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Global stability of a distributed delayed viral model with general incidence rate

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Abstract: In this paper, we discussed a infinitely distributed delayed viral infection model with nonlinear immune response and general incidence rate. We proved the existence and uniqueness of the equilibria. By using the Lyapunov functional and LaSalle invariance principle, we obtained the conditions of global stabilities of the infection-free equilibrium, the immune-exhausted equilibrium and the endemic equilibrium. Numerical simulations are given to verify the analytical results.

Keywords: CTL-response, Lyapunov functional, Basic reproduction number, Viral reproduction number

MSC: 34K20, 34D23

1 Introduction

During recent decades there has been a lot of research regarding mathematical modelling of viruses' dynamics via models of ordinary differential equations. The advances in immunology have lead us to better understand the interactions between populations of virus and the immune system, therefore several nonlinear sytems of ordinary differential equations have been proposed. Nowak and Bengham [1] study the model

$$x'(t) = s - dx(t) - \beta x(t)v(t), \tag{1}$$
$$y'(t) = \beta x(t)v(t) - ay(t) - py(t)z(t), \tag{2}$$
$$v'(t) = ky(t) - uv(t), \tag{3}$$
$$z'(t) = cy(t)z(t) - bz(t). \tag{4}$$

Where $x(t)$ denotes the number of healthy cells, $y(t)$ denotes the infected cells, $v(t)$ denotes the number of mature viruses and $z(t)$ denotes the number of CTL (cytotoxic T lymphocyte response) cells. Uninfected target cells are assumed to be generated at a constant rate s and die at rate d. Infection of target cells by free virus is assumed to occur at rate β. Infected cells die at rate a and are removed at rate p by the CTL immune response. New virus is produced from infected cells at rate k and dies at rate u. The average lifetime of uninfected cells, infected cells and free virus is thus given by $1/d$, $1/a$ and $1/u$, respectively. The parameter c denotes the rate at which the CTL response is produced and b denotes death rate of the CTL response. All given constants are assumed to be positive.

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Generally, the type of incidence function used in a model has an important role in modeling the dynamics of viruses. The most common, is the bilinear incidence rate βxv. However, this rate is not useful all the time. For instance, bilinear incidence suggests, that the model can not describe the infection process of hepatitis B, where individuals with small liver are more resistant to infection than the ones with a bigger liver. Recently, works about models of infections by viruses have used the incidence function of type Beddington-DeAngelis and Crowley-Martin. In [2] the authors propose a model of infection by virus with Crowley-Martin functional response $\frac{\beta x(t)v(t)}{(1+ax(t))(1+bv(t))}$. Li and Fu in [3] study the following system:

$$x'(t) = s - dx(t) - \frac{\beta x(t)v(t)}{(1+ax(t))(1+bv(t))}, \tag{5}$$

$$y'(t) = \frac{\beta x(t-\tau)v(t)e^{-s\tau}}{(1+ax(t-\tau))(1+bv(t-\tau))} - ay(t) - py(t)z(t), \tag{6}$$

$$v'(t) = ky(t) - uv(t), \tag{7}$$

$$z'(t) = cy(t)z(t) - bz(t). \tag{8}$$

They construct a Lyapunov functional to establish the global dynamics of the system. More recently, in [4], the authors consider the system

$$x'(t) = s - dx(t) - \frac{\beta x(t)v(t)}{1+ax(t)+bv(t)}, \tag{9}$$

$$y'(t) = \frac{\beta x(t)v(t)}{1+ax(t)+bv(t)} - ay(t) - py(t)z(t), \tag{10}$$

$$v'(t) = ky(t) - uv(t), \tag{11}$$

$$z'(t) = cy(t-\tau)z(t-\tau) - bz(t). \tag{12}$$

They also give also results of global stability as well as, Hopf bifurcation results.

Yang and Wei in [5] consider a more general incidence rate, they study the system

$$x'(t) = s - dx(t) - x(t)f(v(t)), \tag{13}$$

$$y'(t) = x(t)f(v(t)) - ay(t) - py(t)z(t), \tag{14}$$

$$v'(t) = ky(t) - uv(t), \tag{15}$$

$$z'(t) = cy(t)z(t) - bz(t), \tag{16}$$

giving some results about global stability in terms of the basic reproduction number and the immune response reproduction number. Here the $f(v)$ is assumed to be a continuous function on v that belongs to $(0, \infty)$ and satisfies $f(0) = 0, f'(v) > 0$ for all v greater or equal to 0 and $f''(v) < 0$ for all v greater or equal to 0.

In [6], the authors consider a more general incidence rate $f(x, y, v)v$, where f is assumed to be continuously differentiable in the interior of $\mathbb{R}^3_+$ and satisfies the following hypotheses

i) $f(0, y, v) = 0$, for all $y \geq 0, v \geq 0$.

ii) $\frac{\partial f}{\partial x}(x, y, v) > 0$ for all $x > 0, y > 0, v > 0$.

iii) $\frac{\partial f}{\partial y}(x, y, v) \leq 0$ and $\frac{\partial f}{\partial v}(x, y, v) \leq 0$ for all $x \geq 0, y \geq 0, v \geq 0$.

In [7], authors analyze an infection model by virus , with general incidence and immune response, which generalizes the systems [2, 6, 8], namely,

$$\begin{aligned}
\dot{x} &= s - dx - f(x, y, v)v,\\
\dot{y} &= f(x, y, v)v - ay - pyz,\\
\dot{v} &= ky - uv,\\
\dot{z} &= cyz - bz,
\end{aligned}$$

where $f(x, y, v)$ is a continuous and differentiable function in the interior of $\mathbb{R}^3_+$ and satisfies the conditions (i), (ii), (iii).

Another viral infection model is the studied in [9] given by:

$$\begin{aligned}
\dot{x} &= n(x) - h(x,v),\\
\dot{y} &= \int_0^\infty f_1(\tau)h(x(t-\tau),v(t-\tau))d\tau - ag_1(y) - pw(y,z),\\
\dot{v} &= k\int_0^\infty f_2(\tau)g_1(y(t-\tau))d\tau,\\
\dot{z} &= c\int_0^\infty f_3(\tau)w(y(t-\tau),z(t-\tau))d\tau - bg_3(z).
\end{aligned}$$

Where x, y, v, z denotes the non infected cells, infected cells, virus and specific virus CTL at time t respectively. Conditions on functions f_i,h, w, and g_i are specified in [9]. Related works are [10-14].

Based on the discussion above, we will study a delayed viral infection model with general incidence rate and CTL immune response given by

$$\dot{x} = n(x) - f(x(t),y(t),v(t))v(t), \tag{17}$$

$$\dot{y} = \int_0^\infty f_1(\tau)f(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)e^{-\alpha_1\tau} - a\varphi_1(y(t)) - pw(y(t),z(t)), \tag{18}$$

$$\dot{v} = k\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\varphi_1(y(t-\tau)) - uv(t), \tag{19}$$

$$\dot{z} = c\int_0^\infty f_3(\tau)w(y(t-\tau),z(t-\tau)) - b\varphi_2(z(t)). \tag{20}$$

The dynamics of uninfected cells, x, in the absence of infection is governed by $x' = n(x)$. $n(x)$ is the intrinsic growth rate of uninfected cells accounting for both productions and natural mortality. This is assumed to satisfy the following:

$H_1)$ $n(x)$ is continuously differentiable, and exist $\bar{x} > 0$ such as that $n(\bar{x}) = 0$, $n(x) > 0$ for $x \in [0, \bar{x})$, and $n(x) < 0$ for $x < \bar{x}$. Typical functions appearing in the literature are $n(x) = s - dx$ and $n(x) = s - dx + rx(1 - x/x_{max})$.

$H_2)$ φ_i is strictly increasing on $[0,\infty)$; $\varphi_i(0) = 0$; $\varphi_i'(0) = 1$; $\lim_{y\longrightarrow\infty}\varphi_i(y) = +\infty$; and there exists $k_i > 0$ such as $\varphi_i(y) \geq k_i y$ for any $y_i \geq 0$.

$H_3)$ $w(y,z)$ is continuously differentiable; $\frac{\partial w(y,z)}{\partial z} > 0$ for $y \in (0,\infty)$, $z \in [0,\infty)$; $w(y,z) > 0$ for $y \in (0,\infty)$ and $z \in (0,\infty)$ with $w(y,z) = 0$ if and if only $y = 0$ or $z = 0$.

