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STABILITY OF A DELAYED HIV-1 DYNAMICS MODEL WITH BEDDINGTON-DEANGELIS FUNCTIONAL RESPONSE AND ABSORPTION EFFECT WITH TWO DELAYS

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Abstract. This research examined the stability properties of a set of delay differential equations for HIV-I infection that includes a Beddington-DeAngelis functional response. The model has incorporated with two-time delays namely intracellular time delay and maturation time delay, and the absorption effect in order to make the processes more biologically sensitive. We prove that the infection free equilibrium and the chronic infection equilibrium be locally asymptotically stable if the basic reproduction number $R_0 \leq 1$ and $R_0 > 1$ respectively, by using the characteristic equations of dynamics model and Routh Hurwitz stability criterion. It is shown that, if $R_0 \leq 1$, the infection-free equilibrium is globally asymptotically stable by using appropriate Lyapunov function and LaSalle's invariance principle. Further, we have established the conditions for the permanence of the system. In addition, numerical simulations are performed to illustrate the theoretical results.

Keywords: HIV- I infection model; Beddington – DeAngelis functional response; absorption effect; intracellular delay; maturation delay; global stability.

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1. INTRODUCTION

The Human Immunodeficiency Virus (HIV) is a well-known lentivirus which consist the capability of leading to the disease, Acquired Immunodeficiency Syndrome (AIDS) over time [1]. As the human body is not capable of eliminating HIV completely, once an individual gets infected with the virus, he/she becomes a host of the virus for the lifetime.

HIV attacks the body's immune system, which is made up of various biological structures and processes that protect the host from various infections and diseases. HIV has the potential to infect target cells, such as helper T cells, macrophages, and dendritic cells [2]. Because HIV specifically attacks the $CD4^+$T lymphocytes which is a large portion of white blood cells, the assistance from the $CD4^+$T lymphocytes to fight off infections is reduced. If we do not provide any treatment to the infected body externally, HIV can drastically reduce the number of $CD4^+$T lymphocytes in the human body and make a person more susceptible to infections and related diseases. When a certain amount of $CD4^+$T cells has been destroyed in a body, then that person has badly damaged immune system which is called as "opportunistic infection" and this is the advanced stage of HIV infection(see e.g [3],[4]). This usually happens, if you do not get treated for HIV for a long period of time. Current statistics issued by WHO show that HIV and AIDS are a frequent problem in Sri Lanka and around the world. Although much progress has been made in the prevention and treatment of HIV, there is still a need to develop appropriate drug therapies.

A mathematical model is a powerful tool that can be implemented to understand the dynamics of HIV infection, disease progression, and the interaction of the immune system with HIV. Therefore, mathematical modeling and model analysis of HIV infection have attracted the interest of researchers during recent years (see e.g [5],[6],[7],[8],[9]). Some researchers have focused their attention on stochastic models in the field of epidemiology in order to place the model in the more sound practical ground (see e.g [10], [11]). However, most of the mathematical models of the HIV-I infection are still being under investigation with the possibility of various developments.

Korobeinikov [12] has done complete theoretical analysis on local and global stability properties for the equilibriums of the basic virus Dynamics model (1.1) which is proposed by Bonhoeffer [13] and Nowak [14].

$$\begin{aligned} \dot{x}(t) &= \lambda - \beta x(t)v(t) - dx(t), \\ \dot{y}(t) &= \beta x(t)v(t) - py(t), \\ \dot{v}(t) &= ky(t) - uv(t). \end{aligned} \tag{1.1}$$

In model (1.1), x is the amount of uninfected target cells, y is the number of infected cells which have capability to produce virus and v is the amount free virus. λ, indicates the rate at which non-infected target cells are recruited into the compartment. β is the incidence rate which uninfected target cells and free virus contact with each other and k is the rate which an infected cell creates free virus. d is the death rate of non-infected target cells, p is the death rate of infected cells and u is the free virus death rate. It has been further assumed that all the above-mentioned parameters are nonnegative in biological meanings.

In Model (1.1) it has been assumed that virus particles are produced immediately after a virus binds to a target cell in real-time, without any delay of time. However, it has been biologically proven that there is a gap between the time a virus enters a target cell and the time it takes for a new virus to form from that target cell [15]. This lag is referred to as the intracellular time delay, and more accurate and precise models have been suggested which has taken this delay into account through a delay differential equation, omitting the ordinary differential equation for the infected target cells as in the model (1.1)(see e.g. [16],[5],[8],[17]).

Viral maturation delay is the time it takes for the virus to mature after infected cells reproduce new virus. In Biological sense, without maturation, a newly produced virus cannot directly attach to uninfected target cells([18],[19]). Therefore, the consideration of the maturation time delay in the dynamic model will improve the biological responsiveness of the model.

The term $\beta x(t)v(t)$ of the model (1.1) is the incidence rate between uninfected $CD4^+T$ cells and free virus, which is defined as either bilinear mass functional response, Holling Type I functional response or bilinear incidence rate (see e.g [14],[20],[21]). According to researchers in [22] a nonlinear incidence rate is preferable to a bilinear incidence rate. In this context, some authors have substituted the bilinear incidence rate for Holling type II functional responses (see

e.g.[23],[24]). Moreover, some researchers have used a Beddington-DeAngelis incidence rate function for their mathematical models (see e.g.[25], [6],[26]) and further, some researchers have replaced bilinear incidence rate by the Crowley Martin function response (see e.g. [27]).

When pathogens are engrossed into the uninfected cells, the number of pathogens is decreased in the volume of blood, which is called the absorption effect. The absorption effect has also been included in some of the mathematical models [28]. Pradeep and Ma have presented a mathematical model by including both Beddington-DeAngelis type functional response and absorption effect in [9].

Inspired by the above works, the following mathematical model is suggested by incorporating a Beddington-DeAngelis-type active response, intercellular and maturation delays, and an absorption effect

$$\begin{aligned}
\dot{x}(t) &= \lambda - \frac{\beta x(t)v(t)}{1+ax(t)+bv(t)} - dx(t),\\
\dot{y}(t) &= e^{-p\tau}\frac{\beta x(t-\tau)v(t-\tau)}{1+ax(t-\tau)+bv(t-\tau)} - py(t),\\
\dot{v}(t) &= ke^{-u\sigma}y(t-\sigma) - uv(t) - \frac{\beta x(t)v(t)}{1+ax(t)+bv(t)}.
\end{aligned} \tag{1.2}$$

Here, $a>0, b>0$ and $\tau \geq 0$ is the intercellular time delays, $e^{-p\tau}$ is the probability of surviving from $t-\tau$ to t, and $\sigma \geq 0$ is the maturity time delay, and $e^{-u\sigma}$ accounts for the probability of surviving from time $t-\sigma$ to t. A number of other variables have the same biological significance as the aforementioned model (1.1) and further, all parameters are assumed to be positive.

