GLOBAL STABILITY ANALYSIS OF A GENERALIZED VIRUS DYNAMICS MODEL WITH THE IMMUNE RESPONSE

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ABSTRACT. The aim of this work is to study the global stability of a generalized model of a viral dynamic that includes the adaptive immune response, represented by Cytotoxic Lymphocyte T-cell (CTL-cell). The incidence function introduced in this model is the generalization of a variety of viral models including HIV, influenza, HBV, and HCV. We show that the global stability of this model, using the Lyapunov function, is not only characterized by the basic reproduction number but also by what is called the basic defense number, which represents the level of the infection required to trigger the CTL response. In fact, if the basic defense number is bigger than one, we prove the global stability of the CTL-active equilibrium, which represents a chronic stage of the infection, where the CTL cells could also damage the healthy cells. Otherwise, we have another equilibria that represents the early state of the infection, where the adaptive immune response is not involved yet in the clearance of the infection and only the innate immune response is active.

1 Introduction There is a wealth of papers on the mathematical modeling of the viral infections and the immune response that have tried to contribute to the understanding of the dynamic of the viruses and how the immune system deals with these infections. These studies were either virus specific, such as HIV [17, 18, 25], Influenza [2, 19, 20], HBV [3, 9, 22, 27], and HCV [1, 4] just to mention some or for general viral infection (see for example [5]). In these models, the infection rate is assumed to follow either the mass action, which reflects the adaptation of these models from the ecological models, or a more general incidence rate, such as density dependence [9, 27], Beddington-De Angelis [10, 11, 14, 23], Crowley-Martin [29, 26], sigmoidal function of
the virus concentration [28] or other forms of “mass action” (see [24], for example). All these incidence rates are justified by either the availability of data, or by the depth of understanding of the pathology of viruses, and the mechanism of infection, and its complexity.

The use of these generalized incidence functions has contributed to exploring the rich dynamics of viral infection models, giving more insight into the possible outcomes of infection and immune response such as the determining of a threshold of clearance of the virus by the immune system, and the condition that allows the virus to persist. However, it has made the mathematical analysis more challenging particularly when it comes to global stability analysis. Recent papers have shown the possibility of having global stability results via Lyapunov functions [8, 11, 12, 14, 23, 24, 29, 26].

In recent work of Xu [26], the author has improved the global stability of viral infection model with Crowley-Martin incidence function and no immune response studied by Zhou et al. [29], using Lyapunov function and of La Salle’s invariance principle instead of the theory of competitive systems. We extended this result [8] by considering a more general form of incidence function with a cure rate of infected cells and gave the global stability result via Barbalat’s lemma.

Moreover, Wang et al. [23] has studied the global stability of a virus dynamics model with Beddington-De Angelis incidence rate and CTL immune response. In this model, the authors showed the global stability of the three equilibria (disease free, immune free, and endemic) using the generalized Lyapunov function [12]. In this model, the authors introduced an immune response reproduction number as a threshold of the endemic equilibrium global stability, but did not elaborate on the effect of the immune response on the healthy cells population. More precisely, it was not clear if the CTL response has negative effects or not.

This work is the generalization of the results of [23], [26] and [8] by extending the work of [23] to more general incidence function. Moreover, we will show that the immune response, represented here by the CTL cell, will reduce the pole of healthy cells.

Our paper is organized in the following way: In Section 2, we introduce our model, and we give the positivity and boundedness of solutions. In Section 3, we present the local and global stability analysis, and we give a conclusion and a discussion of our paper in Section 4.
2 Presentation of model and preliminary results

As mentioned previously, our model is the generalization of models presented by [23], and it is presented as follows:

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

where \( x(0) = x_0, y(0) = y_0, v(0) = v_0 \) and \( z(0) = z_0 \) are given.

Susceptible cells \( x \) are produced with the rate \( \lambda \), and decay at a rate \( dx \) and the viruses infect the \( x \) cells at a rate \( f(x, y, v)v \), which lead to increase of the infected cells \( y \), these cells die at a rate \( ay \) and cleared by the CTL immune response at a rate \( pyz \). The infected cells produce the free virus particle \( v \) at a rate \( ky \) and \( v \) decays at a rate \( uv \). Finally, CTL cells \( z \) increase at a rate \( cyz \) as a result of stimulation by the viral antigen of the infected cells and in the absence of the viral antigen, the CTL cells decay at a rate \( bz \).

As in [8], we define the incidence function \( f(x, y, v) \) as continuously differentiable in the interior of \( \mathbb{R}^3_+ \) with the following properties hold:

\begin{align*}
(H_1) \quad & f(0, y, v) = 0, \quad \text{for all } y \geq 0 \text{ and } v \geq 0, \\
(H_2) \quad & \frac{\partial f}{\partial x}(x, y, v) > 0, \quad \text{for all } x > 0, y \geq 0 \text{ and } v \geq 0, \\
(H_3) \quad & \frac{\partial f}{\partial y}(x, y, v) \leq 0 \text{ and } \frac{\partial f}{\partial v}(x, y, v) \leq 0 \\
& \quad \text{for all } x \geq 0, y \geq 0 \text{ and } v \geq 0.
\end{align*}

It is clear that the properties \((H_1)-(H_3)\) of the function \( f \) are generalization of the mass action \( \beta x \), density dependence \( \frac{\beta x}{x+g} \) Beddington-De Angelis \( \frac{\beta x}{1+\alpha x+y} \) and Crowley-Martin incidence functions \( \frac{\beta x}{(1+\alpha x)(1+y)} \), which will make our stability results cover a broad forms of incidence rates. In addition, this generalization will allow us to find the effect of the immune response, CTL cells, on the dynamic of the infection without any restrictive choices of the incidence rate that might be contributed to the study of special cases.

