\rho) & 0 \\ (1-\varepsilon)k & -\mu-(1-\eta)f(\frac{\lambda}{d},0,0) \end{pmatrix}.$$

The next generation matrix is given by

$$F.V^{-1} = \begin{pmatrix} -\dfrac{g(\frac{\lambda}{d},0)}{a+\rho} - \dfrac{(1-\varepsilon)(1-\eta)kf(\frac{\lambda}{d},0,0)}{(a+\rho)\left(\mu+(1-\eta)f(\frac{\lambda}{d},0,0)\right)} & -\dfrac{(1-\mu)f(\frac{\lambda}{d},0,0)}{\mu+(1-\mu)f(\frac{\lambda}{d},0,0)} \\ 0 & 0 \end{pmatrix},$$

and the basic reproduction number of system (2.2) is defined as

$$\mathcal{R}_0 = \rho(-F.V^{-1})$$

where $\rho(A)$ denotes the spectral radius of a matrix A. It follows that :

$$\begin{aligned}\mathcal{R}_0 &= \frac{(1-\varepsilon)(1-\eta)kf(\frac{\lambda}{d},0,0)}{(a+\rho)\left(\mu+(1-\eta)f(\frac{\lambda}{d},0,0)\right)}+\frac{g(T^0,0)}{a+\rho},\\ &= \frac{(1-\varepsilon)(1-\eta)kf(\frac{\lambda}{d},0,0)+(\mu+(1-\eta)f(\frac{\lambda}{d},0,0))g(\frac{\lambda}{d},0)}{(a+\rho)(\mu+(1-\eta)f(\frac{\lambda}{d},0,0))}.\end{aligned}$$

This completes the proof of theorem 3.3. □

Remark 3.2. According to [16], $\mathcal{R}_{01}$ is the basic reproduction number corresponding to virus-to-cell infection mode, whereas $\mathcal{R}_{02}$ is the basic reproduction number corresponding to cell-to-cell transmission mode.

3.3.2. *Infected equilibrium.*

Proposition 3.4. *If $\mathcal{R}_0 > 1$, then system (2.2) has a unique chronic infection equilibrium of the form $E^* = (T^*, I^*, V^*)$ with $T^* \in (0, T^0)$, $I^* > 0$ and $V^* > 0$.*

Proof. To find the other equilibrium of system (2.2), which is named the infected equilibrium, we solve the algebraic system

$$\begin{cases}\lambda - dT - (1-\eta)f(T,I,V)V - g(T,I)I + \rho I = 0, & (3.1)\\ (1-\eta)f(T,I,V)V + g(T,I)I - (a+\rho)I = 0, & (3.2)\\ (1-\varepsilon)kI - \mu V - (1-\eta)f(T,I,V)V = 0. & (3.3)\end{cases}$$

Adding (3.2) and (3.3) one has :

$$V = \frac{1}{\mu}[(1-\varepsilon)k + g(T,I) - (a+\rho)]I. \quad (3.4)$$

Reporting (3.4) into (3.2) yields :

$$[(1-\varepsilon)k + g(T,I) - (a+\rho)](1-\eta)f(T,I,V) + \mu g(T,I) - \mu(a+\rho) = 0. \quad (3.5)$$

Since $I = \frac{1}{a}(\lambda - dT) \geq 0$, we have $T \leq \frac{\lambda}{d}$. Hence, there is no biological equilibrium when $T > \frac{\lambda}{d}$. We define the function ψ on the interval $\left[0, T^0\right]$ by :

$$\psi(T) = [(1-\varepsilon)k + g(T,I) - (a+\rho)](1-\eta)f(T,I,V) + \mu g(T,I) - \mu(a+\rho).$$

We have

$$\psi(0) = -\mu(a+\rho) < 0.$$

Moreover,

$$\begin{aligned}\psi(T^0) =&(1-\varepsilon)k(1-\eta)f(T^0,0,0) + [\mu+(1-\eta)f(T^0,0,0)]g(T^0,0),\\ &-(a+\rho)\left[\mu+(1-\eta)f(T^0,0,0)\right]\\ =&(a+\rho)\left(\mu+(1-\eta)f(T^0,0,0)\right)\\ &\left\{\frac{(1-\varepsilon)k(1-\eta)f(T^0,0,0)+[\mu+(1-\eta)f(T^0,0,0)]g(T^0,0)}{(a+\rho)(\mu+(1-\eta)f(T^0,0,0))}-1\right\},\\ =&(a+\rho)\left(\mu+(1-\eta)f(T^0,0,0)\right)(\mathcal{R}_0-1)\end{aligned}$$

and

$$\begin{aligned}\frac{d\psi}{dT}(T) =&(1-\eta)\left(\frac{\partial g}{\partial T}(T,I)-\frac{d}{a}.\frac{\partial g}{\partial I}(T,I)\right)f(T,I,V)+(1-\eta)\{\frac{\partial f}{\partial T}(T,I,V)\\&-\frac{d}{a}\frac{\partial f}{\partial I}(T,I,V)+\frac{1}{\mu}[(\frac{\partial g}{\partial T}(T,I)-\frac{d}{a}.\frac{\partial g}{\partial I}(T,I))I\\&-\frac{d}{a}((1-\varepsilon)k+g(T,I)-(a+\rho)].\frac{\partial f}{\partial V}(T,I,V)\}\\&[(1-\varepsilon)k+g(T,I)-(a+\rho)]+\mu\left(\frac{\partial g}{\partial T}(T,I)-\frac{d}{a}\frac{\partial g}{\partial I}(T,I)\right),\\=&\left(\frac{\partial g}{\partial T}(T,I)-\frac{d}{a}.\frac{\partial g}{\partial I}(T,I)\right)[\mu+(1-\eta)f(T,I,V)]\\&+(1-\eta)\left(\frac{\partial f}{\partial T}(T,I,V)-\frac{d}{a}\frac{\partial f}{\partial I}(T,I,V)\right)[(1-\varepsilon)k+g(T,I)-(a+\rho)]\\&+(1-\eta)\frac{I}{\mu}\left((\frac{\partial g}{\partial T}(T,I)-\frac{d}{a}.\frac{\partial g}{\partial I}(T,I))\right)[(1-\varepsilon)k+g(T,I)-(a+\rho)]\\&-(1-\eta)\frac{d}{a}\frac{1}{\mu}\frac{\partial f}{\partial V}(T,I,V)\left[(1-\varepsilon)k+g(T,I)-(a+\rho)\right]^2.\end{aligned}$$

We deduce that

$$\frac{d\psi}{dT}(T)>0.$$

Hence, for $\mathcal{R}_0>1$, there exists a unique infected equilibrium $E^*=(T^*,I^*,V^*)$ with $T^*\in\left(0,\frac{\lambda}{d}\right)$, $I^*>0$ and $V^*>0$. This completes the proof of proposition 3.4. □

4. Local stability

In this section, we discuss the local stability of the two equilibria of system (2.2).

