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Global Properties of Latent Virus Dynamics Models with Immune Impairment and Two Routes of Infection

Aeshah A. Raezah [1,2], Ahmed M. Elaiw [1,*] and Badria S. Alofi [1]

[1] Department of Mathematics, Faculty of Science, King Abdulaziz University, P.O. Box 80203, Jeddah 21589, Saudi Arabia; aalraezh@kku.edu.sa (A.A.R.); badoora2al3ofi@gmail.com (B.S.A.)
[2] Department of Mathematics, Faculty of Science, King Khalid University, P.O. Box 25145, Abha 61466, Saudi Arabia
* Correspondence: a_m_elaiw@yahoo.com

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Abstract: This paper studies the global stability of viral infection models with CTL immune impairment. We incorporate both productively and latently infected cells. The models integrate two routes of transmission, cell-to-cell and virus-to-cell. In the second model, saturated virus–cell and cell–cell incidence rates are considered. The basic reproduction number is derived and two steady states are calculated. We first establish the nonnegativity and boundedness of the solutions of the system, then we investigate the global stability of the steady states. We utilize the Lyapunov method to prove the global stability of the two steady states. We support our theorems by numerical simulations.

Keywords: Viral infection; immune impairment; global stability; cell-to-cell transmission

1. Introduction

In the literature, several mathematical models of within-host virus dynamics have been constructed and analyzed [1–9]. The cytotoxic T Lymphocyte (CTL) is one of the central components of the immune system against viral infections. CTLs lyse the viral-infected cells which participate in reducing or clearing the viruses from the body. Several mathematical models have been presented which integrate the effect of the CTL immune response on viral dynamics (see e.g., [10–12]). Nowak and Bangham [10] have presented a mathematical model to characterize the dynamics of the virus (J) with uninfected cells (G), infected cells (I) and CTLs (K) as:

$$\dot{G}(t) = \theta - \mu G(t) - \xi G(t) J(t), \tag{1}$$
$$\dot{I}(t) = \xi G(t) J(t) - \varrho I(t) - \beta I(t) K(t), \tag{2}$$
$$\dot{J}(t) = \vartheta I(t) - c J(t), \tag{3}$$
$$\dot{K}(t) = \rho I(t) K(t) - \epsilon K(t). \tag{4}$$

The uninfected cells are replenished at rate θ, die at rate μG and become infected at rate ξGJ, where ξ is the virus–cell incidence rate constant. βIK is the killer rate of infected cells by CTL and ϱI is the death rate of the infected cells, where β and ϱ are constants. The CTLs are proliferated and die at rates ρIK and ϵK, respectively, where ρ and ϵ are constants.

Models (1)–(4) assume that the presence of antigen can activate the CTL immune response, however, the CTL immune impairment is negelcted. To model the immune impairment, Regoes et al. [13] have modified models (1)–(4) as:

$$\dot{G}(t) = \theta - \mu G(t) - \xi G(t)J(t), \tag{5}$$
$$\dot{I}(t) = \xi G(t)J(t) - \varrho I(t) - \beta I(t)K(t), \tag{6}$$
$$\dot{J}(t) = \vartheta I(t) - cJ(t), \tag{7}$$
$$\dot{K}(t) = \rho I(t) - \epsilon K(t) - hI(t)K(t), \tag{8}$$

where the terms ρI and hIK represents the proliferation rate and the immune impairment, respectively, and h is a constant. Mathematical models of virus dynamics with impairment of CTL functions have been constructed in seveal papers (see e.g., [13–15]). The works presented in [13–15] assume that the virus infects the uninfected cells by virus-to-cell transmission.

The uninfected target cells can be infected via two ways of transmissions, namely, the diffusion-limited virus-to-cell transmission and the direct cell-to-cell transfer using virological synapses [16]. The cell-to-cell transmission has been recognized in several works (see e.g., [17–20]). Recent studies have revealed that over 50% of viral infection is due to cell-to-cell transmission [21] and even with an antiretroviral therapy, the cell-to-cell spread of the virus can still permit ongoing replication [22]. Thus, for some viruses, cell-to-cell transmission seems to be a more powerful means of virus propagation than the virus-to-cell transmission [23,24]. Several mathematical models of virus dynamics with two ways of infection have been developed by many researchers (see [25–30]). However, in these papers, the impairment of CTL functions is not included. In a very recent work, Elaiw et al. [31] have studied the dynamic behavior of virus infection with impairment of CTL functions and two routes of infection, but with one class of infected cells, productively infected cells.

In case of human immunodeficiency virus (HIV) infection, current treatment consisting of several antiretroviral drugs can suppress viral replication to a low level but cannot completely eradicate the HIV [29]. An important reason is that HIV provirus can reside in latently infected cells [32,33]. Latently infected cells live long, are not affected by antiretroviral drugs or immune responses, but can be activated to produce HIV by relevant antigens.

The aim of the present paper is to propose and analyze viral infection models which include (i) both productively infected cells and latently infected cells, (ii) both virus-to-cell and cell-to-cell transmissions, and (iii) impairment of CTL functions. We first show that the solutions of the models are nonnegative and bounded, then we derive the basic reproduction number which determines the existence and global stability of the steady states. We utilize the Lyapunov method to prove the global stability of the two steady states. We support our theorems by numerical simulations.

2. The Model

We study the following model:

$$\dot{G}(t) = \theta - \mu G(t) - \xi_1 G(t)J(t) - \xi_2 G(t)I(t), \tag{9}$$
$$\dot{L}(t) = (1-\nu)(\xi_1 G(t)J(t) + \xi_2 G(t)I(t)) - (b+d)L(t), \tag{10}$$
$$\dot{I}(t) = \nu(\xi_1 G(t)J(t) + \xi_2 G(t)I(t)) - \varrho I(t) - \beta I(t)K(t) + bL(t), \tag{11}$$
$$\dot{J}(t) = \vartheta I(t) - cJ(t), \tag{12}$$
$$\dot{K}(t) = \rho I(t) - \epsilon K(t) - hI(t)K(t), \tag{13}$$

where, L is the concentration of the latently infected cells. The uninfected cells become infected at rates $\xi_1 GJ$ and $\xi_2 GI$ due to virus-to-cell and cell-to-cell infections, respectively, where ξ_1 and ξ_2 are the incidence rate constants. The fractions $1-\nu$ and ν with $0 < \nu \leq 1$ are the probabilities that upon infection, an uninfected cell will becomes either latently infected or productively infected, respectively.

Parameter b denotes the average number of latently infected cells cells that become productively infected cells, and d denotes the death rate constant of the latently infected cells.

2.1. Nonnegativity and Boundedness

Let us define

$$\Omega = \left\{(G, L, I, J, K) \in \mathbb{R}^5_{\geq 0} : 0 \leq G, L, I \leq N_1, 0 \leq J \leq N_2, 0 \leq K \leq N_3\right\}. \tag{14}$$

Lemma 1. *The compact set Ω is positively invariant for system (9)–(13).*

Proof. We observe that

$$\begin{aligned}
\dot{G}\big|_{(G=0)} &= \theta > 0, \\
\dot{L}\big|_{(L=0)} &= (1-\nu)(\xi_1 GJ + \xi_2 GI) \geq 0, && \forall G, J, I \geq 0, \\
\dot{I}\big|_{(I=0)} &= \nu\xi_1 GJ + bL \geq 0, && \forall G, J, L \geq 0, \\
\dot{J}\big|_{(J=0)} &= \vartheta I \geq 0, && \forall I \geq 0, \\
\dot{K}\big|_{(K=0)} &= \rho I \geq 0, && \forall I \geq 0.
\end{aligned}$$

