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Global Stability of General Pathogen Models With CTL Impairment and Distributed Delays

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Abstract. This paper presents a pathogen dynamics models with impaired of cytotoxic T lymphocytes (CTLs) function. The models includes both pathogen-to-cell and cell-to-cell modes of transmission which are represented by general nonlinear functions. The basic reproduction number $\mathcal{R}_0$ is determined and two equilibrium points are calculated. Nonnegativity and boundedness of the solution are proved. Lyapunov function and LaSalle's invariance principle are used to prove the global stability of each equilibria. Simulations are used to illustrate the theoretical results. A study is conducted on the effect of impaired CTL-cell functions and time delays on pathogen dynamics. Finally, we have observed that increasing of time delay will suppress the pathogen replication.

1. Introduction

The dynamics of human pathogens within hosts have been described by a variety of mathematical models in recent years (see [1]- [17]). In several pathogen infection models, cytotoxic T lymphocyte (CTL) immune response has been considered. The presence of antigens stimulate immunity and neglect the impairment of CTL immunity in [19]- [28]. In several studies, immune impairment has been associated with pathogen infection models [29]- [31]. It has been reported in several papers that there are two ways of pathogen transmissions, pathogen-to-cell and cell-to-cell [39]- [47]. Several papers studied the effect of the immune impairment with cell-to-cell transmission [48]- [51]. Elaiw at al. in [48] studied the following model:

$$\dot{U}(t) = \Upsilon - \Phi U(t) - \eta_1 V(t)U(t) - \eta_2 X(t)U(t), \tag{1.1}$$

$$\dot{X}(t) = \eta_1 V(t)U(t) + \eta_2 X(t)U(t) - \Theta X(t) - CX(t)Q(t), \tag{1.2}$$

$$\dot{V}(t) = \Omega X(t)d\gamma - \Sigma V(t), \tag{1.3}$$

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$$\dot{Q}(t) = \Psi X(t) - \Lambda Q(t) - \beta X(t)Q(t), \tag{1.4}$$

where $U(t)$, $X(t)$, $V(t)$ and $Q(t)$ are, respectively, the concentrations of uninfected cells, infected cells, pathogen and CTLs at time t, respectively The uninfected cells are restored at rate Υ and die at rate ΦU. The infected cells are killed by CTLs at rate CXQ and die at rate ΘX. Pathogens proliferate at rate ΩX and die by rate ΣV. CTLs are proliferated at rate ΨX and die by rate ΛQ. The impairment of the CTL is represented by βXQ. The uninfected cells become infected at rate $\eta_1 VU + \eta_2 XU$. After that some research studied the above model by changing the nonlinear incident rate [50]- [51]. In addition, other papers studied this model by adding time delay [49]. In [50], the pathogen-to-cell and cell-to-cell incidence rates were descibed by $K_1(V)M(U)$ and $K_2(X)M(U)$ where K_1, K_2 and M are general functions. However, the intracellular time delay was neglected in [50].

In our research, we studied two general pathogen dynamics models, by taking into account (a) CTL immune impairment, (b) distributed-time delays (c) general pathogen-to-cell and cell-to-cell incidence rates, $H_1(V,U)$ and $H_2(X,U)$, respectively. These incidence rates $H_1(V,U)$ and $H_2(X,U)$ are more general than the model in [50]. In the second model, we take into account two type of infected cells, latently infected cells and actively infected cells. We proved that all solutions are nonnegativity and boundedness. Lyapunov functions are constructed in order to establish the global stability of the equilibrium.

2. Model with general rate of incidence

In this section, we present a pathogen dynamics model with general pathogen-to-cell and cell-to-cell incidences as follows:

$$\dot{U}(t) = \Upsilon - \Phi U(t) - \left[H_1(V(t),U(t)) + H_2(X(t),U(t))\right], \tag{2.1}$$

$$\dot{X}(t) = \int_0^{f_1} e^{-\beta_1\gamma} g_1(\gamma)\left[H_1(V(t-\gamma),U(t-\gamma)) + H_2(X(t-\gamma),U(t-\gamma))\right]d\gamma \\ - \Theta X(t) - CX(t)Q(t), \tag{2.2}$$

$$\dot{V}(t) = \Omega \int_0^{f_2} e^{-\beta_2\gamma} g_2(\gamma) X(t-\gamma)d\gamma - \Sigma V(t), \tag{2.3}$$

$$\dot{Q}(t) = \Psi X(t) - \Lambda Q(t) - \beta X(t)Q(t). \tag{2.4}$$

The uninfected cells are become infected at rate $H_1(V(t),U(t)) + H_2(X(t),U(t))$. Denote $y_n = e^{-\beta_1\gamma} g_1(\gamma), z_n = \int_0^{f_1} y_n d\gamma$. Define $W_1(U) = \lim_{V\to 0^+} \frac{H_1(V,U)}{V} = \frac{\partial}{\partial V} H_1(0,U), W_2(U) = \lim_{X\to 0^+} \frac{H_1(X,U)}{X} = \frac{\partial}{\partial X} H_2(0,U)$. Functions H_1 and H_2 satisfy the following conditions:

(A1) $H_i(V,U)$ is continuously differentiable, $H_i(V,U) > 0$, and $H_i(V,0) = 0, H_i(0,U) = 0$ for all $V,U > 0$ and $i = 1,2$,

(A2) $\frac{\partial H_i(V,U)}{\partial V}, \frac{\partial H_i(V,U)}{\partial U} > 0$ for all $V,U \geq 0$,

(A3) $W_i(U) > 0, \acute{W}_i(U) > 0$,for all $U > 0, i = 1,2$,

(A4) $\frac{\partial}{\partial V}\left(\frac{H_i(V,U)}{V}\right) \leq 0$, for all $V > 0, i = 1,2$.

The initial condition of (2.1)-(2.4) are

$$\begin{aligned} U(r) &= \psi_1(r), \qquad X(r) = \psi_2(r), \\ V(r) &= \psi_3(r), \qquad Q(r) = \psi_4(r), \\ \psi_i(r) &\geq 0, r \in [-\lambda, 0], \quad i = 1,2,3,4, \end{aligned} \tag{2.5}$$

where, $\lambda = \max\{f_1, f_2\}$, $\psi_i \in C([-\lambda, 0], \mathbb{R}_{\geq 0})$ and C is the Banach space of continuous functions mapping from $[-\lambda, 0]$ to $\mathbb{R}_{\geq 0}$ with the norm $\|\psi_i\| = \sup_{-\lambda \leq \theta \leq 0} |\psi_i(\theta)|$ for $\psi_i \in C,\ i = 1,2,...,6$. We note that model (2.1)-(2.4) with initial conditions (2.5) has a unique solution. All parameters of model (2.1)-(2.4) are positive.

2.1. **Basic properties.** We will analyze the non-negativity and finiteness of model (2.1)-(2.4) solutions in this subsection:

Lemma 2.1. *There is a positively invariant compact set for the model (2.1)-(2.4).*

$$\Omega_1 = \left\{(U, X, V, Q) \in \mathbb{R}^4_{\geq 0} : 0 \leq U, X \leq N_2, 0 \leq V \leq N_3, 0 \leq Q \leq N_4\right\}. \tag{2.6}$$

Proof. It is obvious that

$$U|_{(U=0)} = \Upsilon > 0,$$

$$\begin{aligned} X(t) &= \int_0^t e^{-\int_z^t (\Theta + CQ(t))dt} \int_0^{f_1} e^{-\beta_1\gamma} y_1(\gamma) \left[H_1(V(t-\gamma), U(t-\gamma))\right. \\ &\quad \left.+ H_2(X(t), U(t))\right] d\gamma + \psi_2(0) e^{-\int_0^t (\Theta + CQ(t))dt} \\ &\geq 0, \\ V(t) &= \psi_3(0)e^{-\Sigma t} + \Omega \int_0^t e^{-\Sigma(t-z)} \int_0^{f_2} e^{-\beta_2\gamma} X(t-\gamma) d\gamma dz \geq 0, \\ Q(t) &= \int_0^t e^{-\int_z^t (\Lambda + \beta X(t))dt} \Psi X(t) d\gamma + \psi_4(0) e^{-\int_0^t (\Lambda + \beta X(t))dt}. \end{aligned}$$

This is proof that the model (2.1)-(2.4) is positively invariant property of $\mathbb{R}^4_{\geq 0}$.

Let $C_1 = \int_0^{f_1} y_1(\gamma) U(t-\gamma) d\gamma + X$,

$$\begin{aligned} \dot{C}_1 &= \left(\int_0^{f_1} y_1(\gamma) \left\{\Upsilon - \Phi U(t-\gamma) - \left[H_1(V(t-\gamma), U(t-\gamma)) + H_2(X(t-\gamma), U(t-\gamma))\right]\right\} d\gamma\right) \\ &\quad + \int_0^{f_1} y_1(\gamma) \left[H_1(V(t-\gamma), U(t-\gamma)) + H_2(X(t-\gamma), U(t-\gamma))\right] d\gamma - \Theta X(t) - CX(t)Q(t) \\ &= \Upsilon z_1 - \Phi \int_0^{f_1} y_1(\gamma) U(t-\gamma) d\gamma - \Theta X(t) - CX(t)Q(t) \\ &\leq \Upsilon z_1 - \sigma_1 \left(\int_0^{f_1} y_1(\gamma) U(t-\gamma) d\gamma + X(t)\right) \end{aligned}$$

$$\leq \Upsilon z_1 - \sigma_1 C_1,$$

where, $\sigma_1 = \min\{\Phi, \Theta\}$. Then $\lim_{t\to\infty}\sup C_1(t) \leq N_1$, $N_1 = \frac{\Upsilon z_1}{\sigma_1}$. It follows that $0 \leq \lim_{t\to\infty}\sup U(t)$ and $\lim_{t\to\infty}\sup X(t) \leq N_1$ for all $t \geq 0$. Moreover, let $C_2 = \frac{\Theta}{2\Omega}V + \frac{\Theta}{4\Psi}Q$, then

$$\begin{aligned}\dot{C}_2 &= \frac{\Theta}{2\Omega}\left(\Omega\int_0^{f_2} y_2(\gamma)X(t-\gamma)d\gamma - \Sigma V(t)\right) + \frac{\Theta}{4\Psi}\left(\Psi X(t) - \Lambda Q(t) - \beta X(t)Q(t)\right)\\ &= \frac{\Theta}{2}z_2N_1 + \frac{\Theta}{4}N_1 - \frac{\Theta\beta}{4\Psi}X(t)Q(t) - \frac{\Theta\Sigma}{2\Omega}V(t) - \frac{\Theta\Lambda}{4\Psi}Q(t)\\ &\leq \frac{\Theta}{2}z_2N_1 + \frac{\Theta}{4}N_1 - \frac{\Theta\Sigma}{2\Omega}V(t) - \frac{\Theta\Lambda}{4\Psi}Q(t)\\ &\leq \frac{\Theta}{2}z_2N_1 + \frac{\Theta}{4}N_1 - \sigma_2C_2,\end{aligned}$$

where, $\sigma_2 = \min\{\Sigma, \Lambda\}$. Then $\lim_{t\to\infty}\sup C_2(t) \leq N_2$, $N_2 = \frac{\frac{\Theta}{2}z_2N_1 + \frac{\Theta}{4}N_1}{\sigma_2}$. It follows that $0 \leq \lim_{t\to\infty}\sup V(t) \leq N_3$ and $0 \leq \lim_{t\to\infty}\sup Q(t) \leq N_4$ for all $t \geq 0$, where $N_3 = \frac{2\Omega N_2}{\Theta}$ and $N_4 = \frac{4\Psi N_2}{\Theta}$. This prove the boundedness of U, X, V and Q. □

The next lemma will introduce the equilibrium existence for the model (2.1)-(2.4).

Lemma 2.2. *Assume that conditions A1 through A4 have been satisfied, and define $\mathcal{R}_0 > 0$ is the basic reproduction number of model (2.1)-(2.4).*

(i) if $\mathcal{R}_0 \leq 1$, then only one equilibrium Γ_0 exists,

(ii) if $\mathcal{R}_0 > 1$, therefore two equilibria Γ_0 and Γ_1 exist.