Theorem 4.1. *The disease-free equilibrium E^0 is locally asymptotically stable if $\mathcal{R}_0<1$ and becomes unstable if $\mathcal{R}_0>1$.*

Proof. The Jacobian matrix of system (2.2) at the disease-free equilibrium E^0 is given by :

$$J_{E^0}=\begin{pmatrix}-d & -g(T^0,0)+\rho & -(1-\eta)f(T^0,0,0)\\ 0 & g(T^0,0)-(a+\rho) & (1-\eta)f(T^0,0,0)\\ 0 & (1-\varepsilon)k & -\mu-(1-\eta)f(T^0,0,0)\end{pmatrix}.$$

Computing the characteristic equation of J_{E^0}, one has

$$-(X+d)(X^2+a_1X+a_0)=0 \tag{4.1}$$

where

$$\begin{aligned}a_1 &= -g(T^0,0)+(a+\rho)+\mu+(1-\eta)f(T^0,0,0),\\ a_0 &= -g(T^0,0)\left[\mu+(1-\eta)f(T^0,0,0)\right]+(a+\rho)\left[\mu+(1-\eta)f(T^0,0,0)\right]\\&\quad -(1-\varepsilon)(1-\eta)kf(T^0,0,0).\end{aligned}$$

a_0 and a_1 can also be written in the form :

$$a_1=\mu+(1-\eta)f(T^0,0,0)+(a+\rho)(1-\mathcal{R}_{02}),$$

and

$$a_0=(a+\rho)(\mu+(1-\eta)f(T^0,0,0))(1-\mathcal{R}_0).$$

Since $\mathcal{R}_0 < 1$, it follows that a_0 and a_1 are positive. From the Routh-Hurwitz criteria [12] we know that all roots of $X^2 + a_1X + a_0 = 0$ have negative real parts. Thus all roots of (4.1) have negative real parts. Therefore, the disease-free equilibrium E^0 is locally asymptotically stable for $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 < 1$. □

Next, we study the local stability of the chronic infection equilibrium E^*. Note that the equilibrium E^* does not exist if $\mathcal{R}_0 < 1$ and $E^* = E^0$ when $\mathcal{R}_0 = 1$.

Theorem 4.2. *The chronic infection equilibrium E^* is locally asymptotically stable if $\mathcal{R}_0 > 1$, $aI^*\frac{\partial g}{\partial T}(T^*, I^*) > (1-\varepsilon)kd$ and (H_4) are satisfied.*

Proof. The Jacobian matrix of system (2.2) at the chronic infection equilibrium E^* is given by

$$J_{E^*} = \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix}$$

where

$$\begin{aligned}
a_{11} &= -d - (1-\eta)V^*\frac{\partial f}{\partial T}(E^*) - I^*\frac{\partial g}{\partial T}(T^*, I^*),\\
a_{12} &= -(1-\eta)V^*\frac{\partial f}{\partial I}(E^*) - I^*\frac{\partial g}{\partial I}(T^*, I^*) - g(T^*, I^*) + \rho,\\
a_{13} &= -(1-\eta)\left(V^*\frac{\partial f}{\partial V}(E^*) + f(E^*)\right),\\
a_{21} &= (1-\eta)V^*\frac{\partial f}{\partial T}(E^*) + I^*\frac{\partial g}{\partial T}(T^*, I^*),\\
a_{22} &= (1-\eta)V^*\frac{\partial f}{\partial I}(E^*) + I^*\frac{\partial g}{\partial I}(T^*, I^*) + g(T^*, I^*) - (a+\rho),\\
a_{23} &= (1-\eta)\left(V^*\frac{\partial f}{\partial V}(E^*) + f(E^*)\right),\\
a_{31} &= (1-\eta)V^*\frac{\partial f}{\partial T}(E^*),\\
a_{32} &= (1-\varepsilon)k - (1-\eta)V^*\frac{\partial f}{\partial T}(E^*),\\
a_{33} &= -\mu - (1-\eta)\left(V^*\frac{\partial f}{\partial T}(E^*) + f(E^*)\right).
\end{aligned}$$

Computing the characteristic equation of J_{E^*}, one has

$$X^3 + a_2X + a_1X + a_0 = 0, \tag{4.2}$$

where

$$\begin{aligned}
a_2 =& d + a + \rho - g(T^*, I^*) + \mu + (1-\eta)\left(V^*\frac{\partial f}{\partial V}(E^*) + f(E^*)\right) + (1-\eta)V^*\frac{\partial f}{\partial T}(E^*)\\
&- (1-\eta)V^*\frac{\partial f}{\partial I}(E^*) + I^*\frac{\partial g}{\partial T}(T^*, I^*) - I^*\frac{\partial g}{\partial I}(T^*, I^*),\\
a_1 =& d\left[a + \rho - g(T^*, I^*) - I^*\frac{\partial g}{\partial I}(T^*, I^*) + (1-\eta)\left(V^*\frac{\partial f}{\partial V}(E^*) + f(E^*)\right)\right]\\
&+ \left[\mu + (1-\eta)\left(V^*\frac{\partial f}{\partial V}(E^*) + f(E^*)\right)\right]\left[a + \rho - g(T^*, I^*) - I^*\frac{\partial g}{\partial I}(T^*, I^*)\right]\\
&+ (1-\eta)(a+\mu)\frac{\partial f}{\partial T}(E^*) + (1-\eta)aI^*\frac{\partial f}{\partial T}(E^*) - (1-\eta)(1+\mu)V^*\frac{\partial f}{\partial I}(E^*).
\end{aligned}$$

and

$$\begin{aligned}
a_0 =& d\left((a+\rho-g(T^*,I^*)-I^*\frac{\partial g}{\partial I}(T^*,I^*)\right)\left[\mu+(1-\eta)\left(V^*\frac{\partial f}{\partial V}(E^*)+f(E^*)\right)\right]\\
&+(1-\eta)aV^*I^*\frac{\partial f}{\partial V}(E^*)\frac{\partial g}{\partial T}(T^*,I^*)-d(1-\varepsilon)(1-\eta)kV^*\frac{\partial f}{\partial V}(E^*)\\
&-d(1-\varepsilon)(1-\eta)kf(E^*)+a\mu\left(V^*\frac{\partial f}{\partial T}(E^*)+I^*\frac{\partial g}{\partial T}(T^*,I^*)\right)\\
&+aI^*\frac{\partial g}{\partial T}(T^*,I^*)f(E^*)-d\mu V^*\frac{\partial f}{\partial I}(E^*).\\
=& d\left(a+\rho-g(T^*,I^*)-I^*\frac{\partial g}{\partial I}(T^*,I^*)\right)\left[\mu+(1-\eta)\left(V^*\frac{\partial f}{\partial V}(E^*)+f(E^*)\right)\right]\\
&+(1-\eta)\left(V^*\frac{\partial f}{\partial V}(E^*)+f(E^*)\right)\left(aI^*\frac{\partial g}{\partial T}(T^*,I^*)-d(1-\varepsilon)k\right)\\
&-(1-\eta)d\mu V^*\frac{\partial f}{\partial I}(E^*)+a\mu\left((1-\eta)V^*\frac{\partial f}{\partial T}(E^*)+I^*\frac{\partial g}{\partial T}(T^*,I^*)\right).
\end{aligned}$$