This confirms that $(G(t), L(t), I(t), J(t), K(t)) \in \mathbb{R}^5_{\geq 0}$ with $(G(0), L(0), I(0), J(0), K(0)) \in \mathbb{R}^5_{\geq 0}$. Let $F = G + L + I + \frac{\varrho}{2\vartheta}J + \frac{\varrho}{4\rho}K$. Then

$$\begin{aligned}
\dot{F} &= \theta - \mu G - \xi_1 GJ - \xi_2 GI + (1-\nu)(\xi_1 GJ + \xi_2 GI) - (b+d)L + \nu(\xi_1 GJ + \xi_2 GI) - \varrho I \\
&\quad - \beta IK + bL + \frac{\varrho}{2\vartheta}(\vartheta I - cJ) + \frac{\varrho}{4\rho}(\rho I - \epsilon K - hIK) \\
&= \theta - \mu G - dL - \frac{\varrho}{4}I - \left(\beta + \frac{\varrho h}{4\rho}\right)IK - \frac{\varrho c}{2\vartheta}J - \frac{\varrho\epsilon}{4\rho}K \\
&\leq \theta - \mu G - dL - \frac{\varrho}{4}I - \frac{\varrho c}{2\vartheta}J - \frac{\varrho\epsilon}{4\rho}K \\
&\leq \theta - \sigma\left(G + L + I + \frac{\varrho}{2\vartheta}J + \frac{\varrho}{4\rho}K\right) = \theta - \sigma F,
\end{aligned}$$

where, $\sigma = \min\{\mu, d, \frac{\varrho}{4}, c, \epsilon\}$. Hence, $0 \leq F(t) \leq N_1$ for all $t \geq 0$ if $F(0) \leq N_1$, where $N_1 = \frac{\theta}{\sigma}$. Consequently, $0 \leq G(t), L(t), I(t) \leq N_1, 0 \leq J(t) \leq N_2$ and $0 \leq K(t) \leq N_3$ for all $t \geq 0$ if $G(0) + L(0) + I(0) + \frac{\varrho}{2\vartheta}J(0) + \frac{\varrho}{4\vartheta}K(0) \leq N_1$, where $N_2 = \frac{2\vartheta\theta}{\varrho\sigma}$ and $N_3 = \frac{4\rho\theta}{\varrho\sigma}$. This establishes the bondedness of $G(t), L(t), I(t), J(t)$ and $K(t)$. □

Let us define the basic reproduction number of system (9)–(13) as:

$$\mathcal{R}_0 = \frac{\theta\,(d\nu + b)\,(\vartheta\xi_1 + c\xi_2)}{\varrho c\mu(b+d)}. \tag{15}$$

Lemma 2. *For system (9)–(13),*

(i) if $\mathcal{R}_0 \leq 1$ then there exists a disease-free steady state Δ_0,
(ii) if $\mathcal{R}_0 > 1$, then there exist two steady states Δ_0 and endemic steady state Δ_1.

Proof. The steady states of the system satisfy

$$0 = \theta - \mu G - \xi_1 GJ - \xi_2 GI, \tag{16}$$
$$0 = (1-\nu)(\xi_1 GJ + \xi_2 GI) - (b+d)L, \tag{17}$$
$$0 = \nu(\xi_1 GJ + \xi_2 GI) - \varrho I - \beta IK + bL, \tag{18}$$
$$0 = \vartheta I - cJ, \tag{19}$$
$$0 = \rho I - \epsilon K - hIK. \tag{20}$$

By solving Equations (16)–(20) we get two steady states, disease-free steady state $\Delta_0 = (G_0, 0, 0, 0, 0)$ where $G_0 = \dfrac{\theta}{\mu}$. In addition, we have

$$A_1 I^2 + B_1 I + C_1 = 0,$$

where

$$\begin{aligned}
A_1 &= (h\varrho + \beta\rho)(b+d)(\vartheta\xi_1 + c\xi_2),\\
B_1 &= ((\vartheta\xi_1 + c\xi_2)\epsilon + c\mu h)(b+d)\varrho - (\vartheta\xi_1 + c\xi_2)\theta dh\nu - (\vartheta\xi_1 + c\xi_2)b\theta h + (b+d)\beta\rho c\mu,\\
C_1 &= \epsilon(bc\mu\varrho + cd\mu\varrho)\,(1-\mathcal{R}_0)\,.
\end{aligned}$$

Define a function ψ_1 by

$$\psi_1(I) = A_1 I^2 + B_1 I + C_1 = 0.$$

Then, $\psi_1(0) = \epsilon(bc\mu\varrho + cd\mu\varrho)\,(1-\mathcal{R}_0) < 0$ when $\mathcal{R}_0 > 1$ and $\lim\limits_{I\to\infty}\psi_1(I) = \infty$. Hence, there exists $I_1 \in (0,\infty)$ such that $\psi_1(I_1) = 0$. Hence, when $\mathcal{R}_0 > 1$, then

$$\begin{aligned}
G_1 &= \frac{\theta c}{\xi_1\vartheta I_1 + \xi_2 c I_1 + c\mu} > 0, \qquad J_1 = \frac{\vartheta I_1}{c} > 0,\\
L_1 &= \frac{(1-\nu)\theta I_1(\xi_1\vartheta + \xi_2 c)}{(\xi_1\vartheta I_1 + \xi_2 c I_1 + c\mu)(d+b)} > 0, \qquad K_1 = \frac{\rho I_1}{hI_1 + \epsilon} > 0.
\end{aligned}$$

It follows that, an endemic steady state $\Delta_1(G_1, L_1, I_1, J_1, K_1)$, exists if $\mathcal{R}_0 > 1$. □

2.2. Global Stability

We define $\Gamma(\ell) = \ell - 1 - \ln\ell$. We note that $\Gamma(\ell) \geq 0$ for any $\ell > 0$ and $\Gamma(1) = 0$. To investigate the global stability of the steady states, we construct Lyapunov functions using the method presented [4] and followed by [5–7].

Theorem 1. *Let $\mathcal{R}_0 < 1$, then Δ_0 of models (9)–(13), is globally asymptotically stable and it is unstable if $\mathcal{R}_0 > 1$.*

Proof. Constructing a function $\Lambda_0(G, L, I, J, K)$ as:

$$\Lambda_0(G, L, I, J, K) = G_0\Gamma\left(\frac{G}{G_0}\right) + \left(\frac{b}{\nu d + b}\right)L + \left(\frac{b+d}{\nu d + b}\right)I + \frac{\xi_1 G_0}{c}J + \frac{\varrho(1-\mathcal{R}_0)}{\rho}\left(\frac{b+d}{\nu d + b}\right)K.$$

Clearly, $\Lambda_0(G, L, I, J, K)$ for all $G, L, I, J, K > 0$, while $\Lambda_0(G, L, I, J, K)$ reaches its global minimum at Δ_0. Calculating $\frac{d\Lambda_0}{dt}$ along the trajectories of (9)–(13) we get

$$\begin{aligned}\frac{d\Lambda_0}{dt} &= \left(1-\frac{G_0}{G}\right)(\theta-\mu G-\xi_1 GJ-\xi_2 GI)+\left(\frac{b}{\nu d+b}\right)((1-\nu)(\xi_1 GJ+\xi_2 GI)-(d+b)L)\\ &+\left(\frac{b+d}{\nu d+b}\right)(\nu(\xi_1 GJ+\xi_2 GI)-\varrho I+bL-\beta IK)+\frac{\xi_1 G_0}{c}(\vartheta I-cJ)+\frac{\varrho(1-\mathcal{R}_0)}{\rho}\left(\frac{b+d}{\nu d+b}\right)(\rho I-\epsilon K-hIK)\\ &=\left(1-\frac{G_0}{G}\right)(\theta-\mu G)+\varrho\left(\frac{b+d}{\nu d+b}\right)\left(\frac{\xi_2 G_0(\nu d+b)}{\varrho(b+d)}-1+\frac{\xi_1 G_0\vartheta(\nu d+b)}{\varrho c(b+d)}+(1-\mathcal{R}_0)\right)I\\ &-\left(\frac{b+d}{\nu d+b}\right)\left(\beta+\frac{\varrho h(1-\mathcal{R}_0)}{\rho}\right)IK-\frac{\varrho\epsilon(1-\mathcal{R}_0)}{\rho}\left(\frac{b+d}{\nu d+b}\right)K\\ &=-\mu\frac{(G-G_0)^2}{G}-\left(\frac{b+d}{\nu d+b}\right)\left(\beta+\frac{\varrho h(1-\mathcal{R}_0)}{\rho}\right)IK-\left(\frac{b+d}{\nu d+b}\right)\frac{\varrho\epsilon(1-\mathcal{R}_0)}{\rho}K.\end{aligned}$$

Since $\mathcal{R}_0<1$, then for all $G,L,I,J,K>0$ we have $\frac{d\Lambda_0}{dt}\leq 0$. The solutions of the system tend to the largest invariant subset of $\{(G,L,I,J,K):\frac{d\Lambda_0}{dt}=0\}$ [34]. It can be easily show that $\frac{d\Lambda_0}{dt}=0$ at Δ_0. Applying LaSalle's invariance principle (LIP), we get that Δ_0 is globally asymptotically stable.