All parameters are nonnegative and the distributions f_i for $i = 1, 2$ are assumed to satisfy the following (see [9, 14]) :

- $f_i(\tau) \geq 0$, for $\tau \geq 0$.
- $\int_0^\infty f_i(\tau)d\tau = 1$ for $i = 1, 2$.
- $\int_0^\infty f_3(\tau)d\tau \leq 1$ and $\int_0^\infty f_3(\tau)e^{s\tau}d\tau < \infty$ for some $s > 0$.

In addition, the uniqueness and global stability results on the positive equilibrium require the following assumption:

$H_4)$ $w(y,z) = \varphi_1(y)\varphi_2(z)$.

In this paper, we will study the global dynamics model of (17)-(20). Organization is as follows: in section 2, we prove the existence and uniqueness of the infection free equilibrium, the CTL-inactivated infection equilibrium and the CTL-activated infection equilibrium. In section 3, the conditions that allow the global stability of each equilibrium are determined and proved. Section 4, provide several numerical simulations that show the results obtained in section 3 and 4. Finally, in section 5 we summarize the results we have obtained, comparing them with previous models studied in literature, and setting the guidelines for possible future work.

1.1 Positivity and boundedness

For system (17) the suitable space is $\mathcal{C}^4 = \mathcal{C} \times \mathcal{C} \times \mathcal{C} \times \mathcal{C}$, where $\mathcal{C}$ is the Banach space of fading memory type ([15]):

$$C := \{\phi \in C((-\infty, 0], \mathbb{R}), \quad \phi(\theta)e^{\alpha\theta} \quad \text{is uniformly continous for} \quad \theta \in (-\infty, 0] \quad \text{and} \quad \|\phi\| < \infty\},$$

where the norm of a $\phi \in \mathcal{C}$ is defined as $\|\phi\| = \sup_{\theta \le 0} |\phi(\theta)|e^{\alpha\theta}$. The nonnegative cone of $\mathcal{C}$ is defined as $\mathcal{C}_+ = C((-\infty, 0], \mathbb{R}_+)$.

Theorem 1.1. *Under the initial conditions, all solutions of system* (17)-(20) *are positive and ultimately uniformly bounded in X.*

Proof. To see that $x(t)$ is positive, we proceed by contradiction. Let t_1 the first value of time such that $x(t_1) = 0$. From (17) we see that $x'(t_1) = n(0) > 0$ and $x(t_1) = 0$, therefore there exists $\epsilon > 0$ such that $x(t) < 0$ for $t \in (t_1 - \epsilon, t_1)$, this leads to a contradiction. It follows that $x(t)$ is always positive. With a similar argument we see that $y(t)$, $v(t)$ and $z(t)$ are positive for $t \ge 0$.

The hypotheses (H_1) and equation (17) imply that $\limsup_{t\longrightarrow\infty} x(t) \le \bar{x}$.

From (17), (18) and assumption (H_2), we obtain

$$\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}x'(t-\tau)d\tau + y'(t) = \int_0^\infty f_1(\tau)e^{-\alpha_1\tau}n(x(t-\tau))d\tau - a\varphi_1(y) \le M_1G_1 - ak_1y, \tag{21}$$

where $M_1 = \sup_{x\in[0,\bar{x}]} n(x)$ and $G_1 = \int_0^\infty f_1(\tau)e^{-\alpha_1\tau}d\tau$.

Let $e(t) = \int_0^\infty f_1(\tau)e^{-\alpha_1\tau}x(t-\tau)d\tau$, we have that $e(t) \le \bar{x}G_1$ for $t > 0$. Then

$$\begin{aligned}(e(t) + y(t))' &\le M_1G_1 - ak_1y \\ &= M_1G_1 + M_1G_1 - M_1G_1 - ak_1y \\ &\le 2M_1G_1 - \frac{M_1}{\bar{x}}e(t) - ak_1y \\ &\le 2M_1G_1 - \bar{\mu}(e(t) + y(t)) \text{ where } \bar{\mu} = \min\left\{\frac{M_1}{\bar{x}}, ak_1\right\},\end{aligned}$$

and thus $\limsup_{t\longrightarrow\infty}(e(t) + y(t)) \le \frac{2M_1G_1}{\bar{\mu}}$. Since $e(t) \ge 0$, we know that $\limsup_{t\longrightarrow\infty} y(t) \le \frac{2M_1G_1}{\bar{\mu}}$. From (19), we have that,

$$\begin{aligned}\dot{v} &= k\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\varphi_1(y(t-\tau))d\tau - uv(t) \\ &\le kM_2G_2 - uv(t),\end{aligned}$$

where $M_2 = \sup_{y\in\left[0,\frac{2M_1G_1}{\bar{\mu}}\right]} \varphi_1(y)$ and $G_2 = \int_0^\infty f_2(\tau)e^{-\alpha_2\tau}d\tau$, and thus $\limsup_{t\longrightarrow\infty} v(t) \le \frac{kM_2G_2}{u}$.

Using a similar argument, let $G_3 = \int_0^\infty f_3(\tau)d\tau$, $L(t) = \frac{cG_3}{p}y(t) + z(t)$, $\tilde{\mu} = \min\{ak_1, bk_2\}$ and $M_3 = \sup_{(x,y,v)\in[0,\bar{x}]\times[0,\frac{2M_1G_1}{\bar{\mu}}]\times[0,\frac{kM_2G_2}{u}]} f(x,y,v)v$, then

$$\begin{aligned}L'(t) &= \frac{cG_3}{p}G_1f(x,y,v)v - \frac{acG_3}{p}\varphi_1(y) - cG_3\varphi_1(y)\varphi_2(z) + cG_3\varphi_1(y)\varphi_2(z) - b\varphi_2(z) \\ &\le \frac{cG_3G_1}{p}M_3 - \frac{acG_3}{p}k_1y - bk_2z \\ &\le \frac{cG_3G_1}{p}M_3 - \tilde{\mu}\left(\frac{cG_3}{p}y + z\right)\end{aligned}$$

$$= \frac{cG_3G_1}{p}M_3 - \tilde{\mu}L(t),$$

therefore $\limsup_{t\longrightarrow\infty} L(t) \le \frac{cG_1G_3M_3}{p\tilde{\mu}}$. Since $\frac{cG_3}{p}y(t) \ge 0$, we know that $\limsup_{t\longrightarrow\infty} z(t) \le \frac{cG_1G_3M_3}{p\tilde{\mu}}$.

Therefore, $x(t)$, $y(t)$, $v(t)$ and $z(t)$ are ultimately uniformly bounded in $\mathcal{C}^4$. □

Previous theorem implies that the omega limit set of system (17)-(20) is contained in the following bounded feasible region:

$$\Gamma = \left\{(x, y, v, z) \in \mathcal{C}_+^4 : \| x \| \le \bar{x}, \| y \| \le \frac{2M_1G_1}{\bar{\mu}}, \| v \| \le \frac{kM_2G_2}{u}, \| z \| \le \frac{cG_1G_3M_3}{p\tilde{\mu}}\right\}.$$

It can be verified that the region Γ is positively invariant with respect to model (17)-(20) and that the model is well posed.

2 Existence and uniqueness of equilibria of system

At any equilibrium we have

$$n(x) - f(x, y, v)v = 0, \tag{22}$$

$$f(x, y, v)v - \frac{a}{G_1}\varphi_1(y) - \frac{p}{G_1}\varphi_1(y)\varphi_2(z) = 0, \tag{23}$$

$$k\varphi_1(y) - \frac{u}{G_2}v = 0, \tag{24}$$

$$c\varphi_1(y)\varphi_2(z) - \frac{b}{G_3}\varphi_2(z) = 0. \tag{25}$$

System (17)-(20) always has an infection free equilibrium $E_0 = (\bar{x}, 0, 0, 0)$. In addition to E_0, the system could have two types of chronic infection equilibria $E_1 = (x_1, y_1, v_1, 0)$ and $E_2 = (x_2, y_2, v_2, z_2)$ in Γ, where the entries of E_1 and E_2 are strictly positive. The equilibria E_1 and E_2 are called CTL-inactivated infection equilibrium (CTL-IE) and CTL-activated infection equilibrium (CTL-AE), respectively.