Since

$$\mathcal{R}_0>1$$

and

$$\begin{aligned}
a+\rho-g(T^*,I^*)=&\frac{1}{\mu}[(1-\varepsilon)k+g(T^*,I^*)-(a+\rho)](1-\eta)f(T^*,I^*,V^*)\\
=&\frac{V^*}{I^*}(1-\eta)f(T^*,I^*,V^*)>0,
\end{aligned}\tag{4.3}$$

we deduce that a_0, a_1, and a_2 are positive. In fact, firstly, we deduce from (4.3) that $a+\rho-g(T^*,I^*)>0$. Furthermore, using assumptions (H_{01}), (H_{01}), (H_2), (H_3) and (H_4), we obtain respectively, $\frac{\partial g}{\partial T}(T^*,I^*)\geq 0$, $\frac{\partial g}{\partial I}(T^*,I^*)\leq 0$, $\frac{\partial f}{\partial T}(E^*)\geq 0$, $\frac{\partial f}{\partial I}(E^*)\leq 0$ and $V^*\frac{\partial f}{\partial V}(E^*)+f(E^*)\geq 0$. This shows that a_2 is positive. Secondly, from the same arguments used to prove the positivity of a_2, we deduce that a_1 is positive. Finally, in addition to assumptions (H_{01}), (H_{01}), (H_2), (H_3) and (H_4), using the fact that $aI^*\frac{\partial g}{\partial T}(T^*,I^*)-d(1-\varepsilon)k>0$, we deduce that a_0 is positive.

Moreover,

$$\begin{aligned}
a_1a_2-a_0=&da_1+(a+\rho+\mu-g(T^*,I^*)-I^*\frac{\partial g}{\partial I}(T^*,I^*))a_1+(1-\eta)\\
&\left(V^*\frac{\partial f}{\partial T}(E^*)f(E^*)\right)a_1+\left((1-\eta)(V^*\frac{\partial f}{\partial T}(E^*))+I^*\frac{\partial g}{\partial T}(T^*,I^*)\right)a_1\\
&-(1-\eta)V^*\frac{\partial f}{\partial I}(E^*)a_1-(1-\eta)\left(V^*\frac{\partial f}{\partial V}(E^*)+f(E^*)\right)\\
&\left(da+d\rho-dg(T^*,I^*)-dI^*\frac{\partial g}{\partial I}(T^*,I^*)+aI^*\frac{\partial g}{\partial T}(T^*,I^*)-d(1-\varepsilon)k\right)\\
&-d\mu\left(a+\rho-g(T^*,I^*)-I^*\frac{\partial g}{\partial I}(T^*,I^*)-(1-\eta)V^*\frac{\partial f}{\partial I}(E^*)\right)\\
&-a\mu\left[(1-\eta)V^*\frac{\partial f}{\partial T}(E^*)+I^*\frac{\partial g}{\partial T}(T^*,I^*)\right],
\end{aligned}$$

$$
\begin{aligned}
=&(d+\mu)a_1+(1-\eta)\left(V^*\frac{\partial f}{\partial V}(E^*)+f(E^*)\right)\left(a_1-aI^*\frac{\partial g}{\partial T}(T^*,I^*)\right)(a+\rho\\
&-g(T^*,I^*)-I^*\frac{\partial g}{\partial I}(T^*,I^*))\left(a_1-d(1-\eta)\left(V^*\frac{\partial f}{\partial V}(E^*)+f(E^*)\right)-d\mu\right)\\
&-(1-\eta)(a_1-d\mu)V^*\frac{\partial f}{\partial I}(E^*)+\left((1-\eta)V^*\frac{\partial f}{\partial I}(E^*)+I^*\frac{\partial g}{\partial T}(T^*,I^*)\right)\\
&(a_1-a\mu)+d(1-\varepsilon)(1-\eta)k\left(V^*\frac{\partial f}{\partial V}(E^*)+f(E^*)\right).
\end{aligned}
$$

One deduces that $a_1a_2-a_0>0$. From the Routh-Hurwitz criteria in [12] we know that all roots of (4.2) have negative real parts. Thus, the chronic infection equilibrium E^* is locally asymptotically stable for $\mathcal{R}_0>1$. □

5. Global stability

In this section, we investigate the global stability of the disease-free equilibrium E^0 and the chronic infection equilibrium E^*.

For the global stability, we assume that $a\geq d$. Biologically, this assumption is often satisfied because a represents the death rate of infected cells and includes the possibility of death by bursting of infected cells. Furthermore, this assumption is considered by many authors; see, for example, [16, 37, 32, 40]. Particularly in [4], this condition means that the average life-time of infected cells $\frac{1}{a}$ is shorter than the average life-time of infected cells $\frac{1}{d}$.
Therefore, we have the following result.

Theorem 5.1. *If $\mathcal{R}_0<1$ and $a\geq d$ then the uninfected equilibrium E^0 is globally asymptotically stable.*

Proof. Construct the following Lyapunov functional

$$
L(T(t),I(t),V(t))\equiv L(t)=I(t)+\frac{(1-\eta)f(T^0,0,0)}{\mu+(1-\eta)f(T^0,0,0)}V(t).
$$

Calculating the time derivative of $L(t)$ along the positive solution of system (2.2), we have

$$
\begin{aligned}
\frac{dL}{dt}=&\frac{dL}{dT}\frac{dT}{dt}+\frac{dL}{dI}\frac{dI}{dt}+\frac{dL}{dV}\frac{dV}{dt},\\
=&\frac{dI}{dt}+\frac{(1-\eta)f(T^0,0,0)}{\mu+(1-\eta)f(T^0,0,0)}\frac{dV}{dt},\\
=&(1-\eta)f(T,I,V)V+g(T,I)I-(a+\rho)I+\frac{(1-\eta)(1-\varepsilon)kf(T^0,0,0)}{\mu+(1-\eta)f(T^0,0,0)}I\\
&-\mu\frac{(1-\eta)f(T^0,0,0)}{\mu+(1-\eta)f(T^0,0,0)}V-\frac{(1-\eta)^2f(T^0,0,0)}{\mu+(1-\eta)f(T^0,0,0)}f(T,I,V)V,\\
=&\left[f(T,I,V)-\frac{(1-\eta)f(T^0,0,0)}{\mu+(1-\eta)f(T^0,0,0)}\left(\mu+(1-\eta)f(T,I,V)\right)\right]V\\
&+(a+\rho)I\left[\frac{(1-\eta)(1-\varepsilon)kf(T^0,0,0)}{(a+\rho)(\mu+(1-\eta)f(T^0,0,0))}+\frac{g(T,I)}{(a+\rho)}-1\right].
\end{aligned}
$$