Proof. The equilibria satisfy the following equations

$$0 = \Upsilon - \Phi U - \left[H_1(V,U) + H_2(X,U)\right], \tag{2.7}$$

$$0 = z_1\left[H_1(V,U) + H_2(X,U)\right] - \Theta X - CXQ, \tag{2.8}$$

$$0 = z_2\Omega X - \Sigma V, \tag{2.9}$$

$$0 = \Psi X - \Lambda Q - \beta XQ, \tag{2.10}$$

where $z_n = \int_0^\infty \delta(\gamma - \gamma_n))e^{-\gamma\theta_n}d\gamma = e^{-\gamma_n\theta_n}$ $n = 1, 2, 3$. Clear, from Eqs. (2.7)-(2.10) we obtain that the model has uninfected equilibrium $\Gamma_0 = (U_0, 0, 0, 0)$, such that $U_0 = \frac{\Upsilon}{\Phi}$. Also, if $X \neq 0$ we can define another equilibrium $\Gamma = (U, X, V, Q)$ that has satisfied the following equation

$$0 = \frac{z_1\left[H_1(V,U) + H_2(X,U)\right]}{X} - \Theta - CQ,$$

where

$$V = \frac{z_2\Omega X}{\Sigma}, \quad Q = \frac{\Psi X}{\beta X + \Lambda},$$

and U has satisfied the following equation

$$0 = \Upsilon - \Phi U - \left[H_1(V,U) + H_2(X,U)\right],$$

define a function H on $[0,\infty)$ by

$$G(X)=\frac{z_1\left[H_1(V,U)+H_2(X,U)\right]}{X}-\Theta-CQ. \tag{2.11}$$

From Eq (2.11) and the boundedness of H_1 and H_2 we obtain $\lim_{X\to\infty}\frac{H_1(V,U)}{X}=\lim_{X\to\infty}\frac{H_2(X,U)}{X}=0$. Therefore $\lim_{X\to\infty}G(X)=-\Theta-\dfrac{\Psi C}{\beta}<0$ and $\lim_{X\to 0}G(X)=\left(\frac{z_2z_1\Omega}{\Sigma}\frac{\partial}{\partial X}H_1(0,U_0)+z_1\frac{\partial}{\partial X}H_2(0,U_0)\right)-\Theta>0$. Hence there exists $X_1\in(0,\infty)$ and from Eqs. (2.7)-(2.10), we have $V_1=\dfrac{z_2\Omega X_1}{\Sigma}>0$ and $Q_1=\dfrac{\Psi X_1}{\beta X_1+\Lambda}>0$ when $\Theta\left[\left(\frac{z_2z_1\Omega}{\Theta\Sigma}\frac{\partial}{\partial X}H_1(0,U_0)+\frac{z_1}{\Theta}\frac{\partial}{\partial X}H_2(0,U_0)\right)-1\right]>0$. Consequently, the basic infection reproduction number $\mathcal{R}_0$ can be defined as:

$$\mathcal{R}_0=\mathcal{R}_{01}+\mathcal{R}_{02}, \tag{2.12}$$

where $\mathcal{R}_{01}=\frac{z_2z_1\Omega}{\Theta\Sigma}\frac{\partial}{\partial X}H_1(0,U_0)$ and $\mathcal{R}_{02}=\frac{z_1}{\Theta}\frac{\partial}{\partial X}H_2(0,U_0)$. It implies that $\Gamma_1=(U_1,X_1,V_1,Q_1)$ exists if $\mathcal{R}_0>1$. □

2.2. **Global characteristics.** In the next subsection, we will study the global stability of equilibria of the model (2.1)-(2.4) by generating appropriate Lyapunov function. Define a function $g:(0,\infty)\to[0,\infty)$ as $g(v)=v-1-\ln v$.

Theorem 2.1. *For model (2.1)-(2.4), if $\mathcal{R}_0<1$, then Γ_0 is globally asymptotically stable (GAS).*

Proof. Let us create a function $Y_1(U,X,V,Q)$ as:

$$\begin{aligned}Y_1(U,X,V,Q)&=z_1\left(U-U_0-\int_{U_0}^{U}\frac{W_1(U_0)}{W_1(U)}d\theta\right)+X\\&+\int_0^{f_1}y_1(\gamma)\int_0^{\gamma}\left[H_1(V(t-\eta),U(t-\eta))+H_2(X(t-\eta),U(t-\eta))\right]d\eta d\gamma\\&+\frac{\Theta\mathcal{R}_{01}}{z_2}\int_0^{f_2}y_2(\gamma)\int_0^{\gamma}X(t-\eta)\,d\eta d\gamma+\frac{\Theta\mathcal{R}_{01}}{z_2\Omega}V+\frac{\Theta(1-\mathcal{R}_0)}{\Psi}Q.\end{aligned}$$

Obviously, $Y_1(U_0,0,0,0)=0$ and $Y_1(U,X,V,Q)>0$ for all $U,X,V,Q>0$. By calculating $\dfrac{dY_1}{dt}$ along the model (2.1)-(2.4), we get

$$\begin{aligned}\frac{dY_1}{dt}&=z_1\left(1-\frac{W_1(U_0)}{W_1(U)}\right)\left[\Upsilon-\Phi U-(H_1(V,U)+H_2(X,U))\right]\\&+\int_0^{f_1}y_1(\gamma)\left[H_1(V(t-\gamma),U(t-\gamma))+H_2(X(t-\gamma),U(t-\gamma))\right]d\gamma-\Theta X-CXQ\\&+\int_0^{f_1}y_1(\gamma)\left[H_1(V(t),U(t))+H_2(X(t),U(t))\right]d\gamma\\&-\int_0^{f_1}y_1(\gamma)\left[H_1(V(t-\gamma),U(t-\gamma))+H_2(X(t-\gamma),U(t-\gamma))\right]d\gamma\end{aligned}$$

$$+\frac{\Theta}{z_2}\mathcal{R}_{01}\int_0^{f_2} y_2(\gamma)\left[X-X(t-\gamma)\right]d\gamma+\frac{\Theta\mathcal{R}_{01}}{z_2\Omega}\left(\Omega\int_0^{f_2} y_2(\gamma)X(t-\gamma)d\gamma-\Sigma V\right)$$
$$+\frac{\Theta(1-\mathcal{R}_0)}{\Psi}\left(\Psi X-\Lambda Q-\beta XQ\right)$$
$$=z_1\left(1-\frac{W_1(U)}{W_1(U_0)}\right)(\Upsilon-\Phi U)+\frac{z_1W_1(U_0)}{W_1(U)}\left(H_1(V,U)+H_2(X,U)\right)$$
$$-\Theta\mathcal{R}_0X+\frac{\Theta\mathcal{R}_{01}}{z_2}\int_0^{f_2} y_2(\gamma)Xd\gamma-\frac{\Sigma\Theta\mathcal{R}_{01}}{\Omega z_2}V$$
$$-\left(C+\frac{\beta\Theta(1-\mathcal{R}_0)}{\Psi}\right)XQ-\frac{\Theta(1-\mathcal{R}_0)\Lambda}{\Psi}Q.$$

$$\frac{dY_1}{dt}\leq z_1\left(1-\frac{W_1(U_0)}{W_1(U)}\right)(\Upsilon-\Phi U)+\frac{z_1W_1(U_0)}{W_1(U)}\left(W_1(U)V+W_2(U)X\right)$$
$$-\Theta\mathcal{R}_0X+\frac{\Theta\mathcal{R}_{01}}{z_2}\int_0^{f_2} y_2(\gamma)Xd\gamma-\frac{\Theta\mathcal{R}_{01}}{\Sigma\Omega z_2}V$$
$$-\left(C+\frac{\beta\Theta(1-\mathcal{R}_0)}{\Psi}\right)XQ-\frac{\Theta(1-\mathcal{R}_0)\Lambda}{\Psi}Q$$
$$\leq z_1\left(1-\frac{W_1(U_0)}{W_1(U)}\right)(\Upsilon-\Phi U)+z_1\left(W_1(U_0)V+W_2(U_0)X\right)$$
$$-\Theta\mathcal{R}_0X+\frac{\Theta\mathcal{R}_{01}}{z_2}\int_0^{f_2} y_2(\gamma)Xd\gamma-\frac{\Theta\Sigma\mathcal{R}_{01}}{\Omega z_2}V$$
$$-\left(C+\frac{\beta\Theta(1-\mathcal{R}_0)}{\Psi}\right)XQ-\frac{\Theta(1-\mathcal{R}_0)\Lambda}{\Psi}Q,$$
$$\leq z_1\left(1-\frac{W_1(U_0)}{W_1(U)}\right)(\Upsilon-\Phi U)+\left(\frac{\Theta\Sigma\mathcal{R}_{01}}{z_2\Omega}V+\Theta\mathcal{R}_{02}X\right)$$
$$+\frac{\Theta\mathcal{R}_{01}}{z_2}\int_0^{f_2} y_2(\gamma)Xd\gamma-\frac{\Theta\Sigma\mathcal{R}_{01}}{z_2\Omega}V$$
$$-\Theta\mathcal{R}_0X-\left(C+\frac{\beta\Theta(1-\mathcal{R}_0)}{\Psi}\right)XQ-\frac{\Theta(1-\mathcal{R}_0)\Lambda}{\Psi}Q.$$

From Remak 1 and using $\Upsilon=\Phi U_0$ and we obtain

$$\frac{dY_1}{dt}\leq \Upsilon z_1\left(1-\frac{W_1(U_0)}{W_1(U)}\right)\left(1-\frac{U}{U_0}\right)-\left(C+\frac{\beta\Theta(1-\mathcal{R}_0)}{\Psi}\right)XQ-\frac{\Theta(1-\mathcal{R}_0)\Lambda}{\Psi}Q.$$

We have we have $\left(1-\frac{W_1(U_0)}{W_1(U)}\right)\left(1-\frac{U}{U_0}\right)\leq 0$ from assumption A2. Obviously, if $\mathcal{R}_0<1$, then $\frac{dY_1}{dt}\leq 0$ for all $U,X,V,Q>0$. Moreover $\frac{dY_1}{dt}=0$ if and only if $U(t)=U_0$ and $Q(t)=0$. Let $\acute{\mathcal{D}}_0$ be largest invariant subset of $\mathcal{D}_0$ where $\mathcal{D}_0=\left\{(U,X,V,Q):\frac{dY_1}{dt}=0\right\}$. The solutions of the model (2.1)-(2.4) tend to $\acute{\mathcal{D}}_0$. For each element in $\acute{\mathcal{D}}_0$ we $U(t)=U_0$ and $Q(t)=0$. Hence, from Eq. (2.4) we obtain

$$\dot{Q}(t)=0=\Psi X(t)-\Lambda Q(t)-\beta X(t)Q(t),$$

thus $X(t) = 0$. Eq. (2.2) yields

$$\dot{X}(t) = 0 = H_1(V, U_0),$$

then $H_1(V(t)) = 0$ that yields $V(t) = 0$. It follows that $\acute{\mathcal{D}}_0$ has a single point which is $(U_0, 0, 0, 0)$. By using LaSalle's invariance principle (L.I.P), Γ_0 is GAS when $\mathcal{R}_0 < 1$.