The rest content of the paper is organized as follows. The uniqueness, positivity and bounded of the solution of the model (1.2) is discussed in section 2. In Section 3, a discussion is provided concerning the threshold parameter R_0 for model (1.2), and the existence of equilibrium is discussed as it relates to R_0. The detailed discussion of local stabilities of equilibrium is given in Section 4. In Section 5 is given the global stability of the infection free equilibrium. In Section 6 the permanency of the model (1.2) is discussed. The numerical simulations of the model (1.2) is given in Section 7 and the Section 8 concludes with a brief discussion.

2. Positivity and Boundedness

Let $\zeta = max\{\tau, \sigma\}$, Then the initial conditions for the model (1.2) can be consider as:

$$\begin{aligned} x(\theta) = \psi_1(\theta), y(\theta) = \psi_2(\theta) \quad \text{and} \quad v(\theta) = \psi_3(\theta), \\ \psi_i(\theta) \geq 0 \quad \text{for} \quad i = 1,2,3. \end{aligned} \tag{2.1}$$

where $\theta \in [-\zeta, 0]$ and $\psi = (\psi_1(\theta), \psi_2(\theta), \psi_3(\theta)) \in C$, and C represent the Banach space $C([-\zeta, \mathbb{R}^3_+])$ of continuous functions that map the interval $[-\zeta, 0]$ into $\mathbb{R}^3_+$.

Theorem 2.1. *Any non-negative initial conditions (2.1), the model (1.2) has a unique solution. Furthermore, these solutions are non-negative and bounded for all $t \geq 0$.*

Proof. To show that $x(t)$ is non-negative, we proceed with contradiction by assuming $x(t)$ non-positive on the existing interval $[0, T_{max})$. Let $t_1 \in [0, T_{max})$ be the first time, such that $x(t_1) = 0$, and $\dot{x}(t_1) \leq 0$. But from the first equation of the model (1.2), we have that $\dot{x}(t_1) = \lambda > 0$, when $x(t_1) = 0$. This results in a contradiction. Hence, $x(t) > 0$ for all $t_1 \in [0, T_{max})$.

From the second equation of the model (1.2), we have

$$y(t) = y(0)e^{-pt} + \int_0^t \frac{e^{-pt}\beta x(\theta - \tau)v(\theta - \tau)}{1 + ax(\theta - \tau) + bv(\theta - \tau)} e^{-(t-\theta)} d\theta.$$

Therefore, it is easy to see that $y(t)$ is non-negative for all $t_1 \in [0, T_{max})$. Then, by similar argument of $x(t)$, we can show that $v(t) > 0$ for all $t_1 \in [0, T_{max})$.

Next, we need to show that the solutions of the system are bounded.

From the first equation of the model (1.2), we have

$$\dot{x}(t) = \lambda - \frac{\beta x(t)v(t)}{1 + ax(t) + bv(t)} - dx(t) \leq \lambda - dx(t).$$

It has that

$$x(t) \leq x(0)e^{-dt} + \frac{\lambda}{d}(1 - e^{-dt}).$$

Therefore, $\limsup_{t\to\infty} x(t) \leq \frac{\lambda}{d}$, and hence $x(t)$ is bounded on $[0, +\infty)$.

Next for $t \geq 0$, let's define $F(t)$ as follows

$$F(t) = e^{-pt}x(t - \tau) + y(t).$$

Taking the derivative of $F(t)$, we have

$$F'(t) = \lambda e^{-p\tau} - de^{-p\tau}x(t - \tau) - py(t) \leq \lambda e^{-p\tau} - \delta F(t),$$

where $\delta = min(d, p)$. Then, it is follows that

$$\limsup_{t\to\infty} F(t) \leq \frac{\lambda e^{-p\tau}}{\delta}.$$

Hence $x(t)$ and $y(t)$ are bounded.

From the last equation of the model (1.2), it has for $t \geq 0$,

$$\dot{v}(t) \leq ke^{-u\sigma} y(t-\sigma) - uv(t).$$

It implies that,

$$\limsup_{t\to\infty} v(t) \leq \frac{k\lambda e^{-p\tau-u\sigma}}{u\delta}.$$

This confirms that the solutions $x(t), y(t)$, and $v(t)$ are bounded for any $\tau, \sigma \geq 0$. Therefore, every solution can be extended up to any time $t > 0$. Which mean that the solution of the model (1.2) exist globally. □

3. Reproduction Number and Possible Equilibrium

In most of the viral dynamic mathematical models that have been proposed, there are two separate equilibrium states; Namely, infection-free equilibrium and infectious equilibrium.

Since the number of uninfected cells (x), the number of infected cells (y), and the number of free viruses (v) must all change at equilibrium points at the same time, there is no time delay. Therefore, to determine the equilibrium point of the proposed model, the equations in the model (1.2) are equal to zero and the intracellular time delay (τ) and the maturation time delay (σ) have been fixed in the equations.

Then the model (1.2) has the infection-free equilibrium $E_0(\lambda/d, 0, 0)$. The basic reproduction number for model (1.2) was derived from the spectral radius of the next generation matrix, as the similar approach proposed by Van and Watmough in [29] and denoted as R_0.

$$R_0 = \frac{\lambda\beta k e^{-u\sigma-p\tau}}{p(ud + au\lambda + \lambda\beta)}.$$

The Basic reproduction number is the average amount of infected cells formed by a single infected cell as a result of introducing the infected cells in a population of full susceptible cells that has an important impact on the dynamics of the system.

R_0 is useful for us to determine whether or not the virus clears up over time from the body. If $R_0 > 1$, then the model (1.2) has unique chronic infection equilibrium $E_1(x_1, y_1, v_1)$, where

$$x_1 = \frac{\lambda b(ke^{-p\tau-u\sigma} - p) + pu}{(ke^{-p\tau-u\sigma} - p)(db+\beta) - aup}, \quad y_1 = \frac{e^{-p\tau}(ud + \lambda\beta + au\lambda)(R_0 - 1)}{(ke^{-p\tau-u\sigma} - p)(db+\beta) - aup}$$
$$v_1 = \frac{(ke^{-p\tau-u\sigma} - p)(ud + \lambda\beta + au\lambda)(R_0 - 1)}{u[(ke^{-p\tau-u\sigma} - p)(db+\beta) - aup]}.$$

4. Local Stability of the Equilibriums

In this section, the local stability properties of the infection-free equilibrium E_0 and the chronic infection equilibrium E_1 of the model (1.2) were established by analyzing the characteristic equations and the Ruth Hurwitz criteria.

