RESEARCH ARTICLE

Stability properties of a delayed HIV model with nonlinear functional response and absorption effect

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Abstract: This study investigated the impact of latent and maturation delay on the qualitative behaviour of a human immunodeficiency virus-1 (HIV-1) infection model with nonlinear functional response and absorption effect. Basic reproduction number (R_0), which is defined as the average number of infected cells produced by one infected cell after inserting it into a fully susceptible cell population is calculated for the proposed model. As R_o (threshold) depends on the negatively exponential function of time delay, these parameters are responsible to predict the future propagation behaviour of the infection. Therefore, for smaller positive values of delay and larger positive values of infection rate, the infection becomes chronic. Besides, infection dies out with larger delays and lower infection rates. To make the model biologically more sensible, we used the functional form of response function that plays an important role rather than the bilinear response function. Existence of equilibria and stability behaviour of the proposed model totally depend on R_o. Local stability properties of both infection free and chronic infection equilibria are established by utilising the characteristic equation. As it is crucially important to study the global behaviour at equilibria rather than the local behaviour, we used the method of Liapunov functional. By constructing suitable Liapunov functionals and applying LaSalle's invariance principle for delay differential equations, we established that infection free equilibrium is globally asymptotically stable if $R_0 \leq 1$, which biologically means that infection dies out. Moreover, sufficient condition is derived for global stability of chronic infection equilibrium if $R_0 > 1$, which biologically means that infection becomes chronic. Numerical simulations are given to illustrate the theoretical results.

Keywords: Basic reproduction number, HIV-1 infection, latent delay, Liapunov functional, local and global stability, mathematical delay.

INTRODUCTION

It is well known that the human immunodeficiency virus (HIV) has become a serious problem in the world. The leading cause of human deaths in the Sub-Saharan Africa has been identified as HIV-1 and AIDS (acquired immunodeficiency syndrome). Biologically, it has been proved that the prime target of HIV-1 is CD4^{+} T lymphocytes (large portion of white blood cells in the immune system). Mathematical models in epidemiology and immunology have given considerable contribution to understand the behaviour of disease transmission (Rong *et al.*, 2007; Sedaghat *et al.*, 2007; Wedagedera, 2011; Pawelek *et al.*, 2012). Hence, these results play a noticeable role to improve various kinds of drug therapies. Different mathematical models have emerged after Anderson and May's primus model (Anderson & May, 1981), which describes the dynamics of micro-parasites. Mathematical models with various infection functions have been introduced in HIV-1 viral dynamics models and also in other types of viral dynamic models such as hepatitis B (Gourley *et al.*, 2008) and hepatitis C (Wodarz, 2003).

By constructing suitable Liapunov functionals, global asymptotical stability properties of both infected and uninfected equilibria of a basic viral dynamic model with bilinear incidence rate has been established in the recent past (Korobeinikov, 2004). Further, very recently, Tian and Liu (2014) have proposed and analysed the following

virus dynamical model (1) with more general incidence rate and cure rate; the authors have completely studied the global stability for virus free and chronic infection equilibria by utilising Liapunov functional method and the Poincaré-Bendixson property for three dimensional competitive systems, respectively.

$$\begin{cases} \dot{x}(t) = \lambda - \beta f(x, y, v)v(t) - dx(t) + qy(t), \\ \dot{y}(t) = \beta f(x, y, v)v(t) - (p+q)y(t), \\ \dot{v}(t) = ky(t) - uv(t), \end{cases} \quad ...(1)$$

where x, y and v are the number of uninfected target cells, the number of infected cells, which are able to produce virus and the number of free viruses, respectively. The death rates of uninfected target cells, infected cells and free viruses are represented by d, p, and u, respectively. The per capita contact rate is β and the rate of free virus created by infected cells is ky. Furthermore, uninfected target cells are recruited to the compartment at constant rate λ and infected cells are recovered at constant rate q. It is assumed that all the aforementioned parameters are non-negative in order to be biologically sensible.

Models with deviations from classical models can be seen in the literature, for instance, bilinear incidence rate (Nowak *et al.*, 1996; 1997; Perelson *et al.*, 1996), i.e. $x(t)v(t)$, and Holling II functional response (Li & Ma, 2007), i.e. $x(t)v(t) / (1+cx(t))$ where c is the half saturation constant, have been used instead of $f(x, y, v)v$ in model (1) when $q = 0$.

Replacing the incidence rate function, $f(x, y, v)v$ of model (1) by Crowley-Martin type of functional response, Zhou and Cui (2011) have proved that chronic infection equilibrium of model (1) is globally asymptotically stable by means of Liapunov functional and LaSalle's invariance principle. Huang *et al.* (2011) have used the Beddington-DeAngelis type infection rate function instead of $f(x, y, v)v$ in model (1) when $q = 0$, which was introduced by Beddington (1975) and DeAngelis *et al.* (1975). Recently, a great deal of attention has been paid by many researchers on the Beddington-DeAngelis type response function, which has been used in the virus dynamics model (Wang *et al.*, 2010; Huang *et al.*, 2011; Elaiw *et al.*, 2012), and in ecological model (Hsu *et al.*, 2013) and their stability behaviours have been studied. Moreover, a general form of incidence rate function $f(x, v)$ has been considered (Huang *et al.*, 2010).

Most virus dynamic models have been formulated in the recent past ignoring the process that considers absorption of pathogens into the uninfected cells. In this process, the pathogen density in the blood volume reduces with time, as a result of loss of pathogens due to their absorption into susceptible cells. The integral effect of the absorption process depends on the type of disease. For example, in the case of HIV, the amount of pathogens that is absorbed by a susceptible cell is smaller than the amount of decreased pathogens in the blood volume (Perelson *et al.*, 1996). However, some researchers have considered the absorption effect in their models as it has a direct effect on the stability of the model (Anderson *et al.*, 1989). Xu (2012) presented a delayed model with saturation infection rate and absorption effect where he has used suitable Liapunov functionals and LaSalle's invariance principle, and proved that infection free equilibrium and chronic infection equilibrium are globally asymptotically stable. Further, Pradeep and Ma (2014) proposed and analysed a delayed model with Beddington-DeAngelis type response function and absorption ignoring global stability properties of chronic infection equilibrium. Motivated by the above work, in this study, we considered a more general delayed model (2) with general infection function rate, state dependent nonlinear removal rate for infected cells, latent time delay, maturation time delay of newly produced viruses and absorption effect. By means of Liapunov functionals, global stability properties of infection free equilibrium and infected equilibrium were established. Numerical simulations are presented to illustrate our theoretical results.