We define the general reproduction number as

$$R(x, y, v) = \frac{kG_1G_2f(x, y, v)}{au},$$

which is the ratio of the per capita production and decay rates of mature viruses at an equilibrium (x, y, v, z) with $z = 0$. In particular, at the infection free equilibrium, E_0, we denote $R(\bar{x}, 0, 0)$ by R_0, representing the basic production number for viral infection:

$$R_0 = R(\bar{x}, 0, 0) = \frac{kG_1G_2f(\bar{x}, 0, 0)}{au}. \tag{26}$$

From assumption (H2) we have that φ_1 is invertible, so we can define from equation (25):

$$\hat{y} = \varphi_1^{-1}\left(\frac{b}{cG_3}\right), \quad \hat{v} = \frac{k\varphi_1(\hat{y})G_2}{u}.$$

Define also $H(x) = n(x) - f(x, \hat{y}, \hat{v})\hat{v}$, we have $H(0) = n(0) > 0$ and $H(\bar{x}) = -f(\bar{x}, \hat{y}, \hat{v})\hat{v}$, with $f(\bar{x}, \hat{y}, \hat{v}) > f(0, \hat{y}, \hat{v}) = 0$ by (ii), so there exists a $\hat{x} \in (0, \bar{x})$ such that $H(\hat{x}) = 0$. We denote:

$$R_1 = R(\hat{x}, \hat{y}, \hat{v}), \tag{27}$$

and refer it as the viral reproduction number. From assumptions on f it is easy to see that $f(\bar{x}, 0, 0) > f(\bar{x}, y, v)$, for all $y, v > 0$, moreover for all $x \in [0, \bar{x})$ we have $f(x, y, v) < f(\bar{x}, y, v)$, so:

$$R_0 = R(\bar{x}, 0, 0) > R(\bar{x}, y, v) > R(x, y, v), \quad \forall x \in [0, \bar{x}), y, v > 0. \tag{28}$$

Particularly, $R_0 > R_1$. The basic reproduction number for the CTL response is given by:

$$R_{CTL} = \frac{cG_3\varphi_1(y_1)}{b}.$$

In order to prove of the existence and uniqueness of equilibria, we require two additional assumptions. First, we define the following sets:

$$\begin{aligned} X_n &= \{\xi \in [0,\bar{x}] : (n(x) - n(\xi))(x-\xi) < 0 \text{ for } x \neq \xi, x \in [0,\bar{x}]\}, \\ X_f(y,v) &= \{\xi \in [0,\bar{x}] : (f(x,y,v) - f(\xi,y,v))(x-\xi) < 0 \text{ for } x \neq \xi, x \in [0,\bar{x}]\}, \\ X &= \cap_{y,v\in(0,\bar{y})\times(0,\bar{v})} X_f(y,v) \cap X_n. \end{aligned}$$

The following conditions are used to guarantee the uniqueness of the equilibria.
(A_1)The system (17)-(20) has an equilibrium $E_1 = (x_1, y_1, v_1, 0)$ satisfying $x_1 \in X$.
(A_2)The system (17) has an equilibrium $E_2 = (x_2, y_2, v_2, z_2)$ satisfying $X_n \cap X_f(y_2, v_2)$.

Theorem 2.1. *Assume that $i) - iii)$ and $H_1 - H_4$ are satisfied.*
1. *If $R_0 \leq 1$, then $E_0 = (x_0, 0, 0)$ is the unique equilibrium of the system* (17)-(20) .
2. *if $R_1 \leq 1 < R_0$ then in addition to E_0, system* (17)-(20) *has a CTL inactivated infection equilibrium E_1.*
3. *If $R_0 > R_1 > 1$ then, in addition to E_0 and E_1 system* (17) *has a CTL activated infection equilibrium.*

When $x = \bar{x}$ and $y = v = z = 0$ the equations (22)-(25)are satisfied, therefore $E_0 = (x_0, 0, 0, 0)$ is a steady state called the infection free equilibrium. To prove that it is unique when $R_0 < 1$, we look for the existence of a positive equilibrium.

To find a positive equilibrium we proceed as follows: from equation (25) $\varphi_2(z) = 0$ or $\varphi_1(y) = \frac{b}{cG_1}$. If $\varphi_2(z) = 0$ then from assumption (H_2) we get, $z = 0$ and using (22)-(24)

$$n(x) = f(x,y,v)v = \frac{a\varphi_1(y)}{G_1} = \frac{auv}{kG_1G_2}. \tag{29}$$

By (H_2), we know that φ_1^{-1} exists. Solving $n(x) = \frac{a\varphi_1(y)}{G_1}$ for y gives us that

$$y(x) = \phi(x) = \varphi_1^{-1}\left(\frac{n(x)G_1}{a}\right),$$

with $\phi(\bar{x}) = 0$ and $\phi(0) = y^0$ being a unique root of equations $n(0) = \frac{a\varphi_1(y^0)}{G_1}$. Solving (24) for v we obtain:

$$v(x) = \frac{kn(x)G_1G_2}{au}.$$

Note that, from (ii) we have $f(x,y,v) > f(0,y,v) = 0$, $\forall x > 0$. So if $E^* = (x^*, y^*, v^*, z^*)$ is a positive equilibrium, then $n(x^*) = f(x^*, y^*, v^*)v^* > 0$, so $x^* \in (0, \bar{x})$.

Now, using (29) define on the interval $[0, \bar{x})$ the function G,

$$\begin{aligned} G(x) &= f(x, y(x), v(x)) - \frac{n(x)}{v(x)} \\ &= f\left(x, \phi(x), \frac{n(x)kG_1G_2}{au}\right) - \frac{au}{kG_1G_2}, \end{aligned}$$

we have $G(0) = -\frac{au}{kG_1G_2} < 0$, $G(\bar{x}) = f(\bar{x}, 0, 0) - \frac{au}{kG_1G_2} = \frac{au}{kG_1G_2}(R_0 - 1)$. Therefore, if $R_0 > 1$, then $G(x)$ has a root $x^* \in (0, \bar{x})$ such that

$$f(x^*, y(x^*), v(x^*)) - \frac{n(x^*)}{v(x^*)} = 0,$$

or equivalently

$$n(x^*) - f(x^*, y(x^*), v(x^*))v(x^*) = 0.$$

We conclude that, for $R_0 > 1$, there exists another equilibrium $E_1 = (x_1, y_1, v_1, 0)$ with $x_1 = x^* \in (0, \bar{x})$, $y_1 = \phi(x_1)$ and $v_1 = \frac{kG_2\phi(x_1)}{u}$. Moreover, using the fact that $R_0 > R(x, y, v)$, for all $x, y, v > 0$, when $R_0 < 1$ we have $R(x, y, v) < 1$. Using (29) we arrive to

$$n(x) - f(x, y, v)v > 0, \quad \forall x, y, v > 0,$$

so equation (22) never holds. Therefore, E_1 exists iff $R_0 > 1$.

Next we show that $E_1 = (x_1, y_1, v_1, 0)$ is unique. Suppose, to the contrary, that there exists another CTL-IE equilibrium $E_1^* = (x_1^*, y_1^*, v_1^*, 0)$. Without loss of generality, we assume that $x_1^* < x_1$. Then $x_1 \in X_n$ implies that $n(x_1^*) > n(x_1)$. By virtue of $x_1 \in X_h$, we get $f(x_1^*, y_1^*, v_1^*) < f(x_1, y_1, v_1)$. On the other hand, it follows from (29) that $f(x_1^*, y_1^*, v_1^*) = f(x_1, y_1, v_1) = au/kG_1G_2$. This is a contradiction, and thus E_1 is the unique CTL-IE.

Note that the CTL-AE $E_2 = (x_2, y_2, v_2, z_2)$ exists if $(x_2, y_2, v_2, z_2) \in \mathbf{R}_+^4$ satisfies the equilibrium equations (22)-(25) and $\varphi_1(y) = b/cG_3$. Therefore according to system (17)-(20) and (H_2) we have

$$y_2 = \varphi_1^{-1}\left(\frac{b}{cG_3}\right). \tag{30}$$

Note that the values $\hat{x}, \hat{y}, \hat{v}$ are used to define R_1, so they clearly satisfy the equilibrium equations. Solving the equation (23) for z and using (H2) yields $\hat{z} = \phi_2^{-1}\left(\frac{kG_1G_2f(\hat{x},\hat{y},\hat{v})-au}{pu}\right) = \phi_2^{-1}\left(\frac{a(R_1-1))}{p}\right)$. Using the fact that φ_2^{-1} is defined on $[0, \infty)$ we conclude that the CTL-AE $E_2 = (\hat{x}, \hat{y}, \hat{v}, \hat{z})$ exists if and only if $R_1 > 1$.