Theorem 4.1. *For any $\tau \geq 0$ and $\sigma \geq 0$ of model (1.2), if $R_0 < 1$, the infection-free equilibrium E_0 is locally asymptotically stable; if $R_0 > 1$, the infection free equilibrium E_0 is unstable, and if $R_0 = 1$, the infection free equilibrium E_0 is linearly stable.*

Proof. The characteristic equation of model (1.2) at E_0 can be derived as below,

$$(s+d)[(s+p)(s+u+n) - kne^{-u\sigma-s\sigma-p\tau-s\tau}] = 0, \tag{4.1}$$

where $n = \frac{\beta\lambda}{d+a\lambda}$. It is clear that the first factor of the equation (4.1) always has a negative real root as $d = -s$, and the other roots of the equation can be determined by the following equation.

$$(s+p)(s+u+n) - kne^{-u\sigma-s\sigma-p\tau-s\tau} = 0. \tag{4.2}$$

For any τ and σ, when $s = 0$, the equation (4.1) can be written in form

$$dp(u+n)(R_0 - 1) = 0. \tag{4.3}$$

Thus, if $R_0 \neq 1$, for any time delay $\tau, \sigma \geq 0$, $s = 0$ is not a solution of the equation (4.1), and then the other solution of the equation (4.2) can be discussed under the following two cases. Consider the case $\tau, \sigma = 0$. Then the equation (4.2) can be derived as

$$s^2 + Ps + Q = 0. \tag{4.4}$$

where, $P = (u+n+p)$ and $Q = p(u+n)(1-R_0)$. It is so clear that $P > 0$, and $Q > 0$ if $R_0 < 1$. Then according to the Ruth Hurwitz criterion, roots of equation (4.4) have negative real parts. Thus, it was proved that, if $R_0 < 1$, all the roots of the equation (4.1) have negative real parts. It follows that, if $R_0 < 1$, the infection-free equilibrium point E_0 is locally asymptotically stable.

Next, consider $\tau, \sigma > 0$, and assume that $s = \omega i$, where $\omega > 0$, is the pure imaginary root of equation (4.2) (see e.g [6],[30]). Then, it is possible to write equation (4.2) as follows

$$(\omega i + p)(\omega i + u + n) - kne^{-p\tau - u\sigma - i\omega(\tau+\sigma)} = 0. \tag{4.5}$$

As a result of separating the real and imaginary parts of equation (4.5), we have

$$-\omega^2 + p(u+n) \quad = nke^{-u\sigma - p\tau}\cos\omega(\tau+\sigma). \tag{4.6}$$

$$\omega(u+n+p) \quad = -nke^{-u\sigma - p\tau}\sin\omega(\tau+\sigma). \tag{4.7}$$

When the two sides of the equation (4.6) and (4.7) are squared and added together, it gives

$$(\omega^2)^2 + [p^2 + (u+n)^2]\omega^2 + p^2(u+n)^2(1-R_0^2) = 0. \tag{4.8}$$

The equation (4.8) is a quadratic equation with two roots for ω^2 and it is clear that the equation (4.8) has no positive roots if $R_0 < 1$. As a result, all the roots of equation (4.1) have negative real parts, if $R_0 < 1$. Hence, if $R_0 < 1$, the infection-free equilibrium point is locally asymptotically stable [Theorem 3.4.1, [30]].

Further, consider the left-hand side of equation (4.2) as

$$f(s,\tau,\sigma) = (s+p)(s+u+n) - kne^{-u\sigma - s\sigma - p\tau - s\tau} \tag{4.9}$$

For any time-delay $\tau, \sigma \geq 0$, and for $R_0 > 1$, the equation (4.9) can be written as

$$\begin{gathered} f(0,\tau,\sigma) = p(u+n)(1-R_0) < 0 \quad \text{and} \\ \lim_{s\to\infty} f(s,\tau,\sigma) \to +\infty. \end{gathered} \tag{4.10}$$

Hence, it has been confirmed that there is at least one positive root for $f(s,\tau,\sigma) = 0$ if $R_0 > 1$. Therefore infection free equilibrium is unstable if $R_0 > 1$.

Furthermore, if $R_0 = 1$ the equation (4.2) can be written as

$$s^2 + s(p+u+n) + p(u+n)[1 - e^{-s\tau - s\sigma}] = 0. \tag{4.11}$$

It easy to see that $s = 0$ is a simple solution of equation(4.11).

Further, it is possible to show that any other roots of equation (4.11) have only negative roots. Assume that $s = \alpha + i\beta$, for some $\alpha \geq 0, \beta \geq 0, \tau \geq 0$ and $\sigma \geq 0$. Then, by seperatong the real and imaginary part, the equation (4.11) can be written as

$$\alpha^2 - \beta^2 + \alpha(p+u+n) + p(u+n) = p(u+n)e^{-\alpha(\tau+\sigma)}\cos\beta(\tau+\sigma), \tag{4.12}$$

and

$$2\alpha\beta + \beta(p+u+n) = -p(u+n)e^{-\alpha(\tau+\sigma)}\sin\beta(\tau+\sigma). \tag{4.13}$$

By squaring and adding the two sides of equations (4.12) and (4.13) the following inequality can be obtained.

$$\left[\left(\alpha^2 - \beta^2\right) + \alpha(p+u+n) + p(u+n)\right]^2 + [2\alpha\beta + \beta(p+u+n)]^2 \leq [p(u+n)]^2. \tag{4.14}$$

It is obvious that inequality (4.14) cannot be satisfied, which leads to a contradiction. This means that every root in the equation (4.11) has a negative real part other than $s = 0$, when $R_0 = 1$. □

Next, we need to examine the local stability of the chronic infection equilibrium E_1.

Theorem 4.2. *If $R_0 > 1$, the chronic infection equilibrium E_1 of the system (1.2) is locally asymptotically stable for any time delay $\tau \geq 0$ and $\sigma \geq 0$.*

Proof. Let

$$l = \frac{v_1(1+bv_1)}{(1+ax_1+bv_1)^2} \quad \text{and} \quad m = \frac{x_1(1+ax_1)}{(1+ax_1+bv_1)^2}$$

Then, the characteristic equation of model (1.2) at $E_1(x_1, y_1, v_1)$ can be derived as following form

$$\begin{aligned}(s+\beta l+d)[(s+p)(s+u+\beta m) - k\beta m e^{-s\sigma-u\sigma-s\tau-p\tau}] \\ +\beta m[k\beta l e^{-s\sigma-u\sigma-s\tau-p\tau} - \beta l(s+p)] = 0.\end{aligned} \tag{4.15}$$

Furthermore, the equation (4.15) can be simplified as

$$s^3 + P_2 s^2 + P_1 s + P_0 + (sQ_1 + Q_0)e^{-s(\tau+\sigma)} = 0. \tag{4.16}$$

where,

$$P_0 = pu(\beta l + d) + pd\beta m, \quad P_1 = p(u + \beta m) + (\beta l + d)(p + u) + d\beta m,$$

$$P_2 = p + u + d + \beta m + \beta l,$$

$$Q_0 = -dp\left[\frac{u(1+ax_1)}{1+ax_1+bv_1} + \beta m\right], \quad Q_1 = -p\left[\frac{u(1+ax_1)}{1+ax_1+bv_1} + \beta m\right].$$

In the case of $\tau = 0$ and $\sigma = 0$, equation (4.16) can be reduced to the following formula

$$s^3 + P_2 s^2 + (P_1 + Q_1)s + P_0 + Q_0 = 0, \tag{4.17}$$

where,

$$P_2 = p + u + d + \beta(l + m) > 0,$$

$$P_1 + Q_1 = d\beta m + (d + \beta l)(p + u) + \frac{upbv_1}{1 + ax_1 + bv_1} > 0,$$

and

$$P_2(P_1 + Q_1) - (P_0 + Q_0) = (p + u)[dp + (d + \beta l)(u + d + \beta(l + m))] + \beta(p^2 l + d^2 m) + [p + u + \beta(l + m)]\left[\beta dm + \frac{upv_1}{1 + ax_1 + bv_1}\right] > 0.$$

Therefore, according to the Ruth Hurwitz criterion, the infected equilibrium point E_1 of model (1.2) is locally asymmetrically stable when $\tau = 0$ and $\sigma = 0$.