Theorem 2.2. *For the model (2.1)-(2.4), Γ_1 is GAS when $\mathcal{R}_0 > 1$.*

Proof. By constructing a function $Y_2(U, X, V, Q)$ as:

$$\begin{aligned}
Y_2(U,X,V,Q) &= z_1\left(U - U_1 - \int_{U_1}^{U} \frac{H_1(V_1,U_1)}{H_1(V_1,U)} d\theta\right) + X_1 g\left(\frac{X}{X_1}\right) \\
&+ \int_0^{f_1} y_1(\gamma) \int_0^{\gamma} \Bigg[H_1(V_1,U_1) G\left(\frac{H_1(V(t-\eta),U(t-\eta))}{H_1(V_1,U_1)}\right) \\
&+ H_2(X_1,U_1) G\left(\frac{H_2(X(t-\eta),U(t-\eta))}{H_2(X_1,U_1)}\right)\Bigg] d\eta d\gamma \\
&+ \frac{z_1 H_1(V_1,U_1)}{\Sigma V_1} \int_0^{f_2} y_2(\gamma) \int_0^{\gamma} G\left(\frac{\Omega X(t-\eta)}{X_1}\right) d\eta d\gamma \\
&+ \frac{z_1 H_1(V_1,U_1)}{\Sigma V_1} V_1 g\left(\frac{V}{V_1}\right) + \frac{C}{2(\Psi - \beta Q_1)}(Q - Q_1)^2.
\end{aligned}$$

Note that $\Psi - \beta Q_1 = \frac{\Lambda Q_1}{X_1} > 0$. Obviously $Y_2(U, X, V, Q) > 0$ for all $U, X, V, Q > 0$ and $Y_2(U_1, X_1, V_1, Q_1) = 0$. Moreover

$$\begin{aligned}
\frac{dY_2}{dt} &= z_1\left(1 - \frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)[\Upsilon - \Phi U - [H_1(V,U) + H_2(X,U)]] \\
&+ \left(1 - \frac{X_1}{X}\right)\left[\int_0^{f_1} y_1(\gamma)\,[H_1(V(t-\gamma),U(t-\gamma)) + H_2(X(t-\gamma),U(t-\gamma))] - \Theta X - CXQ\right] \\
&+ \int_0^{f_1} y_1(\gamma) H_1(V_1,U_1)\left[\frac{H_1(V,U)}{H_1(V_1,U_1)} - \frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V_1,U_1)} + \ln\left(\frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V,U)}\right)\right] \\
&+ \int_0^{f_1} y_1(\gamma) H_2(X_1,U_1)\left[\frac{H_2(X,U)}{H_2(X_1,U_1)} - \frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X_1,U_1)} + \ln\left(\frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X,U)}\right)\right] \\
&+ \frac{z_1 H_1(V_1,U_1)}{\Sigma V_1} \int_0^{f_2} y_2(\gamma)\left[\Omega X - \Omega X(t-\gamma) + \ln\frac{X(t-\gamma)}{X}\right] \\
&+ \frac{z_1 H_1(V_1,U_1)}{\Sigma V_1}\left(1 - \frac{V_1}{V}\right)(\Omega X(t-\gamma) - \Sigma V) + \frac{C(Q - Q_1)}{(\Psi - \beta Q_1)}(\Psi X - \Lambda Q - \beta XQ) \\
&= z_1\left(1 - \frac{H_1(V_1,U_1))}{H_1(V_1,U)}\right)(\Upsilon - \Phi U) + z_1\left(\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)[H_1(V(t),U(t)) + H_2(X(t),U(t))]
\end{aligned}$$

$$- \Theta\left(X-X_1\right) - CQ\left(X-X_1\right) - \int_0^{f_1} y_1(\gamma)\left[H_1(V(t-\gamma),U(t-\gamma)) + H_2(X(t-\gamma),U(t-\gamma))\right]d\gamma\frac{X_1}{X}$$
$$+ \frac{z_1 H_1(V_1,U_1)}{\Sigma V_1}\left(\Omega X - \Sigma V - \frac{\Omega V_1 X(t-\gamma)}{V} + \Sigma V_1\right)$$
$$+ \frac{C(Q-Q_1)}{(\Psi - hQ_1)}\left(\Psi X - \Lambda Q - \beta X Q\right). \tag{2.13}$$

Applying the equilibrium conditions for Γ_1:

$$\begin{aligned}
\Upsilon - \Phi U_1 &= H_1(V_1,U_1) + H_2(X_1,U_1)\\
z_1\left[H_1(V_1,U_1) + H_2(X_1,U_1)\right] &= \Theta X_1 + C X_1 Q_1,\\
z_2 \Omega X_1 &= \Sigma V_1,\\
\Psi X_1 &= \Lambda Q_1 + \beta X_1 Q_1,
\end{aligned}$$

we get

$$\begin{aligned}
\frac{dY_2}{dt} &= \Phi U_1 z_1\left(1-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)\left(1-\frac{U}{U_1}\right) + z_1\left(\frac{H_1(V,U)}{H_1(V_1,U)} - \frac{V}{V_1}\right)\left[H_1(V_1,U_1)\right]\\
&+ z_1\left(\frac{H_1(V_1,U_1)H_2(X,U)}{H_1(V_1,U)H_2(X_1,U_1)} - \frac{X}{X_1}\right)\left[H_2(X_1,U_1)\right]\\
&+ z_1 H_1(V_1,U_1)\left[2 - \frac{H_1(V_1,U_1)}{H_1(V_1,U)} - \frac{H_1(V(t-\gamma),U(t-\gamma))X_1}{H_1(V_1,U_1)X} - \frac{X}{X_1}\right.\\
&\left.+ \ln\left(\frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V,U)}\right)\right] + z_1 H_2(X_1,U_1)\left[2 - \frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right.\\
&\left.- \frac{H_2(X(t-\gamma),U(t-\gamma))X}{H_2(X_1,U_1)X_1} + \ln\left(\frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X,U)}\right)\right]\\
&+ z_1 H_1(V_1,U_1)\left[\frac{X}{X_1} - \frac{V_1 X(t-\gamma)}{V X_1} + 1 + \ln\left(\frac{X(t-\gamma)}{X}\right)\right]\\
&- C\left(\frac{\Lambda + \beta X}{\Psi - \beta Q_1}\right)(Q-Q_1)^2.
\end{aligned} \tag{2.14}$$

Eq. (2.14) can be simplified as

$$\begin{aligned}
\frac{dY_2}{dt} &= \Phi U_1 z_1\left(1-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)\left(1-\frac{U}{U_1}\right) + z_1 H_1(V_1,U_1)\left(\frac{H_1(V,U)}{H_1(V_1,U)} - \frac{V}{V_1}\right)\\
&\times\left[1 - \frac{H_1(V_1,U)}{H_1(V,U)}\right]\\
&+ z_1 H_2(X_1,U_1)\left(\frac{L(X,U)}{L(X_1,U_1)} - \frac{X}{X_1}\right)\left(1 - \frac{L(X_1,U_1)}{L(X,U)}\right)\\
&+ z_1 H_1(V_1,U_1)\left[4 - \frac{H_1(V_1,U_1)}{H_1(V_1,U)} - \frac{H_1(V(t-\gamma),U(t-\gamma))X}{H_1(V_1,U_1)X_1} - \frac{V_1 X(t-\gamma)}{V X_1}\right.\\
&\left.+ \ln\left(\frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V,U)}\right) + \ln\left(\frac{X(t-\gamma)}{X}\right) - \frac{V H_1(V_1,U)}{V_1 H_1(V,U)}\right]
\end{aligned}$$

$$+ z_1 H_2(X_1,U_1)\left[3 - \frac{H_1(V_1,U_1)}{H_1(V_1,U)} - \frac{H_2(X(t-\gamma),U(t-\gamma))X_1}{H_2(X_1,U_1)X} - \frac{XL(X_1,U_1)}{X_1L(X,U)} + \ln\left(\frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X,U)}\right)\right] - C\left(\frac{\Lambda+\beta X}{\Psi-\beta Q_1}\right)(Q-Q_1)^2.$$

Since

$$\ln\left(\frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V,U)}\right) = \ln\left(\frac{H_1(V(t-\gamma),U(t-\gamma))X_1}{H_1(V_1,U_1)X}\right) + \ln\left(\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right) + \ln\frac{V_1X(t-\gamma)}{VX_1} + \ln\left(\frac{VH_1(V_1,U)}{V_1H_1(V,U)}\right) - \ln\left(\frac{X(t-\gamma)}{X}\right),$$

$$\begin{aligned}\ln\left(\frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X,U)}\right) &= \ln\frac{H_1(V_1,U_1)}{H_1(V_1,U)} + \frac{H_2(X(t-\gamma),U(t-\gamma))X_1}{H_2(X_1,U_1)X} + \ln\frac{XL(X_1,U_1)}{X_1L(X,U)}\\ &= \ln\frac{H_1(V_1,U_1)}{H_1(V_1,U)} + \frac{H_2(X(t-\gamma),U(t-\gamma))X_1}{H_2(X_1,U_1)X}\\ &\quad + \ln\frac{H_1(V_1,U)H_2(X_1,U_1)X}{H_1(V_1,U_1)H_2(X,U)X_1},\end{aligned}$$

we get

$$\begin{aligned}\frac{dY_2}{dt} &= \Phi U_1 z_1\left(1-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)\left(1-\frac{U}{U_1}\right) + z_1H_1(V_1,U_1)\left(\frac{H_1(V,U)}{H_1(V_1,U)} - \frac{V}{V_1}\right)\left[1-\frac{H_1(V_1,U)}{H_1(V,U)}\right]\\ &\quad z_1H_2(X_1,U_1)\left(\frac{L(X,U)}{L(X_1,U_1)} - \frac{X}{X_1}\right)\left[1-\frac{L(X_1,U_1)}{L(X,U)}\right] + z_1H_1(V_1,U_1)\left[G\left(\frac{VH_1(V_1,U)}{V_1H_1(V,U)}\right)\right]\\ &\quad + z_1H_1(V_1,U_1)\left[G\left(\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right) + G\left(\frac{H_1(V(t-\gamma),U(t-\gamma))X}{H_1(V_1,U_1)X_1}\right) + G\left(\frac{V_1X(t-\gamma)}{VX_1}\right)\right]\\ &\quad + z_1H_2(X_1,U_1)\left[G\left(\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right) + G\left(\frac{H_2(X(t-\gamma),U(t-\gamma))X}{H_2(X_1,U_1)X_1}\right) + G\left(\frac{XL(X_1,U_1)}{X_1L(X,U)}\right)\right]\\ &\quad - C\left(\frac{\Lambda+\beta X}{\Psi-\beta Q_1}\right)(Q-Q_1)^2.\end{aligned}$$

Using Remak 2 we get

$$\left(1-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)\left(1-\frac{U}{U_1}\right) \le 0,$$

and

$$\left(\frac{H_1(V,U)}{V} - \frac{H_1(V_1,U)}{V_1}\right)[H_1(V,U) - H_1(V_1,U)] \le 0,$$

it follows

$$\left(\frac{H_1(V,U)}{H_1(V_1,U)} - \frac{V}{V_1}\right)\left[1-\frac{H_1(V_1,U)}{H_1(V,U)}\right] \le 0.$$

Hence, we obtain that $\frac{dY_2}{dt} \le 0$ and $\frac{dY_2}{dt} = 0$ at the point (U_1, X_1, V_1, Q_1). Let $\acute{\mathcal{D}}_1$ the largest invariant subset of the set $\left\{(U,X,V,Q) : \frac{dY_2}{dt} = 0\right\}$. Thus, the solutions of model tend to $\acute{\mathcal{D}}_1$. It is clear that $\acute{\mathcal{D}}_1$ has unique point that is Γ_1. Thus, the global asymptotic stable of Γ_1 obtains from L.I.P. □

3. Model with latently infected cells

In this section, we present a pathogen dynamics model with general pathogen-to-cell and cell-to-cell incidence as follows:

$$\dot{U}(t) = \Upsilon - \Phi U(t) - \left[H_1(V(t), U(t)) + H_2(X(t), U(t))\right], \tag{3.1}$$

$$\begin{aligned}\dot{L}(t) &= (1-n)\int_0^{f_1} e^{-\beta_1\gamma} g_1(\gamma)\left[H_1(V(t-\gamma), U(t-\gamma))\right.\\ &\quad \left.+H_2(X(t-\gamma), U(t-\gamma))\right] d\gamma - (d+b)L(t),\end{aligned} \tag{3.2}$$

$$\begin{aligned}\dot{X}(t) &= n\int_0^{f_2} e^{-\beta_2\gamma} g_2(\gamma)\left[H_1(V(t-\gamma), U(t-\gamma)) + H_2(X(t-\gamma), U(t-\gamma))\right] d\gamma\\ &\quad - \Theta X(t) + bL(t) - CX(t)Q(t),\end{aligned} \tag{3.3}$$

$$\dot{V}(t) = \Omega\int_0^{f_3} e^{-\beta_3\gamma} g_2(\gamma) X(t-\gamma) d\gamma - \Sigma V(t), \tag{3.4}$$

$$\dot{Q}(t) = \Psi X(t) - \Lambda Q(t) - \beta X(t)Q(t), \tag{3.5}$$

where, $L(t)$ and $X(t)$ are the concentration of the latently and productivity infected cells at time t, respectively. The fractions $(1-n)$ and n with $0 < n \leq 1$ are the probabilities that upon infection, uninfected cells will become either latently infected or productively infected, b is the average number of latently infected cells become productively infected cells and d is death rate constant of the latently infected cells. All other parameters have the same meaning as model (5)-(8).

The initial condition of (3.1)-(3.5) are

$$\begin{aligned} &U(r) = \psi_1(r), \qquad L(r) = \psi_2(r),\\ &X(r) = \psi_3(r), \qquad V(r) = \psi_4(r),\\ &Q(r) = \psi_5(r),\\ &\psi_i(r) \geq 0, r \in [-\lambda, 0], \quad k = 1, 2, ..., 5.\end{aligned} \tag{3.6}$$

where, $\lambda = \max\{f_1, f_2, f_3\}$, $\psi_i \in C([-\lambda, 0], \mathbb{R}_{\geq 0})$ and C is the Banach space of continuous functions mapping from $[-\lambda, 0]$ to $\mathbb{R}_{\geq 0}$ with the norm $\left\|\psi_i\right\| = \sup_{-\lambda\leq\theta\leq 0}\left|\psi_i(\theta)\right|$ for $\psi_i \in C,\ i = 1, 2, ..., 6$. We note that model (3.1)-(3.5) with initial conditions (3.6) has a unique solution. All parameters of model (3.1)-(3.5) are positive.