Now we will prove that E_2 is unique. Suppose that there exists another CTL-AE, $E_2^* = (x_2^*, y_2^*, v_2^*, z_2^*)$. Then $y_2 = y_2^*$ and $v_2 = v_2^*$. Without loss of generality, we assume that $x_2^* < x_2$. Then $x_2 \in X_n$ implies $n(x_2^*) > n(x_2)$. Note that $n(x_2^*) = f(x_2^*, y_2, v_2)$ and $n(x_2) = f(x_2, y_2, v_2)$, implies that $f(x_2^*, y_2, v_2) > f(x_2, y_2, v_2)$. This contradicts that $x_2 \in X_f(y_2, v_2)$ and hence E_2 is unique.

3 Global stability

Let R_0 and R_1 be defined as in previous section.

Theorem 3.1. *If $R_0 < 1$, then infection free-Equilibrium E_0 of model* (17)-(20) *is globally asymptotically stable.*

Proof. Define a Lyapunov functional

$$\begin{aligned}
V_1 = x - x_0 + \int_{x_0}^{x} \frac{f(x_0, 0, 0)}{f(s, 0, 0)} ds + \frac{1}{G_1} y + \frac{a}{kG_1G_2} v + \frac{p}{cG_1G_3} z \\
+ \frac{1}{G_1} \int_0^\infty f_1(\tau) e^{-\alpha_1\tau} \int_{t-\tau}^{t} f(x(s), y(s), v(s))v(s) ds d\tau + \frac{a}{G_1G_2} \int_0^\infty f_2(\tau) e^{-\alpha_2\tau} \int_{t-\tau}^{t} \varphi_1(y(s)) ds d\tau \\
+ \frac{p}{G_1G_3} \int_0^\infty f_3(\tau) \int_{t-\tau}^{t} \varphi_1(y(s))\varphi_2(z(s)) ds d\tau,
\end{aligned}$$

where $G_i = \int_0^\infty f_i(\tau), i = 1, 2, 3$.

Calculating the derivative of V_1 along the positive solutions of system (17)-(20) , it follows that

$$\begin{aligned}
\dot{V}_1 = \left(1 - \frac{f(x_0, 0, 0)}{f(x, 0, 0)}\right)\dot{x} + \frac{1}{G_1}\dot{y} + \frac{a}{kG_1G_2}\dot{v} + \frac{p}{cG_1G_3}\dot{z} \\
+ f(x, y, v)v - \frac{1}{G_1} \int_0^\infty f_1(\tau) e^{-\alpha_1\tau} f(x(t-\tau), y(t-\tau), v(t-\tau)) d\tau \\
+ \frac{a}{G_1}\varphi_1(y) - \frac{a}{G_1G_2} \int_0^\infty f_2(\tau) e^{-\alpha_2\tau} \varphi_1(y(t-\tau)) d\tau
\end{aligned}$$

$$
\begin{aligned}
&+\frac{p}{G_1}\varphi_1(y)\varphi_2(z)-\frac{p}{G_1G_3}\int_0^\infty f_3(\tau)\varphi_1(y(t-\tau))\varphi_2(z(t-\tau))d\tau\\
&=\left(1-\frac{f(x_0,0,0)}{f(x,0,0)}\right)(n(x)-f(x,y,v)v)\\
&+\frac{1}{G_1}\left(\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}f(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)-a\varphi_1(y)-p\varphi_1(y)\varphi_2(z)\right)\\
&+\frac{a}{kG_1G_2}\left(k\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\varphi_1(y(t-\tau))-uv\right)+\frac{p}{cG_1G_3}\left(c\int_0^\infty f_3(\tau)\varphi_1(y(t-\tau)\varphi_2(z(t-\tau))-b\varphi_2(z)\right)\\
&+f(x,y,v)v-\frac{1}{G_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}f(x(t-\tau),y(t-\tau),v(t-\tau))d\tau\\
&+\frac{a}{G_1}\varphi_1(y)-\frac{a}{G_1G_2}\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\varphi_1(y(t-\tau))d\tau\\
&+\frac{p}{G_1}\varphi_1(y)\varphi_2(z)-\frac{p}{G_1G_3}\int_0^\infty f_3(\tau)\varphi_1(y(t-\tau))\varphi_2(z(t-\tau))d\tau.
\end{aligned}
$$

Using $n(x_0)=0$ and simplifying, we get

$$
\begin{aligned}
\dot V_1&=(n(x)-n(x_0))\left(1-\frac{f(x_0,0,0)}{f(x,0,0)}\right)+\frac{au}{kG_1G_2}v\left(\frac{f(x,y,v)}{f(x,0,0)}\frac{f(x_0,0,0)kG_1G_2}{au}-1\right)-\frac{pb}{cG_1G_3}\varphi_2(z)\\
&=(n(x)-n(x_0))\left(1-\frac{f(x_0,0,0)}{f(x,0,0)}\right)+\frac{au}{kG_1G_2}v\left(\frac{f(x,y,v)}{f(x,0,0)}R_0-1\right)-\frac{pb}{cG_1G_3}\varphi_2(z)\\
&\le(n(x)-n(x_0))\left(1-\frac{f(x_0,0,0)}{f(x,0,0)}\right)+\frac{au}{kG_1G_2}v\,(R_0-1)-\frac{pb}{cG_1G_3}\varphi_2(z).
\end{aligned}
$$

Using the following inequalities:

$$
\begin{aligned}
n(x)-n(x_0)<0,\quad 1-\frac{f(x_0,0,0)}{f(x,0,0)}\ge 0\ \textit{for}\ x\ge x_0,\\
n(x)-n(x_0)>0,\quad 1-\frac{f(x_0,0,0)}{f(x,0,0)}\le 0\ \textit{for}\ x< x_0.
\end{aligned}
$$

We have that

$$
(n(x)-n(x_0))\left(1-\frac{f(x_0,0,0)}{f(x,0,0)}\right)\le 0.
$$

Since $R_0\le 1$, we have $\dot V_1\le 0$. Therefore the disease free E_1 is stable, $\dot V_1=0$ if and only if $x=x_0, y=0, v=0, z=0$. So, the largest compact invariant set in $\{(x,y,v,z):\dot V_1=0\}$ is just the singleton E_1. From LaSalle invariance principle , we conclude that E_1 is globally asymptotically stable. □

Theorem 3.2. *If $R_0>1$ and $R_1<1$, then CTL-IE E_1, of model (17) is globally asymptotically stable.*

Proof. Consider the following Lyapunov functional:

$$
V_1=\hat L(t)
$$

where

$$
\begin{aligned}
\hat L&=x-x_1-\int_{x_1}^{x}\frac{f(x_1,y_1,v_1)}{f(s,y_1,v_1)}ds+\frac{1}{G_1}\int_{y_1}^{y}\left(1-\frac{\varphi_1(y_1)}{\varphi_1(\sigma)}\right)d\sigma+\frac{a}{kG_1G_2}\int_{v_1}^{v}\left(1-\frac{v_1}{\sigma}\right)d\sigma\\
&+\frac{p}{cG_1G_3}z
\end{aligned}
$$

$$+\frac{f(x_1,y_1,v_1)v_1}{G_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\int_0^\tau H\left(\frac{f(x(t-\omega),y(t-\omega),v(t-\omega))v(t-\omega)}{f(x_1,y_1,v_1)v_1}\right)d\omega d\tau$$
$$+\frac{a\varphi_1(y_1)}{G_1G_2}\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\int_0^\tau H\left(\frac{\varphi_1(t-\omega)}{\varphi_1(y_1)}\right)d\omega d\tau$$
$$+\frac{p}{G_1G_3}\int_0^\infty f_3(\tau)\int_0^\tau \varphi_1(y(t-\omega))\varphi_2(z(t-\omega))d\omega d\tau.$$

At infected equilibrium

$$n(x_1)-f(x_1,y_1,v_1)v_1=0, \tag{31}$$
$$f(x_1,y_1,v_1)v_1=\frac{a\varphi_1(y_1)}{G_1}, \tag{32}$$
$$\frac{u}{kG_2}=\frac{\varphi_1(y_1)}{v_1}. \tag{33}$$