Let's assume that $s = i\omega$ ($\omega > 0$) is the purely imaginary solution of equation (4.18). Then we can separate the real and imaginary parts, and it reduce to the following two equations

$$Q_1\omega \sin\omega(\tau + \sigma) + Q_0 \cos\omega(\tau + \sigma) = P_2\omega^2 - P_0. \tag{4.18}$$

$$Q_1\omega \cos\omega(\tau + \sigma) - Q_0 \sin\omega(\tau + \sigma) = \omega^3 - P_1\omega. \tag{4.19}$$

By squaring both sides of each equation (4.18) and (4.20), and adding them together, it is easy to obtain equation (4.20).

$$(\omega^3)^2 + (P_2^2 - 2P_1)(\omega^2)^2 + (P_1^2 - 2P_0P_1 - Q_1^2)\omega^2 + (P_0^2 - Q_0^2) = 0, \tag{4.20}$$

Let, $L=(P_2^2-2P_1), M=(P_1^2-2P_0P_1-Q_1^2)$, and $N=(P_0^2-Q_0^2)$, and it is not difficult to show that,

$$L=(u+\beta m)^2+2\beta^2 ml+p^2+(d+\beta l)^2>0,$$

$$M=\frac{p^2ubv_1}{1+ax_1+bv_1}\left[u+2\beta m+\frac{u(1+ax_1)}{1+ax_1+bv_1}\right]+2p^2\beta^2 ml+(\beta dm)^2 +(d+\beta l)^2(u^2+p^2)+2\beta dum(d+\beta l)>0,$$

$$N=P^2u\left(\beta l+\frac{bdv_1}{1+ax_1+bv_1}\right)\left[u(d+\beta l)+2\beta dm+\frac{du(1+ax_1)}{1+ax_1+bv_1}\right]>0.$$

Therefore, according to the Routh-Hurwitz criterion, equation (4.20) does not have positive roots for ω^2. It follows that it is impossible to have a purely imaginary root in (4.17). Thus, according to Kuang's theory on characteristic equation of delay differential equations [30], if $R_0>1$, the chronic infection equilibrium E_1 of the model (1.2) is locally asymptotically stable. □

5. Global Stability of the Equilibriums

In this section we discuss, if $R_0<1$, the infection-free equilibrium E_0 is globally asymptotically stable. Hence, all solution stating in $\mathbb{R}^3_+$ reach to E_0.

Theorem 5.1. *If $R_0\leq 1$, the infection-free equilibrium E_0 is globally asymptotically stable for any time delay $\tau,\sigma\geq 0$.*

Proof. The proof of Theorem 5.1 has to be discussed under two cases.

Case I: If $ke^{-u\sigma-p\tau}-p>0$ Consider the Lyapunov function as

$$V_1=x-x_0-\int_{x_0}^{x}\lim_{v\to 0^+}\frac{f(x_0,v)}{f(\eta,v)}d\eta+k_1y+k_2v+k_3I+k_4J. \tag{5.1}$$

where k_1,k_2,k_3 and k_4 are constants need to be determined later, and

$$I=\int_{-\tau}^{0}\beta f(x(t+\eta),v(t+\eta))d\eta,\quad J=\int_{-\sigma}^{0}y(t+\eta)d\eta,\quad \text{and}\quad f(x,v)=\frac{xv}{1+ax+bv}.$$

Taking the derivative of V_1 along the solutions of model (1.2), it shows that for $t\geq 0$.

$$\dot{V}_1=\left(1-\lim_{v\to 0^+}\frac{f(x_0,v)}{f(\eta,v)}\right)(\lambda-\beta f(x,v)-dx)+k_1\left(e^{-p\tau}\beta f(x(t-\tau),v(t-\tau))-py\right) +k_2\left(e^{-u\sigma}ky(t-\sigma)-uv-\beta f(x,v)\right)+k_3\dot{I}+k_4\dot{J}, \tag{5.2}$$

where,

$$\dot{I} = \beta(f(x,v) - f(x(t-\tau), v(t-\tau))), \quad \text{and} \quad \dot{J} = y - y(t-\sigma).$$

Based on the fact that $\lambda = dx_0$, and considering $k_1 = kk_2e^{-u\sigma}/p$, $\quad k_2 = p/(ke^{-u\sigma-p\tau})$, $k_3 = k_1e^{-p\tau,}$ and $k_4 = kk_2e^{-u\sigma}$, equation (5.2) can be derived as follows

$$\dot{V}_1 = \left(1 - \lim_{v\to 0^+} \frac{f(x_0,v)}{f(x,v)}\right)(\lambda - dx) + k_2uv\left(\frac{\beta}{k_2u}\frac{f(x,v)}{v}\lim_{v\to 0^+}\frac{f(x_0,v)}{f(x,v)} - 1\right). \tag{5.3}$$

The equation (5.3) further can be simplified as

$$\dot{V}_1 = -\frac{d(x-x_0)^2}{x(1+ax_0)} - \frac{\beta\lambda bv^2}{(d+a\lambda)(1+ax+bv)} + \frac{puv(ud+\beta\lambda+au\lambda)(R_0-1)}{u(d+a\lambda)(ke^{-u\sigma-p\tau}-p)}. \tag{5.4}$$

It is clear that the first and second terms of the equation (5.4) is negative for all $x, v > 0$ and last term be negative for $R_0 < 1$. That is, if $R_0 \leq 1$, it follows that $\dot{V}_1 \leq 0$. The equality exists if and only if $x = x_0$ and $v = 0$. Then from the third equation of the model (1.2), we have $y = 0$. This is show that the infection equilibrium is stable. This is shown that $M_1 = \{E_0\}$ is the largest invariant subset of $E_1 = \{\psi = (x(t), y(t), v(t)) \in C \mid \dot{V}_1(\psi) = 0\}$. By LaSalle's invariance principle, the infection free equilibrium E_0 is globally asymptotically stable when it is $R_0 \leq 1$.