According to Remark 3.1, we consider solutions for which $T(t) \leq \frac{\lambda}{d}$. Using the expression of $\mathcal{R}_0$, one has

$$\begin{aligned}
\frac{dL}{dt} \leq & \left[f(T,0,0) - \frac{(1-\eta)f(T^0,0,0)}{\mu + (1-\eta)f(T^0,0,0)} \left(\mu + (1-\eta)f(T,I,V)\right) \right] V \\
& + (a+\rho)I \left[\frac{(1-\eta)(1-\varepsilon)kf(T^0,0,0) + (\mu + (1-\eta)f(T^0,0,0))g(T^0,0)}{(a+\rho)(\mu + (1-\eta)f(T^0,0,0))} - 1 \right], \\
\leq & \frac{\mu f(T,0,0) + f(T,0,0)f(T^0,0,0) - \mu f(T^0,0,0) - f(T^0,0,0)f(T,0,0)}{\mu + (1-\eta)f(T^0,0,0)} \\
& + (a+\rho)I[\mathcal{R}_0 - 1], \\
\leq & \frac{\mu \left(f(T,0,0) - f(T^0,0,0) \right)}{\mu + (1-\eta)f(T^0,0,0)} + (a+\rho)I[\mathcal{R}_0 - 1], \\
\leq & (a+\rho)I[\mathcal{R}_0 - 1].
\end{aligned}$$

Consequently, $\frac{dL}{dt} \leq 0$ for $\mathcal{R}_0 < 1$. Moreover, it is easy to show that the largest compact invariant set $\mathcal{I}$ in

$$\begin{aligned}
\mathcal{V} = & \{(T,I,V) \ / \ \frac{dL}{dt} = 0\}, \\
= & \{(T,I,V) \ / \ I = V = 0\}
\end{aligned}$$

is the singleton $\{E^0\}$. By the LaSalle invariance principle[19], the disease-free equilibrium E^0 is globally asymptotically stable for $\mathcal{R}_0 < 1$. □

We now investigate the global dynamics of system (2.2) when $\mathcal{R}_0 > 1$. Firstly, we need the following lemma.

Lemma 5.2. *If $\mathcal{R}_0 > 1$, then differential system (2.2) is uniformly persistent.*

Proof. Considering the notations as in theorem 4.5 of [11], we denote by $X_1 = Int(\mathbb{R}^3_+)$ the interior of $\mathbb{R}^3_+$ and by $X_2 = Bd(\mathbb{R}^3_+)$ the boundary of $\mathbb{R}^3_+$. Since (T,I,V) is bounded, there exists a compact set B of $\mathbb{R}^3_+$ in which all the solutions of the differential system (2.2) initiated in $\mathbb{R}^3_+$ finally enter and stay there forever. Let us denote by $\omega(x_0)$ the omega limit set of the solution $x = x(t,x_0)$ of the system (2.2) (By the criterion of Poincaré-Bendixson, and the fact that the solutions of (2.2) remain in a compact, and the omega limit set always exists). We need to determine Ω_2 defined as in Theorem 4.5 in [11] by

$$\Omega_2 = \bigcup_{y \in Y_2} \omega(y) \tag{5.1}$$

with,

$$Y_2 = \{x \in X_2 \ / \ \phi_t(x) \in X_2; \ \forall t > 0\}.$$

Setting $Y_2 = \{(T,I,V)^T \in Bd(\mathbb{R}^3_+) \ / \ I = V = 0\}$, one has $\Omega_2 = \{E^0 = (T^0,0,0)\}$ where $T^0 = \dfrac{\lambda}{d}$.
Thus, solutions initiated on the T-axis converge to E^0, then E_0 is an isolated recovering of Ω_2 (since E^0 is an equilibrium of (2.2)) and secondly acyclic (because there is no non-trivial solution in $Bd(\mathbb{R}^3_+)$ which links E^0 to itself). Finally, if it is shown that E^0 is a weak repeller for X_1, the proof will be achieved.
By definition, E^0 is a weak repeller for X_1 if for each solution with initial data $(t_0,x_0) \in J \times X$ we have :

$$\lim_{t \to +\infty} \sup d(x(t,x_0), E^0) > 0. \tag{5.2}$$

Inequality (5.2) holds if

$$V^s(E^0) \cap Int(\mathbb{R}^3_+) = \emptyset, \tag{5.3}$$

where $V^s(E^0)$ denotes the stable manifold of E^0.

Suppose that (5.2) does not hold for a solution $x = x(t, x_0)$ with initial data $x_0 \in X_1$. Considering the fact that the closed positive orthant is positively invariant with respect to the system (2.2), then,

$$\lim_{t\to+\infty} \sup\, d(x(t,x_0), E_0)) = \lim_{t\to+\infty} \inf\, d(x(t,x_0), E_0)) = 0.$$

Therefore, we will have $\lim_{t\to+\infty} x(t, x_0) = E^0$ which is clearly impossible if (5.3) is verified.

It remains to show that (5.3) is valid in order to achieve a contradiction. For this, let us recall that the Jacobian matrix associated with the system (2.2) in E_0 is given by

$$\nabla F(E^0) = \begin{pmatrix} -d & -g(T^0,0)+\rho & -(1-\eta)f(T^0,0,0) \\ 0 & g(T^0,0)-(a+\rho) & (1-\eta)f(T^0,0,0) \\ 0 & (1-\varepsilon)k & -\mu-(1-\eta)f(T^0,0,0) \end{pmatrix}.$$

The characteristic polynomial of $\nabla F(E^0)$ is given by

$$P_{\nabla F(E^0)}(X) = -(X+d)\Big(X^2 + a_1X + a_0\Big).$$

Since the product of the real parts of the roots of the polynomial $T(X) = X^2 + a_1X + a_0$ worth $a_0 = (a+\rho)(\mu+(1-\eta)f(T^0,0,0))(1-\mathcal{R}_0) \leq 0$, then the point E^0 is unstable for the system (2.2). This implies that the matrix $\nabla F(E^0)$ defined previously has an eigenvalue with a positive real part denoted x_+ and two others with negative real parts x^1_- and x^2_- which may or may not coincide with x^1_-. The eigenspace associated with the eigenvalue x^1_- is the vector space generated by the vector (1.0.0). If $x^1_- \neq x^2_-$, then the eigenspace associated with x^2_- has the structure $(0, v_2, v_3)$ with v_2 and v_3 verifying the following equation :

$$\begin{pmatrix} g(T^0,0)-(a+\rho) & (1-\eta)f(T^0,0,0) \\ (1-\varepsilon)k & -\mu-(1-\eta)f(T^0,0,0) \end{pmatrix} \cdot \begin{pmatrix} v_2 \\ v_3 \end{pmatrix} = x^2_- \begin{pmatrix} v_2 \\ v_3 \end{pmatrix}. \tag{5.4}$$