$$\begin{cases} \dot{x}(t) = \lambda - \beta x(t)f(v(t)) - dx(t), \\ \dot{y}(t) = e^{-a\tau}\beta x(t-\tau)f(v(t-\tau)) - pg(y(t)), \\ \dot{v}(t) = ke^{-b\sigma}g(y(t-\sigma)) - uv(t) - \beta x(t)f(v(t)). \end{cases} \quad ...(2)$$

Here, τ is the time period taken for viral entry into an uninfected target cell and produce new viruses from it. The term, $e^{-a\tau}$ accounts for the probability of surviving from time $t - \tau$ to t where $a > 0$ is the death rate of the infected cells from time $t - \tau$ to t. The time period taken for the newly produced virion to become mature and then infectious is denoted by the parameter σ. The term $e^{-b\sigma}$ represents the probability of surviving from time $t - \sigma$ to t where $b > 0$ is the death rate of viruses from time $t - \sigma$ to t. Other parameters have the same biological meaning as aforementioned model (1). We assumed throughout this study that the functions $f(v)$ and $g(y)$ satisfy the following conditions:

(H1) $f \in C^2[0, +\infty)$, $f(0) = 0$, $f'(0) > 0$, $f'(v) > 0$, and $f''(v) < 0$ $(\forall v > 0)$,

(H2) $g \in C^1[0, +\infty)$, $g(0) = 0$, $\lim_{y \to +\infty} g(y) = K \le +\infty$, and $g'(y) > L \ (\forall y > 0)$, where L is a positive constant and K is a positive constant or $+\infty$.

Let $C = C([-r, 0], R_+^3)$ be a Banach space of continuous functions mapping from interval $[-r, 0]$ to R_+^3 equipped with sup-norm. Further, initial conditions for model (2) are given as follows,

$$x(\theta) = \phi_1(\theta), \quad y(\theta) = \phi_2(\theta), \quad v(\theta) = \phi_3(\theta), \quad (-r \le \theta \le 0),$$
$$...(3)$$

where $r = \max\{\tau, \sigma\}$ and in biological meaning, $\phi_i(\theta)$ ($i = 1, 2, 3$) are real functions, which are continuous and non-negative on the interval $[-r, 0]$. From the fundamental theory of delay differential equations (Kuang, 1993), it is easy to prove that the existence and uniqueness of solutions $(x(t), y(t), v(t))^T$ of model (2) for time $t \ge 0$ with initial conditions (3).

METHODS AND MATERIALS

In this section, we investigate the non-negativity of solutions as state variables represent populations and ultimately boundedness of solutions of model (2) as there are some limitations for state variables. Model (2) is analysed for two equilibria, which are based on the reproduction number. Local stability properties of both equilibria are analysed by using the well known Ruth Hurwitz criterion when time delays are not present, and some theorems from Kuang (1993) are used to analyse model (2) when time delays are present. Global stability properties for both equilibria are established by the method of Liapunov functional and LaSalle's invariance principle.

The following theorem shows the non-negativity and the boundedness of any solution of model (2).

Theorem 1. *Any solution $(x(t), y(t), v(t))^T$ of model (2) is non-negative for $t \ge 0$ and ultimately bounded under initial conditions (3).*

Proof. For any $\varepsilon > 0$, consider the following initial conditions

$$x(\theta) = \phi_1(\theta) + \varepsilon, \quad y(\theta) = \phi_2(\theta) + \varepsilon, \quad v(\theta) = \phi_3(\theta) + \varepsilon, \quad ...(4)$$

where (ϕ_1, ϕ_2, ϕ_3) is aforementioned initial condition (3).

For any $\varepsilon > 0$, let $(x(t,\varepsilon), y(t,\varepsilon), v(t,\varepsilon))^T$ be the solution of model (2) under conditions (4), and its maximal

existence interval is denoted by $[0, T_\varepsilon)$, where $0 < T_\varepsilon \le +\infty$. For $\varepsilon = 0$, let us show that the solution $(x(t), y(t), v(t))^T$ is non-negative on $[0, T_0)$.

In fact, for any close interval $[0, b] \subset [0, T_0)$, from the solution $(x(t,\varepsilon), y(t,\varepsilon), v(t,\varepsilon))^T$ is a continuous function with the parameter ε, for sufficiently small $\varepsilon > 0$ the solution $(x(t,\varepsilon), y(t,\varepsilon), v(t,\varepsilon))^T$ is uniformly existent on $[0, b]$.

Assume that $x(t)$ loses its non-negativity on some local existence interval $[0, b]$. According to the initial conditions, it has a non-negative function on $[-r, 0]$, then there exists $t_1 \ge 0$ such that $x(t_1) = 0$ and $\dot{x}(t_1) \le 0$. However, from the first equation of model (2) one can obtain that $\dot{x}(t_1) = \lambda > 0$. It is clear that this is a contradiction. Therefore, $x(t, \varepsilon)$ is always positive on $(0, b]$.

Further, from the second equation of model (2), we assume that $y(t)$ loses its non-negativity on $(0, b]$. Let $\bar{t} = \inf\{t \in (0, b] \mid y(t) = 0\}$, then $y(\bar{t}) = 0$ and $\dot{y}(\bar{t}) \le 0$. It is easy to verify that $v(t, \varepsilon) > 0$ for $[-r, \bar{t}]$ as $y(t, \varepsilon) > 0$ for $[-r, \bar{t}]$. However, $\dot{y}(\bar{t}) = e^{-\alpha t} \beta x(\bar{t} - \tau) f(v(\bar{t} - \tau)) > 0$ This leads to a contradiction. Therefore, $y(t, \varepsilon) > 0$ for all $t \in [0, b]$. Along this line, from the third equation of model (2), we can prove similarly that $v(t, \varepsilon) > 0$ for all $t \in [0, b]$.

Letting $\varepsilon \to 0^+$, for any $t \in [0, b]$, it has that $x(t, 0) \ge 0$, $y(t, 0) \ge 0$, $v(t, 0) \ge 0$. Thus, for any $t \in [0, T_0)$, it has that $x(t) \ge 0$, $y(t) \ge 0$, $v(t) \ge 0$. Further, for any $t \in [0, T_0)$, it is easy to see that $x(t) \ge 0$, $y(t) \ge 0$, $v(t) \ge 0$.