2.1 Positivity and boundedness of solutions

As the first and important step to validate our model (1) as model that represents the
evolution of cells, we prove, in the following result, that the cell number is nonnegative and bounded.

**Proposition 1.** All solutions with nonnegative initial conditions exist, remain non-negative and bounded. In addition, we have following inequalities:

i) \[ x(t) \leq x_0 + \frac{\lambda}{d}, \]

ii) \[ y(t) \leq y_0 + \max \left( 1, 2 - \frac{d}{a} \right) x_0 + \max \left( \frac{\lambda}{a}, \frac{\lambda}{d} \right), \]

iii) \[ v(t) \leq v_0 + \frac{k}{u} \|y\|_\infty, \]

iv) \[ z(t) \leq z_0 + \frac{c}{u} \max \left( 1, 2 - \frac{d}{b} \right) x_0 + y_0 + \max \left( \frac{\lambda}{b}, \frac{\lambda}{d} \right) \]
\[ + \max \left( 0, 1 - \frac{a}{b} \right) \|y\|_\infty \].

**Proof.** To prove this result, we use a standard technique (see, for example, [27]). More precisely, for positivity, we show that any solution starting in nonnegative orthant \( \mathbb{R}_+^4 = \{(x, y, v, z) \in \mathbb{R}^4 : x \geq 0, y \geq 0, v \geq 0, z \geq 0 \} \) stays orthant. In fact, \((x(t), y(t), v(t), z(t)) \in \mathbb{R}_+^4\), we have

\[ \dot{x} \big|_{x=0} = \lambda > 0, \quad \dot{y} \big|_{y=0} = f(x, 0, v) v \geq 0, \]
\[ \dot{v} \big|_{v=0} = ky \geq 0, \quad \dot{z} \big|_{z=0} = 0 \geq 0. \]

Hence, we have positivity of all solutions initiating in \( \mathbb{R}_+^4 \).

For boundedness, we first use the equation \( \dot{x} = \lambda - dx - f(x, y, v)v \) to get \( \dot{x} + dx \leq \lambda \), Hence,

\[ x(t) \leq x_0 e^{-dt} + \frac{\lambda}{d} (1 - e^{-dt}), \]

which proves the inequality i)

From the second equation of our model we have

\[ \dot{y} = f(x, y, v)v - ay - pyz \leq f(x, y, v)v = \lambda - dx - \dot{x}, \]

which implies

\[ \dot{y} + ay \leq \lambda - (\dot{x} + dx). \]
Thus,

\[ y(t)e^{at} - y_0 \leq \frac{\lambda}{a}(e^{at} - 1) - \int_0^t e^{(a-d)s} \frac{d}{ds} (x(s)e^{ds}) \, ds. \]

By integration by parts, we have

(3) \[ y(t) \leq (x_0 + y_0)e^{-at} + \frac{\lambda}{a}(1 - e^{-at}) - x(t) + (a - d) \int_0^t x(s)e^{a(s-t)} \, ds. \]

If \( a - d \leq 0 \), then

(4) \[ y(t) \leq x_0 + y_0 + \frac{\lambda}{a}, \]

and if \( a - d \geq 0 \), then

\[ y(t) \leq x_0 + y_0 + \frac{\lambda}{a} + (a - d) \int_0^t x(s)e^{a(s-t)} \, ds. \]

Using the previous result i), we have

\[ y(t) \leq x_0 + y_0 + \frac{\lambda}{a} + (a - d) \left( x_0 + \frac{\lambda}{d} \right) \left( 1 - e^{-at} \right). \]

Hence,

(5) \[ y(t) \leq y_0 + \left( 2 - \frac{d}{a} \right) x_0 + \frac{\lambda}{d}. \]

From (4) and (5), we prove ii).

To show iii), we use the equation \( \dot{v} = ky - uv \), and by simple integrating factor method, we can easily see

\[ v(t) \leq v_0 + \frac{k}{u} \| y \|_{\infty} (1 - e^{-tu}). \]

and deduce iii).

Finally, we prove the last inequality iv). From the equation \( \dot{z} = cyz - bz \) we get

\[ \dot{z} + bz = cyz = \frac{c}{p} \left[ \lambda - (\dot{x} + dx) - (\dot{y} + ay) \right]. \]
By the integrating factor,
\[ z(t)e^{bt} - z_0 = \frac{c}{p} \left[ \frac{\lambda}{b} (e^{bt} - 1) - \int_0^t e^{(b-d)s} \frac{d}{ds} (x(s)e^{ds}) \, ds \right. \\
\left. - \int_0^t e^{(b-a)s} \frac{d}{ds} (y(s)e^{as}) \, ds \right]. \]

Using integration by parts, we can solve the last two integrals and simplify previous equation to
\[ z(t) = \left[ \frac{c}{p} \left( x_0 + y_0 - \frac{\lambda}{b} \right) + z_0 \right] e^{-bt} \\
+ \frac{c}{p} \left\{ \frac{\lambda}{b} + \int_0^t [(b-d)x(s) + (b-a)y(s)] e^{(s-t)} \, ds - x(t) - y(t) \right\}. \]