In the case of equality between x^2_- and x^1_-, we note that the squared matrix at the left side of (5.4) will be not diagonalizable. Indeed if it was diagonalizable, it would be similar to the matrix $D = \begin{pmatrix} x^2_- & 0 \\ 0 & x^2_- \end{pmatrix}$, and this would imply that

$$\begin{pmatrix} x^2_- & 0 \\ 0 & x^2_- \end{pmatrix} = \begin{pmatrix} g(T^0,0)-(a+\rho) & (1-\eta)f(T^0,0,0) \\ (1-\varepsilon)k & -\mu-(1-\eta)f(T^0,0,0) \end{pmatrix}$$

which is absurd.

Therefore, the structure of the eigenvector associated with x^2_- will have the structure (v_1, v_2, v_3), where v_1 satisfies the equation

$$\nabla F(E^0). \begin{pmatrix} v_1 \\ v_2 \\ v_3 \end{pmatrix} = x^2_- \begin{pmatrix} v_1 \\ v_2 \\ v_3 \end{pmatrix}.$$

In both cases (i.e., the cases $x^2_- = x^1_-$ and $x^2_- \neq x^1_-$), we will always have $(v_2, v_3) \notin \mathbb{R}^2_+$. Indeed, the matrix defined in (5.4) is a Metzler matrix and irreducible. Hence, the stability modulus of x_+ of this Metzler matrix will be an eigenvalue to which will correspond an eigenvector u of the positive orthant. The vector u being unique, this implies that (v_1, v_2, v_3) is not contained in this positive orthant, i.e., $(v_1, v_2, v_3) \notin \mathbb{R}^3_+$. Therefore,

$$V^s(E^0) \cap int(\mathbb{R}^3_+) = \emptyset$$

which completes the proof.. □

Remark 5.1. According to [5], we can deduce from lemma 5.2 the existence of a compact absorbing set in Ω.

Next, we focus on the global stability of the chronic infection equilibrium E^* by assuming that $\mathcal{R}_0 > 1$ and the incidence function f satisfies the hypothesis (H_4). To prove the global stability of E^*, we apply the geometrical approach developed by Li and Muldowney [21].

Theorem 5.3. *Assume that $\mathcal{R}_0 > 1$, $(1-\eta)\ \overline{q_1} < \delta$ and (H_4) hold, then the chronic infection equilibrium E^* is globally asymptotically stable where*

$$\overline{q_1} = \frac{1}{t}\int_0^t \left(I(s)\frac{\partial f}{\partial T} - I(s)\frac{\partial f}{\partial I} - V(s)\frac{\partial f}{\partial V}\right) ds$$

Proof. The second additive compound matrix of the Jacobian matrix J, of the system (2.2) is defined by

$$J^{[2]} = \begin{pmatrix} J_{11}+J_{22} & J_{23} & -J_{13} \\ J_{32} & J_{11}+J_{33} & J_{12} \\ -J_{31} & J_{21} & J_{22}+J_{33} \end{pmatrix} = \begin{pmatrix} c_{11} & c_{12} & c_{13} \\ c_{21} & c_{22} & c_{23} \\ c_{31} & c_{32} & c_{33} \end{pmatrix}$$

where

$$\begin{aligned}
c_{11} &= -(a+d+\rho) - I\frac{\partial g}{\partial T} - (1-\eta)\left(V\frac{\partial f}{\partial T} + V\frac{\partial f}{\partial I}\right) + I\frac{\partial g}{\partial I} + g,\\
c_{12} &= (1-\eta)\left(V\frac{\partial f}{\partial V} + f\right),\\
c_{13} &= (1-\eta)\left(V\frac{\partial f}{\partial V} + f\right),\\
c_{21} &= (1-\varepsilon)k - (1-\eta)V\frac{\partial f}{\partial I},\\
c_{22} &= -\left[d+\mu+(1-\eta)V\frac{\partial f}{\partial T} + I\frac{\partial g}{\partial T} + (1-\eta)\left(V\frac{\partial f}{\partial V}+f\right)\right],\\
c_{23} &= \rho - (1-\eta)V\frac{\partial f}{\partial I} - I\frac{\partial g}{\partial I} - g,\\
c_{31} &= (1-\eta)V\frac{\partial f}{\partial T},\\
c_{32} &= (1-\eta)V\frac{\partial f}{\partial T} + I\frac{\partial g}{\partial T},\\
c_{33} &= -\left[a+\rho+\mu+(1-\eta)\left(V\frac{\partial f}{\partial V}+f\right)\right] + (1-\eta)V\frac{\partial f}{\partial I} + I\frac{\partial g}{\partial I} + g,
\end{aligned}$$

and $J_{ij}; i,j = 1,2,3$ is the (k,l)th entry of the matrix J.
We consider the matrix

$$P(T,I,V) = diag\left(1, \frac{I}{V}, \frac{I}{V}\right)$$

which has inverse given by

$$P^{-1} = diag\left(1, \frac{V}{I}, \frac{V}{I}\right)$$

and the matrix P_f which is obtained by replacing each entry p_{ij} of P by its derivative in the direction of the solution of system (2.2). Thus

$$P_f = diag\left(0, \frac{I'V - V'I}{V^2}, \frac{I'V - V'I}{V^2}\right)$$

with $I' = \dfrac{dI}{dt}$ and $V' = \dfrac{dV}{dt}$. It follows that,

$$P_f P^{-1} = diag\left(0, \frac{I'}{I} - \frac{V'}{V}, \frac{I'}{I} - \frac{V'}{V}\right).$$