Calculating the derivative of $\hat{L}$ along the positive solutions of (17), we get

$$\begin{aligned}
\dot{V}_1 &= \left(1-\frac{f(x_1,y_1,v_1)}{f(x,y_1,v_1)}\right)\dot{x}+\frac{1}{G_1}\left(1-\frac{\varphi_1(y_1)}{\varphi_1(y)}\right)\dot{y}+\frac{a}{kG_1G_2}\left(1-\frac{v_1}{v}\right)\dot{v}+\frac{p}{cG_1G_2}\dot{z}\\
&+\frac{f(x_1,y_1,v_1)v_1}{G_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\\
&\left(H\left(\frac{f(x,y,v)v}{f(x_1,y_1,v_1)v_1}\right)-H\left(\frac{f(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{f(x_1,y_1,v_1)v_1}\right)\right)d\tau\\
&+\frac{a\varphi_1(y_1)}{G_1G_2}\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\left(H\left(\frac{\varphi_1(y)}{\varphi_1(y_1)}\right)-H\left(\frac{\varphi_1(y(t-\tau))}{\varphi_1(y_1)}\right)\right)d\tau\\
&+\frac{p}{G_1}\varphi_1(y)\varphi_2(z)-\frac{p}{G_1G_3}\int_0^\infty f_3(\tau)\varphi_1(y(t-\tau))\varphi_2(z(t-\tau))d\tau\\
&=\left(1-\frac{f(x_1,y_1,v_1)}{f(x,y_1,v_1)}\right)(n(x)-f(x,y,v)v)\\
&+\frac{1}{G_1}\left(1-\frac{\varphi_1(y_1)}{\varphi_1(y)}\right)\left(\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}f(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)-a\varphi_1(y)-p\varphi_1(y)\varphi_2(z)\right)\\
&+\frac{a}{kG_1G_2}\left(1-\frac{v_1}{v}\right)\left(k\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\varphi_1(y-\tau)-uv\right)\\
&+\frac{p}{cG_1G_2}\left(c\int_0^\infty f_3(\tau)\varphi_1(y(t-\tau))\varphi_2(z(t-\tau))-b\varphi_2(z)\right)\\
&+\frac{f(x_1,y_1,v_1)v_1}{G_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\left(H\left(\frac{f(x,y,v)v}{f(x_1,y_1,v_1)v_1}\right)-H\left(\frac{f(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{f(x_1,y_1,v_1)v_1}\right)\right)d\tau\\
&+\frac{a\varphi_1(y_1)}{G_1G_2}\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\left(H\left(\frac{\varphi_1(y)}{\varphi_1(y_1)}\right)-H\left(\frac{\varphi_1(y(t-\tau))}{\varphi_1(y_1)}\right)\right)d\tau\\
&+\frac{p}{G_1}\varphi_1(y)\varphi_2(z)-\frac{p}{G_1G_3}\int_0^\infty f_3(\tau)\varphi_1(y(t-\tau))\varphi_2(z(t-\tau))d\tau.
\end{aligned}$$

Using (31)-(33), we, get

$$\begin{aligned}
\dot{V}_1 &= (n(x)-n(x_1))\left(1-\frac{f(x_1,y_1,v_1)}{f(x,y_1,v_1)}\right)\\
&+\frac{a\varphi_1(y_1)}{G_1}\left(1-\frac{f(x_1,y_1,v_1)}{f(x,y_1,v_1)}+\frac{f(x,y,v)v}{f(x,y_1,v_1)v_1}\right)\\
&+\frac{a\varphi_1(y_1)}{G_1}\left(1-\frac{1}{G_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\frac{\varphi_1(y_1)}{\varphi_1(y)}\frac{v(t-\tau)}{v_1}\frac{f(x(t-\tau),y(t-\tau),v(t-\tau)))}{f(x_1,y_1,v_1)}\right)d\tau\\
&+\frac{a\varphi_1(y_1)}{G_1}\left[\frac{1}{G_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\ln\left(\frac{f(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{f(x_1,y_1,v_1)v_1}\right)d\tau\right]\\
&+\frac{a\varphi_1(y_1)}{G_1}\left[\frac{1}{G_2}\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\ln\left(\frac{\varphi_1(y(t-\tau))}{\varphi_1(y_1)}d\tau\right)-\ln\left(\frac{f(x,y,v)v\varphi_1(y)}{f(x_1,y_1,v_1)v_1\varphi_1(y_1)}\right)\right]\\
&+\frac{pb\varphi_1(z)}{cG_1G_3}\left(\frac{cG_3\varphi_1(y_1)}{b}-1\right).
\end{aligned}$$

Therefore

$$\begin{aligned}
\dot{V}_1 &= (n(x)-n(x_1))\left(1-\frac{f(x_1,y_1,v_1)}{f(x,y_1,v_1)}\right)\\
&+\frac{a\varphi_1(y_1)}{G_1}\left(1-\frac{v}{v_1}+\frac{f(x,y_1,v_1)}{f(x,y,v)}+\frac{f(x,y,v)v}{f(x,y_1,v_1)v_1}\right)\\
&-\frac{a\varphi_1(y_1)}{G_1}\left[H\left(\frac{f(x_1,y_1,v_1)}{f(x,y_1,v_1)}\right)+H\left(\frac{f(x,y_1,v_1)}{f(x,y,v)}\right)\right]\\
&-\frac{a\varphi_1(y_1)}{G_1}\left[\frac{1}{G_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}H\left(\frac{\varphi_1(y_1)}{\varphi_1(y)}\frac{v(t-\tau)}{v_1}\frac{f(x(t-\tau),y(t-\tau),z(t-\tau))}{f(x_1,y_1,v_1)}\right)d\tau\right]\\
&-\frac{a\varphi_1(y_1)}{G_1}\left[\frac{1}{G_2}\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}H\left(\frac{\varphi_1(y(t-\tau))v_1}{\varphi_1(y_1)v}\right)d\tau\right]\\
&+\frac{pb\varphi_1(z)}{cG_1G_3}(R_1-1).
\end{aligned}$$

Using the inequalities:

$$\begin{aligned}
n(x)-n(x_1)<0,\quad 1-\frac{f(x_1,y_1,v_1)}{f(x,y_1,v_1)}\geq 0\ \ for\ x\geq x_1,\\
n(x)-n(x_1)>0,\quad 1-\frac{f(x_1,y_1,v_1)}{f(x,y_1,v_1)}\leq 0\ \ for\ x< x_1.
\end{aligned}$$

We have that

$$\left(1-\frac{x}{x_1}\right)\left(1-\frac{f(x_1,y_1,v_1)}{f(x,y_1,v_1)}\right)\leq 0,$$

$$\begin{aligned}
&-1-\frac{v}{v_1}+\frac{f(x,y_1,v_1)}{f(x,y,v)}+\frac{v}{v_1}\frac{f(x,y,v)}{f(x,y_1,v_1)}\\
&=\left(1-\frac{f(x,y,v)}{f(x,y_1,v_1)}\right)\left(\frac{f(x,y_1,v_1)}{f(x,y,v)}-\frac{v}{v_1}\right)\leq 0.
\end{aligned}$$

Since $R_1 \leq 1$, we have $\dot{V}_1 \leq 0$, thus E_1 is stable. $\dot{V}_1 = 0$ if and only if $x = x_1, y = y_1, v =_1, z = 0$. So, the largest compact invariant set in $\{(x,y,v,z) : \dot{v}_1 = 0\}$ is the singleton E_1. From LaSalle invariance principle, we conclude that E_1 is globally asymptotically stable. □

Theorem 3.3. *Assume that $(i)-(iii)$, H_1-H_4 hold and $f_3(\tau)=\delta(\tau)$. If $R_1>1$, then the CTL-AE, E_2 is Globally asymptotically stable.*

Proof. Define a Lyapunov functional for E_2.

$$
\begin{aligned}
V_2 &= x - x_2 - \int_{x_2}^{x} \frac{f(x_2,y_2,v_2)}{f(s,y_2,v_2)}ds + \frac{1}{G_1}\int_{y_2}^{y}\left(1-\frac{\varphi_1(y_2)}{\varphi_1(\sigma)}\right)d\sigma + \frac{a+p\varphi_2(z_2)}{kG_1G_2}\int_{v_2}^{v}\left(1-\frac{v_2}{\sigma}\right)d\sigma \\
&+ \frac{p}{cG_1}\int_{z_2}^{z}\left(1-\frac{\varphi_2(z_2)}{\varphi_2(\sigma)}\right)d\sigma \\
&+ \frac{1}{G_1}f(x_2,y_2,v_2)v_2\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\int_{t-\tau}^{t} H\left(\frac{f(x(s),y(s),v(s))v(s)}{f(x_2,y_2,v_2)v_2}\right)dsd\tau \\
&+ \frac{a+p\varphi_2(z_2)}{kG_1G_2}\varphi_1(y_2)\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\int_{t-\tau}^{t} H\left(\frac{\varphi_1(y(s))}{\varphi_1(y_2)}\right)dsd\tau.
\end{aligned}
$$