We calculate the characteristic equation at the steady state Δ_0 as:

$$(\lambda+\mu)(\lambda+\epsilon)(\lambda^3+a_1\lambda^2+a_2\lambda+a_3)=0, \tag{21}$$

where

$$a_1=-\xi_2\nu G_0+\varrho+b+c+d, \tag{22}$$
$$a_2=((-\xi_2\nu G_0+\varrho+b+d)c-(\xi_2 b+\nu(\xi_1\vartheta+\xi_2 d))G_0+\varrho(d+b), \tag{23}$$
$$a_3=(-\xi_2(\nu d+b)cG_0-\xi_1\vartheta G_0((\nu d+b)))+\varrho c(d+b)=\varrho c(d+b)(1-\mathcal{R}_0). \tag{24}$$

Define

$$\psi_2(\lambda)=\lambda^3+a_1\lambda^2+a_2\lambda+a_3.$$

We have $\psi_2(0)=\varrho c(d+b)(1-\mathcal{R}_0)$. Hence, $\psi_2(0)<0$ when $\mathcal{R}_0>1$. We have also $\lim_{\lambda\to\infty}\psi_2(\lambda)=\infty$, which shows that ψ_2 has a positive real root and then, Δ_0 is unstable for $\mathcal{R}_0>1$. □

Theorem 2. *For system (9)–(13), if $\mathcal{R}_0>1$, then Δ_1 is globally asymptotically stable.*

Proof. Let a function $\Lambda_1(G,L,I,J,K)$ be defined as:

$$\begin{aligned}\Lambda_1(G,L,I,J,K)&=G_1\Gamma\left(\frac{G}{G_1}\right)+\left(\frac{b}{\nu d+b}\right)L_1\Gamma\left(\frac{L}{L_1}\right)+\left(\frac{b+d}{\nu d+b}\right)I_1\Gamma\left(\frac{I}{I_1}\right)+\frac{\xi_1 G_1}{c}J_1\Gamma\left(\frac{J}{J_1}\right)\\ &+\frac{\beta}{2(\rho-hK_1)}\left(\frac{b+d}{\nu d+b}\right)(K-K_1)^2.\end{aligned}$$

Clearly, $\Lambda_1(G,L,I,J,K)>0$ for all $G,L,I,J,K>0$, and $\Lambda_1(G_1,L_1,I_1,J_1,K_1)=0$. Calculating $\frac{d\Lambda_1}{dt}$ along the trajectories of (9)–(13) we get

$$\begin{aligned}\frac{d\Lambda_1}{dt}&=\left(1-\frac{G_1}{G}\right)(\theta-\mu G-\xi_1 GJ-\xi_2 GI)+\left(\frac{b}{\nu d+b}\right)\left(1-\frac{L_1}{L}\right)((1-\nu)(\xi_1 GJ+\xi_2 GI)-(d+b)L)\\ &+\left(\frac{b+d}{\nu d+b}\right)\left(1-\frac{I_1}{I}\right)(\nu(\xi_1 GJ+\xi_2 GI)-\varrho I+bL-\beta IK)\\ &+\frac{\xi_1 G_1}{c}\left(1-\frac{J_1}{J}\right)(\vartheta I-cJ)+\frac{\beta}{\rho-hK_1}\left(\frac{b+d}{\nu d+b}\right)(K-K_1)(\rho I-\epsilon K-hIK)\\ &=\left(1-\frac{G_1}{G}\right)(\theta-\mu G)+\xi_2 G_1 I-\left(\frac{b}{\nu d+b}\right)\frac{L_1}{L}(1-\nu)(\xi_1 GJ+\xi_2 GI)+\left(\frac{b(d+b)}{\nu d+b}\right)L_1\\ &-\nu\left(\frac{b+d}{\nu d+b}\right)\frac{I_1}{I}(\xi_1 GJ+\xi_2 GI)-\varrho\left(\frac{b+d}{\nu d+b}\right)(I-I_1)-b\left(\frac{b+d}{\nu d+b}\right)\frac{I_1}{I}L-\beta\left(\frac{b+d}{\nu d+b}\right)(I-I_1)K+\frac{\vartheta\xi_1 G_1}{c}I\\ &-\frac{\vartheta\xi_1 G_1}{c}\frac{J_1}{J}I+\xi_1 G_1 J_1+\frac{\beta}{\rho-hK_1}\left(\frac{b+d}{\nu d+b}\right)(K-K_1)(\rho I-\epsilon K-hIK).\end{aligned} \tag{25}$$

Simplifying Equation (25) and applying the following conditions for Δ_1:

$$\theta - \mu G_1 = \xi_1 G_1 J_1 + \xi_2 G_1 I_1, \quad (1-\nu)\left(\xi_1 G_1 J_1 + \xi_2 G_1 I_1\right) = (d+b)L_1,$$
$$\nu\left(\xi_1 G_1 J_1 + \xi_2 G_1 I_1\right) + bL_1 = \varrho I_1 + \beta I_1 K_1, \quad \vartheta I_1 = cJ_1, \quad \rho I_1 = \epsilon K_1 + hI_1 K_1,$$
$$\left(\frac{b+d}{\nu d+b}\right)(\varrho I_1 + \beta I_1 K_1) = \xi_1 G_1 J_1 + \xi_2 G_1 I_1,$$

we get

$$\begin{aligned}\frac{d\Lambda_1}{dt} = &-\left(\mu + \xi_2 I_1 \frac{(b+d)\nu}{\nu d+b}\right)\frac{(G-G_1)^2}{G} - \beta\left(\frac{\epsilon + hI}{\rho - hK_1}\right)\left(\frac{b+d}{\nu d+b}\right)(K-K_1)^2 \\ &+ \xi_1 G_1 J_1\left(\frac{b(1-\nu)}{\nu d+b}\right)\left(4 - \frac{G_1}{G} - \frac{L_1 GJ}{LG_1 J_1} - \frac{I_1 L}{IL_1} - \frac{J_1 I}{JI_1}\right) \\ &+ \xi_1 G_1 J_1\left(\frac{(b+d)\nu}{\nu d+b}\right)\left(3 - \frac{G_1}{G} - \frac{I_1 GJ}{IG_1 J_1} - \frac{J_1 I}{JI_1}\right) \\ &+ \xi_2 G_1 I_1\left(\frac{b(1-\nu)}{\nu d+b}\right)\left(3 - \frac{G_1}{G} - \frac{L_1 GI}{LG_1 I_1} - \frac{I_1 L}{I_1 L_1}\right). \end{aligned} \tag{26}$$

We have if $\mathcal{R}_0 > 1$, then $G_1, L_1, I_1, J_1, K_1 > 0$. The geometrical and arithmetical means relationship implies that

$$4 \le \frac{G_1}{G} + \frac{L_1 GJ}{LG_1 J_1} + \frac{I_1 L}{IL_1} + \frac{J_1 I}{JI_1},$$
$$3 \le \frac{G_1}{G} + \frac{I_1 GJ}{IG_1 J_1} + \frac{J_1 I}{JI_1},$$
$$3 \le \frac{G_1}{G} + \frac{L_1 GI}{LG_1 I_1} + \frac{I_1 L}{I_1 L_1}.$$

Hence for all $G, L, I, J, K > 0$ we have $\frac{d\Lambda_1}{dt} \le 0$ and $\frac{d\Lambda_1}{dt} = 0$ when $G = G_1$, $L = L_1$, $I = I_1$, $J = J_1$ and $K = K_1$. Utilizing LIP we obtain that if $\mathcal{R}_0 > 1$, then Δ_1 is globally asymptotically stable. □

3. Model with Saturated Incidence Rate

The rate of infection in model (9)–(13) is bilinear in the virus and the uninfected cell. Actual incidence rates are probably not strictly linear. A less than linear response in viruses and infected cells could occur due to saturation at high virus or infected cell concentrations [35]. Therefore, it is reasonable for us to assume that the infection rate of modeling viral infection is given by saturated mass action. In this section, we study a vial infection model with saturation:

$$\dot{G} = \theta - \mu G - \frac{\xi_1 GJ}{1+\alpha_1 J} - \frac{\xi_2 GI}{1+\alpha_2 I}, \tag{27}$$
$$\dot{L} = (1-\nu)\left(\frac{\xi_1 GJ}{1+\alpha_1 J} + \frac{\xi_2 GI}{1+\alpha_2 I}\right) - (d+b)L, \tag{28}$$
$$\dot{I} = \nu\left(\frac{\xi_1 GJ}{1+\alpha_1 J} + \frac{\xi_2 GI}{1+\alpha_2 I)}\right) - \varrho I + bL - \beta IK, \tag{29}$$
$$\dot{J} = \vartheta I - cJ, \tag{30}$$
$$\dot{K} = \rho I - \epsilon K - hIK, \tag{31}$$

where α_1, α_2 are saturation constants. All parameters and variables have the same meaning as (9)–(13).