Furthermore, one has

$$B = P_f P^{-1} + P(J^{[2]}P^{-1} = \begin{pmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{pmatrix},$$

where

$$B_{11} = -(a+d+\rho) - I\frac{\partial g}{\partial T} - (1-\eta)\left(V\frac{\partial f}{\partial T} + V\frac{\partial f}{\partial I}\right) + I\frac{\partial g}{\partial I} + g,$$

$$B_{12} = \left((1-\eta)\frac{V}{I}\left(V\frac{\partial f}{\partial V} + f\right) \qquad (1-\eta)\frac{V}{I}\left(V\frac{\partial f}{\partial V} + f\right)\right),$$

$$B_{21} = \begin{pmatrix} \left((1-\varepsilon)k - (1-\eta)V\frac{\partial f}{\partial I}\right)\frac{I}{V} \\ \\ \left((1-\eta)V\frac{\partial f}{\partial T}\right)\frac{I}{V} \end{pmatrix},$$

$$B_{22} = \begin{pmatrix} -\left(d+\mu+(1-\eta)V\frac{\partial f}{\partial T} + I\frac{\partial g}{\partial T} + (1-\eta)\left(V\frac{\partial f}{\partial V} + f\right)\right) + \left(\frac{I'}{I} - \frac{V'}{V}\right) & \rho - (1-\eta)V\frac{\partial f}{\partial I} - I\frac{\partial g}{\partial I} - g \\ \\ (1-\eta)V\frac{\partial f}{\partial T} + I\frac{\partial g}{\partial T} & -\left(a+\rho+\mu+(1-\eta)\left(V\frac{\partial f}{\partial V} + f\right)\right) + (1-\eta)V\frac{\partial f}{\partial I} + I\frac{\partial g}{\partial I} + g + \left(\frac{I'}{I} - \frac{V'}{V}\right) \end{pmatrix}.$$

We define the norm on $\mathbb{R}^3$ as $\|(u,v,w)\| = \max\{|u|, |v|+|w|\}$ for all $(u,v,w) \in \mathbb{R}^3$ Then the Lozinskii measure μ with respect to the norm $\|\cdot\|$ can be estimated as follows (see [25]):

$$\mu(B) \leq sup\{g_1, g_2\} \tag{5.5}$$

where

$$g_1 = \mu_1(B_{11}) + \|B_{12}\| \text{ et } g_2 = \mu_1(B_{22}) + \|B_{21}\|.$$

Here, μ_1 denotes the Lozinskii measure with respect to the l_1 vector norm, and $\|B_{12}\|$ and $\|B_{21}\|$ are matrix norms with respect to the l_1 norm. Moreover, we have

$$\mu_1(B_{11}) = -(a+d+\rho) - I\frac{\partial g}{\partial T} - (1-\eta)\left(V\frac{\partial f}{\partial T} + V\frac{\partial f}{\partial I}\right) + I\frac{\partial g}{\partial I} + g. \tag{5.6}$$

$$\|B_{12}\| = (1-\eta)\frac{V}{I}\left(V\frac{\partial f}{\partial V} + f\right). \tag{5.7}$$

According to the second equation of system (2.2), (5.7) becomes:

$$\|B_{12}\| = \frac{I'}{I} + (1-\eta)\frac{V^2}{I}\frac{\partial f}{\partial V} + a + \rho - g.$$

$$\mu_1(B_{22}) = \frac{I'}{I} - \frac{V'}{V} - \mu - (1-\eta)\left(V\frac{\partial f}{\partial V} + f\right) + \max\{-d; -a\}, \tag{5.8}$$

$$= \frac{I'}{I} - \frac{V'}{V} - \mu - (1-\eta)\left(V\frac{\partial f}{\partial V} + f\right) - \delta \tag{5.9}$$

and

$$\|B_{21}\| = \left[(1-\varepsilon)k - (1-\eta)V\frac{\partial f}{\partial I} + (1-\eta)V\frac{\partial f}{\partial T}\right]\frac{I}{V}. \tag{5.10}$$

Hence, we obtain :

$$\begin{array}{rcl} g_1 & = & \frac{I'}{I} - d + (1-\eta)\frac{V^2}{I}\frac{\partial f}{\partial V} - (1-\eta)\left(V\frac{\partial f}{\partial T} + V\frac{\partial f}{\partial I}\right) + I\frac{\partial g}{\partial I} - I\frac{\partial g}{\partial T}, \\ & \leq & \frac{I'}{I} - \delta, \text{ since } a \geq d. \end{array} \tag{5.11}$$

By using the first equation of (2.2), (5.8) and (5.10), one also has :

$$\begin{aligned} g_2 &= \frac{I'}{I} - \frac{V'}{V} - \mu - (1-\eta)\left(V\frac{\partial f}{\partial V} + f\right) - \delta \\ &\quad + \left[(1-\varepsilon)k - (1-\eta)V\frac{\partial f}{\partial I} + (1-\eta)V\frac{\partial f}{\partial T}\right]\frac{I}{V}, \\ &= \frac{I'}{I} - \delta + (1-\eta)\left(I\frac{\partial f}{\partial T} - I\frac{\partial f}{\partial I} - V\frac{\partial f}{\partial V}\right). \end{aligned} \tag{5.12}$$

From (5.5), (5.11) and (5.12), we get :

$$\mu(B) \leq \frac{I'}{I} - \delta + (1-\eta)\left(I\frac{\partial f}{\partial T} - I\frac{\partial f}{\partial I} - V\frac{\partial f}{\partial V}\right).$$

From Lemma 5.2 we know that the system (2.2) is uniformly persistent when $\mathcal{R}_0 > 1$. Then there exists a compact absorbing set $K \subset \Omega$ [5]. Along each solution $(T(t), I(t), V(t))$ of (2.2) with $X_0 = (T(0), I(0), V(0))$, we have

$$\frac{1}{t}\int_0^t (\mu(B(X(s), X_0)))\, ds \leq (1-\eta)\frac{1}{t}\ln\left(\frac{I(t)}{I_0}\right) - \delta + \frac{1}{t}\int_0^t \left(I(s)\frac{\partial f}{\partial T} - I(s)\frac{\partial f}{\partial I} - V(s)\frac{\partial f}{\partial V}\right) ds,$$

which implies that

$$\begin{aligned} &\limsup_{t\to\infty} \sup_{X_0\in K} \frac{1}{t}\int_0^t (\mu(B(X(s), X_0)))\, ds \\ \leq\ & -\delta + \limsup_{t\to\infty} \sup_{X_0\in K} (1-\eta)\frac{1}{t}\int_0^t \left(I(s)\frac{\partial f}{\partial T} - I(s)\frac{\partial f}{\partial I} - V(s)\frac{\partial f}{\partial V}\right) ds, \\ \leq\ & -\delta + (1-\eta)\ \overline{q_1}, \\ <\ & 0. \end{aligned}$$

Then, based on Theorem 3.5 in [21], we deduce that the chronic infection equilibrium E^* is globally asymptotically stable. This completes the proof of the theorem 5.3. □