3.1. **Basic properties.**

In this subsection we will discuss the non-negativity and finiteness of model (3.1)-(3.5) solutions:

Lemma 3.1. *For the model (3.1)-(3.5), a positively invariant compact set exists*

$$\Omega_1 = \left\{(U, L, X, V, Q) \in \mathbb{R}^4_{\geq 0} : 0 \leq U, L, X \leq N_2, 0 \leq V \leq N_3, 0 \leq Q \leq N_4\right\}. \tag{3.7}$$

Proof. Clearly

$$\dot{U}|_{(U=0)} = \Upsilon > 0,$$

$$L(t) = (1-n)\int_0^t e^{-(d+b)(t-z)}\int_0^{f_1} e^{-\beta_1\gamma} g_1(\gamma)\left[H_1(V(t-\gamma),U(t-\gamma))\right.$$
$$\left.+H_2(X(t-\gamma),U(t-\gamma))\right]d\gamma + \psi_2(0)e^{-(d+b)t} \geq 0,$$
$$X(t) = \int_0^t e^{-\int_z^t(\Theta+CQ(t))dt}\int_0^{f_2} ne^{-\beta_2\gamma}y_2(\gamma)\left[H_1(V(t-\gamma),U(t-\gamma))\right.$$
$$\left.+H_2(X(t),U(t))\right] + bL(t)d\gamma + \psi_3(0)e^{-\int_0^t(\Theta+CQ(t))dt} \geq 0,$$
$$V(t) = \psi_4(0)e^{-\Sigma t} + \Omega\int_0^t e^{-\Sigma(t-z)}\int_0^{f_2} e^{-\beta_2\gamma}X(t-\gamma)d\gamma dz \geq 0,$$
$$Q(t) = \int_0^t e^{-\int_z^t(\Lambda+\beta X(t))dt}\Psi X(t)d\gamma + \psi_5(0)e^{-\int_0^t(\Lambda+\beta X(t))dt} \geq 0,$$

This is an evidence for the positively invariant property of $\mathbb{R}^5_{\geq 0}$ for the model (3.1)-(3.5). Let $C_1 = (1-n)\int_0^{f_1} y_1(\gamma)U(t-\gamma)d\gamma + n\int_0^{f_2} y_2(\gamma)U(t-\gamma)d\gamma + L + X$,

$$\dot{C}_1 = (1-n)\int_0^{f_1} y_1(\gamma)\{\Upsilon - \Phi U(t-\gamma) - [H_1(V(t-\gamma),U(t-\gamma)) + H_2(X(t-\gamma),U(t-\gamma)]\}d\gamma$$
$$+n\int_0^{f_2} y_2(\gamma)\{\Upsilon - \Phi U(t-\gamma) - [H_1(V(t-\gamma),U(t-\gamma)) + H_2(X(t-\gamma),U(t-\gamma)]\}d\gamma$$
$$+(1-n)\int_0^{f_1} y_1(\gamma)\left[H_1(V(t-\gamma),U(t-\gamma)) + H_2(X(t-\gamma),U(t-\gamma)\right]d\gamma - (d+b)L(t)$$
$$+n\int_0^{f_2} y_2(\gamma)\left[H_1(V(t-\gamma),U(t-\gamma)) + H_2(X(t-\gamma),U(t-\gamma))\right]d\gamma - \Theta X(t)$$
$$-CX(t)Q(t) + bL(t).$$

Then

$$\begin{aligned}\dot{C}_1 &= \Upsilon(1-n)z_1 + \Upsilon nz_2 - \Phi\int_0^{f_1} y_1(\gamma)U(t-\gamma)d\gamma \\ &- \Phi\int_0^{f_2} y_2(\gamma)U(t-\gamma)d\gamma - \Theta X(t) - CX(t)Q(t) - dL(t) \\ &\leq \Upsilon(1-n)z_1 + \Upsilon nz_2 - \Phi\int_0^{f_1} y_1(\gamma)U(t-\gamma)d\gamma \\ &- \Phi\int_0^{f_2} y_2(\gamma)U(t-\gamma)d\gamma - \Theta X(t) - dL(t) \\ &\leq \Upsilon(1-n)z_1 + \Upsilon nz_2 - \sigma_2 C_1,\end{aligned}$$

where, $\sigma_1 = \min\{\Phi,\Theta,d\}$. Then $\lim_{t\to\infty}\sup C(t) \leq N_1$, $N_1 = \frac{\Upsilon(1-n)z_1+\Upsilon nz_2}{\sigma_2}$. It follows that $0 \leq \lim_{t\to\infty}\sup U(t), \lim_{t\to\infty}\sup L(t), \lim_{t\to\infty}\sup X(t) \leq N_1$, for all $t \geq 0$. Moreover, let $C_2 = \frac{\Theta}{2\Omega}V + \frac{\Theta}{4\Psi}Q$

$$\dot{C}_2 = \frac{\Theta}{2\Omega}\left(\Omega\int_0^{f_2} y_2(\gamma)X(t-\gamma)d\gamma - \Sigma V(t)\right) + \frac{\Theta}{4\Psi}\left(\Psi X(t) - \Lambda Q(t) - \beta X(t)Q(t)\right)$$

$$\begin{aligned}\dot{C}_2 &\leq \frac{\Theta z_2}{2}N_1 + N_1 - \Phi\int_0^{f_1} y_1(\gamma)U(t-\gamma)d\gamma \\ &- \frac{\Theta\Sigma}{2\Omega}V(t) - \frac{\Theta\beta}{4\Psi}X(t)Q(t) - \frac{\Theta\Lambda}{4\Psi}Q(t) \\ &\leq \frac{\Theta}{2}z_2N_1 + \frac{\Theta}{4}X(t) - \sigma_2C_2,\end{aligned}$$

where $\sigma_2 = \min\{\Sigma, \Lambda\}$. Then $\lim_{t\to\infty}\sup C(t) \leq N_2$, $N_2 = \frac{\frac{\Theta z_2}{2}N_1+N_1}{\sigma_2}$. It follows that $0 \leq \lim_{t\to\infty}\sup V(t) \leq N_3$ and $0 \leq \lim_{t\to\infty}\sup Q(t) \leq N_4$ for all $t \geq 0$ if, where $N_3 = \frac{2\Omega N_2}{\Theta}$ and $N_4 = \frac{4\Psi N_2}{\Theta}$. This prove the boundedness of U, L, X, V and Q. □

The equilibrium's existence for the model (3.1)-(3.5) will be introduced in the following lemma.

Lemma 3.2. *Suppose that Assumption A1-A4 are satisfied and let $\mathcal{R}_0 > 0$ be the basic reproduction number of model (3.1)-(3.5).*

(i) if $\mathcal{R}_0 \leq 1$, then only one equilibrium Γ_0 exists,

(ii) if $\mathcal{R}_0 > 1$, therefore two equilibria Γ_0 and Γ_1 exist.

Proof. To calculate the equilibria we let

$$0 = \Upsilon - \Phi U - \left[H_1(V,U) + H_2(X,U)\right], \tag{3.8}$$

$$0 = z_1(1-n)\left[H_1(V,U) + H_2(X,U)\right] - (d+b)L(t), \tag{3.9}$$

$$0 = z_2 n\left[H_1(V,U) + H_2(X,U)\right] - \Theta X - CXQ, \tag{3.10}$$

$$0 = z_3\Omega X - \Sigma V, \tag{3.11}$$

$$0 = \Psi X - \Lambda Q - \beta XQ. \tag{3.12}$$

From Eqs. (3.8)-(3.12) we find that the model has uninfected equilibrium $\Gamma_0 = (U_0, 0, 0, 0, 0)$, where $U_0 = \dfrac{\Upsilon}{\Phi}$ and If $X \neq 0$ we can define another equilibrium $\Gamma = (U, L, X, V, Q)$ satisfying the following equation

$$0 = z_1z_2(1-n)\left[H_1(V,U) + H_2(X,U)\right] - (d+b)z_2L,$$

$$0 = z_1z_2n\left[H_1(V,U) + H_2(X,U)\right] - \Theta z_1X + bz_1L - Cz_1XQ,$$

$$0 = z_1z_2\left[H_1(V,U) + H_2(X,U)\right] - \Theta z_1X - Cz_1XQ + \left(bz_1 - (d+b)z_2\right)L,$$

such that

$$\frac{z_1(1-n)\left[H_1(V,U) + H_2(X,U)\right]}{(d+b)} = L(t),$$

$$0=\frac{bz_1^2\,(1-n)\,[H_1(V,U)+H_2(X,U)]}{(d+b)}+nz_1z_2\,[H_1(V,U)+H_2(X,U)]-\Theta z_1X-Cz_1XQ,$$
$$0=\frac{bz_1^2\,(1-n)\,[H_1(V,U)+H_2(X,U)]}{(d+b)X}+\frac{nz_1z_2}{X}\,[H_1(V,U)+H_2(X,U)]-\Theta z_1-Cz_1Q,$$
$$V=\frac{z_3\Omega X}{\Sigma},\quad Q=\frac{\Psi X}{\beta X+\Lambda},$$

and U satisfy the following equation

$$0=\Upsilon-\Phi U-[H_1(V,U)+H_2(X,U)],$$

define a function H on $[0,\infty)$ by

$$G(X)=\frac{bz_1^2\,(1-n)\,[H_1(V,U)+H_2(X,U)]}{(d+b)X}+\frac{nz_1z_2}{X}\,[H_1(V,U)+H_2(X,U)]-\Theta z_1-Cz_1Q,\quad (3.13)$$

Eq (3.13) and the boundedness of H_1 and H_2 imply that $\lim_{X\to\infty}\frac{H_1(V,U)}{X}=\lim_{X\to\infty}\frac{H_2(X,U)}{X}=0$. Hence $\lim_{X\to\infty}G(X)=-\Theta z_1-\dfrac{\Psi z_1C}{\beta}<0$ and $\lim_{X\to 0}G(X)=\frac{bz_1^2(1-n)\left[\frac{z_3\Omega}{\Sigma}\frac{\partial}{\partial X}H_1(0,U_0)+\frac{\partial}{\partial X}H_2(0,U_0\right]}{(d+b)}+nz_1z_2\left[\frac{z_3\Omega}{\Sigma}\frac{\partial}{\partial X}H_1(0,U_0)+\frac{\partial}{\partial X}H_2(0,U_0\right]-\Theta z_1>0$. Consequently there exists $X_1\in(0,\infty)$ and from Eqs. (3.8)-(3.12), we have $V_1=\dfrac{z_3\Omega X_1}{\Sigma}>0$ and $Q_1=\dfrac{\Psi X_1}{\beta X_1+\Lambda}>0$ when $\Theta z_1\left[\frac{bz_1(1-n)}{(d+b)\Theta}\left[\frac{z_3\Omega}{\Sigma}\frac{\partial}{\partial X}H_1(0,U_0)+\frac{\partial}{\partial X}H_2(0,U_0)\right]+\frac{nz_2}{\Theta}\left[\frac{z_3\Omega}{\Sigma}\frac{\partial}{\partial X}H_1(0,U_0)+\frac{\partial}{\partial X}H_2(0,U_0)\right]-1\right]>0$. Thus, we can define the basic infection reproduction number $\mathcal{R}_0$ as:

$$\mathcal{R}_0=\mathcal{R}_{01}+\mathcal{R}_{02},\quad (3.14)$$

where $\mathcal{R}_{01}=\mathcal{R}_{11}+\mathcal{R}_{21}$, $\mathcal{R}_{02}=\mathcal{R}_{12}+\mathcal{R}_{22}$, $\mathcal{R}_{11}=\frac{nz_2}{\Theta}\frac{z_3\Omega}{\Sigma}\frac{\partial}{\partial X}H_1(0,U_0)$, $\mathcal{R}_{12}=\frac{nz_2}{\Theta}\frac{\partial}{\partial X}H_2(0,U_0)$, $\mathcal{R}_{21}=\frac{bz_1(1-n)}{(d+b)\Theta}\frac{z_3\Omega}{\Sigma}\frac{\partial}{\partial X}H_1(0,U_0)$ and $\mathcal{R}_{22}=\frac{bz_1(1-n)}{(d+b)\Theta}\frac{\partial}{\partial X}H_2(0,U_0)$. It follow that $\Gamma_1=(U_1,L_1,X_1,V_1,Q_1)$ exists if $\mathcal{R}_0>1$. □

3.2. **Global characteristics.** In the following subsection we are going to confirm the global stability of the model (3.1)-(3.5) equilibria by creating appropriate Lyapunov function.