3.1. Basic Properties

The next lemma shows the nonnegativity and boundedness of the solutions of system (27)–(31)

Lemma 3. *The compact set Ω is positively invariant for system (27)–(31).*

The proof is similar to that of Lemma 1.
The basic reproduction number of system (27)–(31) is the same as given by Equation (15).

Lemma 4. *Consider models (27)–(31), then*

(i) A disease-free steady state Δ_0 exists when $\mathcal{R}_0 \leq 1$,
(ii) An endemic steady state Δ_1 exists when $\mathcal{R}_0 > 1$.

Proof. Let

$$0 = \theta - \mu G - \frac{\xi_1 GJ}{1+\alpha_1 J} - \frac{\xi_2 GI}{1+\alpha_2 I}, \tag{32}$$

$$0 = (1-\nu)\left(\frac{\xi_1 GJ}{1+\alpha_1 J} + \frac{\xi_2 GI}{1+\alpha_2 I}\right) - (d+b)L, \tag{33}$$

$$0 = \nu\left(\frac{\xi_1 GJ}{1+\alpha_1 J} + \frac{\xi_2 GI}{1+\alpha_2 I}\right) + bL - \varrho I - \beta IK, \tag{34}$$

$$0 = \vartheta I - cJ, \tag{35}$$

$$0 = \rho I - \epsilon K - hIK. \tag{36}$$

By solving the algebraic Equations (32)–(36) we obtain a disease-free steady state $\Delta_0 = (G_0, 0, 0, 0, 0)$. Moreover we have

$$A_2 I^3 + B_2 I^2 + C_2 I + D_2 = 0,$$

$$\begin{aligned}
A_2 &= \vartheta(h\varrho + \beta\rho)(\mu\alpha_1\alpha_2 + \xi_1\alpha_2 + \xi_2\alpha_1)(b+d),\\
B_2 &= (\vartheta(\mu\alpha_1 + \xi_1)(\epsilon\alpha_2\varrho + h\varrho + \beta\rho) + (\vartheta\epsilon\alpha_1\varrho + ch\varrho + c\beta\rho)\xi_2 + c\mu\alpha_2(h\varrho + \beta\rho))(b+d)\\
&\quad - (\xi_1\alpha_2 + \xi_2\alpha_1)\theta h\vartheta(d\nu + b),\\
C_2 &= ((\vartheta\mu\alpha_1 + c\mu\alpha_2 + \vartheta\xi_1 + c\xi_2)\varrho\epsilon + (h\varrho + \rho\beta)c\mu)(b+d) - ((\xi_1\alpha_2 + \xi_2\alpha_1)\epsilon\vartheta + (\vartheta\xi_1 + c\xi_2)h)\theta(d\nu + b),\\
D_2 &= \frac{\epsilon}{c\mu\varrho}(1 - \mathcal{R}_0),
\end{aligned}$$

where $\mathcal{R}_0$ is defined by Equation (15). Define

$$\psi_3(I) = A_2 I^3 + B_2 I^2 + C_2 I + D_2 = 0.$$

We have

$$\psi_3(0) = \frac{\epsilon}{c\mu\varrho}(1 - \mathcal{R}_0),$$
$$\lim_{I\to\infty} \psi_3(I) = \infty.$$

Since $\mathcal{R}_0 > 1$, then $\psi_3(0) < 0$ and there exists $I_1 \in (0, \infty)$ such that $\psi_3(I_1) = 0$. Hence

$$G_1 = \frac{\theta(\alpha_1\vartheta I_1 + c)(\alpha_2 I_1 + 1)}{(\alpha_1\alpha_2\mu + \xi_1\alpha_2 + \xi_2\alpha_1)\vartheta I_1^2 + (\alpha_1\mu\vartheta + \alpha_2 c\mu + \xi_1\vartheta + \xi_2 c)I_1 + c\mu} > 0, \tag{37}$$

$$L_1 = \frac{(1-\nu)(\vartheta(\xi_1\alpha_2 + \xi_2\alpha_1)I_1 + \xi_2 c + \xi_1\vartheta))\theta I_1}{((\alpha_1\alpha_2\mu + \xi_1\alpha_2 + \xi_2\alpha_1)\vartheta I_1^2 + (\alpha_1\mu\vartheta + \alpha_2 c\mu + \xi_1\vartheta + \xi_2 c)I_1 + c\mu)(d+b)} > 0, \tag{38}$$

$$J_1 = \frac{\vartheta I_1}{c} > 0, \quad K_1 = \frac{\rho I_1}{hI_1 + \epsilon} > 0. \tag{39}$$

Hence, the endemic steady state $\Delta_1(G_1, L_1, I_1, J_1, K_1)$ exists when $\mathcal{R}_0 > 1$. □

3.2. Global Properties

Theorem 3. *Let $\mathcal{R}_0 < 1$, then Δ_0 of system (27)–(31) is globally asymptotically stable and it is unstable if $\mathcal{R}_0 > 1$.*

Proof. Define $\Lambda_0^G(G, L, I, J, K)$ as the following

$$\Lambda_0^G(G, L, I, J, K) = G_0\Gamma\left(\frac{G}{G_0}\right) + \left(\frac{b}{\nu d + b}\right)L + \left(\frac{b+d}{\nu d + b}\right)I + \frac{\xi_1 G_0}{c}J + \frac{\varrho(1-\mathcal{R}_0)}{\rho}\left(\frac{b+d}{\nu d + J}\right)K.$$

It is seen that $\Lambda_0^G(G, L, I, J, K) > 0$ for all $G, L, I, J, K > 0$ while $\Lambda_0^G(G, L, I, J, K)$ reaches its global minimum at Δ_0. We calculate $\frac{d\Lambda_0^G}{dt}$ as:

$$\begin{aligned}
\frac{d\Lambda_0^G}{dt} &= \left(1 - \frac{G_0}{G}\right)\left(\theta - \mu G - \frac{\xi_1 GJ}{1+\alpha_1 J} - \frac{\xi_2 GI}{1+\alpha_2 I}\right) + \left(\frac{b}{\nu d + b}\right)\left((1-\nu)\left(\frac{\xi_1 GJ}{1+\alpha_1 J} + \frac{\xi_2 GI}{1+\alpha_2 I}\right) - (d+b)L\right) \\
&+ \left(\frac{b+d}{\nu d + b}\right)\left(\nu\left(\frac{\xi_1 GJ}{1+\alpha_1 J} + \frac{\xi_2 GI}{1+\alpha_2 I}\right) + bL - \varrho I - \beta IK\right) + \frac{\xi_1 G_0}{c}(\vartheta I - cJ) \\
&+ \frac{\varrho(1-\mathcal{R}_0)}{\rho}\left(\frac{b+d}{\nu d + b}\right)(\rho I - \epsilon K - hIK) \\
&= \mu\left(1 - \frac{G_0}{G}\right)(G_0 - G) + \frac{\xi_1 G_0 J}{1+\alpha_1 J} + \frac{\xi_2 G_0 I}{1+\alpha_2 I} + \varrho\left(\frac{b+d}{\nu d + b}\right)(1 - 1 - \mathcal{R}_0)I + \frac{\xi_1 G_0}{c}(\vartheta I - cJ) \\
&- \left(\frac{b+d}{\nu d + b}\right)\left(\left(\beta + \frac{\varrho h(1-\mathcal{R}_0)}{\rho}\right)IK + \frac{\varrho(1-\mathcal{R}_0)\epsilon}{\rho}K\right) \\
&= -\left(\mu\frac{(G-G_0)^2}{G} + \frac{\alpha_1\xi_1 G_0 J^2}{1+\alpha_1 J} + \frac{\alpha_2\xi_2 G_0 I^2}{1+\alpha_2 I}\right) + \varrho\left(\frac{b+d}{\nu d + b}\right)\left(\frac{\xi_1 G_0\vartheta(\nu d + b)}{\varrho c(b+d)} + \frac{\xi_2 G_0(\nu d + b)}{\varrho(b+d)} - \mathcal{R}_0\right)I \\
&- \left(\frac{b+d}{\nu d + b}\right)\left(\left(\beta + \frac{\varrho h(1-\mathcal{R}_0)}{\rho}\right)IK + \frac{\varrho(1-\mathcal{R}_0)\epsilon}{\rho}K\right) \\
&= -\mu\frac{(G-G_0)^2}{G} - \frac{\alpha_1\xi_1 G_0 J^2}{1+\alpha_1 J} - \frac{\alpha_2\xi_2 G_0 J^2}{1+\alpha_2 J} - \left(\frac{b+d}{\nu d + b}\right)\left((\beta + \frac{\varrho h(1-\mathcal{R}_0)}{\rho})IK + \frac{\varrho(1-\mathcal{R}_0)\epsilon}{\rho}K\right).
\end{aligned} \tag{40}$$