In order to find an upper bound to this integral, we study all possible cases as follows: If \( b - d \leq 0 \) and \( b - a \leq 0 \), then
\[ z(t) \leq z_0 + \frac{c}{p} \left( x_0 + y_0 \right). \] (6)

If \( b - d \leq 0 \) and \( b - a \geq 0 \), we have
\[ z(t) \leq z_0 + \frac{c}{p} \left( \frac{\lambda}{b} + x_0 + y_0 + \left( 1 - \frac{a}{b} \right) \|y\|_\infty \right). \] (7)

If \( b - d \geq 0 \) and \( b - a \leq 0 \), we get
\[ z(t) \leq z_0 + \frac{c}{p} \left[ \frac{\lambda}{d} + \left( 2 - \frac{d}{b} \right) x_0 + y_0 \right]. \] (8)

Finally, if \( b - d \geq 0 \) and \( b - a \geq 0 \), then
\[ z(t) \leq z_0 + \frac{c}{p} \left[ \frac{\lambda}{d} + \left( 2 - \frac{d}{b} \right) x_0 + y_0 + \left( 1 - \frac{a}{b} \right) \|y\|_\infty \right]. \] (9)

From (6)–(9), we conclude iv).

3 Equilibria and their stability  
Next, we show the existence of three possible equilibria: the disease-free, the immune response-free, and infection equilibrium points. The aim is also to find the conditions that guarantee the local and global asymptotically stabilities of these three equilibria.
3.0.1 Equilibria. We characterize the existence of the equilibria with the respect of basic reproduction number \( R_0 \), which can be define as follows:

\[
R_0 = \left( \frac{\text{amount of viruses generated an during its survival period}}{\text{incidence function at the begin of the infection}} \right) \times \left( \frac{\text{average life expectancy of viruses}}{e^{-a \text{incidence function at the begin of the infection}}} \right).
\]

First, we note that \( 1/a \) is the average life expectancy of the infected cells, and since the virus is produced by infected cells at a rate \( k y \), then \( k/a \) represents the amount of virus generated from living infected cell. Second, the number of susceptible cells at beginning of the infection is \( d \), which means that \( f(\lambda/d, 0, 0) \) is the value of the incidence function when all cells are uninfected. Finally, the average life expectancy of viruses is \( 1/u \). We conclude that

\[
R_0 = \frac{\lambda f(\lambda/d, 0, 0)}{au}.
\]

It is clear that the basic reproduction number \( R_0 \) is not affected by the CTL immune response level. This is not necessarily the case in all viral infection models, but we will show that the stability of the no disease-free equilibria actually depends on another threshold that characterize the intensity of the immune response.

As it is the case for all the mathematical models of viral infections, our model has a disease-free steady state \( E_f(\lambda/d, 0, 0, 0) \). This steady state is unique if \( R_0 \leq 1 \).

To find the other equilibrium, we follow the standard method, which means that the following equations hold:

\[
\begin{align*}
\lambda - dx - f(x, y, v)v &= 0, \\
f(x, y, v)v - ay - pyz &= 0, \\
ky - uw &= 0, \\
cyz - bz &= 0.
\end{align*}
\]

By (14) we get

\[
z = 0 \quad \text{or} \quad y = \frac{b}{c}.
\]
If \( z = 0 \) and using (11)–(13) we have

\[
(15) \quad f \left( x, \frac{\lambda - dx}{a}, \frac{k(\lambda - dx)}{au} \right) = \frac{au}{k}.
\]

Moreover \( y = \lambda - dx/a \geq 0 \) implies that \( x \leq \lambda/d \). Therefore, if \( x > \lambda/d \),
then there is no equilibrium point.

Now, we define on interval \([0, \lambda/d]\) the function \( g_1 \) by

\[
g_1(x) = f \left( x, \frac{\lambda - dx}{a}, \frac{k(\lambda - dx)}{au} \right) - \frac{au}{k}.
\]

We have \( g_1(0) = -\frac{au}{k} < 0 \), \( g_1(\frac{\lambda}{d}) = \frac{au}{k}(R_0 - 1) \) and

\[
g_1'(x) = \frac{\partial f}{\partial x} - \frac{d}{a} \frac{\partial f}{\partial y} - \frac{kd}{au} \frac{\partial f}{\partial v} > 0.
\]

Therefore, if \( R_0 > 1 \), in addition to \( E_f \), there exists another equilibrium
\( E_1(x_1, y_1, v_1, 0) \) with \( x_1 \in (0, \frac{\lambda}{d}) \), \( y_1 = \frac{\lambda - dx_1}{a} \) and \( v_1 = \frac{ky_1}{u} \).

This equilibrium represents an early stage of the infection, where the healthy cell’s count is reduced to below \( \lambda/d \), and the infection cell’s count increases and respectively the virus load, but without the specific immune response considered in our model, which means that the infection did not reach the necessary threshold to activate the CTL cell and respond to the infection. More specifically this is the stage where the innate immune cells are the dominating arm of the immune response in clearing the viral infection. We will call this equilibrium point: the CTL-inactivated infection equilibrium.