The derivative of V_2 along with the solutions of system (17) is

$$
\begin{aligned}
\dot{V}_2 &= \left(1-\frac{f(x_2,y_2,v_2)}{f(x,y_2,v_2)}\right)\dot{x} + \frac{1}{G_1}\left(1-\frac{\varphi_1(y_2)}{\varphi_1(y)}\right)\dot{y} + \frac{a+p\varphi_2(z_2)}{kG_1G_2}\left(1-\frac{v_2}{v}\right)\dot{v} \\
&+ \frac{p}{cG_1}\int_{z_2}^{z}\left(1-\frac{\varphi_2(z_2)}{\varphi_2(z)}\right)\dot{z} + \frac{1}{G_1}f(x_2,y_2,v_2)v_2\int_0^\infty f_1(\tau)e^{-\alpha_1\tau} \\
&\left[H\left(\frac{f(x,y,v)v}{f(x_2,y_2,v_2)v_2}\right) - H\left(\frac{f(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{f(x_2,y_2,v_2)v_2}\right)\right]d\tau \\
&+ \frac{a+p\varphi_2(z_2)}{kG_1G_2}\varphi_1(y_2)\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\left[H\left(\frac{\varphi_1(y)}{\varphi_1(y_2)}\right) - H\left(\frac{\varphi_1(y(t-\tau))}{\varphi_1(y_2)}\right)\right]d\tau.
\end{aligned}
$$

Applying $n(x_2) = f(x_2,y_2,v_2)v_2, f(x_2,y_2,v_2)v_2 = \frac{1}{G_1}(a\varphi_1(y_1)+p\varphi_1(y_1)\varphi_2(z_2)), \varphi_1(y_1) = \frac{b}{c}, \frac{u}{kG_2} = \frac{\varphi_1(y_2)}{v_2}$, we obtain

$$
\begin{aligned}
\dot{V}_2 &= (n(x)-n(x_1))\left(1-\frac{f(x_2,y_2,v_2)}{f(x,y_2,v_2)}\right) \\
&+ \frac{a\varphi_1(y_2)+p\varphi_1(y_2)\varphi_2(z_2)}{G_1}\left(1-\frac{f(x_2,y_2,v_2)}{f(x,y_2,v_2)}+\frac{f(x,y,v)v}{f(x,y_2,v_2)v_2}\right) \\
&+ \frac{a\varphi_1(y_2)+p\varphi_1(y_2)\varphi_2(z_2)}{G_1}\left(1-\frac{1}{G_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\frac{\varphi_1(y_2)}{\varphi_1(y)}\frac{v(t-\tau)}{v_2}\frac{f(x(t-\tau,y(t-\tau),v(t-\tau)))}{f(x_1,y_2,v_2)}\right)d\tau \\
&+ \frac{a\varphi_1(y_2)+p\varphi_1(y_2)\varphi_2(z_2)}{G_1}\left[\frac{1}{G_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}\ln\left(\frac{f(x(t-\tau),y(t-\tau),v(t-\tau))v(t-\tau)}{f(x_2,y_2,v_2)v_2}\right)d\tau\right] \\
&+ \frac{a\varphi_1(y_2)+p\varphi_1(y_2)\varphi_2(z_2)}{G_1}\left[\frac{1}{G_2}\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}\ln\left(\frac{\varphi_1(y(t-\tau))}{\varphi_1(y_2)}d\tau\right) - \ln\left(\frac{f(x,y,v)v\varphi_1(y)}{f(x_2,y_2,v_2)v_2\varphi_1(y_2)}\right)\right].
\end{aligned}
$$

Therefore

$$
\begin{aligned}
\dot{V}_2 &= (n(x)-n(x_1))\left(1-\frac{f(x_2,y_2,v_2)}{f(x,y_2,v_2)}\right) \\
&+ \frac{a\varphi_1(y_2)+p\varphi_1(y_2)\varphi_2(z_2)}{G_1}\left(1-\frac{v}{v_2}+\frac{f(x,y_2,v_2)}{f(x,y,v)}+\frac{f(x,y,v)v}{f(x,y_2,v_2)v_2}\right) \\
&- \frac{a\varphi_1(y_2)+p\varphi_1(y_2)\varphi_2(z_2)}{G_1}\left[H\left(\frac{f(x_2,y_2,v_2)}{f(x,y_2,v_2)}\right)+H\left(\frac{f(x,y_2,v_2)}{f(x,y,v)}\right)\right] \\
&- \frac{a\varphi_1(y_2)+p\varphi_1(y_2)\varphi_2(z_2)}{G_1}\left[\frac{1}{G_1}\int_0^\infty f_1(\tau)e^{-\alpha_1\tau}H\left(\frac{\varphi_1(y_2)}{\varphi_1(y)}\frac{v(t-\tau)}{v_2}\frac{f(x(t-\tau),y(t-\tau),z(t-\tau))}{f(x_2,y_2,v_2)}\right)d\tau\right]
\end{aligned}
$$

$$-\frac{a\varphi_1(y_2)+p\varphi_1(y_2)\varphi_2(z_2)}{G_1}\left[\frac{1}{G_2}\int_0^\infty f_2(\tau)e^{-\alpha_2\tau}H\left(\frac{\varphi_1(y(t-\tau))v_2}{\varphi_1(y_2)v}\right)d\tau\right].$$

Therefore $\dot{V}_2 \le 0$, thus E_2 is stable. $\dot{V}_2 = 0$ if and only if $x = x_2, y = y_2, v = v_2, z = z_3$. So, the largest compact invariant set in $\{(x, y, v, z) : \dot{V}_2 = 0\}$ is the singleton E_2. From LaSalle invariance principle, we conclude that E_2 is globally asymptotically stable. □

4 Numerical simulations

In this section we present some numerical simulations to illustrate the results of stability, obtained in our theorems from previous sections.

Example 4.1. *Consider the functions* $n(x) = \lambda - dx + rx\left(1 - \frac{x}{K}\right)$, $\phi_1(y) = y$, $\phi_2(z) = z$, $w(y, z) = yz$ *and* $f(x, y, v) = \frac{\beta x}{\alpha y+\gamma x}$. *Let* $\tau_1, \tau_2 \in [0, \infty)$ *two fixed delays, and set* $f_1(\tau) = \delta(\tau-\tau_1)$, $f_2(\tau) = \delta(\tau-\tau_2)$, $f_3(\tau) = \delta(\tau)$, *where* δ *is the Dirac delta function defined as*

$$\int_0^\infty \delta(\tau-\tau_i)F(\tau)d\tau = F(\tau_i).$$

Then, the model takes the form:

$$\dot{x} = \lambda - dx + rx\left(1-\frac{x}{K}\right) - \frac{\beta xv}{\alpha y+\gamma x}, \tag{34}$$

$$\dot{y} = \frac{\beta x(t-\tau_1)v(t-\tau_1)}{\alpha y(t-\tau_1)+\gamma x(t-\tau_1)}e^{-\mu\tau_1} - ay - pyz, \tag{35}$$

$$\dot{v} = ke^{-\alpha_2\tau_2}y(t-\tau_2) - uv, \tag{36}$$

$$\dot{z} = cyz - bz, \tag{37}$$

Fix the parameters as $\lambda = 200, d = 0.1, r = 0.6, K = 500, p = 1, k = 0.8, \alpha_2 = 0.05, u = 3.5, c = 0.03, b = 0.75, \tau_1 = 5, \tau_2 = 10, \mu = 0.1, \alpha = \gamma = 0.001$. *The trivial equilibrium point is given by* $E_0 = (666.6666, 0, 0, 0)$, *so the basic reproduction number* $\mathcal{R}_0$ *is obtained by:*

$$R_0 = \frac{kG_1G_2f(x_0,0,0)}{au} = \frac{ke^{-\mu\tau_1}e^{-\alpha_2\tau_2}\beta}{au\gamma} = 105.10841176326923474\beta.$$

$\mathcal{R}_0 \le 1$ *iff* $\beta \le 0.009513986$. *We set* $\beta = 0.003$. *By Theorem 2.1 i), we have the single equilibrium* $E_0 = (666.6666, 0, 0, 0)$ *which is globally asymptotically stable by Theorem 3.1. Using a constant history function* $S = (25, 50, 10, 5)$ *for* $t \in (0, 10)$ *and the tool DDE 23 from Matlab, we can compute numerically the solution of system (34)-(37) for* $t \in (10, 200)$. *The results are shown in Figure 1, where we can see that the solution goes to the equilibria point* E_0.