Clearly if $\mathcal{R}_0 < 1$, then for all $G, L, I, J, K > 0$, we have $\frac{d\Lambda_0^G}{dt} \leq 0$, and $\frac{d\Lambda_0^G}{dt} = 0$ when $G = G_0, L = 0, I = 0, J = 0$ and $K = 0$. Applying LIP implies we get that if $\mathcal{R}_0 < 1$, then Δ_0 is globally asymptotically stable. Similar to the previous section we can easily show that if $\mathcal{R}_0 > 1$, then Δ_0 is unstable. □

Theorem 4. *Let $\mathcal{R}_0 > 1$ then Δ_1 of system (27)–(31) is globally asymptotically stable.*

Proof. Define a function $\Lambda_1^G(G, L, I, J, K)$ as:

$$\begin{aligned}
\Lambda_1^G(G, L, I, J, K) &= G_1\Gamma\left(\frac{G}{G_1}\right) + \left(\frac{b}{\nu d + b}\right)L_1\Gamma\left(\frac{L}{L_1}\right) + \left(\frac{b+d}{\nu d + b}\right)I_1\Gamma\left(\frac{I}{I_1}\right) + \frac{\xi_1 G_1}{c(1+\alpha_1 J_1)}J_1\Gamma\left(\frac{J}{J_1}\right) \\
&+ \frac{\beta}{2(\rho - hK_1)}\left(\frac{b+d}{\nu d + b}\right)(K - K_1)^2.
\end{aligned}$$

It is seen that $\Lambda_1^G(G, L, I, J, K) > 0$ for all $G, L, I, J, K > 0$ while $\Lambda_1^G(G, L, I, J, K)$ reaches its global minimum at Δ_1. Calculating $\frac{d\Lambda_1^G}{dt}$ as:

$$\begin{aligned}
\frac{d\Lambda_1^G}{dt} &= \left(1-\frac{G_1}{G}\right)\left(\theta-\mu G-\frac{\xi_1 GJ}{1+\alpha_1 J}-\frac{\xi_2 GI}{1+\alpha_2 I}\right)\\
&+\left(\frac{b}{\nu d+b}\right)\left(1-\frac{L_1}{L}\right)\left((1-\nu)\left(\frac{\xi_1 GJ}{1+\alpha_1 J}+\frac{\xi_2 GI}{1+\alpha_2 I}\right)-(d+b)L\right)\\
&+\left(\frac{b+d}{\nu d+b}\right)\left(1-\frac{I_1}{I}\right)\left(\nu\left(\frac{\xi_1 GJ}{1+\alpha_1 J}+\frac{\xi_2 GI}{1+\alpha_2 I}\right)+bL-\varrho I-\beta IK\right)\\
&+\frac{\xi_1 G_1}{c(1+\alpha_1 J_1)}\left(1-\frac{J_1}{J}\right)(\vartheta I-cJ)+\frac{\beta}{\rho-hK_1}\left(\frac{b+d}{\nu d+b}\right)(K-K_1)(\rho I-\epsilon K-hIK)\\
&=\left(1-\frac{G_1}{G}\right)(\theta-\mu G)+\frac{\xi_1 G_1 J}{1+\alpha_1 J}+\frac{\xi_2 G_1 I}{1+\alpha_2 I}-\left(\frac{(1-\nu)b}{\nu d+b}\right)\left(\frac{\xi_1 GJ}{1+\alpha_1 J}+\frac{\xi_2 GI}{1+\alpha_2 I}\right)\frac{L_1}{L}\\
&+\frac{b(d+b)}{\nu d+b}L_1-\nu\left(\frac{b+d}{\nu d+b}\right)\left(\frac{\xi_1 GJ}{1+\alpha_1 J}+\frac{\xi_2 GI}{1+\alpha_2 I}\right)\frac{I_1}{I}-\varrho\left(\frac{b+d}{\nu d+b}\right)(I-I_1)\\
&-\beta\left(\frac{b+d}{\nu d+b}\right)(I-I_1)K-\left(\frac{b(b+d)}{\nu d+b}\right)\frac{I_1}{I}L+\frac{\vartheta\xi_1 G_1}{c(1+\alpha_1 J_1)}I-\frac{\xi_1 G_1 J}{1+\alpha_1 J_1}\\
&-\frac{\vartheta\xi_1 G_1}{c(1+\alpha_1 J_1)}\frac{J_1}{J}I+\frac{\xi_1 G_1 J_1}{1+\alpha_1 J_1}+\frac{\beta}{\rho-hK_1}\left(\frac{b+d}{\nu d+b}\right)(K-K_1)(\rho I-\epsilon K-hIK). \qquad (41)
\end{aligned}$$

The steady state conditions of Δ_1 implies that:

$$\begin{aligned}
\theta-\mu G_1=\frac{\xi_1 G_1 J_1}{1+\alpha_1 J_1}+\frac{\xi_2 G_1 I_1}{1+\alpha_2 I_1},\quad (b+d)L_1=(1-\nu)\left(\frac{\xi_1 G_1 J_1}{1+\alpha_1 J_1}+\frac{\xi_2 G_1 I_1}{1+\alpha_2 I_1}\right),\\
\varrho I_1+\beta I_1 K_1=\nu\left(\frac{\xi_1 G_1 J_1}{1+\alpha_1 J_1}+\frac{\xi_2 G_1 I_1}{1+\alpha_2 I_1}\right)+bL_1,\quad \vartheta I_1=cJ_1,\quad \rho I_1=\epsilon K_1+hI_1K_1,\\
\left(\frac{b+d}{\nu d+b}\right)(\varrho I_1+\beta I_1 K_1)=\frac{\xi_1 G_1 J_1}{1+\alpha_1 J_1}+\frac{\xi_2 G_1 I_1}{1+\alpha_2 I_1},
\end{aligned}$$

we get

$$\begin{aligned}
\frac{d\Lambda_1^G}{dt} &= -\mu\frac{(G-G_1)^2}{G}-\frac{\xi_1 G_1 J_1}{1+\alpha_1 J_1}\left(\frac{\alpha_1(J-J_1)^2}{J_1(1+\alpha_1 J)(1+\alpha_1 J_1)}\right)-\frac{\xi_2 G_1 I_1}{1+\alpha_2 I_1}\left(\frac{\alpha_2(I-I_1)^2}{I_1(1+\alpha_2 I)(1+\alpha_2 I_1)}\right)\\
&+\frac{\xi_1 G_1 J_1}{1+\alpha_1 J_1}\left(\frac{b(1-\nu)}{\nu d+b}\right)\left(5-\frac{G_1}{G}-\frac{L_1 GJ(1+\alpha_1 J_1)}{LG_1 J_1(1+\alpha_1 J)}-\frac{I_1 L}{IL_1}-\frac{J_1 I}{JI_1}-\frac{1+\alpha_1 J}{1+\alpha_1 J_1}\right)\\
&+\frac{\xi_1 G_1 J_1}{1+\alpha_1 J_1}\left(\frac{(b+d)\nu}{\nu d+b}\right)\left(4-\frac{G_1}{G}-\frac{I_1 GJ(1+\alpha_1 J_1)}{IG_1 J_1(1+\alpha_1 J)}-\frac{IJ_1}{I_1 J}-\frac{1+\alpha_1 J}{1+\alpha_1 J_1}\right)\\
&+\frac{\xi_2 G_1 I_1}{1+\alpha_2 I_1}\left(\frac{b(1-\nu)}{\nu d+b}\right)\left(4-\frac{G_1}{G}-\frac{L_1 GI(1+\alpha_2 I_1)}{LG_1 I_1(1+\alpha_2 I)}-\frac{I_1 L}{IL_1}-\frac{1+\alpha_2 I}{1+\alpha_2 I_1}\right)\\
&+\frac{\xi_2 G_1 I_1}{1+\alpha_2 I_1}\left(\frac{(b+d)\nu}{\nu d+b}\right)\left(3-\frac{G_1}{G}-\frac{G(1+\alpha_2 I_1)}{G_1(1+\alpha_2 I)}-\frac{1+\alpha_2 I}{1+\alpha_2 I_1}\right)-\beta\left(\frac{\epsilon+hI}{\rho-hK_1}\right)\left(\frac{b+d}{\nu d+b}\right)(K-K_1)^2.
\end{aligned}$$