Next, we consider the boundedness of solutions. Define $H(t)$ as below,

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

Taking derivation along the solution and using (H1), (H2) and mean value theorem,

$$\dot{H}(t) = e^{-\alpha \tau} \lambda - de^{-\alpha \tau} x(t-\tau) - pg(y(t))$$
$$= e^{-\alpha \tau} \lambda - de^{-\alpha \tau} x(t-\tau) - pg'(\xi) y(t) \ (\xi \in [0, y])$$
$$\le e^{-\alpha \tau} \lambda - mH(t).$$

where $m = \min\{d, pL\}$. By the non-negativity of $x(t)$ and $y(t)$, hence, the well-known comparison principle implies that $x(t)$ and $y(t)$ are all bounded on $[0, T_0)$, i.e. $M = \sup_{t \in [0, T_0)} H(t) < +\infty$. Again from the third equation of model (2), it has that

$$\dot{v}(t) \le ke^{-b\sigma} g(y(t-\sigma)) - uv(t) = ke^{-b\sigma} A - uv(t),$$

where $A = \max_{0 \le y \le M} \{g(y)\}$. Hence, we also have from comparison principle that $v(t)$ is bounded on $[0, T_0)$. Boundedness of the solution $(x(t), y(t), v(t))^T$ implies that the above discussion can be extended to $[0, +\infty)$. Hence, the solution $(x(t), y(t), v(t))^T$ is existent and non - negative on $[0, +\infty)$. We have $\lim \sup_{t \to +\infty} H(t) \le e^{-a\tau} \lambda/m$. By the non-negativity of $x(t)$ and $y(t)$, this implies that $x(t)$ and $y(t)$ are ultimately bounded.

Model (2) always has an infection free equilibrium $E_0(x_0, 0, 0)$ where $x_0 = \lambda/d$. By following a similar technique used by Diekmann *et al.* (1990) and Van den Driessche and Watmough (2002), we obtain the basic reproduction number (spectral radius of next generation matrix) for model (2) as

$$R_0 = \frac{\lambda \beta k f'(0) e^{-a\tau - b\sigma}}{p(ud + \lambda \beta f'(0))}.$$

Here, we define R_0 to be the average number of infected cells produced by one infected cell after introducing an infected cell into a fully susceptible cell population. The following theorem shows the existence of chronic infection equilibrium E^*.

Theorem 2. *Suppose that $R_0 > 1$ and $K \ge \frac{\beta x^* f(v^*) e^{-\tau a}}{p}$, then model (2) has a unique chronic infection equilibrium $E^*(x^*, y^*, v^*)$, where $v^* \in (0, v_1)$ and $v_1 = \frac{\lambda}{pu} (ke^{-a\tau - b\sigma} - p)$,*

$$x^* = \frac{\lambda}{d + \beta f(v^*)} \quad and \quad y^* = g^{-1}\left(\frac{\beta x^* f(v^*) e^{-a\tau}}{p}\right)$$

Proof. At any equilibrium point from model (2), we have that

$$\lambda - \beta x f(v) - dx = 0,$$
$$e^{-a\tau} \beta x f(v) - pg(y) = 0,$$
$$ke^{-b\sigma} g(y) - uv - \beta x f(v) = 0.$$

By simple computation, we have that

$$\lambda - dx = \beta x f(v) = pg(y)e^{a\tau} = \frac{pe^{a\tau + b\sigma}}{k}[uv + \beta x f(v)].$$

We can obtain the following equation for v, by substituting x by v:

$$G(v) = \beta f(v)(\lambda ke^{-a\tau - b\sigma} - puv - \lambda p) - pduv = 0.$$

It can be seen that $G(0) = 0$ and there is $v_1 = \frac{\lambda}{pu}(ke^{-a\tau - b\sigma} - p) > 0$ such that $G(v_1) = -pduv_1 < 0$. Differentiation yields for $G(v)$,

$$G'(v) = \beta f'(v)(\lambda ke^{-a\tau - b\sigma} - puv - \lambda p) - pu\beta f(v) - pdu.$$

It is not difficult to find that $G'(v)$ is strictly decreasing on $[0, v_1]$. Further, we have that $\qquad G'(0) = p(\lambda \beta f'(0) + du)(R_0 - 1) > 0 \qquad$ and $G'(v_1) = -pu\beta f(v_1) - pdu < 0$. Therefore, there exists a unique $v^* \in (0, v_1)$ such that $G(v^*) = 0$.

Again from simple calculation, we have that

$$g(y) = \frac{\beta x^* f(v^*) e^{-\tau a}}{p}.$$

Let

$$F(y) = g(y) - \frac{\beta x^* f(v^*) e^{-\tau a}}{p}.$$

Clearly, $F(0) = -\frac{\beta x^* f(v^*) e^{-\tau a}}{p} < 0$ and $F'(y) = g'(y) > 0$. Further,

$$\lim_{y \to +\infty} F(y) = \lim_{y \to +\infty} g(y) - \frac{\beta x^* f(v^*) e^{-\tau a}}{p} = K - \frac{\beta x^* f(v^*) e^{-\tau a}}{p} \ge 0.$$

Hence, there is some value $y^* \in (0, +\infty)$ such that $F(y^*) = 0$ by the monotonicity of the function $g(y)$, we get that

$$y^* = g^{-1}\left(\frac{\beta x^* f(v^*) e^{-\tau a}}{p}\right).$$

Thus, there is a chronic infection equilibrium $E^*(x^*, y^*, v^*)$ for model (2) such that $x^* < x_0$ when $R_0 > 1$.

RESULTS

Local stability

In this subsection, we consider the local stability of infection free equilibrium and chronic infection equilibrium of model (2) by analysing the transcendental characteristic equations. The mathematical results that

we established are given in the following theorems.