In addition to \( R_0 \), we define the basic defense number by CTL response \( R_1 \) of our model. In a similar way, as in \([6, 15]\), this number represents the threshold level of infection required to trigger the CTL cells response. In fact, the mean life expectation of CTL cells is \( 1/b \),

plus after the infection reaches the steady state level \( y_1 \), the CTL cell can be produced on average \( cy_1 \). Therefore, we define \( R_1 \) as follows:

\[
(16) \quad R_1 = \frac{cy_1}{b}.
\]

We will be using the basic defense number to discuss the possibility of the existence of another equilibrium. In fact, for the case \( z \not= 0 \), we have \( y = b/c \) and \( v = kb/(uc) \). By using (11) and (12), we get the following equation

\[
(17) \quad f \left( x, \frac{b}{c}, \frac{kb}{uc} \right) = \frac{uc}{kb}(\lambda - dx).
\]
The fact that $z = \frac{\lambda - dx - \left(\frac{ab}{c}\right)}{(p+q)/c} \geq 0$ implies that $x \leq \frac{\lambda}{d} - \frac{ab}{dc}$. Hence, there is no equilibrium point if $x > \frac{\lambda}{d} - \frac{ab}{dc}$ or $\frac{\lambda}{d} - \frac{ab}{dc} \leq 0$.

Now, we consider the function $g_2$ defined on interval $[0, \frac{\lambda}{d} - \frac{ab}{dc}]$ by

$$g_2(x) = f\left(x, \frac{b}{c} \cdot \frac{kb}{uc}\right) - \frac{uc}{kb}(\lambda - dx).$$

We have $g_2(0) = -\frac{uc\lambda}{kb} < 0$ and

$$g_2'(x) = \frac{\partial f}{\partial x} + \frac{ucd}{kb} > 0.$$

Therefore, if $R_1 < 1$, then $y_1 < \frac{b}{c}$, $x_1 > \frac{\lambda}{d} - \frac{ab}{dc}$ and

$$g_2\left(\frac{\lambda}{d} - \frac{ab}{dc}\right) = f\left(\frac{\lambda}{d} - \frac{ab}{dc}, \frac{b}{c} \cdot \frac{kb}{uc}\right) - \frac{ua}{k} < f(x_1, y_1, v_1) - \frac{ua}{k}.$$

Hence, $g_2\left(\frac{\lambda}{d} - \frac{ab}{dc}\right) < 0$. So, there is no equilibrium point if $R_1 < 1$.

If $R_1 > 1$, then $y_1 > \frac{b}{c}$, $x_1 < \frac{\lambda}{d} - \frac{ab}{dc}$ and $g_2\left(\frac{\lambda}{d} - \frac{ab}{dc}\right) > 0$. Therefore, if $R_1 > 1$, there exists an infection equilibrium $E_2(x_2, y_2, v_2, z_2)$ with $x_2 \in (0, \frac{\lambda}{d} - \frac{ab}{dc})$, $y_2 = \frac{b}{c}$, $v_2 = \frac{ku}{u}$ and $z_2 = \frac{\lambda - dx_2 - ay_2}{py_2}$. Finally, it easy to see that if $R_1 = 1$, then $E_1 = E_2$.

The infection equilibrium $E_2$ represents the state where the CTL cells response is activated and healthy cell count $x_2$ is below the count of the healthy cells in the case of the CTL-inactivated infection equilibrium $E_1$. This is very well known in some viral infections, such as $HBV$, where the majority of the damage of the healthy tissue is due to the CTL cells response. We also have to mention that condition of existence of $E_2$, $R_1 > 1$ means that the infection needs to reach a threshold level so that the CTL cells can kill the infected cell and clear the infection.

We summarize the above in the following theorem.

**Theorem 2.**

1. If $R_0 \leq 1$, then the system (1) has a unique infection-free equilibrium of the form $E_f(\frac{\lambda}{d}, 0, 0, 0)$.
2. If $R_0 > 1$, then the system (1) has a CTL-inactivated infection equilibrium of the form $E_1(x_1, y_1, v_1, 0)$ besides $E_f$, where $x_1 \in (0, \frac{\lambda}{d})$, $y_1 = \frac{\lambda - dx_1}{a}$ and $v_1 = \frac{ku}{u}$.
3. If $R_1 > 1$, then the system (1) has a CTL-activated infection equilibrium of the form $E_2(x_2, y_2, v_2, z_2)$ besides $E_f$ and $E_1$, where $x_2 \in (0, \frac{\lambda}{d} - \frac{ab}{dc})$, $y_2 = \frac{b}{c}$, $v_2 = \frac{ku}{u}$ and $z_2 = \frac{\lambda - dx_2 - ay_2}{py_2}$. 
3.1 Local and global stability of disease-free equilibrium $E_f$

After determining the existence conditions for all possible equilibria, we will focus, in this section, on its stability analysis. For an arbitrary equilibrium $E(x, y, v, z)$, we have the following characteristic equation

$$
\begin{vmatrix}
-d - \frac{\partial f}{\partial x} v - \xi & -\frac{\partial f}{\partial y} v + \rho & -\frac{\partial f}{\partial v} v - f(x, y, v) & 0 \\
\frac{\partial f}{\partial x} v - a - pz - \xi & \frac{\partial f}{\partial y} v + f(x, y, v) & -py & 0 \\
0 & k & -u - \xi & 0 \\
0 & cz & 0 & cy - b - \xi
\end{vmatrix} = 0.
$$

The following proposition gives the characterization of the local stability of the disease-free equilibrium.

**Theorem 3.** Let us define $R_0 = \frac{k f(\lambda/d, 0, 0)}{au}$.

- If $R_0 < 1$, then $E_f$ is locally asymptotically stable.
- If $R_0 > 1$, then $E_f$ is unstable.