Theorem 3.1. *For model (3.1)-(3.5), if $\mathcal{R}_0<1$, then Γ_0 is GAS.*

Proof. Define $Y_1(U,L,X,V,Q)$ as:

$$Y_1(U,L,X,V,Q)=\left(\frac{bz_1\,(1-n)}{(d+b)}+nz_2\right)\left(U-U_0-\int_{U_0}^{U}\frac{W_1(U_0)}{W_1(U)}d\theta\right)+\frac{b}{(d+b)}L+X$$
$$+\frac{b\,(1-n)}{(d+b)}\int_0^{f_1}y_1(\gamma)\int_0^{\gamma}[H_1(V(t-\eta),U(t-\eta))+H_2(X(t-\eta),U(t-\eta))]\,d\eta d\gamma$$
$$+n\int_0^{f_2}y_2(\gamma)\int_0^{\gamma}[H_1(V(t-\eta),U(t-\eta))+H_2(X(t-\eta),U(t-\eta))]\,d\eta d\gamma$$

$$+\frac{\Theta}{z_3}\{\mathcal{R}_{21}+\mathcal{R}_{11}\}\int\limits_0^{f_3} y_3(\gamma)\int\limits_0^{\gamma} X(t-\eta)\,d\eta d\gamma$$
$$+\frac{\Theta}{z_3\Omega}\{\mathcal{R}_{21}+\mathcal{R}_{11}\}V+\frac{\Theta(1-\mathcal{R}_0)}{\Psi}Q.$$

Clearly, $Y_1(U,X,V,Q)>0$ for all $U,X,V,Q>0$ and $Y_1(U_0,0,0,0)=0$. Calculating $\frac{dY_1}{dt}$ along the model (2.1)-(2.4), we get

$$\begin{aligned}
\frac{dY_1}{dt} &= \left(\frac{bz_1(1-n)}{(d+b)}+nz_2\right)\left(1-\frac{W_1(U_0)}{W_1(U)}\right)[\Upsilon-\Phi U-(H_1(V,U)+H_2(X,U))] \\
&+\frac{b(1-n)}{(d+b)}\int_0^{f_1} e^{-\beta_1\gamma}g_1(\gamma)\,[H_1(V(t-\gamma),U(t-\gamma))+H_2(X(t-\gamma),U(t-\gamma))]\,d\gamma \\
&-\frac{b(d+b)}{(d+b)}L(t)+n\int_0^{f_2} e^{-\beta_2\gamma}g_2(\gamma)\,[H_1(V(t-\gamma),U(t-\gamma))+H_2(X(t-\gamma),U(t-\gamma))]\,d\gamma \\
&-\Theta X(t)-CX(t)Q(t)+bL(t) \\
&+\frac{b(1-n)}{(d+b)}\int\limits_0^{f_1} y_1(\gamma)\,[H_1(V(t),U(t))+H_2(X(t),U(t))]\,d\gamma \\
&-\frac{b(1-n)}{(d+b)}\int\limits_0^{f_1} y_1(\gamma)\,[H_1(V(t-\gamma),U(t-\gamma))+H_2(X(t-\gamma),U(t-\gamma))]\,d\gamma \\
&+n\int\limits_0^{f_2} y_2(\gamma)\,[H_1(V(t),U(t))+H_2(X(t),U(t))]\,d\gamma \\
&-n\int\limits_0^{f_2} y_2(\gamma)\,[H_1(V(t-\gamma),U(t-\gamma))+H_2(X(t-\gamma),U(t-\gamma))]\,d\gamma \\
&+\frac{\Theta}{z_3}\{\mathcal{R}_{21}+\mathcal{R}_{11}\}\int_0^{f_3} y_3(\gamma)\,[X-X(t-\gamma)]\,d\gamma \\
&+\frac{\Theta}{z_3\Omega}\{\mathcal{R}_{21}+\mathcal{R}_{11}\}\left(\Omega\int_0^{f_3} y_3(\gamma)X(t-\gamma)d\gamma-\Sigma V(t)\right) \\
&+\frac{\Theta(1-\mathcal{R}_0)}{\Psi}(\Psi X-\Lambda Q-\beta XQ).
\end{aligned}$$

Using $\Upsilon=\Phi U_0$ and from Remak 1 we get

$$\frac{dY_1}{dt}\le\left(\frac{bz_1(1-n)}{(d+b)}+nz_2\right)\left(1-\frac{W_1(U_0)}{W_1(U)}\right)\left(1-\frac{U}{U_0}\right)-\left(C+\frac{\beta\Theta(1-\mathcal{R}_0)}{\Psi}\right)XQ-\frac{\Theta(1-\mathcal{R}_0)\Lambda}{\Psi}Q.$$

From assumption A2 we have we have $\left(1-\frac{W_1(U_0)}{W_1(U)}\right)\left(1-\frac{U}{U_0}\right)\le 0$. Clearly if $\mathcal{R}_0<1$, then $\frac{dY_1}{dt}\le 0$ for all $U,L,X,V,Q>0$. Moreover $\frac{dY_1}{dt}=0$ if and only if $U(t)=U_0$ and $Q(t)=0$. Let

$\mathcal{D}_0 = \left\{(U, L, X, V, Q) : \dfrac{dY_1}{dt} = 0\right\}$ and $\acute{\mathcal{D}}_0$ be largest invariant subset of $\mathcal{D}_0$. The solutions of the model (3.1)-(3.5) tend to $\acute{\mathcal{D}}_0$. For each element in $\acute{\mathcal{D}}_0$ we $U(t) = U_0$ and $Q(t) = 0$. Thus Eq. (3.5) yields

$$\dot{Q}(t) = 0 = \Psi X(t) - \Lambda Q(t) - \beta X(t)Q(t),$$

hence $X(t) = 0$. From Eq. (3.3) we have

$$\dot{X}(t) = 0 = H_1(V, U_0),$$

then $H_1(V(t)) = 0$. which yields $V(t) = 0$. it fllows that $\acute{\mathcal{D}}_0$ contains a single point which is $(U_0, 0, 0, 0, 0)$. L.I.P implies that Γ_0 is GAS when $\mathcal{R}_0 < 1$.

Theorem 3.2. *For the model (3.1)-(3.5), Γ_1 is GAS when $\mathcal{R}_0 > 1$.*

Proof. Constructing a function $Y_2(U, L, X, V, Q)$ as:

$$\begin{aligned}
Y_2(U, L, X, V, Q) = &\left(\frac{bz_1\,(1-n)}{(d+b)} + nz_2\right)\left(U - U_1 - \int\limits_{U_1}^{U} \frac{H_1(V_1, U_1)}{H_1(V_1, U)} d\theta\right) \\
&+ \frac{b}{(d+b)} L_1 g\left(\frac{L}{L_1}\right) + X_1 g\left(\frac{X}{X_1}\right) \\
&+ \frac{b\,(1-n)}{(d+b)} \int\limits_0^{f_1} y_1\,(\gamma)\, H_1(V_1, U_1) \int\limits_0^{\gamma} G\left(\frac{H_1(V(t-\eta), U(t-\eta))}{H_1(V_1, U_1)}\right) d\eta d\gamma \\
&+ \frac{b\,(1-n)}{(d+b)} \int\limits_0^{f_1} y_1\,(\gamma)\, H_2(X_1, U_1) \int\limits_0^{\gamma} G\left(\frac{H_2(X(t-\eta), U(t-\eta))}{H_2(X_1, U_1)}\right) d\eta d\gamma \\
&+ n \int\limits_0^{f_2} y_2\,(\gamma) \int\limits_0^{\gamma} H_1(V_1, U_1) G\left(\frac{H_1(V(t-\eta), U(t-\eta))}{H_1(V_1, U_1)}\right) d\eta d\gamma \\
&+ n \int\limits_0^{f_2} y_2\,(\gamma) \int\limits_0^{\gamma} H_2(X_1, U_1) G\left(\frac{H_2(X(t-\eta), U(t-\eta))}{H_2(X_1, U_1)}\right) d\eta d\gamma \\
&+ \frac{H_1(V_1, U_1)}{\Sigma V_1}\left(\frac{bz_1\,(1-n)}{(d+b)} + nz_2\right) \int\limits_0^{f_3} y_3\,(\gamma) \int\limits_0^{\gamma} G\left(\frac{\Omega X\,(t-\eta)}{X_1}\right) d\eta d\gamma \\
&+ \frac{H_1(V_1, U_1)}{\Sigma V_1}\left(\frac{bz_1\,(1-n)}{(d+b)} + nz_2\right) V_1 g\left(\frac{V}{V_1}\right) + \frac{C}{2(\Psi - \beta Q_1)} (Q - Q_1)^2.
\end{aligned}$$

Note that $\Psi - \beta Q_1 = \frac{\Lambda Q_1}{X_1} > 0$. Clearly $Y_2(U, L, X, V, Q) > 0$ for all $U, L, X, V, Q > 0$ and $Y_2(U_1, L_1, X_1, V_1, Q_1) = 0$. Moreover

$$\frac{dY_2}{dt} = \left(\frac{bz_1\,(1-n)}{(d+b)} + nz_2\right)\left(1 - \frac{H_1(V_1, U_1)}{H_1(V_1, U)}\right)[\Upsilon - \Phi U - [H_1(V, U) + H_2(X, U)]]$$

$$+\frac{b}{(d+b)}\left(1-\frac{L_1}{L}\right)\Bigg[(1-n)\int_0^{f_1} y_1(\gamma)\,[H_1(V(t-\gamma),U(t-\gamma))+H_2(X(t-\gamma),U(t-\gamma))]$$

$$-(b+d)\,L]+\left(1-\frac{X_1}{X}\right)\Bigg[n\int_0^{f_2} y_2(\gamma)\,[H_1(V(t-\gamma),U(t-\gamma))+H_2(X(t-\gamma),U(t-\gamma))]$$

$$-\Theta X-CXQ+bL]$$

$$+\frac{b\,(1-n)}{(d+b)}\int_0^{f_1} y_1(\gamma)H_1(V_1,U_1)\Bigg[\frac{H_1(V,U)}{H_1(V_1,U_1)}$$

$$-\frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V_1,U_1)}+\ln\left(\frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V,U)}\right)\Bigg]$$

$$+\frac{b\,(1-n)}{(d+b)}\int_0^{f_1} y_1(\gamma)H_2(X_1,U_1)\Bigg[\frac{H_2(X,U)}{H_2(X_1,U_1)}-\frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X_1,U_1)}$$

$$+\ln\left(\frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X,U)}\right)\Bigg]+n\int_0^{f_2} y_2(\gamma)H_1(V_1,U_1)\Bigg[\frac{H_1(V,U)}{H_1(V_1,U_1)}$$

$$-\frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V_1,U_1)}+\ln\left(\frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V,U)}\right)\Bigg]+n\int_0^{f_2} y_2(\gamma)H_2(X_1,U_1)$$

$$\times\Bigg[\frac{H_2(X,U)}{H_2(X_1,U_1)}-\frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X_1,U_1)}+\ln\left(\frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X,U)}\right)\Bigg]$$

$$+\frac{H_1(V_1,U_1)}{\Sigma V_1}\left(\frac{bz_1\,(1-n)}{(d+b)}+nz_2\right)\int_0^{f_3} y_3\,(\gamma)\left[\Omega X-\Omega X(t-\gamma))+\ln\frac{X(t-\gamma)}{X}\right]d\gamma$$

$$+\frac{H_1(V_1,U_1)}{\Sigma V_1}\left(\frac{bz_1\,(1-n)}{(d+b)}+nz_2\right)\left(1-\frac{V_1}{V}\right)\left(\Omega\int_0^{f_3} y_3\,(\gamma)\,X(t-\gamma))d\gamma-\Sigma V\right)$$

$$+\frac{C(Q-Q_1)}{(\Psi-\beta Q_1)}\,(\Psi X-\Lambda Q-\beta XQ)$$

$$=\left(\frac{bz_1\,(1-n)}{(d+b)}+nz_2\right)\left(1-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)(\Upsilon-\Phi U)+bL_1+\frac{bLX_1}{X}$$

$$+\left(\frac{bz_1\,(1-n)}{(d+b)}+nz_2\right)\left(1-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)\left(\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)[H_1(V(t),U(t))+H_2(X(t),U(t))]$$

$$-\frac{b}{(d+b)}\frac{L_1}{L}\left[(1-n)\int_0^{f_1} y_1(\gamma)\,[H_1(V(t-\gamma),U(t-\gamma))+H_2(X(t-\gamma),U(t-\gamma))]\right]d\gamma$$

$$-\Theta\,(X-X_1)-CQ\,(X-X_1)$$

$$-\int_0^{f_2} ny_2(\gamma)\,[H_1(V(t-\gamma),U(t-\gamma))+H_2(X(t-\gamma),U(t-\gamma))]\,d\gamma\frac{X_1}{X}$$

$$+\frac{H_1(V_1,U_1)}{\Sigma V_1}\left(\frac{bz_1\,(1-n)}{(d+b)}+nz_2\right)\int_0^{f_3} y_3\,(\gamma)\left[\Omega X-\Omega X(t-\gamma))+\ln\frac{X(t-\gamma)}{X}\right]d\gamma$$

$$+\frac{H_1(V_1,U_1)}{\Sigma V_1}\left(\frac{bz_1(1-n)}{(d+b)}+nz_2\right)\left(\Omega\int_0^{f_3}y_3(\gamma)X(t-\gamma))d\gamma-\Sigma V\right)$$
$$-\frac{H_1(V_1,U_1)}{\Sigma V_1}\left(\frac{bz_1(1-n)}{(d+b)}+nz_2\right)\left(\Omega\int_0^{f_3}y_3(\gamma)X(t-\gamma))d\gamma\frac{V_1}{V}+\Sigma V_1\right)$$
$$+\frac{C(Q-Q_1)}{(\Psi-hQ_1)}(\Psi X-\Lambda Q-\beta XQ). \tag{3.15}$$