Example 4.2. *Now, set* $\beta = 0.0096$, *so* $R_0 > 1$. *Computing* R_1 *from its definition we have* $R_1 = \frac{ke^{-\mu\tau_1}e^{-\alpha_2\tau_2}}{au}f(\hat{x},\hat{y},\hat{v})$, *where*

$$\hat{y} = \frac{b}{c}, \quad \hat{v} = \frac{\hat{y}ke^{-\alpha_2\tau_2}}{u}, \quad n(\hat{x}) - f(\hat{x},\hat{y},\hat{v})\hat{v} = 0,$$

therefore $R_1 = 0.97091 < 1$ *and we have then, a second equilibrium*

$$E_1 = (659.461141, 5.962025, 0.826548, 0).$$

Using the history function from previous example we can plot the solution with Matlab. By Theorem 3.2, E_1 *is globally asymptotically stable as we can see in Figure 2.*

Fig. 1. Global stability of infection free equilibrium for $\mathcal{R}_0 < 1$.

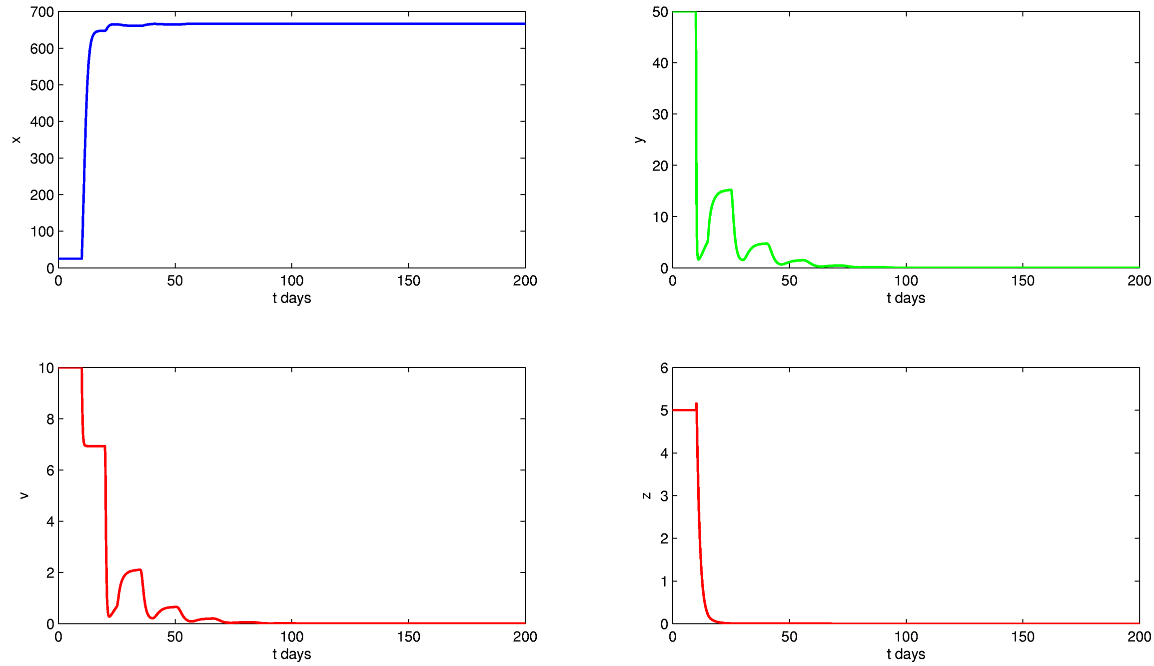
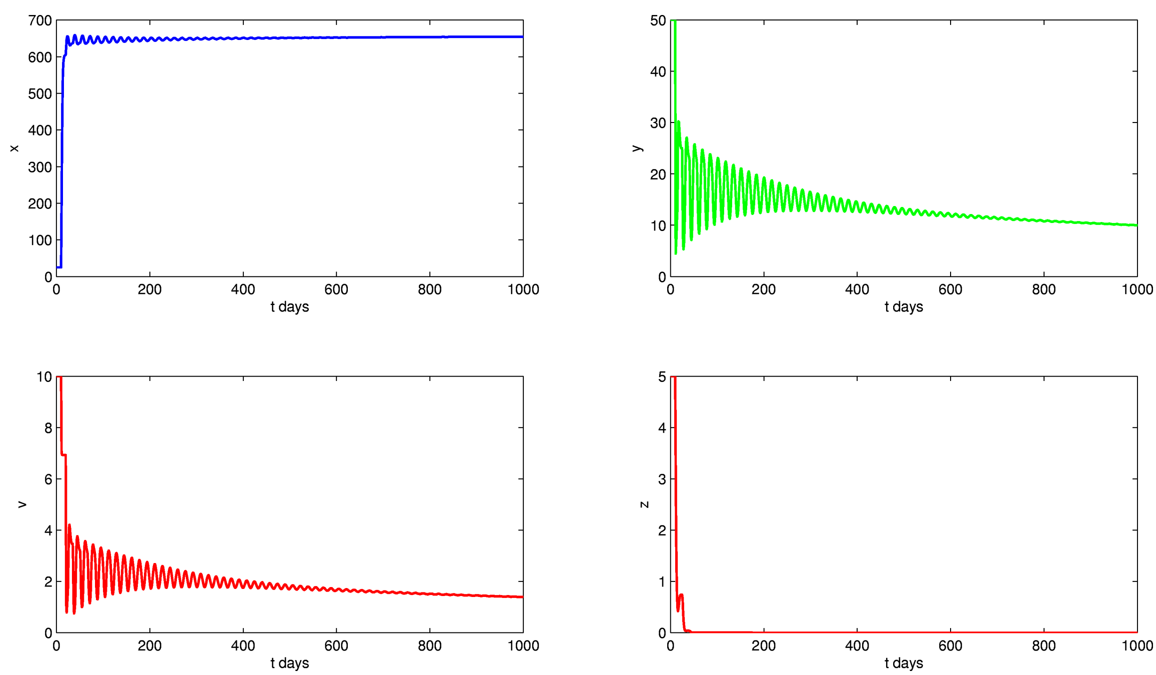


Fig. 2. Global stability of CTL-IE E_1 for $\mathcal{R}_0 > 1 > R_1$.



Finally, for $\beta = 1$, *we have* $R_0 > 1$ *and* $R_1 = 6.088529$, *so there exists an infection free equilibrium* E_0 *and two equilibria*

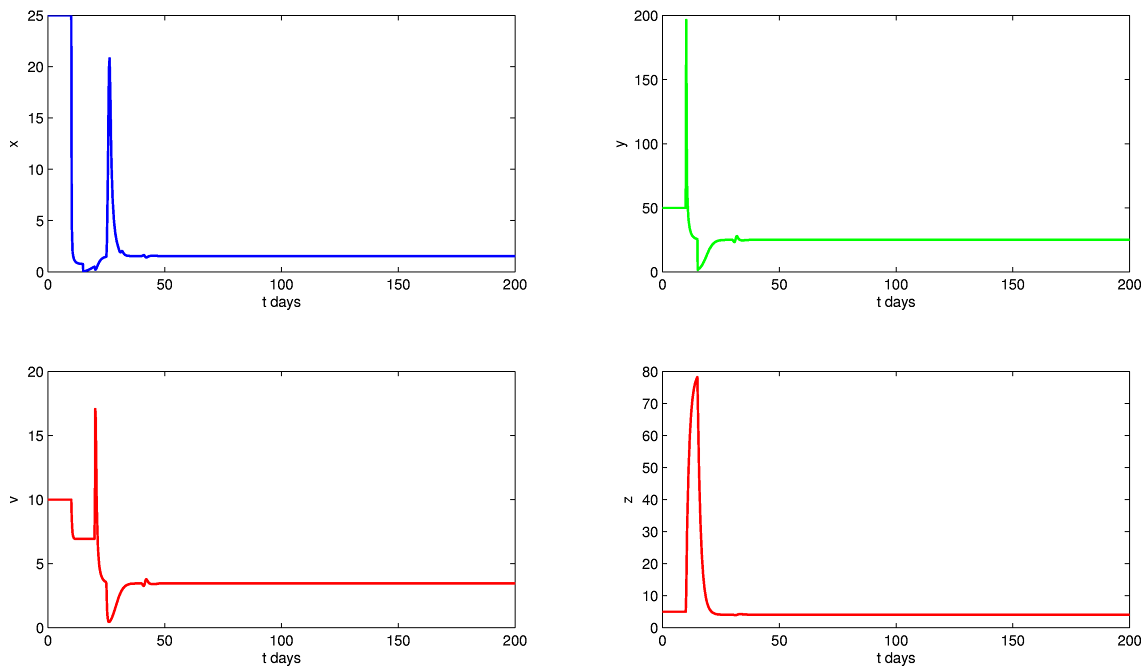
$$E_1 = (1.461792, 152.184859, 21.098236, 0),$$

and

$$E_2 = (1.537198, 25, 3.465889, 4.070823).$$

By Theorem 3.3 we have global stability of equilibrium E_2. We can see in Figure 3 that the solutions approach to E_2.