**Proof.** At $E_f$, (18) reduces to

$$(\xi + b)(\xi + d) \left[ \xi^2 + (a + u)\xi + au + kf \left( \frac{\lambda}{d}, 0, 0 \right) \right] = 0,$$

where the roots are

$$
\xi_1 = -b, \quad \xi_2 = -d, \\
\xi_3 = \frac{-(a + u) - \sqrt{(a + u)^2 - 4au(1 - R_0)}}{2}, \\
\xi_4 = \frac{-(a + u) + \sqrt{(a + u)^2 - 4au(1 - R_0)}}{2}.
$$

It is clear that $\xi_1$, $\xi_2$ and $\xi_3$ are negative. Moreover, $\xi_4$ is negative when $R_0 < 1$ and it is positive if $R_0 > 1$. This proves the theorem. \qed

Theorem 3 only establishes local stability of $E_f$. However, the following theorem establishes the globally asymptotic stability of this disease-free equilibrium.

**Theorem 4.** If $R_0 \leq 1$, the disease-free equilibrium, $E_f$, is globally asymptotically stable.
Proof. Consider the following Lyapunov functional

\[
W_0(x, y, v, z) = x - x_0 - \int_{x_0}^{x} \frac{f(x_0, 0, 0)}{f(x, 0, 0)} ds + y + \frac{a}{k} v + \frac{p}{c} z,
\]

where \(x_0 = \lambda/d\). Calculating the time derivation of \(W_0(x, y, v, z)\) along the positive solutions of model (1), we get

\[
\dot{W}_0(1) = \left(1 - \frac{f(x_0, 0, 0)}{f(x, 0, 0)}\right) \dot{x} + \dot{y} + \frac{a}{k} \dot{v} + \frac{p}{c} \dot{z}
\]

\[
= dx_0 \left(1 - \frac{x}{x_0}\right) \left(1 - \frac{f(x_0, 0, 0)}{f(x, 0, 0)}\right) + \frac{a}{k} v \left(\frac{f(x, y, v)}{f(x, 0, 0)} R_0 - 1\right) - \frac{p}{c} z
\]

\[
\leq dx_0 \left(1 - \frac{x}{x_0}\right) \left(1 - \frac{f(x_0, 0, 0)}{f(x, 0, 0)}\right) + \frac{au}{k} v(R_0 - 1) - \frac{pb}{c} z.
\]

Using the following trivial inequalities

\[
1 - \frac{f(x_0, 0, 0)}{f(x, 0, 0)} \geq 0 \text{ for } x \geq x_0,
\]

\[
1 - \frac{f(x_0, 0, 0)}{f(x, 0, 0)} < 0 \text{ for } x < x_0.
\]

Thus, we have

\[
\left(1 - \frac{x}{x_0}\right) \left(1 - \frac{f(x_0, 0, 0)}{f(x, 0, 0)}\right) \leq 0.
\]

Since \(R_0 \leq 1\), we have \(\dot{W}_0(1) \leq 0\). Thus, the disease-free equilibrium \(E_f\) is stable, and \(\dot{W}_0(1) = 0\) if and only if \(x = x_0\), \(v = 0\) and \(z = 0\). So, the largest compact invariant set in \(\Gamma = \{(x, y, v, z) | \dot{W}_0 = 0\}\) is just the singleton \(E_f\). From LaSalle invariance principle [13], we conclude that \(E_f\) is globally asymptotically stable. \(\square\)

3.2 Local and global stability of CTL infection equilibrium \(E_1\) and \(E_2\) In this section, we focus on local and global stability of the CTL-unactivated infection equilibrium \(E_1\) and the CTL-activated infection equilibrium \(E_2\).

For the CTL-unactivated infection equilibrium, it is easy to verify that point \(E_1\) does not exist if \(R_0 < 1\) and \(E_1 = E_f\) when \(R_0 = 1\). If \(R_0 > 1\), then we have the following result.
Theorem 5. Assume $R_0 > 1$.

- If $R_1 < 1$, then $E_1$ is locally asymptotically stable.
- If $R_1 > 1$, then $E_1$ is unstable.

Proof. We assume that $R_0 > 1$. At $E_1$, (18) reduces to

\[
(cy_1 - b - \xi)(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3) = 0,
\]

where

\[
a_1 = u + d + a + \frac{\partial f}{\partial x}v_1 - \frac{\partial f}{\partial y}v_1,
\]

\[
a_2 = ud + ad + (u + a)\frac{\partial f}{\partial x}v_1 - (u + d)\frac{\partial f}{\partial y}v_1 - k\frac{\partial f}{\partial v}v_1,
\]

\[
a_3 = au\frac{\partial f}{\partial x}v_1 - ud\frac{\partial f}{\partial y}v_1 - kd\frac{\partial f}{\partial v}v_1.
\]

Then, $cy_1 - b = b(R_1 - 1)$ is a real root of (19), which is negative if $R_1 < 1$ and positive if $R_1 > 1$.

On the other hand, we have $a_1$, $a_2$, $a_3$ are nonnegative. Plus,

\[
\left| \begin{array}{cc}
    a_1 & 1 \\
    a_3 & a_2
  \end{array} \right| = a \left( a_2 - \frac{\partial f}{\partial x}v_1 \right) + d \left( a_2 + k\frac{\partial f}{\partial v}v_1 \right)
- \frac{\partial f}{\partial y}v_1(a_2 - ud) + \left( u + \frac{\partial f}{\partial x}v_1 \right)a_2 > 0.
\]

Using the Routh-Hurwitz Theorem [7], the other roots of (19) have negative real parts. Consequently, $E_1$ is unstable when $R_1 > 1$ and locally asymptotically stable when $R_1 < 1$.