The geometrical and arithmetical means relationship implies that

$$\begin{aligned}
5&\leq\frac{G_1}{G}+\frac{L_1 GJ(1+\alpha_1 J_1)}{LG_1 J_1(1+\alpha_1 J)}+\frac{I_1 L}{IL_1}+\frac{J_1 I}{JI_1}+\frac{1+\alpha_1 J}{1+\alpha_1 J_1},\\
4&\leq\frac{G_1}{G}+\frac{I_1 GJ(1+\alpha_1 J_1)}{IG_1 J_1(1+\alpha_1 J)}+\frac{IJ_1}{I_1 J}+\frac{1+\alpha_1 J}{1+\alpha_1 J_1},\\
4&\leq\frac{G_1}{G}+\frac{L_1 GI(1+\alpha_2 I_1)}{LG_1 I_1(1+\alpha_2 I)}+\frac{I_1 L}{IL_1}+\frac{1+\alpha_2 I}{1+\alpha_2 I_1},\\
3&\leq\frac{G_1}{G}+\frac{G(1+\alpha_2 I_1)}{G_1(1+\alpha_2 I)}+\frac{1+\alpha_2 I}{1+\alpha_2 I_1}.
\end{aligned}$$

Thus $\frac{d\Lambda_1^G}{dt}\leq 0$ for all $G, L, I, J, K>0$ and $\frac{d\Lambda_1^G}{dt}=0$ at Δ_1. Using LIP one can easily show that Δ_1 is globally asymptotically stable. □

4. Numerical Simulations

In this section, we solve system (27)–(31) numerically with values of the parameters given as: $\theta = 270$, $\mu = 0.2$, $\xi_2 = 0.005$, $b = 0.1$, $d = 0.2$, $\varrho = \vartheta = 5.5$, $c = 3$, $\rho = 0.5$, $\epsilon = 0.1$ and $\nu = 0.5$. The parameters ξ_1, α_1, α_2, β and h will be varied. We take $\alpha = \alpha_1 = \alpha_2$ and choose different initial conditions as:

IC1: $G(0) = 900, L(0) = 200, I(0) = 15, J(0) = 30, K(0) = 4$,
IC2: $G(0) = 600, L(0) = 150, I(0) = 10, J(0) = 20, K(0) = 3$,
IC3: $G(0) = 400, L(0) = 75, I(0) = 5, J(0) = 10, K(0) = 2$,
IC4: $G(0) = 900, L(0) = 200, I(0) = 140, J(0) = 100, K(0) = 4.2$,
IC5: $G(0) = 900, L(0) = 140, I(0) = 15, J(0) = 100, K(0) = 4$.

Case(1) Stability of steady states:

We take $\alpha = 0, h = 0.1, \beta = 0.04$ and ξ_1 is varied as:

(i) $\xi_1 = 0.0005$, then $\mathcal{R}_0 = 0.9682 < 1$. Figure 1 shows that, the solution of the system with different initial conditions IC1–IC3 tends to Δ_0. This result implies that Δ_0 is globally asymptotically stable which confirms Theorem 3.

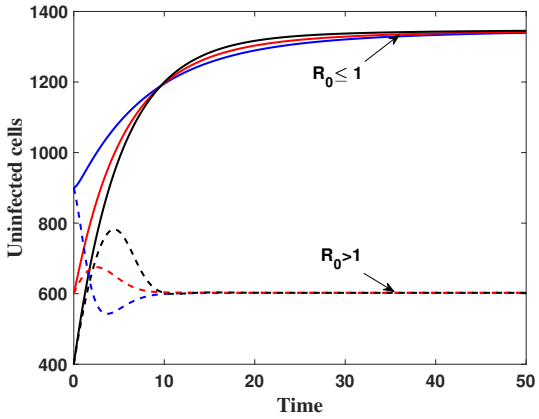
(ii) $\xi_1 = 0.005$ then, $\mathcal{R}_0 = 2.3182 > 1$. The numerical results show that the solutions of the system tends to the steady state $\Delta_1 = (602.3861, 249.2046, 17.5212, 32.1223, 4.7300)$ for all IC1–IC3. This supports the global stability result of Theorem 4.

Case(2) Virus dynamics with variation of α:

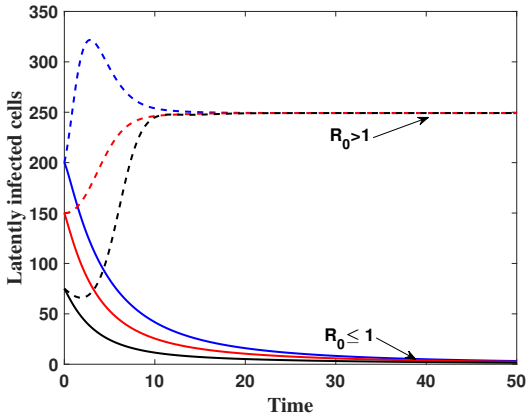
In this case, we fix $\xi_1 = 0.005, h = 0.1, \beta = 0.4$ and α is changed. We solve the system numerically with the initial condition IC4. In Figure 2, we show the effect of saturated incidence parameter α. We can see that the concentration of the uninfected cells is increased as α is increased. Moreover, the concentration of latently infected cells, productively infected, viruses and CTLs are decreased as α is increased.

Case(3) Effect of h on the virus dynamics:

Here, we fix $\xi_1 = 0.005, \alpha = 0.05, \beta = 0.4$ and h is changed. The system is solved with initial condition IC5, Figure 3 shows that the increasing of h will increase both $G(t)$ and $K(t)$ and decrease all of $L(t)$, $I(t)$ and $J(t)$.

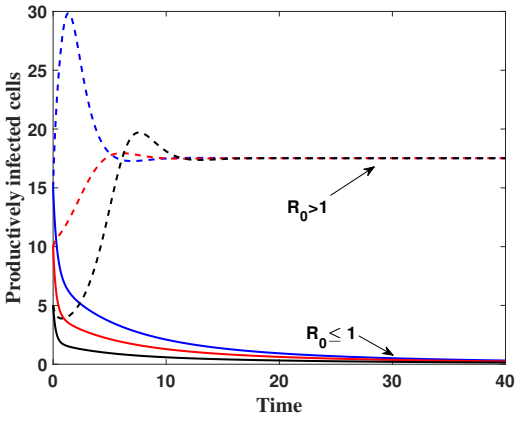


(a) Uninfected cells

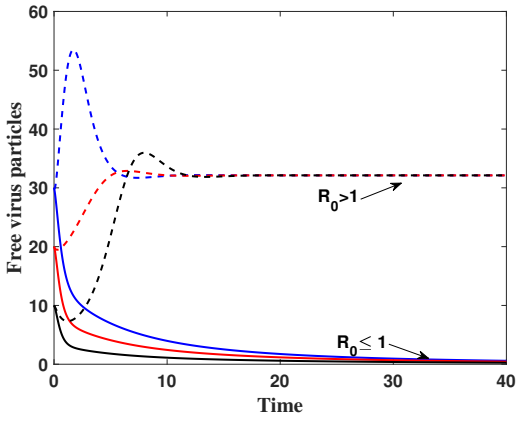


(b) Latently infected cells

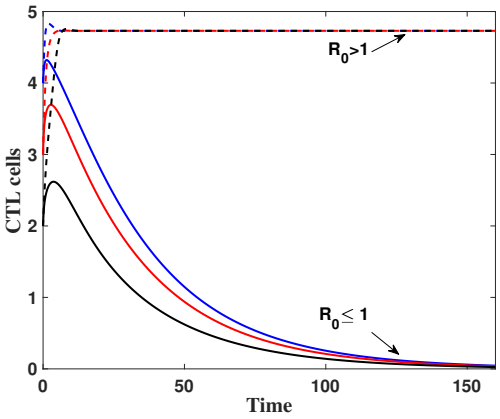
Figure 1. *Cont.*



(c) Productively infected cells

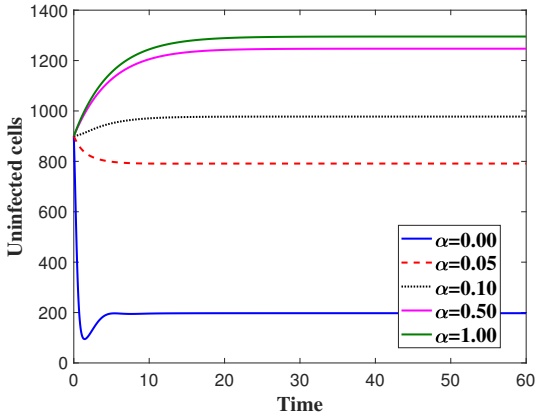


(d) Free virus particles

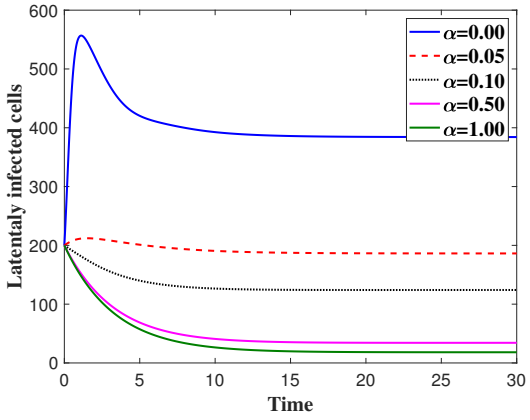


(e) CTLs

Figure 1. The simulation of trajectories of system (27)–(31) with IC1–IC3.