Theorem 3. *Model (2) holds the following conclusions for any time delays τ, σ ≥ 0. (a) If $R_0 < 1$, E_0 is locally asymptotically stable, (b) If $R_0 > 1$, E_0 is unstable, (c) critical case if $R_0 = 1$.*

Proof. The characteristic equation at E_0 for model (2) can be given as below:

$$(s+d)\left[(s+l)(s+u+m) - ne^{-s(\sigma+\tau)}\, e^{-a\tau-b\sigma}\right] = 0, \qquad ...(5)$$

where $l = pg'(0)$, $m = \frac{\beta\lambda f'(0)}{d}$ and $n = \frac{\beta k\lambda}{d} g'(0) f'(0)$. It is clear that the first factor $s + d$ always has negative real root. Therefore, we can determine the other roots of equation (5) by the following equation,

$$f(s, \tau, \sigma) = (s+l)\left[(s+u+m) - ne^{-s(\sigma+\tau)}\, e^{-a\tau-b\sigma}\right] = 0. \qquad ...(6)$$

Let us consider case $\tau = 0$ and $\sigma = 0$. Then, equation (6) becomes $s^2 + As + B = 0$, where $A = u + l + m$ and $B = l(u + m)(1-R_0)$. It is obvious that $A > 0$ and $B > 0$ if $R_0 < 1$. Then, by Ruth Hurwitz criterion it has roots with negative real parts, which means that if $R_0 < 1$, E_0 is locally asymptotically stable.

Next, we consider the case $\tau > 0$ and $\sigma > 0$. Then, let us take $s = \omega i$ is a root of the equation (6) where $\omega \geq 0$. It has that

$$-\omega^2 + (u+l+m)\omega i + l(u+m) - ne^{-a\tau-b\sigma}\, e^{-(\sigma+\tau)\omega i} = 0.$$

By separating real and imaginary parts, we have that

$$l(u+m) - \omega^2 = ne^{-a\tau-b\sigma} \cos\left((\sigma + \tau)\omega\right),$$

$$(u+l+m)\,\omega = -ne^{-a\tau-b\sigma} \sin\left((\sigma + \tau)\omega\right).$$

Squaring both sides and adding, one can obtain that

$$\omega^4 + \left((u + m)^2 + l^2\right)\omega^2 + l^2(u + m)^2(1-R_0^2) = 0. \qquad ...(7)$$

Equation (7) does not have positive real roots for ω^2 if $R_0 < 1$. In case $R_0 < 1$, E_0 is locally asymptotically stable from Theorem 3.4.1 in Kuang (1993).

When $R_0 > 1$ it is not difficult to show that $\lim_{s \to +\infty} f(s,\tau,\sigma) = +\infty$ and $f(0,\tau,\sigma) = l(u+m)(1-R_0) < 0$. Clearly, $f(s,\tau,\sigma) = 0$ has at least one positive root. Therefore, E_0 is unstable if $R_0 > 1$.

When $R_0 = 1$, from equation (6), we have that

$$s^2 + (u+m+l)s + l(u+m)(1-e^{-s(\sigma+\tau)}) = 0. \qquad ...(8)$$

It is easy to see that $s = 0$ is a simple root of equation (8). Then, we are going to prove that any other root of equation (8) has only negative real part. Hence, let us suppose that $s = \varphi + \psi i$ for $\varphi \geq 0$, $\psi \geq 0$ for any $\tau, \sigma \geq 0$. From equation (8), we get that

$$\varphi^2 - \psi^2 + (u+m+l)\varphi + l(u+m) = l(u+m)\bar{c}e^{-\varphi(\sigma+\tau)},$$
$$2\varphi\psi + (u+m+l)\psi = -l(u+m)\bar{s}e^{-\varphi(\sigma+\tau)}, \qquad ...(9)$$

where $\bar{c} = \cos((\sigma+\tau)\psi)$ and $\bar{s} = \sin((\sigma+\tau)\psi)$. By squaring both sides of (9) and taking the addition, we have

$$\left[\varphi^2 - \psi^2 + (u+m+l)\varphi + l(u+m)\right]^2 + \left[2\varphi\psi + (u+m+l)\psi\right]^2 =$$

$$l^2(u+m)^2 e^{-2\varphi(\sigma+\tau)} \leq l^2(u+m)^2.$$

It is obvious that the aforementioned inequality is never satisfied when $\varphi \geq 0$, which leads to a contradiction. Therefore, equation (8) has roots with negative real parts except $s = 0$. Hence, E_0 is stable.

Next, we consider local stability analysis of chronic infection equilibrium E^*.

Theorem 4. *Chronic infection equilibrium E^* is locally asymptotically stable for any time delays τ, $\sigma \geq 0$.*

The corresponding quasi-polynomial at E^* takes the following form

$$s^3 + P_2 s^2 + P_1 s + P_0 + (Q_1 s + Q_0)e^{-s(\sigma+\tau)} = 0, \qquad ...(10)$$

where

$$P_0 = pg'(y^*)\left(u\bar{m} + \beta dx^* f'(v^*)\right), \qquad P_2 = \bar{l} + \bar{m} + pg'(y^*),$$
$$P_1 = pg'(y^*)(\bar{l} + \bar{m}) + u\bar{m} + d\beta x^* f'(v^*), \quad \bar{l} = u + \beta x^* f'(v^*),$$
$$Q_0 = -pdg'(y^*)\left(\frac{u v^* f'(v^*)}{f(v^*)} + \beta x^* f'(v^*)\right) \qquad \bar{n} = \frac{1}{f(v^*)}\left(f(v^*) - v^* f'(v^*)\right),$$
$$Q_1 = -pg'(y^*)\left(\frac{u v^* f'(v^*)}{f(v^*)} + \beta x^* f'(v^*)\right) \qquad \bar{m} = d + \beta f(v^*).$$

Equation (10) is reduced to the following form when $\tau = \sigma = 0$,

$$s^3 + P_2 s^2 + (P_1 + Q_1)s + P_0 + Q_0 = 0, \qquad \ldots(11)$$

where

$$P_0 + Q_0 = pug'(y^*)\left(d\bar{n} + \beta f(v^*)\right),$$

$$P_1 + Q_1 = pg'(y^*)\left(\bar{n}u + \bar{m}\right) + u\bar{m} + d\beta x^* f'(v^*)$$

and

$$P_2(P_1 + Q_1) - (P_0 + Q_0) = pg'(y^*)\left(\bar{l} + \bar{m} + pg'(y^*)\right)\left[\left(\bar{n}u + \bar{m}\right) + \left(u\bar{m} + d\beta x^* f'(v^*)\right)\right]$$

$$- pug'(y^*)\left(d\bar{n} + \beta f(v^*)\right),$$

$$= pg'(y^*)\left[\left(\bar{l} + pg'(y^*)\right)\left(\bar{n}u + \bar{m}\right) + \bar{m}^2 + d\bar{l} + \bar{n}u\beta f(v^*)\right]$$

$$+ (\bar{l} + \bar{m})(u\bar{m} + d\beta x^* f'(v^*)).$$

Noting that the function $f(v)$ is concave and $f(v^*) > v^* f'(v^*)$, we have that $P_0 + Q_0 > 0$, $P_1 + Q_1 > 0$, and $P_2(P_1 + Q_1) - (P_0 + Q_0) > 0$. Hence, equation (11) has roots with negative real parts from the Ruth Hurwitz criterion. Thus, E^* is locally asymptotically stable when $\tau = \sigma = 0$.