For $R_0 > 1$, we investigate the global stability of the CTL-inactivated infection equilibrium, $E_1$ and the CTL-activated infection equilibrium, $E_2$, by introducing the global stability condition for a giving infection equilibrium $E_? = (x_?, y_?, v_?, z_?)$ as follows:

\[
(20) \left( 1 - \frac{f(x, y, v)}{f(x_?, y_?, v_?)} \right) \frac{\frac{f(x, y_?, v_?)}{f(x, y, v)} - \frac{u}{v_?}}{\frac{f(x, y_?, v_?)}{f(x, y, v)}} \leq 0 \quad \text{for all} \ x, y, v > 0.
\]

It is easy to verify that the inequality (20) holds for the mass action, for the Beddington-DeAngelis incident function as well as for the Crowley-Martin incident function. For the density dependent incident function, we study the condition under which this condition holds.

For the global stability of the CTL-inactivated infection equilibrium, $E_1$ we have the following result
Theorem 6. If $R_1 \leq 1$ and (20) hold for $E_1$, then CTL-inactivated infection equilibrium is globally asymptotically stable.

Proof. Consider the following Lyapunov functional

$$W_1(x, y, v, z) = x - x_1 - \int_{x_1}^{x} \frac{f(x_1, y_1, u_1)}{f(s, y_1, v_1)} ds + y - y_1$$

$$- y_1 \ln \frac{y}{y_1} + \frac{a}{k} \left( v - v_1 - v_1 \ln \frac{v}{v_1} \right) + \frac{p}{c} z.$$

Calculating the time derivation of $W_1(x, y, v, z)$ along the positive solutions of model (1), we get

$$\dot{W}_1|_{(1)} = \left( 1 - \frac{f(x_1, y_1, v_1)}{f(x, y_1, v_1)} \right) \dot{x} + \left( 1 - \frac{y_1}{y} \right) \dot{y} + \frac{a}{k} \left( 1 - \frac{v_1}{v} \right) \dot{v} + \frac{p}{c} \dot{z}.$$

Noting that $\lambda = dx_1 + ay_1$, $f(x_1, y_1, v_1)v_1 = ay_1$ and $\frac{y}{v} = \frac{u_1}{v_1}$. Hence,

$$\dot{W}_1|_{(1)} = dx_1 \left( 1 - \frac{x}{x_1} \right) \left( 1 - \frac{f(x_1, y_1, v_1)}{f(x, y_1, v_1)} \right)$$

$$+ ay_1 \left( 1 - \frac{f(x_1, y_1, v_1)}{f(x, y_1, v_1)} + \frac{v}{v_1} f(x, y, v) \right)$$

$$+ ay_1 \left( 1 - \frac{y_1}{y} \frac{f(x, y, v)}{v_1 f(x_1, y_1, v_1)} \right)$$

$$+ ay_1 \left( 1 - \frac{v}{v_1} \frac{y_v}{y_1 v} \right) + pz \left( y_1 - \frac{b}{c} \right)$$

$$= dx_1 \left( 1 - \frac{x}{x_1} \right) \left( 1 - \frac{f(x_1, y_1, v_1)}{f(x, y_1, v_1)} \right)$$

$$+ ay_1 \left( 4 - \frac{f(x_1, y_1, v_1)}{f(x, y_1, v_1)} - \frac{y_1}{y} \frac{v}{v_1} f(x, y, v) \right)$$

$$- \frac{y v_1}{y_1 v} \frac{f(x, y_1, v_1)}{f(x, y, v)}$$

$$+ ay_1 \left( 1 - \frac{v}{v_1} + \frac{f(x, y_1, v_1)}{f(x, y, v)} + \frac{v}{v_1} f(x, y_1, v_1) \right)$$

$$+ \frac{p b}{c} (R_1 - 1) z.$$
Using the following trivial inequalities
\[
1 - \frac{f(x_1, y_1, v_1)}{f(x, y_1, v_1)} \geq 0 \quad \text{for } x \geq x_1,
\]
\[
1 - \frac{f(x_1, y_1, v_1)}{f(x, y_1, v_1)} < 0 \quad \text{for } x < x_1.
\]

Thus, we have
\[
\left(1 - \frac{x}{x_1}\right)\left(1 - \frac{f(x_1, y_1, v_1)}{f(x, y_1, v_1)}\right) \leq 0.
\]

From (20) we have
\[
-1 - \frac{\nu}{v_1} + \frac{f(x, y_1, v_1)}{f(x, y, v)} + \frac{\nu}{v_1} \frac{f(x, y, v)}{f(x, y_1, v_1)} = \left(1 - \frac{f(x, y, v)}{f(x, y_1, v_1)}\right)\left(\frac{f(x, y_1, v_1)}{f(x, y, v)} - \frac{\nu}{v_1}\right) \leq 0.
\]

Using the arithmetic-geometric inequality, we have that
\[
4 - \frac{f(x_1, y_1, v_1)}{f(x, y_1, v_1)} - \frac{y_1}{y} \frac{v}{v_1} \frac{f(x, y, v)}{f(x_1, y_1, v_1)} - \frac{y_1}{y} \frac{v}{v_1} \leq 0.
\]

Since \( R_1 \leq 1 \), we have \( \dot{W}_1(1) \leq 0 \). Thus, \( E_1 \) is stable, and \( \dot{W}_1(1) = 0 \) if and only if \( x = x_1, y = y_1, v = v_1 \) and \( z = 0 \). So, the largest compact invariant set in \( \Gamma = \{(x, y,v,z)|\dot{W}_1 = 0\} \) is just the singleton \( E_1 \). From LaSalle invariance principle \([13]\), we conclude that \( E_1 \) is globally asymptotically stable.