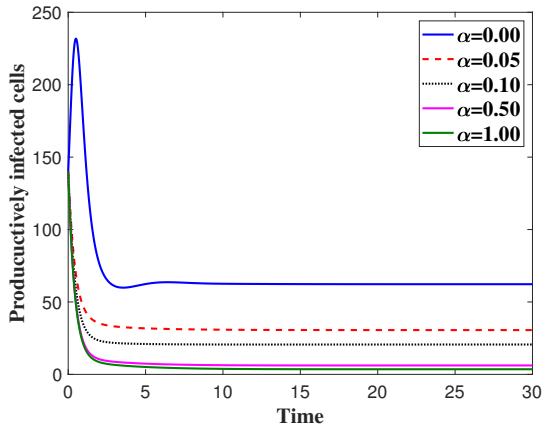


(a) Uninfected cells

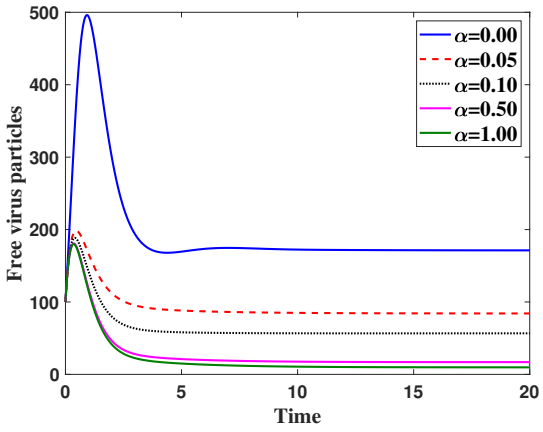


(b) Latently Infected cells

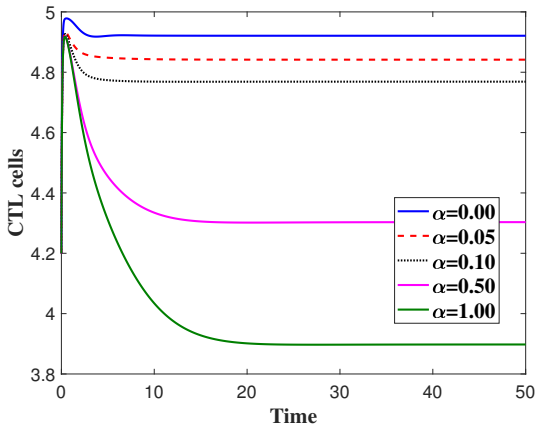
Figure 2. *Cont.*



(c) Productively Infected cells

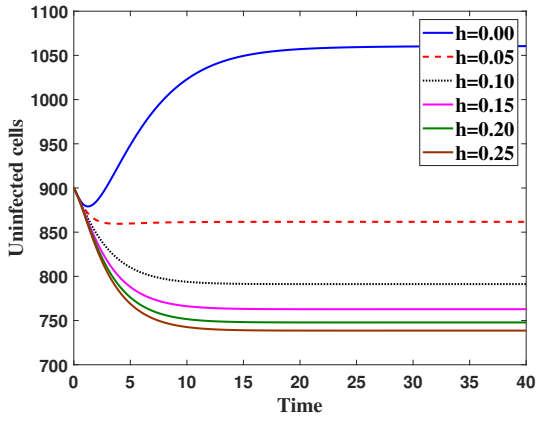


(d) Free virus particles

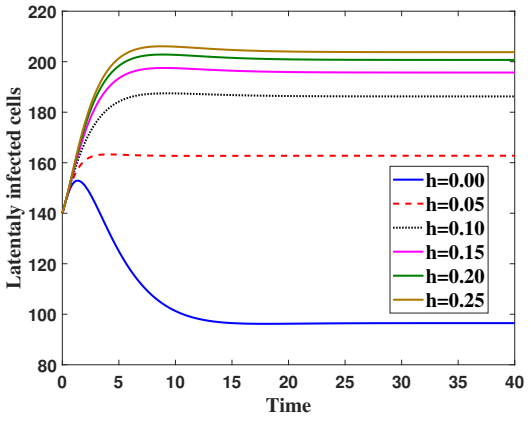


(e) CTLs

Figure 2. The simulation of trajectories of system (27)–(31) with different values of α.

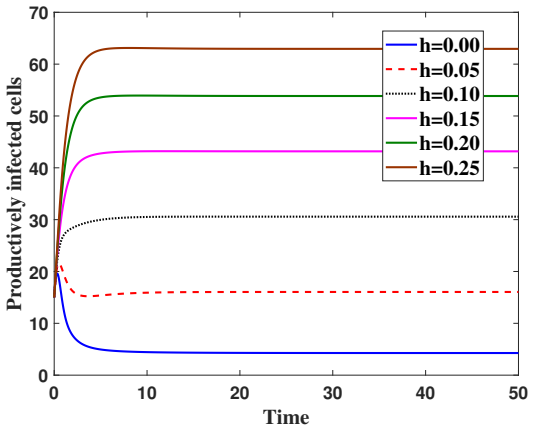


(a) Uninfected cells

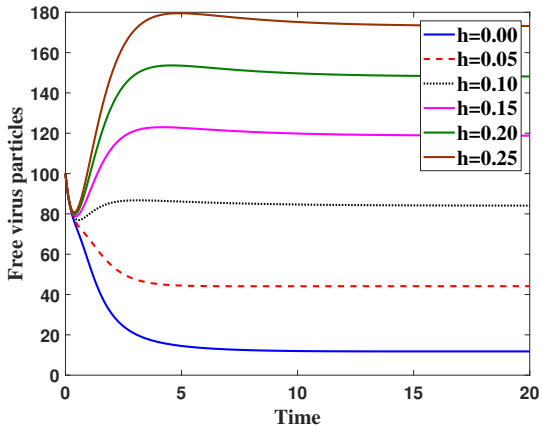


(b) Latently Infected cells

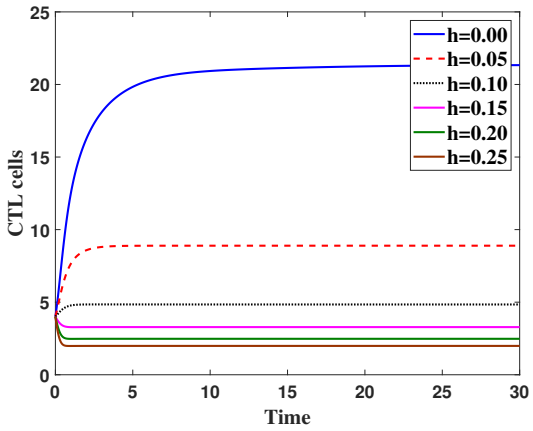
Figure 3. *Cont.*



(c) Productively infected cells



(d) Free virus particles



(e) CTLs

Figure 3. The simulation of trajectories of system (27)–(31) with different value h.

5. Discussion and Conclusions

In this paper, we have proposed two virus dynamics models with impairment of CTL functions. We consider that the healthy cells are infected by two ways, viral and cellular infections. We have considered both latently and productively infected cells. The incidence rate is represented by bilinear and saturation in the first and second models, respectively. We have established the well-posedness of the model. We have derived the basic reproduction numbers $\mathcal{R}_0$ which determine the existence and stability of the disease-free steady state Δ_0 and endemic steady state Δ_1 of the model. We have investigated the global stability of the steady states of the model by using the Lyapunov method and LaSalle's invariance principle. We have proven that (i) if $\mathcal{R}_0 < 1$, then Δ_0 is globally asymptotically stable and the viruses is cleared (ii) if $\mathcal{R}_0 > 1$, then Δ_1 exists then it is globally asymptotically stable. This case corresponds to the persistence of the viruses. The effects of saturation and CTL impairment have been studied. We have supported the theoretical results by numerical simulations.