Now, let us consider the case τ, $\sigma > 0$. If ωi ($\omega > 0$) is a root of the equation (10), it has from separating real and imaginary parts that

$$Q_1 \omega \cos \omega(\tau + \sigma) - Q_0 \sin \omega(\tau + \sigma) = \omega^3 - P_1 \omega,$$

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

Squaring and taking the addition, it is easy to obtain that

$$\omega^6 + P\omega^4 + Q\omega^2 + R = 0, \qquad \ldots(12)$$

where

$$P = P_2^2 - 2P_1, \quad Q = P_1^2 - 2P_2 P_0 - Q_1^2$$

and

$$R = P_0^2 - Q_0^2.$$

Now, we are going to show that $P > 0$, $Q > 0$, and $R > 0$.

$$P = \bar{l}^2 + \bar{m}^2 + (pg(y^*))^2 + 2\beta^2 x^* f'(v^*) f(v^*),$$

$$R = pug(y^*)(P_0 - Q_0)\left(d\bar{n} + \beta f(v^*)\right),$$

$$Q = \left[pg'(y^*)\left(\bar{l} + \bar{m}\right) + u\bar{m} + d\beta x^* f'(v^*)\right]^2 - (pg'(y^*))^2\left(\frac{uv^* f'(v^*)}{f(v^*)} + \beta x^* f'(v^*)\right)^2$$

$$- 2pg'(y^*)\left(\bar{l} + \bar{m} + pg'(y^*)\right)\left(u\bar{m} + \beta dx^* f'(v^*)\right),$$

$$= (pg'(y^*))^2\left(\bar{m}^2 + 2\beta^2 x^* f'(v^*) f(v^*)\right) + \left(u\bar{m} + \beta dx^* f'(v^*)\right)^2$$

$$+ (pg'(y^*))^2 \bar{n}u\left(\bar{l} + \beta x^* f'(v^*) + \frac{uv^* f'(v^*)}{f(v^*)}\right)$$

It can be seen that equation (12) does not have positive real roots for ω^2 as the function $f(v)$ is concave and $f(v^*) > v^* f'(v^*)$. Hence, $P > 0$, $Q > 0$, and $R > 0$. Consequently, E^* is locally asymptotically stable from Theorem 3.4.1 in Kuang (1993).

Global stability of equilibria

In this subsection, we discuss the global stability properties of infection free equilibrium and chronic infection equilibrium. The mathematical results are given in the following theorem.

Theorem 5. *Following conclusions hold for any time delays $\tau, \sigma \geq 0$.*

(a) If $R_0 \leq 1$, then E_0 is globally asymptotically stable.

(b) If (H3) : $d(ke^{-a\tau - b\sigma} - p) \geq \beta pf(v^*)$, then E^* is globally asymptotically stable.

Proof. The proof of part (a) of Theorem 5 is given under two cases.

Case I: when $ke^{-a\tau - b\sigma} > p$

Define the following Liapunov functional

$$V = V_1 + k_3 \int_{-\tau}^{0} x(t+s) f(v(t+s))ds + k_4 \int_{-\sigma}^{0} g(y(t+s))ds,$$

where

$$V_1 = x - x_0 - x_0 \ln \frac{x}{x_0} + k_1 y + k_2 v,$$

and constants k_1, k_2, k_3 and k_4 are determined later. By considering the derivative along the solutions, we have that

$$\dot{V} = \left(1 - \frac{x_0}{x}\right)\left[\lambda - dx - \beta x f(v)\right] + k_1[e^{-a\tau}\beta x(t-\tau)f(v(t-\tau)) - pg(y)]$$

$$+ k_2\left[ke^{-b\sigma}g(y(t-\sigma)) - uv - \beta xf(v)\right]$$

$$+ k_3[xf(v) - x(t-\tau)f(v(t-\tau))] + k_4[g(y(t)) - g(y(t-\sigma))].$$

Noting that $\lambda = dx_0$ and choosing the constants as $k_1 = \frac{k_3}{\beta}e^{a\tau}$, $k_2 = \frac{p}{ke^{-a\tau - b\sigma} - p}$, $k_3 = (k_2 + 1)\beta$ and $k_4 = k_2 ke^{-b\sigma}$, we have that

$$\dot{V} = dx_0\left(2 - \frac{x_0}{x} - \frac{x}{x_0}\right) + \left(\frac{\beta\lambda}{ud}\frac{f(v)}{v} - \frac{p}{ke^{-a\tau - b\sigma} - p}\right)uv.$$

From the concavity of the function $f(v)$, we have that

$$\dot{V} \le dx_0\left(2 - \frac{x_0}{x} - \frac{x}{x_0}\right) + \frac{p(\beta\lambda f'(0) + ud)(R_0 - 1)v}{d(ke^{-a\tau - b\sigma} - p)}.$$

It can be seen that if $R_0 \le 1$ for $t \ge 0$, $\dot{V} \le 0$. Therefore, infection free equilibrium E_0 is stable.