For density dependence incident function, the global stability condition can be written as
\[
\left(1 - \frac{x + y_1}{x + y}\right)\left(\frac{x + y}{x + y_1} - \frac{\nu}{v_1}\right) \leq 0,
\]

using the fact that \( y_1 = \frac{\lambda - dx_1}{a} \) and \( v_1 = \frac{k y_1}{a} \).
3.3 Local and global stability of CTL-activated infection equilibrium $E_2$. This section focuses on local and global stability of the chronic infection equilibrium $E_2$. In fact, it is not difficult to verify that the point $E_2$ does not exist if $R_1 < 1$ and $E_2 = E_1$ when $R_1 = 1$.

We assume that $R_1 > 1$. For $E_2$, equation (18) reduces to

$$
\lambda^4 + b_1 \lambda^3 + b_2 \lambda^2 + b_3 \lambda + b_4 = 0,
$$

where

\begin{align*}
    b_1 &= u + d + a + pz_2 + \frac{\partial f}{\partial x} v_2 - \frac{\partial f}{\partial y} v_2, \\
    b_2 &= ud + ad + p(d + b)z_2 + (u + a + pz_2) \frac{\partial f}{\partial x} v_2 - (u + d) \frac{\partial f}{\partial y} v_2 - k \frac{\partial f}{\partial v} v_2, \\
    b_3 &= (a + pz_2)u \frac{\partial f}{\partial x} v_2 - ud \frac{\partial f}{\partial y} v_2 - kd \frac{\partial f}{\partial v} v_2 + pbz_2 \left( u + d + \frac{\partial f}{\partial x} v_2 \right), \\
    b_4 &= pbuz_2 \left( d + \frac{\partial f}{\partial x} v_2 \right).
\end{align*}

By using the Routh-Hurwitz Theorem, all eigenvalues of (22) have a real negative part if and only if

\begin{equation}
    b_1 > 0, \quad b_4 > 0, \quad \begin{vmatrix} b_1 & 1 \\ b_3 & b_2 \end{vmatrix} > 0 \quad \text{and} \quad \begin{vmatrix} b_1 & 1 & 0 \\ b_3 & b_2 & b_1 \\ 0 & b_4 & b_3 \end{vmatrix} > 0.
\end{equation}

It is clear that $b_1$, $b_2$, $b_3$, and $b_4$ are nonnegative and

\begin{equation}
    \begin{vmatrix} b_1 & 1 \\ b_3 & b_2 \end{vmatrix} = (a + pz_2) \left( b_2 - u \frac{\partial f}{\partial x} v_2 \right) + d \left( b_2 + k \frac{\partial f}{\partial v} v_2 - pbz_2 \right)
    \end{equation}

\begin{equation}
    - \frac{\partial f}{\partial y} v_2 (b_2 - ud) + \left( u + \frac{\partial f}{\partial x} v_2 \right) (b_2 - pbz_2) > 0.
\end{equation}

The proof of the last relation $\begin{vmatrix} b_1 & 1 & 0 \\ b_3 & b_2 & b_1 \\ 0 & b_4 & b_3 \end{vmatrix} > 0$ is tedious and can be verified using Matlab to be true when $R_0 > 1$.

We summarize these findings in the following theorem.

**Theorem 7.** If $R_1 > 1$, then $E_2$ is locally asymptotically stable.
For the global stability of $E_2$, we assume that $R_1 > 1$ and the function $f$ satisfies the following:

$$
(24) \quad \left(1 - \frac{f(x, y, v)}{f(x, y_2, v_2)}\right) \left(\frac{f(x, y_2, v_2)}{f(x, y, v)} - \frac{v}{v_2}\right) \leq 0 \text{ for all } x, y, v > 0.
$$

**Theorem 8.** Assume (24) holds. If $R_1 > 1$, the CTL-activated infection equilibrium, $E_2$, is globally asymptotically stable.

**Proof.** Consider the following Lyapunov functional

$$
W_2(x, y, v, z) = x - x_2 - \int_{x_2}^{x} \frac{f(x_2, y_2, v_2)}{f(x, y_2, v_2)} \, ds + y - y_2 - y_2 \ln \frac{y}{y_2} + \frac{a + p_2z_2}{k} \left(v - v_2 - v \ln \frac{v}{v_2}\right) + \frac{p}{c} \left(z - z_2 - z_2 \ln \frac{z}{z_2}\right).
$$