Case II: When $ke^{-u\sigma-p\tau} - p \leq 0$, define a Lyapunov functional as follows

$$V_2 = k_5y + k_6v + k_7\int_{-\rho}^{0} ky(t+\eta)d\eta + \int_{-\tau}^{0}\beta f(x(t+\eta), v(t+\eta))d\eta. \tag{5.5}$$

where k_5, k_6, and k_7 are constants need to be determined later. Taking the derivative of V_2 along the solutions of model (1.2), it shows that for $t \geq 0$.

$$\begin{aligned}\dot{V}_2 = {} & k_5\left[e^{-p\tau}\beta f(x(t-\tau), v(t-\tau)) - py\right] + k_6\left[e^{-u\sigma}ky(t-\sigma) - uv - \beta f(x,v)\right] \\ & + k_7\left[\beta f(x,v) - \beta f(x(t-\tau), v(t-\tau))\right] + \left[ky - ky(t-\sigma)\right].\end{aligned} \tag{5.6}$$

Taking $k_5 = e^{p\tau}, k_6 = \frac{pe^{u\sigma+p\tau}}{k}$ and $k_7 = k_6e^{-u\sigma}$, equation (5.6) can be derive as follows.

$$\dot{V}_2 = -\frac{puve^{u\sigma+p\tau}}{k} + \frac{xv\beta e^{u\sigma+p\tau}(ke^{-u\sigma-p\tau}-p)}{k(1+ax+bv)}. \tag{5.7}$$

It is clear that $\dot{V}_2 \leq 0$ for all $x, v > 0$, and equality exist if and only if $v = 0$. Then from model (1.2) $y = 0$. This is shown that $M_2 = \{E_0\}$ is the largest invariant subset of $E_2 = \{\psi = (x(t), y(t), v(t)) \in C \mid \dot{V}_2(\psi) = 0\}$. By LaSalle's invariance principle, the infection free equilibrium E_0 is globally asymptotically stable when it is $R_0 \leq 1$. □

6. PERMANENCE

In this section our interest is to present the permanence of system (1.2) with initial condition (2.1). The biological meaning of permanence or uniform persistence implies that the infected cells y(t) and virus particles v(t) cannot be completely eliminated and will eventually persist.

Definition 6.1. *(see,* [31]*)The system (1.2) is said to be persistent if there are two positive constants, m_l, m_u such that for each positive solution $(x(t), y(t), v(t))$ of the system (1.2) with the initial conditions (2.1) satisfy conditions*

$$\begin{aligned} m_l \leq \underline{x} = \liminf_{t\to\infty} x(t) \leq \overline{x} = \limsup_{t\to\infty} x(t) \leq m_u, \\ m_l \leq \underline{y} = \liminf_{t\to\infty} y(t) \leq \overline{y} = \limsup_{t\to\infty} y(t) \leq m_u, \\ m_l \leq \underline{v} = \liminf_{t\to\infty} v(t) \leq \overline{v} = \limsup_{t\to\infty} v(t) \leq m_u, \end{aligned} \tag{6.1}$$

where, $m_l = min\{\underline{x}, \underline{y}, \underline{z}\}$ and $m_u = max\{\overline{x}, \overline{y}, \overline{z}\}$.

From theorem (2.1), we have prove that any solution of system (1.2) is bounded and from the first equation of the system (1.2), we can show that (see e.g [25])

$$\dot{x}(t) = \lambda - \frac{\beta}{b} dx(t) - dx(t).$$

It has that

$$\liminf_{t\to\infty} x(t) \geq \frac{\lambda b}{bd + \beta}.$$

To prove the uniform persistence of the model (1.2), here we presented the persistence theory for infinite dimensional system presented by Hale in [32]. Also, we refer the conditions of Theorem 5.1 in [33] and methods and techniques have been used in ([25], [34],[31], [35]).

Definition 6.2. *(see,* [36],[32]*)A matrix A is call Metzler matrix if and only if all the off-diagonal elements of A are non-negative*

Lemma 6.1. *(see,* [31] *) Perron-Frobenius theorem implies that, if A is an irreducible Metzle matrix there is a positive eigenvector V for the associated maximum eigenvalue λ_m of A.*

Now, assume that X be a complete metric space. suppose $X^0 \in X, \partial X^0 \in X$ and $X = X^0 \cup \partial X^0$, where ∂X^0(non-empty) is the boundary of X^0. Further suppose that $U(t)$ is a C^0- semigroup on X satisfies

$$\begin{aligned} U(t) : X^0 &\longrightarrow X^0. \\ U(t) : \partial X^0 &\longrightarrow \partial X^0. \end{aligned} \tag{6.2}$$

Let $U_b(t) = U(t)|_{\partial X^0}$ and let A_∂ be the global attractor for $U_b(t)$.

Lemma 6.2. *(see* [32]*) Suppose that $U(t)$ satisfies the (6.2) and we have*

(i) there is $t_0 \geq 0$ such that $U(t)$ compact for $t > t_0$.

(ii) $U(t)$ is point dissipative in X.

(iii) $\tilde{A}_b = \cup_{x \in A_b} \omega(x)$ is isolated and has an acyclic covering M, where $\tilde{M} = \{M_1, M_2, \ldots, M_n\}$.

(iv) $W^s(M_i) \cap X^0 = \phi$, for $i = 1, 2, \ldots, n$.

Then ∂X^0 uniform repeller with respect to X^0, that is, there is an $\varepsilon > 0$ such that for any $x \in X^0$,

$$\liminf_{t \to \infty} d(U(t)x, \partial X^0) \geq \varepsilon,$$

where d is distance of $U(t)x$ from ∂X^0.

Theorem 6.1. *If $R_0 > 1$, then the system (1.2) is permanent for any time delay $\tau \geq 0$ and $\sigma \geq 0$ with the initial condition 2.1.*

Proof. We begin by proving that the boundary planes of R^3_+ not attracted to the positive solutions of the system (1.2) uniformly. Let us to define a set

$$C_0 = \{(\psi, \phi_1, \phi_2) \in C([-\tau, 0], \mathbb{R}^3_+) : \psi(\theta) \neq 0, \phi_1(\theta) = \phi_2(\theta) = 0, (\theta \in [-\tau, 0])\}.$$

If $C^0 = intC([-\tau, \mathbb{R}^3_+)$, it is enough to prove that there exist $\varepsilon_0 > 0$ such that for any solution $T(t)$ of system(1.2) Starting from C^0, $\liminf_{t \to \infty} d(T(t), C_0) \geq \varepsilon_0$. To this end, we tend to verify that the conditions of Lemma 6.2 are fulfilled. It is not difficult to see that C^0 and C_0 are positively invariant. Also, conditions (i) and (ii) of Lemma 6.2 are satisfied. In this way, we just have to confirm the conditions (iii) and (iv). There is a consistent arrangement E_0 in C_0, to $x(t) = x_0, y(t) = 0$ and $v(t) = 0$. If $(x(t), y(t), v(t))$ is a solution of the system (1.2) initiating from C_0, then $x(t) \to x_0, y(t) \to 0, v(t) \to 0$ as $t \to +\infty$. Hence, it is obvious that E_0 is an isolated

invariant set. Now we need to show that $W^s(E_0)\cap C^0=\phi$. To prove this result we can assume the contrary, then we have positive solution $(\tilde{x}(t),\tilde{y}(t),\tilde{v}(t))$ for the system (1.2) such that

$$\lim_{t\to\infty}\tilde{x}(t)=x_0,\quad \lim_{t\to\infty}\tilde{y}(t)=0,\quad \lim_{t\to\infty}\tilde{v}(t)=0. \tag{6.3}$$