6. Applications and numerical simulations

As an application of our theoretical results, we consider the system

$$\begin{cases} \dfrac{dT}{dt} = \lambda - dT - \dfrac{(1-\eta)\beta_1 TV}{\alpha_0 + \alpha_1 T + \alpha_2 V + \alpha_3 TV} - \beta_2 TI + \rho I, \\ \dfrac{dI}{dt} = \dfrac{(1-\eta)\beta_1 TV}{\alpha_0 + \alpha_1 T + \alpha_2 V + \alpha_3 TV} + \beta_2 TI - (a+\rho)I, \\ \dfrac{dV}{dt} = (1-\varepsilon)kI - \mu V - \dfrac{(1-\eta)\beta_1 TV}{\alpha_0 + \alpha_1 T + \alpha_2 V + \alpha_3 TV}, \end{cases} \tag{6.1}$$

which is a particular case of system (2.2) by letting

$$f(T, I, V) = \frac{\beta_1 T}{\alpha_0 + \alpha_1 T + \alpha_2 V + \alpha_3 TV}$$

and

$$g(T, I) = \beta_2 T$$

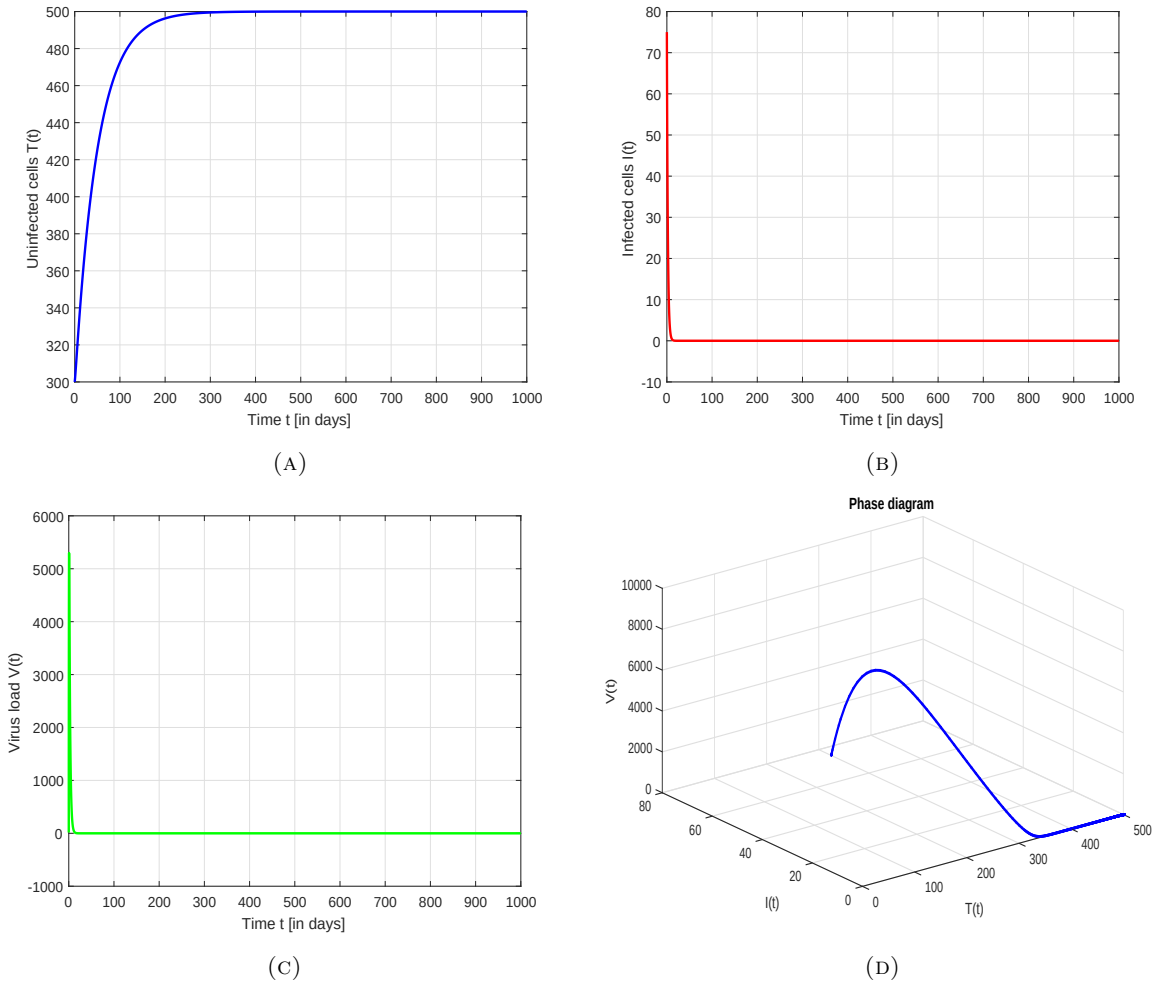
where β_1, β_2, α_1, α_2, α_3 and α_4 are non negative constants. The functions g and f satisfy (H_{01}), (H_{02}) conditions and (H_1), (H_2), (H_3) conditions, respectively. We have

$$f(T, I, V) + V\frac{\partial f}{\partial V}(T, I, V) = \frac{\beta_1 T(\alpha_0 + \alpha_1 T)}{(\alpha_0 + \alpha_1 T + \alpha_2 V + \alpha_3 TV)^2} \geq 0$$

and we conclude that assumption (H_4) is also satisfied. Other state variables and parameters are the same as in model (2.2). The threshold number, $\mathcal{R}_0$ takes the following form

$$\mathcal{R}_0 = \frac{((1-\eta)(1-\varepsilon)k\beta_1\lambda d + (\mu(\alpha_0 d + \alpha_1\lambda) + (1-\eta)\beta_1\lambda)\,\beta_2\lambda}{d(a+\rho)\,(\mu(\alpha_0 d + \alpha_1\lambda) + (1-\eta)\beta_1\lambda)}.$$

Firstly, we simulate the model (6.1) by using the following parameter values : $\lambda = 10$ cells mm^{-3} day^{-1} [15], $\eta = 0.4$, $\beta_1 = 0.000024$ mm^{3}virion^{-1}day^{-1} [15], $\rho = 0.01$ [38], $d = 0.02 day^{-1}$[15]; $\varepsilon = 0.5$, $k = 600$ virions cell^{-1}day^{-1}, $\mu = 3$ day^{-1} [15], $\alpha_0 = 1$, $\alpha_1 = 0.1$, $\alpha_2 = 0.01$, $\alpha_3 = 0.00001$, $\beta_2 = 0.0001$ [38], $a = 0.5$ day^{-1} [15]. According to the values of these parameters, $\mathcal{R}_0 = 0.1257 < 1$, which means that $\mathcal{R}_0$ satisfies the conditions mentioned in Theorem 4.1 and Theorem 5.1. This implies that the disease- free equilibrium $E^0 = (500, 0, 0)$ is globally asymptotically stable. Furthermore, numerical simulation shown in Figure 1 confirms the result.