Calculating the time derivation of $W_2(x, y, v, z)$ along the positive solutions of model (1), we get

$$
\dot{W}_1|_{(1)} = dx_2 \left(1 - \frac{x}{x_2}\right) \left(1 - \frac{f(x_2, y_2, v_2)}{f(x, y_2, v_2)}\right)
$$

$$
+ (ay_2 + py_2z_2) \left(1 - \frac{f(x_2, y_2, v_2)}{f(x, y_2, v_2)}\right) \frac{v}{v_2} \frac{f(x, y, v)}{f(x, y_2, v_2)}
$$

$$
+ (ay_2 + py_2z_2) \left(1 - \frac{y_2}{y_2} \frac{f(x, y, v)}{y_2 \frac{f(x, y_2, v_2)}{v_2}}\right)
$$

$$
+ (ay_2 + py_2z_2) \left(1 - \frac{v}{v_2} \frac{f(x, y_2, v_2)}{v_2 \frac{f(x, y, v)}{v_2}}\right)
$$

$$
= dx_2 \left(1 - \frac{x}{x_2}\right) \left(1 - \frac{f(x_2, y_2, v_2)}{f(x, y_2, v_2)}\right)
$$

$$
+ (ay_2 + py_2z_2) \left(4 - \frac{f(x_2, y_2, v_2)}{f(x, y_2, v_2)} - \frac{y_2}{y_2} \frac{v}{v_2} \frac{f(x, y, v)}{f(x, y_2, v_2)}\right)
$$

$$
- \frac{yv_2}{y_2v} \frac{f(x, y_2, v_2)}{f(x, y, v)}
$$

$$
+ (ay_2 + py_2z_2) \left(-1 - \frac{v}{v_2} + \frac{f(x, y_2, v_2)}{f(x, y, v)} + \frac{v}{v_2} \frac{f(x, y_2, v_2)}{f(x, y_2, v_2)}\right).
$$
Using the following trivial inequalities
\[ 1 - \frac{f(x_2, y_2, v_2)}{f(x, y_2, v_2)} \geq 0 \quad \text{for } x \geq x_2, \]
\[ 1 - \frac{f(x_2, y_2, v_2)}{f(x, y_2, v_2)} < 0 \quad \text{for } x < x_2, \]
we have
\[ \left(1 - \frac{x}{x_2}\right)\left(1 - \frac{f(x_2, y_2, v_2)}{f(x, y_2, v_2)}\right) \leq 0. \]

From (24) we have
\[ -1 - \frac{v}{v_2} + \frac{f(x, y_2, v_2)}{f(x, y, v)} + \frac{v}{v_2} f(x, y_2, v_2) \]
\[ = \left(1 - \frac{f(x, y, v)}{f(x, y_2, v_2)}\right)\left(\frac{f(x, y_2, v_2)}{f(x, y, v)} - \frac{v}{v_2}\right) \leq 0. \]

Using the arithmetic-geometric inequality, we have that
\[ 4 - \frac{f(x_2, y_2, v_2)}{f(x, y_2, v_2)} - \frac{y_2}{y} \frac{f(x_2, y_2, v_2)}{y_2} \frac{v_2}{v} - \frac{f(x_2, y_2, v_2)}{f(x, y, v)} \leq 0. \]

Since \( R_1 > 1 \), we have \( \dot{W}_2|_{(1)} \leq 0 \). Thus, \( E_2 \) is stable, and \( \dot{W}_2|_{(1)} = 0 \) if and only if \( x = x_2, y = y_2 \) and \( v = v_2 \). So, the largest compact invariant set in \( \Gamma = \{(x, y, v, z)|W_2 = 0\} \) is the singleton \( E_2 \). From LaSalle invariance principle, we conclude that \( E_2 \) is globally asymptotically stable.

For density dependance incident function, we can write the global stability condition as
\[ \frac{1}{(x+y)} \left(1 - \frac{x+y}{(x+y)}\right) \left(\frac{x+y}{(x+y)} - \frac{v}{v_2}\right) \leq 0. \]

The conditions under which this inequality hold will be study for each infected equilibrium. Using the fact that \( y_2 = b/c \) and \( v_2 = \frac{k}{u} y_2 \), the inequality (20) holds if
\[ y_2 \leq y \leq \frac{u}{k} v \quad \text{or} \quad \frac{u}{k} v \leq y \leq y_2. \]

In terms of the global stability of \( E_2 \), we expect the number of infected cells to be below the level of the CTL-unactivated infected cell which is \( b/c \). Therefore, (24) holds if
\[ \frac{u}{k} v \leq y. \]
Discussion and conclusion  In this paper, we focused on investigating the global stability analysis of a virus infection model with generalized incidence function. This generalization represents different types of the incidence rate including: mass action, density dependence, Beddington-DeAngelis and Crowley-Martin. We showed that our model has three possible equilibria that represent different stages of the viral infection, no infection, early infection, and chronic infection. The local and global stability analysis of these equilibria was not only constrained by the basic reproduction number $R_0$, but also by what is called the basic defense number $R_1$. This number represents the level of the infection required to trigger the CTL response. Our analysis showed that if $R_1 > 1$ we have global stability of the CTL-activated infected equilibrium, which represent a chronic stage of the infection, where the CTL-cells response has a negative effect on the healthy cells. On the other hand, if $R_1 < 1$, then CTL-unactivated infected equilibrium, which represents the early state of the infection, exist and it is globally stable if the condition (20) holds. This situation refers to the fact that the adaptive immune response is not yet involved in the clearance of the infection and only the innate immune response is taking on to clear the infection.

Our work does not only generalize the recent results by [29] and [23] in the type incident function we studied, but also gives an additional condition of the stability of the early infection stage, which is very important in early diagnosis of any viral infection and will help to design the adequate drug treatment that should be beneficial in reducing the burden of the infection.

Our study did not take in consideration the role of the innate immune response, as it is the case in our study [27]. Therefore, the next normal step of this work is to consider the innate immune response as another arm of the humoral response which would help us to investigate more biological relevant conditions that characterize the stability of the CTL-inactived infected equilibrium.

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