Let us select any sufficiently small enough constant $\varepsilon>0$ and sufficiently large enough $t_0>0$ such that

$$\frac{\lambda}{d}-\varepsilon<\tilde{x}(t)<\frac{\lambda}{d}+\varepsilon,\quad o<\tilde{y}(t)<\varepsilon,\quad 0<\tilde{v}(t)<\varepsilon,$$

for $t>t_0-\tau$ and $t>t_0-\sigma$. Then we have for $t>t_0$

$$\begin{aligned}\dot{\tilde{y}}(t)&\geq\frac{e^{-p\tau}\beta(x_0-\varepsilon)\tilde{v}(t-\tau)}{1+a(x_0-\varepsilon)+b\varepsilon}-p\tilde{y}(t),\\ \dot{\tilde{v}}(t)&\geq ke^{-u\sigma}\tilde{y}(t-\sigma)-u\tilde{v}(t)-\frac{\beta(x_0-\varepsilon)\tilde{v}(t)}{1+a(x_0-\varepsilon)+b\varepsilon}.\end{aligned} \tag{6.4}$$

Now let us consider the matrix defined as follows

$$A_\varepsilon=\begin{pmatrix}-p & \frac{e^{p\tau}\beta(x_0-\varepsilon)}{1+a(x_0-\varepsilon)+b\varepsilon}\\ ke^{-u\sigma} & -\left[u+\frac{\beta(x_0-\varepsilon)}{1+a(x_0-\varepsilon)+b\varepsilon}\right]\end{pmatrix}.$$

It is clear that the non-diagonal elements of the matrix A_ε are positive. Thus, by the Perron - Frobenius theorem, there is a nonnegative eigenvector v(say v_1,v_2) for the maximum eigenvalue λ_1 of the variational matrix A_ε (see e.g. [35], [37]). The characteristic equation of A_ε is

$$\begin{aligned}\lambda^2+\lambda\left[u+\frac{\beta(x_0-\varepsilon)}{1+a(x_0-\varepsilon)+b\varepsilon}+p\right]+p\left[u+\frac{\beta(x_0-\varepsilon)}{1+a(x_0-\varepsilon)+b\varepsilon}\right]\\ -\frac{e^{-p\tau-u\sigma}k\beta(x_0-\varepsilon)}{1+a(x_0-\varepsilon)+b\varepsilon}=0.\end{aligned} \tag{6.5}$$

Since ε is sufficiently small enough arbitrarily constant, equation (6.5) can be further simplified as

$$\begin{aligned}\lambda^2+\lambda\left[u+\frac{\beta(x_0-\varepsilon)}{1+a(x_0-\varepsilon)+b\varepsilon}+p\right]+\frac{p(ud+au\lambda+\beta\lambda)}{d+a\lambda}[1-R_0]\\ -\frac{\beta\varepsilon(p-ke^{-p\tau-u\sigma})}{1+a(x_0-\varepsilon)+b\varepsilon}=0.\end{aligned} \tag{6.6}$$

It is more clear that equation (6.6) has maximum positive eigenvalue λ_1, when $R_0>1$ and $\beta\varepsilon(p-ke^{-p\tau-u\sigma})>0$.

Let us consider

$$\begin{aligned} \dot{y}(t) &= \frac{e^{-p\tau}\beta(x_0-\varepsilon)v(t-\tau)}{1+a(x_0-\varepsilon)+b\varepsilon} - py(t), \\ \dot{v}(t) &= ke^{-u\sigma}y(t-\sigma) - uv(t) - \frac{\beta(x_0-\varepsilon)v(t)}{1+a(x_0-\varepsilon)+b\varepsilon}. \end{aligned} \tag{6.7}$$

Let $v(t) = (v_1(t), v_2(t))$ and $l > 0$ be small enough satisfy the conditions

$$lv_1(t) < \tilde{y}(t_0+\theta),$$

$$lv_2(t) < \tilde{v}(t_0+\theta).$$

for $\theta \in [-\varsigma, 0]$, where $\varsigma = max\{\tau, \sigma\}$, if $(y(t), v(t))$ be the solution of system (6.7) satisfying $y(t) = lv_1(t)$ and $v(t) = lv_2(t)$ for $t_0 - \varsigma < t < t_0$.

Then, it is obvious that, $\begin{pmatrix} y(t) \\ v(t) \end{pmatrix} = \begin{pmatrix} me^{\lambda_1 t}v_1(t) \\ me^{\lambda_2 t}v_2(t) \end{pmatrix}$, where λ_1, λ_2 be the characteristic roots of the system (6.7).

It is clear that both $y(t)$ and $v(t)$ are strictly increasing function of t, also $(y(t), v(t)) \to \infty$, as $t \to \infty$. Note that $\tilde{y}(t) \geq y(t)$ and $\tilde{v}(t) \geq v(t)$ for $t > t_0$. We have $\tilde{y}(t) \to \infty, \tilde{v}(t) \to \infty$ as $t \to \infty$. In this case, we can conclude from the bounded of solutions that C_0 repels the positive solution of system (1.2) uniformly. By incorporating this into Lemma (6.2) the theorem (2.1), we know the system (1.2) is permanent. □

7. NUMERICAL SIMULATIONS

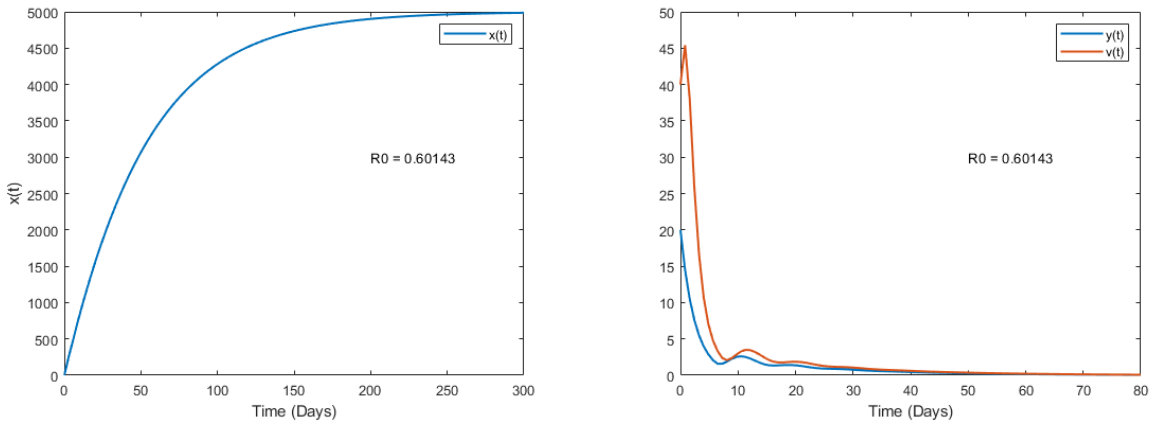
The objective in this section is to demonstrate the validity of the theoretical results that we obtained in Sections 4 and 5, by using the literature-reported parameter values in [6] that be recorded in Table 1. Initially, we choose $\tau = 6$ and $\sigma = 0.9$. Then the numerical simulation