Now, let us show that infection free equilibrium E_0 is globally attractive. Define the subset

$$E = \{\phi = (\phi_1, \phi_2, \phi_3)^T \mid \dot{V}(\phi_1, \phi_2, \phi_3) = 0\},$$

and let M be the largest invariance subset in E with respect to model (2). It is clear that M contains at least one point E_0. For any $\phi = (\phi_1, \phi_2, \phi_3)^T \in M$, let $(x_t, y_t, v_t)^T$ be any solution of model (2) with the initial condition (3), where

$$x_t(\theta) = x(t+\theta), \, y_t(\theta) = y(t+\theta), \, v_t(\theta) = v(t+\theta)(-r \le \theta \le 0).$$

We have from invariance of M that $(x_t, y_t, v_t)^T \in M \subset E$ for any $t \in R$. If $R_0 \le 1$, for any $t \in R$, we have that $x_t(0) = x(t) = x_0$. From the invariance of M we have that $x_t = \phi_1 = x_0$. From the first and third equations of model (2), it has that $f(v_t(0)) = 0$ and $g(y_t(0)) = 0$. Hence, $v_t(0) = v(t) = 0$ and $y_t(0) = y(t) = 0$ for any $t \in R$. This proves that $\phi = (x_0, 0, 0)^T$, i.e., $M = \{E_0\}$. By LaSalle's invariance principle in Kuang (1993), all positive solutions of model (2) converge to E_0. Therefore, infection free equilibrium E_0 of model (2) is globally asymptotically stable if $R_0 \le 1$.

Case II when $ke^{-a\tau - b\sigma} \le p$

Now, we are going to prove that infection free equilibrium E_0 is globally asymptotically stable when $ke^{-a\tau - b\sigma} \le p$. Let us define a Liapunov functional

$$W = c_1 y + c_2 v + \frac{\beta e^{b\sigma}}{k}\int_{-\tau}^{0} x(t+\theta)f(v(t+\theta))d\theta + \int_{-\sigma}^{0} g(y(t+\theta))d\theta,$$

where c_1 and c_2 are due to be determined later. Then, consider the derivative along the solution

$$\dot{W} = c_1\left[e^{-a\tau}\beta x(t-\tau)f(v(t-\tau)) - pg(y(t))\right]$$
$$+ c_2\left[ke^{-b\sigma}g(y(t-\sigma)) - uv(t) - \beta x(t)f(v(t))\right]$$
$$+ \frac{\beta e^{b\sigma}}{k}\left[x(t)f(v(t)) - x(t-\tau)f(v(t-\tau))\right] + g(y) - g(y(t-\sigma)),$$

By choosing $c_1 = \frac{e^{b\sigma + a\tau}}{k}$ and $c_2 = \frac{e^{b\sigma}}{k}$, it has that

$$\dot{W} = -\frac{e^{b\sigma}uv}{k} + \frac{e^{b\sigma + a\tau}}{k}\left[ke^{-b\sigma - a\tau} - p\right]g(y).$$

It is clear that $\dot{W} \le 0$ if $ke^{-b\sigma - a\tau} \le p$. From the third equation of model (2), we have that $y(t) = 0$ if $v(t) = 0$. Thus, $\dot{W} = 0$ if and only if $v(t) = 0$ any $y(t) = 0$. From the first equation, one can obtain that $x(t) = x_0$ as $t \to +\infty$. By following a similar procedure as in case I, we can show that infection free equilibrium E_0 is globally asymptotically stable for case II.

Again, define a Liapunov functional as given below, noting that we use the notations $x_\tau = x(t-\tau)$ and $y_\sigma = y(t-\sigma)$ to reduce excess usage of brackets,

$$Z = x - x^* - x^*\ln\frac{x}{x^*} + \frac{k_1}{p}\left(y - y^* - \int_{y^*}^{y}\frac{g(y^*)}{g(\theta)}d\theta\right)$$
$$+ \frac{k_1}{ke^{-b\sigma}}\left(v - v^* - \int_{v^*}^{v}\frac{f(v^*)}{f(\theta)}d\theta\right) + \frac{\beta k_1}{p}e^{-a\tau}U_1^* + k_1 U_2^*,$$

where k_1 is a constant due to be determined later and

$$U_1^* = \int_{t-\tau}^{t}\left(x(t)f(v(t)) - x^*f(v^*) - x^*f(v^*)\ln\frac{x(t)f(v(t))}{x^*f(v^*)}\right)d\theta,$$

$$U_2^* = \int_{t-\sigma}^{t}\left(g(y(t)) - g(y^*) - g(y^*)\ln\frac{g(y(t))}{g(y^*)}\right)d\theta.$$

By considering the derivative along the solution, we have that

$$\dot{Z} = \left(1 - \frac{x^*}{x}\right)[\lambda - dx - \beta xf(v)]$$

$$+ \frac{k_1}{p}\left(1 - \frac{g(y^*)}{g(y)}\right)[e^{-a\tau}\beta x_\tau f(v_\tau) - pg(y)]$$

$$+ \frac{k_1}{ke^{-b\sigma}}\left(1 - \frac{f(v^*)}{f(v)}\right)[ke^{-b\sigma}g(y_\sigma) - uv - \beta xf(v)]$$

$$+ \frac{\beta k_1}{p}e^{-a\tau}\left[xf(v) - x_\tau f(v_\tau) + x^*f(v^*)\ln\frac{x_\tau f(v_\tau)}{xf(v)}\right]$$

$$+ k_1\left[g(y) - g(y_\sigma) + g(y^*)\ln\frac{g(y_\sigma)}{g(y)}\right]$$

$$= \left(1 - \frac{x^*}{x}\right)[\lambda - dx] + \beta x^*f(v) - \frac{\beta k_1 e^{-a\tau}}{p}\frac{g(y^*)}{g(y)}x_\tau f(v_\tau)$$

$$+ k_1 g(y^*) - \frac{k_1 u}{ke^{-b\sigma}}v - \frac{k_1 f(v^*)}{f(v)}g(y_\sigma) + \frac{k_1}{ke^{-b\sigma}}\frac{f(v^*)u}{f(v)}v + \frac{\beta k_1 f(v^*)}{ke^{-b\sigma}}x$$

$$+ \frac{\beta k_1 x^*}{p}f(v^*)e^{-a\tau}\ln\frac{x_\tau f(v_\tau)}{xf(v)} + k_1 g(y^*)\ln\frac{g(y_\sigma)}{g(y)}.$$