Fig. 3. Global stability of CTL-AE E_2 for $R_0 > 1, R_1 > 1$.



Example 4.3. *In order to show that our model, generalizes the previous articles, we propose the following incidence function to show our results:*

$$f(x,y,v) = \frac{\beta x}{(1+\alpha y)(1+\gamma v)}.$$

This function is not included in the cases studied by [9], since the general form in that work is $h(x,v)$. Our function f includes the three variables x, y, v and satisfies our conditions (i)-(iii) to be an admisible incidence rate.

i) $f(0,y,v) = 0, \quad \forall y, v \geq 0.$
ii) $\frac{\partial f}{\partial x} = \frac{\beta}{(1+\alpha y)(1+\gamma v)} > 0, \quad \forall x, y, v > 0.$
iii a) $\frac{\partial f}{\partial y} = -\frac{\beta x \alpha}{(\alpha y+1)^2(\gamma v+1)} \leq 0 \quad \forall x, y, v \geq 0.$
iii b) $\frac{\partial f}{\partial v} = -\frac{\beta x \gamma}{(\alpha y+1)(\gamma v+1)^2} \leq 0, \quad \forall x, y, v \geq 0.$
Setting the other functions and parameters, as in Example 4.1, then we obtain model:

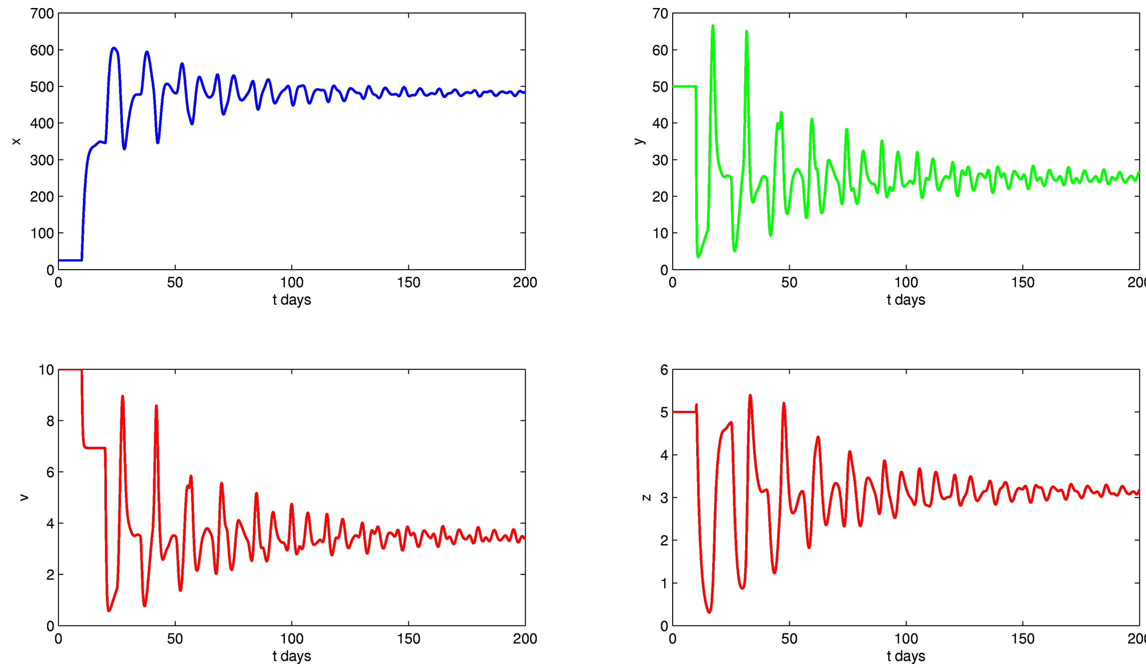
$$\begin{aligned}
\dot{x} &= \lambda - dx + rx\left(1 - \frac{x}{K}\right) - \frac{\beta x v}{(1+y)(1+v)}, \\
\dot{y} &= \frac{\beta x(t-\tau_1)v(t-\tau_1)}{(1+y(t-\tau_1))(1+v(t-\tau_1))}e^{-\mu\tau_1} - ay - pyz, \\
\dot{v} &= ke^{-\alpha_2\tau_2}y(t-\tau_2) - uv, \\
\dot{z} &= cyz - bz,
\end{aligned}$$

The infection free equilibrium is $E_0 = (666.6666, 0, 0, 0)$ as in previous cases, with $R_0 = 70.0722745\beta$, so $R_0 > 1$ iff $\beta > 0.01427097$. Therefore, if we set $\beta = 0.1$ then we have $R_0 > 1$, $R_1 = 4.9234560677357286281$ and there exists two more equilibria points,

$$E_1 = (115.436331, 183.268932, 25.407594, 0), \quad E_2 = (481.791432, 25, 3.465889, 3.138764)$$

with E_2 globally asymptotically stable. Figure 4 shows how the solutions approach to the equilibrium E_2.

Fig. 4. Global stability of CTL-AE E_2 for $f(x, y, v) = \frac{\beta x}{(1+\alpha y)(1+\gamma v)}$, with $R_0 > 1, R_1 > 1$.



5 Conclusions

In this paper we studied the global properties of a model of infinitely distributed delayed viral infection. That considers a nonlinear CTL immune response, given by $w(y, z) = \phi_1(y)\phi_2(z)$ and a general incidence function of the form $f(x, y, v)v$, where w and f satisfy certain conditions derived from previous works and biological meanings. Even when there exists variety of papers that include the CTL immune response (see for example [1, 3–5, 7]) and general incidence functions of various types (see [5, 7, 9]), the model proposed in this article includes a family of the works studied by several authors, and their conclusions can be seen as a particular case of our theorems. There lies its importance and relevance.

The model always presents an infection free positive equilibrium $E_0 = (\bar{x}, 0, 0, 0)$, and two types of chronic infection equilibria: the CTL inactivated infection equilibrium (CTL-IE) $E_1 = (x_1, y_1, v_1, 0)$ and the CTL activated infection equilibrium (CTL-AE) $E_2 = (x_2, y_2, v_2, z_2)$. The coexistence of these equilibria is determined by the basic reproduction number R_0 and the viral reproduction number R_1. These were defined in section 2 and are given in terms of parameters and the functions $f(x, y, v), f_i(\tau), \phi_1(y)$ and $\phi_2(z)$. The results show that $R_0 > R_1$ and the system admits always a positive infection free equilibrium E_0, which is the unique equilibrium when $R_0 \leq 1$. If $R_0 > 1$ which in addition to E_0 provides only the CTL-IE (when $R_1 \leq 1$), or the coexistence of the CTL-IE and CTL-AE ($R_1 > 1$).

We proved, by construction of a Lyapunov function, that whenever the equilibrium E_0 is unique ($R_0 \leq 1$) and $R_0 \neq 1$, E_0 is globally asymptotically stable. Moreover when $R_0 > 1$ and $R_1 < 1$ the CTL-IE, E_1 is globally asymptotically stable. In the case of CTL-AE, E_2 we obtained conditions for global stability only in the case $f_3(\tau) = \delta(\tau)$, i.e., when the equation $\dot{z}$ does not present delay. The results indicate that in this case, the equilibrium E_2 is globally asymptotically stable when $R_1 > 1$ and conditions $(i) - (iii)$, $H_1 - H_4$ hold. It will be of interest to find conditions that guarantee the global stability of the E_2 with a general $f_3(\tau)$, this topic can be taken as a future work.

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