TABLE 1. Literature reported parameter values

Parameter	Range	Value	Parameter	Range	Value
λ	0 - 100 cells mm^{-3}	100	p	0.2 - 0.5 day^{-1}	0.4
β	0.00025 - 0.5 virons	0.45	k	29 - 376 day^{-1}	50
d	0.01 - 0.03 day^{-1}	0.02	a	0.001 - 50 day^{-1}	0.22
u	1.5 - 3 day^{-1}	2.4	b	0.5 - 100 day^{-1}	2

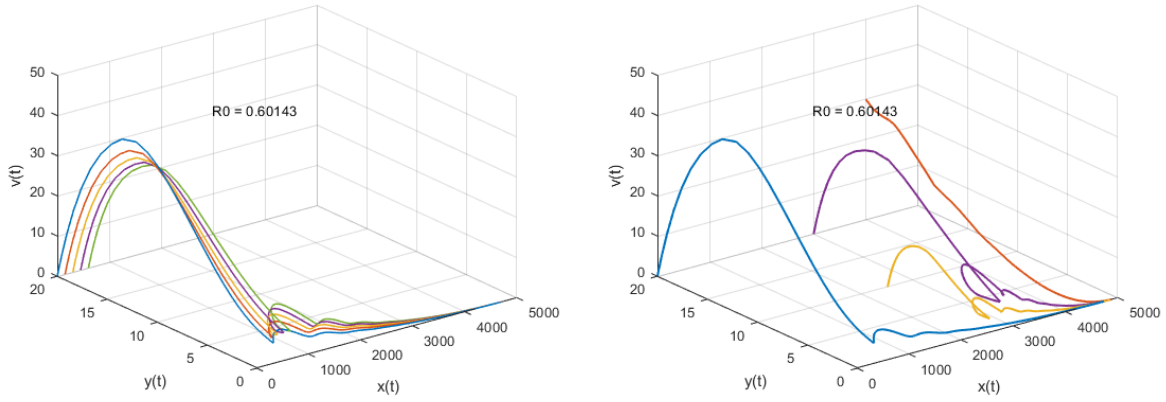
gives that $R_0 = 0.601434 < 1$ and the Theorem 5.1 shows that the infection-free equilibrium $E_0(\lambda/d, 0, 0) = (5000, 0, 0)$ is globally asymptotically stable if $R_0 \leq 1$. This conclusion numerically confirm by the Figures 1 and Figure 2. Secondly, we choose $\tau = 5$ and $\sigma = 0.85481$ the numerical simulation gives that $R_0 = 1$, then the Theorem 5.1 given that infection free equilibrium point $E_0(\lambda/d, 0, 0)$ is globally asymptotically stable and Figure 3 confirm the theoretical result. Thirdly, we consider $\tau = 3$ and $\sigma = 0.2$, the numerical simulation gives that $R_0 = 10.714104 > 1$ and the Theorem 4.2 shows that the chronic infection equilibrium $E_1(x_1, y_1, v_1) = (429.1213, 68.8361, 849.2976)$ is locally asymptotically stable if $R_0 > 1$. The Figure 4 and Figure 5 numerically show that the chronic infection equilibrium is global asymptotically stabile.

It clear that the reproduction ratio $R_0 = \frac{\lambda\beta k e^{-p\tau - u\sigma}}{p(ud + au\lambda + \lambda\beta)}$ is a decreasing function on the time delay τ and σ. In Figure (6a) can be seen that R_0 decreasing as τ increasing when $\sigma = 0$. It further can be observed that $R_0 < 1$ when τ approximately greater that 10.2 and $\sigma = 0$, then the virus is cleared up from the system. Similarly, from Figure (6b) it can be observed that R_0 decreasing as σ increasing when $\tau = 0$ and $R_0 < 1$ when σ approximately grater than 1.7. Finally, all these figures show that for sufficient large τ and σ, the virus is eliminated form the system.



(A) (B)

FIGURE 1. The infection-free equilibrium point $E_0(5000, 0, 0)$ of the model (1.2) is globally asymptotically stable when $\tau = 6$ and $\sigma = 0.9$.



(A) (B)

FIGURE 2. phase diagram of infection-free equilibrium point $E_0(5000,0,0)$ of the model (1.2) is globally asymptotically stable when $\tau = 6$ and $\sigma = 0.9$.

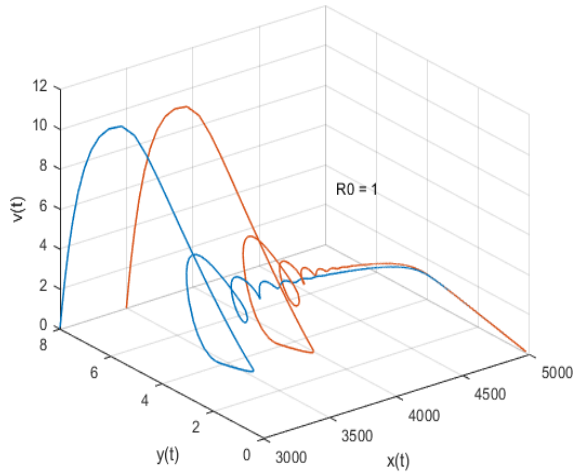
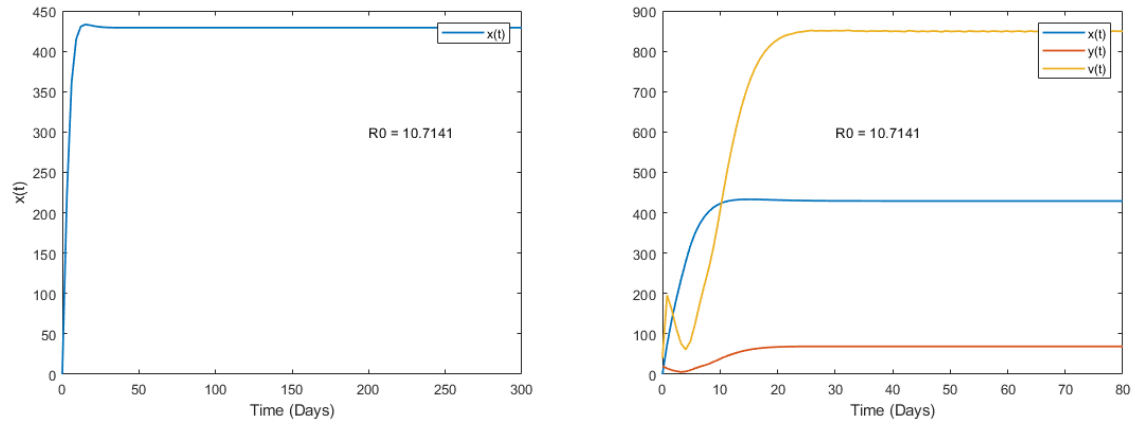
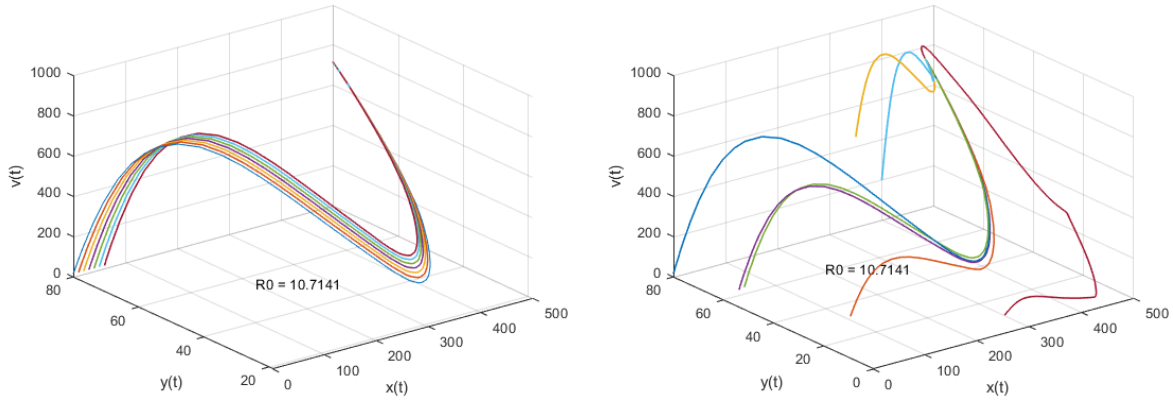