Models (1)–(4) have three steady states; disease-free steady state Δ_0^C, endemic steady state without a CTL immune response Δ_1^C and endemic steady state with a CTL immune response Δ_2^C. Moreover, the existence and stability of the steady states are determined by two threshold parameters, the basic reproduction number R_0^C (which determines whether or not the disease will progress) and the CTL

immune response activation number R_1^C (which determines whether or not a persistent CTL immune response can be established), where

$$\mathcal{R}_0^C = \frac{\theta\vartheta\xi}{\varrho c\mu}, \quad \mathcal{R}_1^C = \frac{\mathcal{R}_0^C}{1+\frac{\epsilon\vartheta\xi}{c\mu\rho}}.$$

In contrast, models (5)–(8) as well as our proposed models (9)–(13) and (27)–(31) have two steady states (Δ_0 and Δ_1) and their existence and stability are determined by only the basic reproduction number R_0.

It has been reported in several works (see e.g., [10,13,36]) that viruses mutate fast and there is a generation of quasi species that may vary in infectivity. In fact, mutations are one of the ways of immune evasion whereby viruses can evade CTL activity. The high mutation rate of viruses naturally leads to the study of the interplay between immune response and virus diversity for a number of different strains [36]. A viral infection model with CTL immune response and mutations has been proposed in [10] as:

$$\dot{G}(t) = \theta - \mu G(t) - \sum_{i=1}^{n} \xi_i G(t) J_i(t), \tag{42}$$

$$\dot{I}_i(t) = \sum_{i=1}^{n} \xi_i G(t) J_i(t) - \varrho_i I_i(t) - \beta_i I_i(t) K_i(t), \quad i = 1, 2, ..., n \tag{43}$$

$$\dot{J}_i(t) = \vartheta_i I_i(t) - c_i J_i(t), \qquad i = 1, 2, ..., n \tag{44}$$

$$\dot{K}_i(t) = \rho_i I_i(t) K_i(t) - \epsilon_i K_i(t), \qquad i = 1, 2, ..., n \tag{45}$$

where, I_i is the concentration of actively infected cells with virus strain i, J_i denotes the concentration of different strains of virus particles and K_i denotes the concentration of strain specific immune responses. It has been assumed that there are n diffierent strains of virus. Models (42)–(45) can be extended to take into account (i) cell-to-cell transmision, (ii) latently infected cells, (iii) immune impairment, and (iv) time delay as:

$$\dot{G}(t) = \theta - \mu G(t) - \sum_{i=1}^{n} G(t) \left[\xi_{1,i} J_i(t) + \xi_{2,i} I_i(t)\right], \tag{46}$$

$$\dot{L}_i(t) = (1-\nu_i) \sum_{i=1}^{n} e^{-\gamma_i \tau_i} G(t-\tau_i) \left[\xi_{1,i} J_i(t-\tau_i) + \xi_{2,i} I_i(t-\tau_i)\right] - (b_i + d_i) L_i(t), \qquad i = 1, 2, ..., n \tag{47}$$

$$\dot{I}_i(t) = \nu_i \sum_{i=1}^{n} e^{-\kappa_i \omega_i} G(t-\omega_i) \left[\xi_{1,i} J_i(t-\omega_i) + \xi_{2,i} I_i(t-\omega_i)\right] - \rho_i I_i(t) - \beta_i I_i(t) K_i(t) + b_i L_i(t), i = 1, 2, ..., n \tag{48}$$

$$\dot{J}_i(t) = \theta_i e^{-\phi_i \kappa_i} I_i(t-\kappa_i) - c_i J_i(t), \qquad i = 1, 2, ..., n \tag{49}$$

$$\dot{K}_i(t) = \rho_i I_i(t) - \epsilon_i K_i(t) - h_i I_i(t) K_i(t), \qquad i = 1, 2, ..., n \tag{50}$$

where L_i is the concentration of latently infected cells with virus strain i. Here, τ_i is the time between a virus strain i entering an uninfected cell to become latently infected cell with virus strain i, and ω_i is the time between a virus strain i entering an uninfected cell and the production of immature viruses of type i. The immature viruses of type i need time κ_i to be mature. The factors $e^{-\gamma_i \tau_i}$, $e^{-\kappa_i \omega_i}$ and $e^{-\phi_i \kappa_i}$ represent the probability of surviving to the age of τ_i, ω_i and κ_i, respectively, where γ_i, κ_i and, ϕ_i are positive constants. It is worth stressing that the role of the delay term does not only take into account the delay in the dynamical response of the interacting entities, but also their heterogeneity. This can be accounted for by modeling interactions as shown in [37].

Effects of Latent Infection on the Virus Dynamics

In this subsection, we show the effect of the presence of latently infected cells on virus dynamics. Let us incorporate an antiviral drug with efficacy η where $\eta \in [0,1)$. The virus dynamics model (9)–(13) under the effect of treatment is given by:

$$\dot{G}(t) = \theta - \mu G(t) - (1-\eta)\left[\xi_1 J(t) + \xi_2 I(t)\right] G(t), \tag{51}$$
$$\dot{L}(t) = (1-\nu)(1-\eta)\left[\xi_1 J(t) + \xi_2 I(t)\right] G(t) - (b+d)L(t), \tag{52}$$
$$\dot{I}(t) = \nu(1-\eta)\left[\xi_1 J(t) + \xi_2 I(t)\right] G(t) - \varrho I(t) - \beta I(t)K(t) + bL(t), \tag{53}$$
$$\dot{J}(t) = \vartheta I(t) - cJ(t), \tag{54}$$
$$\dot{K}(t) = \rho I(t) - \epsilon K(t) - hI(t)K(t). \tag{55}$$

The basic reproduction number R_0^L for system (51)–(55) is given by

$$\mathcal{R}_0^L(\eta) = (1-\eta)\frac{\theta\left(d\nu + b\right)\left(\vartheta\xi_1 + c\xi_2\right)}{\varrho c\mu(b+d)}.$$

When the population of the latently infected cells are not modeled then models (51)–(55) will become:

$$\mathcal{R}_0^L(\eta) < 1, \quad \text{for all} \quad \eta_{crit}^L < \eta < 1,$$
$$\mathcal{R}_0^W(\eta) < 1, \quad \text{for all} \quad \eta_{crit}^W < \eta < 1,$$

and stabilize the disease-free steady state for systems (51)–(55) and (56)–(59). Now, we calculate η_{crit}^W and η_{crit}^L as:

$$\dot{G}(t) = \theta - \mu G(t) - (1-\eta)\left[\xi_1 J(t) + \xi_2 I(t)\right] G(t), \tag{56}$$
$$\dot{I}(t) = (1-\eta)\left[\xi_1 J(t) + \xi_2 I(t)\right] G(t) - \varrho I(t) - \beta I(t)K(t), \tag{57}$$
$$\dot{J}(t) = \vartheta I(t) - cJ(t), \tag{58}$$
$$\dot{K}(t) = \rho I(t) - \epsilon K(t) - hI(t)K(t). \tag{59}$$

The basic reproduction number R_0^W for system (56)–(59) is given by

$$\mathcal{R}_0^W(\eta) = (1-\eta)\frac{\theta\left(\vartheta\xi_1 + c\xi_2\right)}{\varrho c\mu}.$$

Since $0 < \nu < 1$, then

$$\mathcal{R}_0^L(\eta) = (1-\eta)\frac{\theta\left(d\nu + b\right)\left(\vartheta\xi_1 + c\xi_2\right)}{\varrho c\mu(b+d)} < (1-\eta)\frac{\theta\left(\vartheta\xi_1 + c\xi_2\right)}{\varrho c\mu} = \mathcal{R}_0^W(\eta).$$

Clearly, the presence of latently infected cells deceases the basic reproduction number of the system. Now, we aim to determine the minimum drug efficacy that can clear the viruses from the body. We determine η_{crit}^L and η_{crit}^W that make

$$\eta_{crit}^L = \max\left\{0, \frac{\mathcal{R}_0^L(0) - 1}{\mathcal{R}_0^L(0)}\right\},$$
$$\eta_{crit}^W = \max\left\{0, \frac{\mathcal{R}_0^W(0) - 1}{\mathcal{R}_0^W(0)}\right\}.$$

Clearly, $R_0^L(0) < R_0^W(0)$ and thus $\eta_{crit}^L < \eta_{crit}^W$. Therefore, the drug efficacy necessary to steer the states of the system to the disease-free steady state is actually less for system (51)–(55) than that for system (56)–(59).

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