Applying the equilibrium conditions for Γ_1:

$$\begin{aligned}\Upsilon-\Phi U_1&=H_1(V_1,U_1)+H_2(X_1,U_1)\\ z_1(1-n)\left[H_1(V_1,U_1)+H_2(X_1,U_1)\right]&=(b+d)L_1,\\ nz_2\left[H_1(V_1,U_1)+H_2(X_1,U_1)\right]+bL_1&=\Theta X_1+CX_1Q_1,\\ z_3\Omega X_1&=\Sigma V_1,\\ \Psi X_1&=\Lambda Q_1+\beta X_1Q_1,\end{aligned}$$

we get

$$\begin{aligned}\frac{dY_2}{dt}&=\Phi U_1\left(\frac{bz_1(1-n)}{(d+b)}+nz_2\right)\left(1-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)\left(1-\frac{U}{U_1}\right)\\
&+\left(\frac{bz_1(1-n)}{(d+b)}+nz_2\right)\left(\frac{H_1(V,U)}{H_1(V_1,U)}-\frac{V}{V_1}\right)[H_1(V_1,U_1)]\\
&+\left(\frac{bz_1(1-n)}{(d+b)}+nz_2\right)\left(\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\frac{H_2(X,U)}{H_2(X_1,U_1)}-\frac{X}{X_1}\right)[H_2(V_1,U_1)]+bL_1+bL_1\left(1-\frac{X}{X_1}\right)\\
&+b\frac{LX_1}{X}+\left(\frac{bz_1(1-n)}{(d+b)}\right)H_1(V_1,U_1)\left[1-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right.\\
&\left.-\frac{H_1(V(t-\gamma),U(t-\gamma))L_1}{H_1(V_1,U_1)L}+\ln\left(\frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V,U)}\right)\right]\\
&+nz_2H_1(V_1,U_1)\left[2-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right.\\
&\left.-\frac{H_1(V(t-\gamma),U(t-\gamma))X_1}{H_1(V_1,U_1)X}-\frac{X}{X_1}+\ln\left(\frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V,U)}\right)\right]\\
&+\left(\frac{bz_1(1-n)}{(d+b)}\right)H_2(X_1,U_1)\left[1-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}+\frac{X}{X_1}\right.\\
&\left.-\frac{H_2(X(t-\gamma),U(t-\gamma))L_1}{H_2(X_1,U_1)L}+\ln\left(\frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X,U)}\right)\right]\\
&+(nz_2)H_2(X_1,U_1)\left[2-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}-\frac{X}{X_1}+\frac{X}{X_1}\right.\\
&\left.-\frac{H_2(X(t-\gamma),U(t-\gamma))X_1}{H_2(X_1,U_1)X}+\ln\left(\frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X,U)}\right)\right]\end{aligned}$$

$$+\left(\frac{bz_1(1-n)}{(d+b)}+nz_2\right)H_1(V_1,U_1)\left[\frac{X}{X_1}-\frac{V_1X(t-\gamma)}{VX_1}+1+\ln\left(\frac{X(t-\gamma)}{X}\right)\right]$$
$$-C\left(\frac{\Lambda+\beta X}{\Psi-\beta Q_1}\right)(Q-Q_1)^2.$$

Eq. (2.14) can be simplified as

$$\begin{aligned}
\frac{dY_2}{dt} &= \Phi U_1\left(\frac{bz_1(1-n)}{(d+b)}+nz_2\right)\left(1-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)\left(1-\frac{U}{U_1}\right)\\
&+\left(\frac{bz_1(1-n)}{(d+b)}+nz_2\right)\left(\frac{H_1(V,U)}{H_1(V_1,U)}-\frac{V}{V_1}\right)[H_1(V_1,U_1)]\left[1-\frac{H_1(V_1,U)}{H_1(V,U)}\right]\\
&+\left(\frac{bz_1(1-n)}{(d+b)}+nz_2\right)H_2(X_1,U_1)\left(\frac{L_s(X,U)}{L_s(X_1,U_1)}-\frac{X}{X_1}\right)\left(1-\frac{L_s(X_1,U_1)}{L_s(X,U)}\right)\\
&+\left(\frac{bz_1(1-n)}{(d+b)}\right)H_1(V_1,U_1)\left[4-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}-\frac{LX_1}{L_1X}-\frac{X}{X_1}\right.\\
&\left.-\frac{H_1(V(t-\gamma),U(t-\gamma))L_1}{H_1(V_1,U_1)L}+\ln\left(\frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V,U)}\right)-\frac{VH_1(V_1,U)}{V_1H_1(V,U)}\right]\\
&+nz_2H_1(V_1,U_1)\left[3-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}-\frac{VH_1(V_1,U)}{V_1H_1(V,U)}\right.\\
&\left.-\frac{H_1(V(t-\gamma),U(t-\gamma))X_1}{H_1(V_1,U_1)X}-\frac{X}{X_1}+\ln\left(\frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V,U)}\right)\right]\\
&+\left(\frac{bz_1(1-n)}{(d+b)}\right)H_2(X_1,U_1)\left[4-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}-\frac{LX_1}{L_1X}-\frac{X}{X_1}+\frac{X}{X_1}\right.\\
&\left.-\frac{H_2(X(t-\gamma),U(t-\gamma))L_1}{H_2(X_1,U_1)L}+\ln\left(\frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X,U)}\right)-\frac{L_s(X_1,U_1)}{L_s(X,U)}\right]\\
&+(nz_2)H_2(X_1,U_1)\left[3-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}-\frac{L_s(X_1,U_1)}{L_s(X,U)}\right.\\
&\left.-\frac{H_2(X(t-\gamma),U(t-\gamma))X_1}{H_2(X_1,U_1)X}+\ln\left(\frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X,U)}\right)\right]\\
&+\left(\frac{bz_1(1-n)}{(d+b)}+nz_2\right)H_1(V_1,U_1)\left[\frac{X}{X_1}-\frac{V_1X(t-\gamma)}{VX_1}+1+\ln\left(\frac{X(t-\gamma)}{X}\right)\right]\\
&-C\left(\frac{\Lambda+\beta X}{\Psi-\beta Q_1}\right)(Q-Q_1)^2,
\end{aligned}$$

we get

$$\begin{aligned}
\frac{dY_2}{dt} &= \Phi U_1\left(\frac{bz_1(1-n)}{(d+b)}+nz_2\right)\left(1-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)\left(1-\frac{U}{U_1}\right)\\
&+\left(\frac{bz_1(1-n)}{(d+b)}+nz_2\right)\left(\frac{H_1(V,U)}{H_1(V_1,U)}-\frac{V}{V_1}\right)[H_1(V_1,U_1)]\left[1-\frac{H_1(V_1,U)}{H_1(V,U)}\right]\\
&+\left(\frac{bz_1(1-n)}{(d+b)}+nz_2\right)H_2(X_1,U_1)\left(\frac{L_s(X,U)}{L_s(X_1,U_1)}-\frac{X}{X_1}\right)\left(1-\frac{L_s(X_1,U_1)}{L_s(X,U)}\right)
\end{aligned}$$

$$
\begin{aligned}
&+\left(\frac{bz_1\,(1-n)}{(d+b)}\right)H_1(V_1,U_1)\left[5-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}-\frac{LX_1}{L_1X}-\frac{V_1X(t-\gamma)}{VX_1}+\ln\left(\frac{X(t-\gamma)}{X}\right)\right.\\
&\left.-\frac{H_1(V(t-\gamma),U(t-\gamma))L_1}{H_1(V_1,U_1)L}+\ln\left(\frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V,U)}\right)-\frac{VH_1(V_1,U)}{V_1H_1(V,U)}\right]\\
&+nz_2H_1(V_1,U_1)\left[4-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}-\frac{VH_1(V_1,U)}{V_1H_1(V,U)}+\ln\left(\frac{X(t-\gamma)}{X}\right)\right.\\
&\left.-\frac{H_1(V(t-\gamma),U(t-\gamma))X_1}{H_1(V_1,U_1)X}-\frac{V_1X(t-\gamma)}{VX_1}+\ln\left(\frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V,U)}\right)\right]\\
&+\left(\frac{bz_1\,(1-n)}{(d+b)}\right)H_2(X_1,U_1)\left[4-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}-\frac{LX_1}{L_1X}-\frac{X}{X_1}+\frac{X}{X_1}\right.\\
&\left.-\frac{H_2(X(t-\gamma),U(t-\gamma))L_1}{H_2(X_1,U_1)L}+\ln\left(\frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X,U)}\right)-\frac{L_s(X_1,U_1)}{L_s(X,U)}\right]\\
&+(nz_2)\,H_2(X_1,U_1)\left[3-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}-\frac{L_s(X_1,U_1)}{L_s(X,U)}\right.\\
&\left.-\frac{H_2(X(t-\gamma),U(t-\gamma))X_1}{H_2(X_1,U_1)X}+\ln\left(\frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X,U)}\right)\right]\\
&-C\left(\frac{\Lambda+\beta X}{\Psi-\beta Q_1}\right)(Q-Q_1)^2.
\end{aligned}
$$

We get

$$
\begin{aligned}
\frac{dY_2}{dt}&=\Phi U_1\left(\frac{bz_1\,(1-n)}{(d+b)}+nz_2\right)\left(1-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)\left(1-\frac{U}{U_1}\right)\\
&+\left(\frac{bz_1\,(1-n)}{(d+b)}+nz_2\right)\left(\frac{H_1(V,U)}{H_1(V_1,U)}-\frac{V}{V_1}\right)[H_1(V_1,U_1)]\left[1-\frac{H_1(V_1,U)}{H_1(V,U)}\right]\\
&+\left(\frac{bz_1\,(1-n)}{(d+b)}+nz_2\right)H_2(X_1,U_1)\left(\frac{L(X,U)}{L(X_1,U_1)}-\frac{X}{X_1}\right)\left(1-\frac{L(X_1,U_1)}{L(X,U)}\right)\\
&-\left(\frac{bz_1\,(1-n)}{(d+b)}\right)H_1(V_1,U_1)\left[G\left(\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)+G\left(\frac{LX_1}{L_1X}\right)+G\left(\frac{V_1X(t-\gamma)}{VX_1}\right)\right.\\
&\left.+G\left(\frac{VH_1(V_1,U)}{V_1H_1(V,U)}\right)+G\left(\frac{H_1(V(t-\gamma),U(t-\gamma))L_1}{H_1(V_1,U_1)L}\right)\right]\\
&-nz_2H_1(V_1,U_1)\left[+G\left(\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)+G\left(\frac{V_1X(t-\gamma)}{VX_1}\right)\right.\\
&\left.G\left(\frac{H_1(V(t-\gamma),U(t-\gamma))X_1}{H_1(V_1,U_1)X}\right)+G\left(\frac{VH_1(V_1,U)}{V_1H_1(V,U)}\right)\right]\\
&-\left(\frac{bz_1\,(1-n)}{(d+b)}\right)H_2(X_1,U_1)\left[G\left(\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)+G\left(\frac{LX_1}{L_1X}\right)+G\left(\frac{XL_s(X_1,U_1)}{X_1L_s(X,U)}\right)\right.\\
&\left.G\left(\frac{H_2(X(t-\gamma),U(t-\gamma))L_1}{H_2(X_1,U_1)L}\right)\right]\\
&-(nz_2)\,H_2(X_1,U_1)\left[G\left(\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)+G\left(\frac{X}{X_1}\right)+G\left(\frac{XL(X_1,U_1)}{X_1L(X,U)}\right)\right.
\end{aligned}
$$

$$G\left(\frac{H_2(X(t-\gamma),U(t-\gamma))X_1}{H_2(X_1,U_1)X}\right)\Bigg]$$
$$-C\left(\frac{\Lambda+\beta X}{\Psi-\beta Q_1}\right)(Q-Q_1)^2.$$