FIGURE 3. Phase diagram of infection-free equilibrium point $E_0(5000,0,0)$ of the model (1.2) is globally asymptotically stable when $\tau = 5$ and $\sigma = 0.85481$.



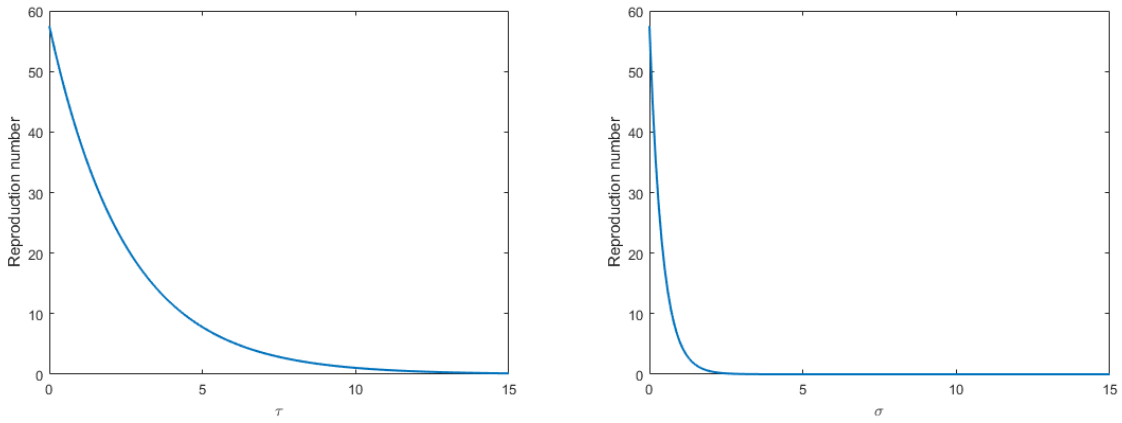
(A) (B)

FIGURE 4. The chronic infection equilibrium point $E_1(429.1213, 68.8361, 849.2976)$ of the model (1.2) is globally asymptotically stable when $\tau = 3$ and $\sigma = 0.2$.



(A) (B)

FIGURE 5. Phase diagram of the chronic infection equilibrium point $E_1(429.1213, 68.8361, 849.2976)$ of the model (1.2) is globally asymptotically stable when $\tau = 3$ and $\sigma = 0.2$.



(A) Reproduction Ratio vs τ when $\sigma = 0$ (B) Reproduction Ratio vs σ when $\tau = 0$

FIGURE 6. Basic reproduction number R_0 as τ and σ increasing.

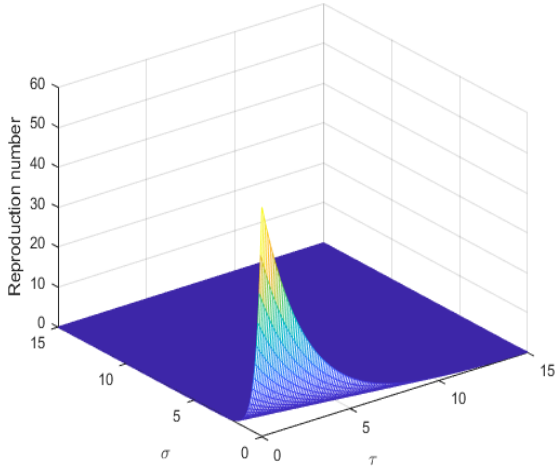


FIGURE 7. Plot of the basic reproduction number when both τ and σ increasing.

8. DISCUSSION

In this paper, we have proposed and concentrated on a delay HIV-1 dynamics model with absorption effect and Beddington-DeAngelis functional response by incorporating both maturation time delay (σ) and intercellular time delay (τ) into the model.

The local stability of both the infection-free equilibrium point E_0 and the chronic infection equilibrium point E_1 is verified in detail by studying the characteristic equations of system (1.2) at each equilibrium point as given in Theorem 4.1 and Theorem 4.2, respectively. If the initial

reproduction number R_0 is less than or equal unity, the infection-free equilibrium E_0 is locally asymmetric stable, which biologically implies that the respective virus can be controlled by drug treatment or activating of the body's immune system. In this case the host will not get be infected and the disease will be cured within a certain period of time. Furthermore, the above theorems clearly show that if the initial reproduction number is greater than unity, the infection-free equilibrium point E_0 is unstable and the chronic infection equilibrium point E_1 is locally asymptotically stable, which biologically implying that the host cannot control disease recruitment.

To analyze the global stability of the infection-free equilibrium, two Lyapunov functions were constructed and the LaSalles invariance principle was used to check the stability. we have shown that the system (1.2) is uniformly persistence in Section (6) for any delay $\sigma, \tau \geq 0$. The numerical simulations clearly suggest that the chronic infection equilibrium E_1 in model (1.2) is globally asymptotically stable if $R_0 > 1$.

It is confirmed by the result in Figure (7), when all the other parameters are constant we can find sufficiently large delay τ and σ such that the basic reproduction number less than or equal unity which make virus clean up. In biological terms, we can draw the following conclusion: the both τ and σ play an important role in the viral infection process to eliminate the virus and adequately large τ and σ can be eliminated virus from the system.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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