Note that $k_1 = \frac{pke^{-b\sigma}}{(ke^{-a\tau - b\sigma} - p)} > 0$ as $ke^{-a\tau - b\sigma} > p$ when $R_0 > 1$, $\lambda = dx^* + \beta x^*f(v^*)$, $g(y^*) = \frac{\beta x^*}{p}f(v^*)e^{-a\tau}$, and $\frac{k_1 u}{ke^{-b\sigma}} = \beta x^*\frac{f(v^*)}{v^*}$, it has that

$$\dot{Z} = dx^*\left(2 - \frac{x}{x^*} - \frac{x^*}{x}\right) + \frac{\beta k_1 x^*}{p} f(v^*)e^{-\alpha\tau}\left[1 - \frac{x^*}{x} + \ln\frac{x^*}{x}\right]$$

$$+ \beta x^* f(v^*)\left[\frac{f(v)}{f(v^*)} + \frac{f(v^*)v}{f(v)v^*} - \frac{v}{v^*} - 1\right]$$

$$+ \beta x^* f(v^*)\left[2 - \frac{x^*}{x} + \frac{k_1}{ke^{-b\sigma}}\frac{x}{x^*} + \left(\frac{k_1}{ke^{-b\sigma}} + 1\right)\left(\frac{x^*}{x} - 2\right)\right]$$

$$+ \frac{\beta k_1 x^*}{p} f(v^*)e^{-\alpha\tau}\left[1 - \frac{g(y^*)}{g(y)}\frac{x_\tau f(v_\tau)}{x^* f(v^*)} + \ln\frac{g(y^*)}{g(y)}\frac{x_\tau f(v_\tau)}{x^* f(v^*)}\right]$$

$$+ \frac{\beta k_1 x^*}{p} f(v^*)e^{-\alpha\tau}\left[1 - \frac{f(v^*)}{f(v)}\frac{g(y_\sigma)}{g(y^*)} + \ln\frac{f(v^*)}{f(v)}\frac{g(y_\sigma)}{g(y^*)}\right]$$

$$= -\frac{(x-x^*)^2}{x}\left(\frac{d(ke^{-\alpha\tau-b\sigma} - p) - \beta pf(v^*)}{(ke^{-\alpha\tau-b\sigma} - p)}\right) + \frac{\beta k_1 x^* f(v^*)}{pe^{\alpha\tau}}\left[1 - \frac{x^*}{x} + \ln\frac{x^*}{x}\right]$$

$$+ \beta x^* f(v^*)\left(\frac{v}{v^*} - \frac{f(v)}{f(v^*)}\right)\left(\frac{f(v^*)}{f(v)} - 1\right)$$

$$+ \frac{\beta k_1 x^* f(v^*)}{pe^{\alpha\tau}}\left[1 - \frac{g(y^*)}{g(y)}\frac{x_\tau f(v_\tau)}{x^* f(v^*)} + \ln\frac{g(y^*)}{g(y)}\frac{x_\tau f(v_\tau)}{x^* f(v^*)}\right]$$

$$+ \frac{\beta k_1 x^* f(v^*)}{pe^{\alpha\tau}}\left[1 - \frac{f(v^*)}{f(v)}\frac{g(y_\sigma)}{g(y^*)} + \ln\frac{f(v^*)}{f(v)}\frac{g(y_\sigma)}{g(y^*)}\right].$$

According to the properties of concavity and monotonicity of $f(v)$, it holds the following inequalities,

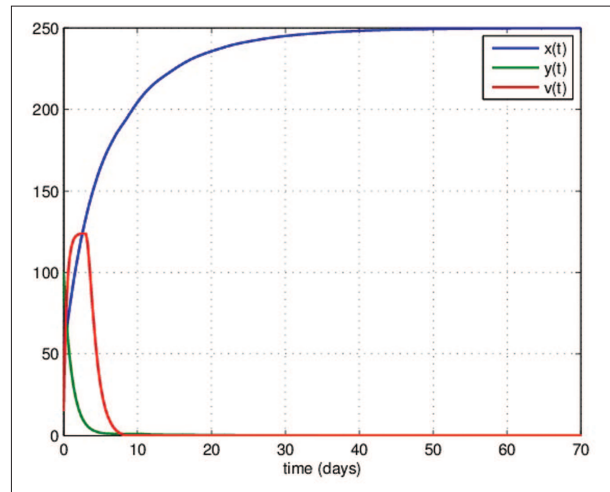$$\begin{cases} 1 \le \dfrac{f(v^*)}{f(v)} \le \dfrac{v^*}{v}, & 0 < v \le v^*, \\[2mm] 1 \ge \dfrac{f(v^*)}{f(v)} \ge \dfrac{v^*}{v}, & v \ge v^*. \end{cases}$$

From which it has that

$$\left(\frac{v}{v^*} - \frac{f(v)}{f(v^*)}\right)\left(\frac{f(v^*)}{f(v)} - 1\right) \le 0.$$
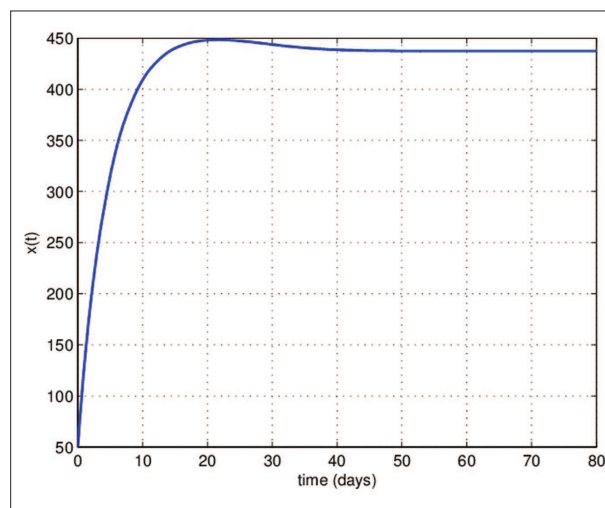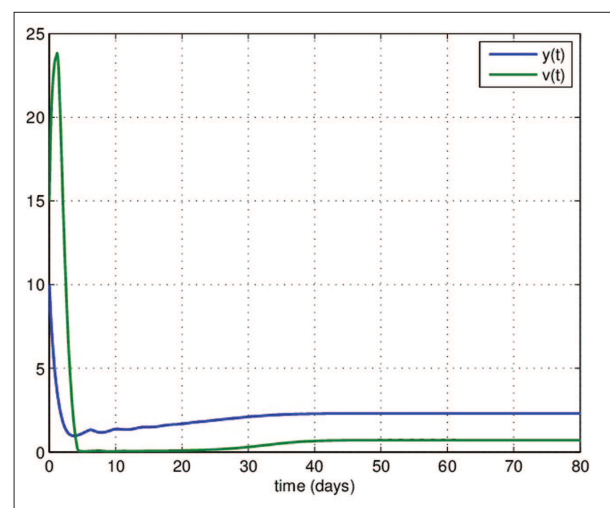

Figure 1: Time evolutions of model (2) with initial values (50; 100; 15). E_0 is globally asymptotically stable

When $d(ke^{-\alpha\tau-b\sigma} - p) \ge \beta pf(v^*)$, then $\dot{Z} \le 0$. This implies that infection equilibrium E^* is stable.