Since

$$\ln\left(\frac{H_1(V(t-\gamma),U(t-\gamma))}{H_1(V,U)}\right)=\ln\left(\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)+\ln\left(\frac{LX_1}{L_1X}\right)+\ln\frac{V_1X(t-\gamma)}{VX_1}$$
$$+\ln\left(\frac{VH_1(V_1,U)}{V_1H_1(V,U)}\right)+\ln\left(\frac{H_1(V(t-\gamma),U(t-\gamma))L_1}{H_1(V_1,U_1)L}\right)-\ln\left(\frac{X(t-\gamma)}{X}\right),$$

$$\ln\left(\frac{H_2(X(t-\gamma),U(t-\gamma))}{H_2(X,U)}\right)=\ln\frac{H_1(V_1,U_1)}{H_1(V_1,U)}+\ln\frac{LX_1}{L_1X}+\ln\frac{XL_s(X_1,U_1)}{X_1L_s(X,U)}$$
$$+\ln\frac{H_2(X(t-\gamma),U(t-\gamma))L_1}{H_2(X_1,U_1)L}$$
$$=\ln\frac{H_1(V_1,U_1)}{H_1(V_1,U)}+\ln\frac{LX_1}{L_1X}+\ln\frac{XH_1(V_1,U)H_2(X_1,U_1)}{X_1H_1(V_1,U_1)H_2(X,U)}$$
$$+\ln\frac{H_2(X(t-\gamma),U(t-\gamma))L_1}{H_2(X_1,U_1)L}.$$

Using Remak 2 we get

$$\left(1-\frac{H_1(V_1,U_1)}{H_1(V_1,U)}\right)\left(1-\frac{U}{U_1}\right)\le 0,$$

and

$$\left(\frac{H_1(V,U)}{V}-\frac{H_1(V_1,U)}{V_1}\right)[H_1(V,U)-H_1(V_1,U)]\le 0,$$

it follows

$$\left(\frac{H_1(V,U)}{H_1(V_1,U)}-\frac{V}{V_1}\right)\left[1-\frac{H_1(V_1,U)}{H_1(V,U)}\right]\le 0.$$

Hence, we obtain that $\frac{dY_2}{dt}\le 0$ and $\frac{dY_2}{dt}=0$ at the point (U_1,L_1,X_1,V_1,Q_1). Let $\acute{\mathcal{D}}_1$ the largest invariant subset of the set $\left\{(U,L_1,X,V,Q):\frac{dY_2}{dt}=0\right\}$. Thus, the solutions of model tend to $\acute{\mathcal{D}}_1$. It is clear that $\acute{\mathcal{D}}_1$ contains unique point which is Γ_1. The global asymptotic stability of Γ_1 follows from L.I.P. □

4. Numerical simulations and dissection

In this section, we propose example and carry out numerical simulations to approve our theoretical results shown in this paper. All of numerical computations are carried out by MATLAB.

4.1. **Example of the model (2.1)-(2.4).** To perform numerical simulations and demonstrate the global asymptotic stability of the equilibria of models, we choose the following functions , $H_1(V,U) = \frac{\eta_1 UV}{1+\alpha_1 V}$ and $H_2(X,U) = \frac{\eta_2 UX}{1+\alpha_2 X}$, where $\eta_1, \eta_2, \alpha_1, \alpha_1$ are nonnegative constants. We can easily see that $H_1(V,U)$ and $H_2(X,U)$ are continuously differentiable functions, moreover, they satisfy the following:

$H_i(V,U) > 0$ and $H_i(0,U) = H_i(V,0) = 0, i = 1,2,$ for all $U > 0$ and $V > 0$, thus, A1 is satisfied. We have

$$\frac{\partial H_1(V,U)}{\partial U} = \frac{\eta_1 V}{1+\alpha_1 V} > 0, \frac{\partial H_1(V,U)}{\partial V} = \frac{\eta_1 U}{(1+\alpha_1 V)^2} > 0,$$
$$\frac{\partial H_2(X,U)}{\partial U} = \frac{\eta_1 X}{1+\alpha_1 X} > 0, \frac{\partial H_2(X,U)}{\partial U} = \frac{\eta_1 U}{(1+\alpha_1 X)^2} > 0,$$

for all $X, V, U > 0$, hence A2 is satisfied, $W_1(U) = \frac{\partial H_1(0,U)}{\partial V} = U > 0, W_2(U) = \frac{\partial H_2(0,U)}{\partial X} = U > 0$, for $U > 0$. Hence $W_1(U) = W_2(U) = 1 > 0$, it means A3 satisfied. Moreover, we have

$$\frac{\partial}{\partial V}\left(\frac{H_1(V,U)}{V}\right) = \frac{-\eta_1\alpha_1 V}{(1+\alpha_1 V)^2} < 0, \text{ forall } V, U > 0,$$
$$\frac{\partial}{\partial X}\left(\frac{H_2(X,U)}{X}\right) = \frac{\eta_1\alpha_1 X}{(1+\alpha_1 X)^2} < 0, \text{ forall } X, U > 0,$$

Then, A4 is satisfied. In addition, we choose particular form of probability distributed function as follows:

$$g_n(\gamma) = \delta(\gamma - \gamma_n) \quad n = 1,2,$$

where $\delta(.)$ is Dirac delta function we have

$$\int_0^\infty g_n(\gamma)d\gamma = 1 \quad n = 1,2,$$

we have

$$z_n = \int_0^\infty \delta(\gamma-\gamma_n))e^{-\gamma\theta_n}d\gamma = e^{-\gamma_n\theta_n} \quad n = 1,2,$$

$$\int_0^\infty \delta(\gamma-\gamma_1))e^{-\gamma\theta_1}H_i(V(t-\gamma),U(t-\gamma))d\gamma = e^{-\gamma_1\theta_1}H_i(V(t-\gamma_1),U(t-\gamma_1)),$$
$$\int_0^\infty \delta(\gamma-\gamma_2))e^{-\gamma\theta_2}X(t-\gamma)d\gamma = e^{-\gamma_2\theta_2}X(t-\gamma_2).$$

Hence, the model becomes

$$\dot{U} = \Upsilon - \Phi U - \left(\frac{\eta_1(1-a_1)VU}{1+\alpha_1 V} + \frac{\eta_2(1-a_2)XU}{1+\alpha_2 X}\right), \tag{4.1}$$

$$\dot{X} = \left(\frac{\eta_1 e^{-\gamma_1\theta_1}(1-a_1)V(t-\gamma_1)U(t-\gamma_1)}{1+\alpha_1 V} + \frac{\eta_2 e^{-\gamma_1\theta_1}(1-a_2)X(t-\gamma_1)U(t-\gamma_1)}{1+\alpha_2 X}\right)$$
$$-\Theta X - CXQ, \tag{4.2}$$

$$\dot{V} = \Omega e^{-\gamma_2\theta_2}(1-a_3)X(t-\gamma_2) - \Sigma V, \tag{4.3}$$

$$\dot{Q} = \Psi X - \Lambda Q - \beta XQ, \tag{4.4}$$

where the efficacy of drug a_1 is introduced to reduce the transmission of infection through cell-free mode. This efficacy is mainly reverse transcriptase inhibitors (RTIs) in the case of HIV. The efficacy of drug a_2 is introduced to block cell-to-cell infection that targets the factors required for synapse formation under the assumption that such a drug exists. The third efficacy of drug a_3 is applied to prevent the pathogen protease from cleaving the pathogen polyprotein into functional units which is called protease inhibitors (PIs) in the case of HIV.We have $0 \leq a_n < 1, n = 1, 2$. The basic reproduction number of models is given by

$$R_0 = \left[\frac{\Omega e^{-\gamma_2\theta_2} e^{-\gamma_1\theta_1} \eta_1 \left(1 - a_1\right) \left(1 - a_3\right)}{\Theta\Sigma} + \frac{\eta_2 e^{-\gamma_1\theta_1} \left(1 - a_2\right)}{\Theta}\right] U_0.$$

We shall carry out numerical simulations for the model (4.1)-(4.4) using the parameters values given in Table 1. We choose three initial conditions as:

IC1: $U(0) = 600, X(0) = 8.5, V(0) = 15, Q(0) = 3.5$,

IC2: $U(0) = 1150, X(0) = 3, V(0) = 12, Q(0) = 2.5$, and

IC3: $U(0) = 800, X(0) = 5, V(0) = 8, Q(0) = 1.5$.

Case (1) To study the effect of η_1 on equilibria stability:

We choose, $\alpha_1 = \alpha_2 = 0.1$ $\beta = 0.1$ and η_1 is varied as:

(i) if $\eta_1 = 0.1$, then we compute $\mathcal{R}_0 = 12.2780 > 1$. Lemma 2 states that the model has two equilibria Γ_0 and Γ_1. As we can see from Figure 1 that numerical results agree with theoretical results of Theorem 2 and the model solutions converge to the equilibrium $\Gamma_1 = (323.309, 9.4310, 13.517, 3.6161)$ for all IC1-IC3.

(ii) if $\eta_1 = 0.001$ then, $\mathcal{R}_0 = 0.9149 < 1$. From Lemma 2, the model has only one equilibrium Γ_0. For Figure 1 we note that, uninfected cells concentration is growing up to its original value $U_0 = 1667$, while the concentration of infected cells, pathogens and CTL cells are decreasing and approaching zero for IC1-IC3. It shows that, Γ_0 is GAS and this means that the pathogens are cleaned up, so it supports Theorem 1.

Case(2) Effect of saturation parameter: We choose $\alpha = \alpha_1 = \alpha_2$ on the pathogen dynamics. parameter Moreover, we take the following initial condition IC4: $U(0) = 1250, X(0) = 3, V(0) = 5, Q(0) = 3.2$. Figure 2 shows that as α increased, the concentration of the uninfected target cells is increased while the the concentrations of infected cells, pathogen particles, and CTL cells are decreased. We note that the parameter α has no effect on the stability of equilibria since $\mathcal{R}_0$ does not depend on α.

Case(3) Effect of antiviral treatment on the stability of equilibria:

To study the effect of antiviral treatment on pathogen dynamics. The basic reproduction number of the model is given by $\mathcal{R}_0 = (1-a)\mathcal{R}_{02} + (1-a)^2\mathcal{R}_{01}$. Since the target of antiviral drugs is to clear the pathogen particles from the body, then we have to determine the minimum drug efficacy a_{min} such that $\mathcal{R}_0 < 1$ for all $a_{min} < a \leq 1$. We can find the value of a_{min} by solving the following

Parameter	Value	Parameter	Value	Parameter	Value
Υ	250	η_2	0.01	Σ	3
Φ	0.15	Θ	5.4	Ψ	0.4
r	1	q	0.04	Λ	0.1
β	0.1	Ω	5	$\eta_1, \alpha_1, \alpha_2$	varied

Table 1. Parameters values of the model (4.1)-(4.4).

Algebraic equation:

$$\mathcal{R}_0 = (1-a)\,\mathcal{R}_{02} + (1-a)^2\,\mathcal{R}_{01} = 1,$$

let $b = 1-a$, then $(1-a)\,\mathcal{R}_{02} + (1-a)^2\,\mathcal{R}_{01} - 1 = 0$. The roots given by

$$b\mathcal{R}_{02} + b^2\mathcal{R}_{01} - 1 = 0,$$

hence

$$b = \frac{\mathcal{R}_{02} \pm \sqrt{\mathcal{R}_{02}^2 + 4\mathcal{R}_{01}}}{2},$$

$$a = 1 - \frac{\mathcal{R}_{02} \pm \sqrt{\mathcal{R}_{02}^2 + 4\mathcal{R}_{01}}}{2}.$$

For this purpose, we let $\eta_1 = 0.001, \alpha = 0.1$, and a is varied. Suppose a new set of initial conditions as: IC5: $U(0) = 1500, X(0) = 1, V(0) = 1.3, Q(0) = 2$. As it is illustrated in Figure 3 that as a is increased, the uninfected cells concentrations are increased. While the infected cells concentration and the pathogens are decayed as a result of CTL cells concentration is increased.