(A) (B) (C) (D)

FIGURE 1. Time evolutions of model (2.2) with initial values (300; 100; 15). E^0 is globally asymptotically stable

In Figure 1 (a), the proliferation of uninfected cells reaches its equilibrium value at $\frac{\lambda}{d}$ and $T(t)$ converges to $\frac{\lambda}{d} = 500$ whereas in Figure 1 (b) and in Figure 1 (c), Infected cells $I(t)$ and viral load $V(t)$

converge to zero.

Secondly, we choose $\beta_1 = 0.000024$ mm^{3}virion^{-1}day^{-1} [15] and the other parameter values are the same as above. The reason to just modify the parameter β_1 is based on the fact that $\mathcal{R}_0$ is an increasing function with respect to β_1. By calculating, we $\mathcal{R}_0 = 1.2571 > 1$, which means that it satisfies the conditions mentioned in Theorem 4.1 and Theorem 5.3. This implies that the chronic infection equilibrium $E^* = (405, 12.10, 1275)$ is globally asymptotically stable. In addition to this, numerical simulations shown in Figure 2 confirms the result.

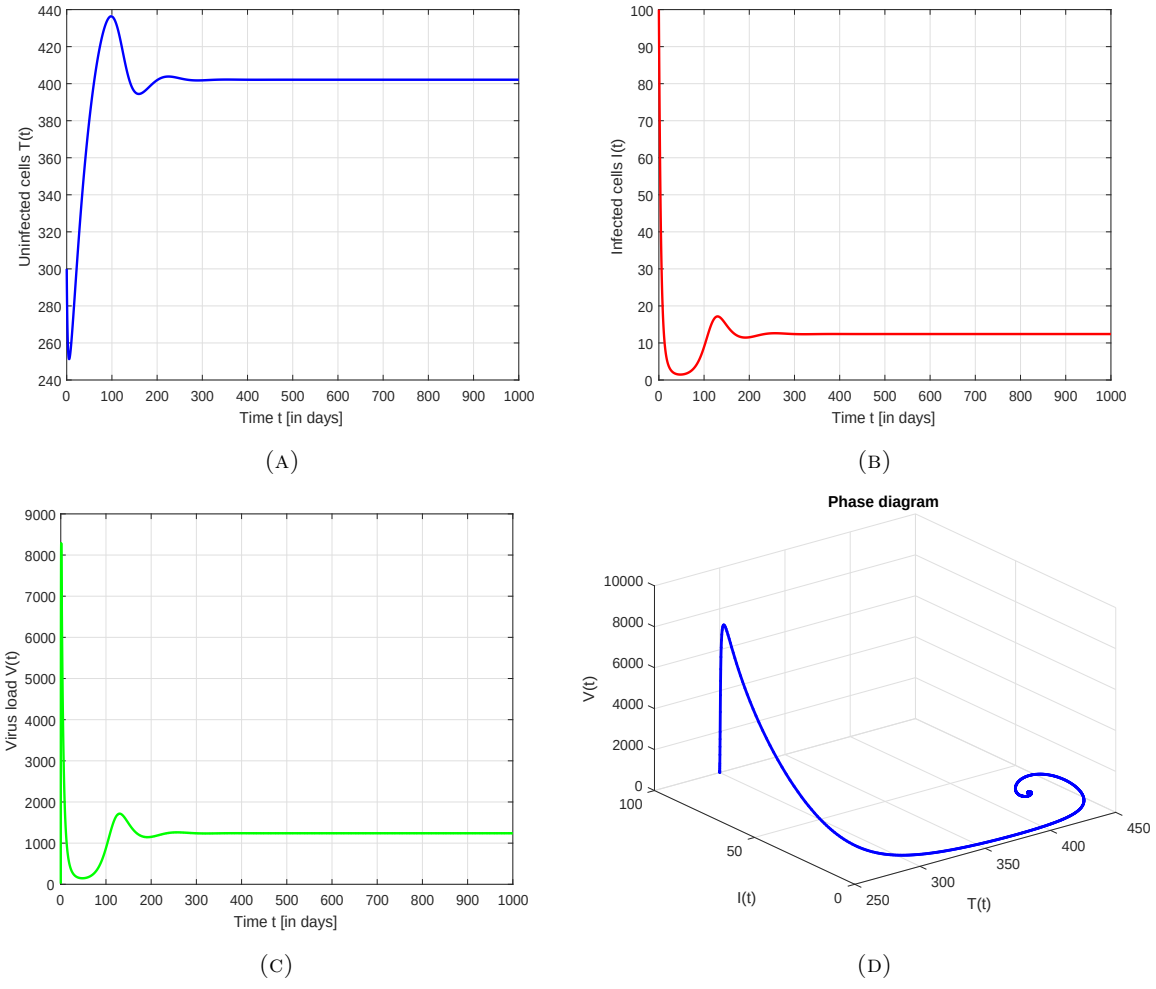


FIGURE 2. Time evolutions of model (2.2) with initial values (300; 75; 15). E^* is globally asymptotically stable

In Figure 2, we observe damped oscillations at the beginning of the simulation. Infection will not become totally extinct, but a considerable reduction of the viral load and infected cells will be observed. Particularly, in Figure 2 (a), the number of uninfected cells $T(t)$ decrease rapidly and then increase slightly until equilibrium is reached whereas in Figure 2 (b), infected cells $I(t)$ do not tend to zero as t increases and in Figure 2 (c) viruses persist in the presence of treatment leading to the system going to an endemic equilibrium.

7. Conclusion

In this study, we have proposed and studied a virus dynamic model with a generalized functional response, treatment and absorption effect. By analyzing the characteristic equations of model (2.2) at the disease-free equilibrium point, it has been completely established that the disease-free equilibrium is locally asymptotically stable if the basic reproduction number $\mathcal{R}_0$ is less than or equal to one ($\mathcal{R}_0 \leq 1$). The local stability result of the chronic infection equilibrium of model (2.2) is shown in Theorem 4.2. If the basic reproduction number is greater than one ($\mathcal{R}_0 > 1$), then the disease-free equilibrium is unstable and the chronic infection equilibrium is locally asymptotically stable. The global behaviour of the model is investigated by constructing an appropriate Lyapunov functional for disease-free equilibrium and by applying Li-Muldowney global stability-criterion to the chronic infection equilibrium. Numerical simulations are carried out, performed in MATLAB, to confirm obtained theoretical result in a particular case. Furthermore, for model (2.2), we found that the basic reproduction number is less than that of a model without absorption effect. From the above discussion, it can be seen that there is a positive effect on eliminating viruses from the blood vessel than the model without absorption effect. Finally, it should be noted that most of the results contained in this work extend and complete the results of the works in [14] and [17]. It would be interesting to incorporate time delay into the current model. Also, taking into account random phenomena could be a serious issue. These two challenges will be the concerns of future investigation.

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