For any $\phi = (\phi_1, \phi_2, \phi_3)^T \in M$, let us show that $M = \{E^*\}$. We have that $\dot{V} = 0$ if and only if

$$\frac{x_t(0)}{x^*} = \frac{g(y^*)}{g(y_t(0))}\frac{x_t(-\tau)f(v_t(-\tau))}{x^* f(v^*)} = \frac{f(v^*)}{f(v_t(0))}\frac{g(y_t(-\sigma))}{g(y^*)} = \frac{f(v^*)}{f(v_t(0))} = 1.$$

Therefore, it gives that $x_t(0) = x(t) = x^*$ and $v_t(0) = v(t) = v^*$. From the third equation of model (2) and (H2), it can be obtained that $y_t(0) = y(t) = y^*$. This proves that $\phi = (x^*, y^*, v^*)^T$, i.e., $M = \{E^*\}$. By LaSalle's invariance principle in Kuang (1993), all positive solutions of model (2)

(a)

(b)

Figure 2: Time evolutions of model (2) with initial values (50;10;15). E^* is globally asymptotically stable
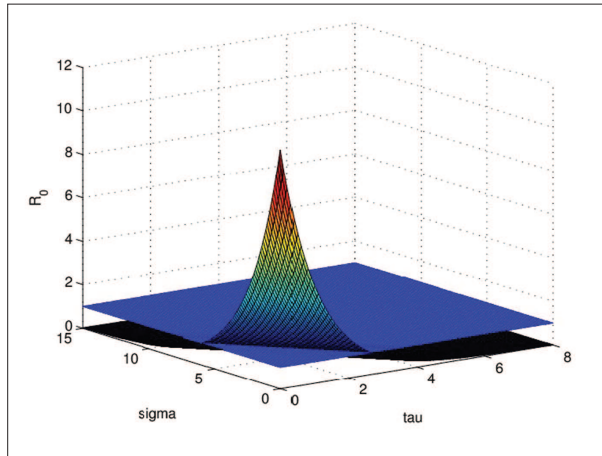
Figure 3: The variation of R_0 with respect to $\tau > 0$ and $\sigma > 0$.

converge to E^*. Therefore, the infected equilibrium E^* of model (2) is globally asymptotically stable.

For an example, to show the validity of our theoretical results, we substitute $f(v(t)) = \frac{v(t)}{1+cv(t)}$ where c is an arbitrary positive constant and $g(y(t)) = y(t)$. The functions $f(v(t))$ and $g(y(t))$ satisfies (H1) and (H2) conditions, respectively. Other state variables and parameters are the same as model (2). Further, all the parameter values are estimated as $\lambda = 50$, $\beta = 0.9$, $d = 0.2$, $a = 0.9$, $p = 0.9$, $k = 10$, $b = 0.4$, $u = 2.4$ and $c = 30$. As we pre-decide the parameter values, they are kept at fixed. Moreover, It is also clear that R_0 of model (2) totally depends on both time delays, namely, $\tau > 0$ and $\sigma > 0$. The threshold, R_0 reduces to the following form

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

First, we select $\tau = 2$ and then easily we can find the value for $\sigma = 3$ such that $R_0 < 1$ from Figure 3. Then, we have that $R_0 = 0.54735 < 1$, which means that it satisfied the conditions mentioned in Theorem 3 (a) and Theorem 5 (a). It implies that the infection free equilibrium E_0 (250,0,0) is globally asymptotically stable. Further, numerical simulation shown in Figure 1 confirmed the result.

Next, $\tau = 2$, again by Figure 3, we can select $\sigma = 1.2$ such that $R_0 > 1$. Then we have that $R_0 = 1.13046 > 1$, which implies that all conditions are satisfied noted in Theorem 3(b) as well as Theorem 5(b) without (H3). However,

numerical simulations depicted in Figure 2 show that the chronic infection equilibrium E^* (437.33, 2.30, 0.71) is globally asymptotically stable.

DISCUSSION AND CONCLUSION

In this study, we have proposed and studied a delayed virus dynamic model with nonlinear functional response, nonlinear state dependent removal function and absorption effect. By analysing the characteristic equations of model (2) at infection free equilibrium, it has been completely established that infection free equilibrium is locally asymptotically stable if the basic reproduction number (R_0) is less than or equal to one ($R_0 \leq 1$). We can see from the expression for basic reproduction number, that it directly depends on both time delays, negatively exponential function of time delays, and also on infection rate when other parameters are fixed. The mathematical result is given in Theorem 3. Viruses can be cleaned from the body if the latent period (τ) delays and the maturation (σ) increases, in this case, the basic reproduction number decreases. Local stability result of the chronic infection equilibrium of model (2) is shown in Theorem 4. If the basic reproduction number is greater than one ($R_0 > 1$), then infection free equilibrium is unstable and chronic infection equilibrium is locally asymptotically stable. Some parameters of model (2) are positively and others are negatively involved to reduce the reproduction number, however, the death rate of infected cells (p), infection rate (β) and both time delays (τ and σ) show drastic impacts. Increasing or decreasing some parameter values are limited to some levels. Yet, latent time delay and maturation time delay can be increased (by some therapies) to reduce the reproduction number to less than unity in order to eliminate the virus propagation, which can be clearly seen from Figure 3.

Regarding global stability analysis, Huang *et al.* (2010), McClueskey (2009) and Saito (2002) have given elegant Liapunov functionals on various models. By these motivations, we have shown that infection free equilibrium of model (2) is globally asymptotically stable. Moreover, chronic infection equilibrium of model (2) is globally asymptotically stable with condition (H3). The mathematical results are shown in Theorem 5. However, by numerical simulations, we conjectured that chronic infection equilibrium of model (2) is globally asymptotically stable when $R_0 > 1$, that is without condition (H3). According to the global stability results, we have more strong results on stability properties than local stability results. Further, for model (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.

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