(i) Γ_1 when if $0 < a < 0.2810$.

(ii) Γ_0 when $a > 0.2810$.

Case (4) Effect of time delay on the pathogen dynamics:

For this, let $\eta_1 = 0.001$, and $\alpha_1 = \alpha_2 = 0.1$ is varied. We suppose the initial conditions

IC6: $U(0) = 1250, X(0) = 4, V(0) = 7, Q(0) = 3.5$. By solving $\mathcal{R}_0(\gamma) = 1$, we get $\gamma = 1.3944$. It follows

(i) $\Gamma_1$when $0 < \gamma < 1.3944$.

(ii) Γ_0 when $\gamma > 1.3944$.

We observe that the increases of time delays play the same influence of treatment.

Figures 4 with Theorem 2 have proved the compatibility of numerical and theoretical results.

4.2. **Example of the model (3.1)-(3.5).** In this subsection, we will implement numerical simulations for a special case of the model (3.1)-(3.5) as:

$$\dot{U} = \Upsilon - \Phi U - \left(\frac{\eta_1\,(1-a_1)\,VU}{1+\alpha_1 V} + \frac{\eta_2\,(1-a_2)\,XU}{1+\alpha_2 X}\right), \tag{4.5}$$

$$\dot{L} = (1-n)\left(\frac{\eta_1 e^{-\gamma_1\theta_1}(1-a_1)V(t-\gamma_1)U(t-\gamma_1)}{1+\alpha_1 V} + \frac{\eta_2 e^{-\gamma_1\theta_1}(1-a_2)X(t-\gamma_1)U(t-\gamma_1)}{1+\alpha_2 X}\right)$$
$$-(d+b)L, \tag{4.6}$$
$$\dot{X} = n\left(\frac{\eta_1 e^{-\gamma_{21}\theta_2}(1-a_1)V(t-\gamma_2)U(t-\gamma_2)}{1+\alpha_1 V} + \frac{\eta_2 e^{-\gamma_2\theta_2}(1-a_2)X(t-\gamma_2)U(t-\gamma 2)}{1+\alpha_2 X}\right)$$
$$-\Theta X - CXQ + bL, \tag{4.7}$$
$$\dot{V} = \Omega e^{-\gamma_3\theta_3}(1-a_3)X(t-\gamma_3) - \Sigma V, \tag{4.8}$$
$$\dot{Q} = \Psi X - \Lambda Q - \beta XQ, \tag{4.9}$$

where the parameters values given in Table 1. We suppose that $\alpha_1 = \alpha_2 = \alpha$ with no loss of generality.

The basic reproduction number of models is given by

$$R_0 = \left(\frac{b(1-n)e^{-\gamma_1\theta_1}}{(d+b)}\right)\left[\frac{\Omega e^{-\gamma_3\theta_3}\eta_1(1-a_1)(1-a_3)}{\Theta\Sigma} + \frac{\eta_2(1-a_2)}{\Theta}\right]U_0$$
$$+\left(ne^{-\gamma_2\theta_2}\right)\left[\frac{\Omega e^{-\gamma_3\theta_3}\eta_1(1-a_1)(1-a_3)}{\Theta\Sigma} + \frac{\eta_2(1-a_2)}{\Theta}\right]U_0.$$

We will choose three sets of initial conditions as:

IC1: $U(0) = 900, L(0) = 8.5, X(0) = 15, V(0) = 200, Q(0) = 0.06$,

IC2: $U(0) = 800, L(0) = 7, X(0) = 10, V(0) = 150, Q(0) = 0.6$, and

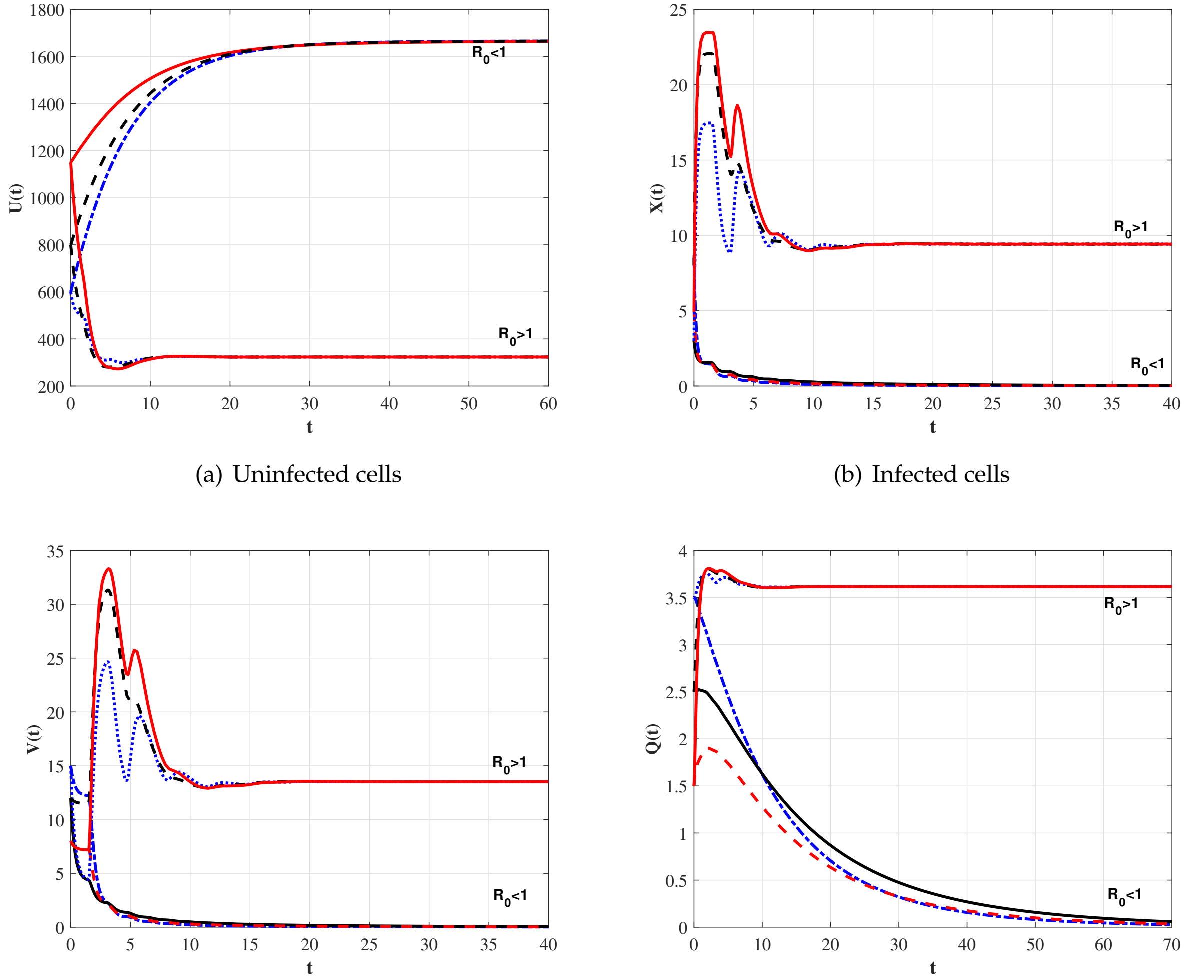
IC3: $U(0) = 600, L(0) = 5, X(0) = 5, V(0) = 100, Q(0) = 0.4$.

Case (1) Effect of η_1 on equilibria stability:

We choose $\alpha = 0.01, \beta = 0.1, n = 0.5, c = 0.1, a = 0.9$ and η_1 is varied as:

(i) if $\eta_1 = 0.001, \eta_2 = 0.001$, then we compute $\mathcal{R}_0 = 0.7478 < 1$. From Lemma 4 we have that the model has only one equilibrium Γ_0. We observe from Figure 5 that, uninfected cells concentration is rising and tends its free-disease value $U_0 = 1350$, on the other hand we find that the concentrations of latently infected cells, productively infected, pathogens and CTL cells are decreasing and tend to zero for IC1-IC3. This proves that, Γ_0 is GAS, the pathogen will be cleared and this consistent with Theorem 3.

(ii) if $\eta_1 = 0.001, \eta_2 = 0.01$, then, $\mathcal{R}_0 = 2.1862 > 1$. As we discussed before in Lemma 4 that the model has two positive equilibria Γ_0 and Γ_1. We note that Figure 5 results are consistent with Theorem 4 results. It is seen that, the solutions of the model converge to the endemic equilibrium $\Gamma_1 = (726.1863, 17.9913, 126.3050, 458.4638, 0.9932)$ for all IC1-IC3.



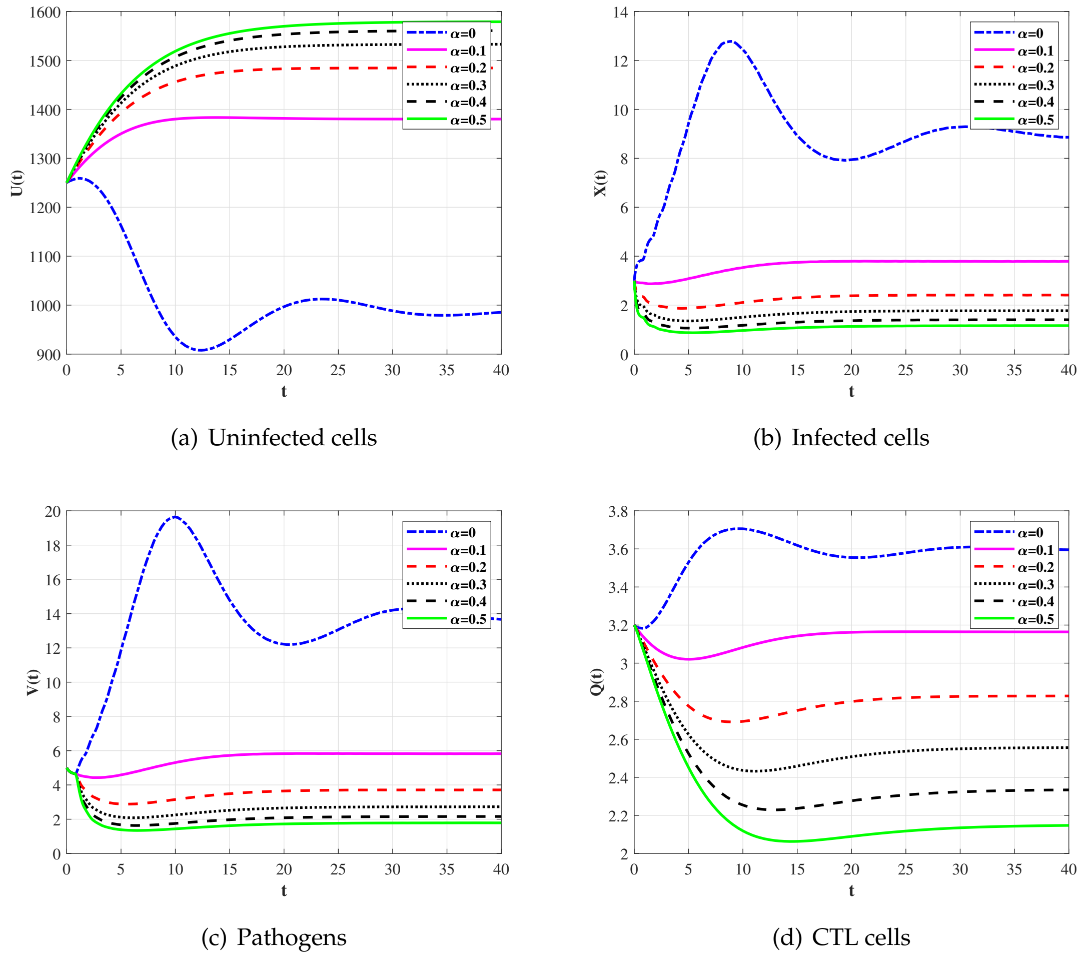
(a) Uninfected cells

(b) Infected cells

(c) Pathogens

(d) CTL cells

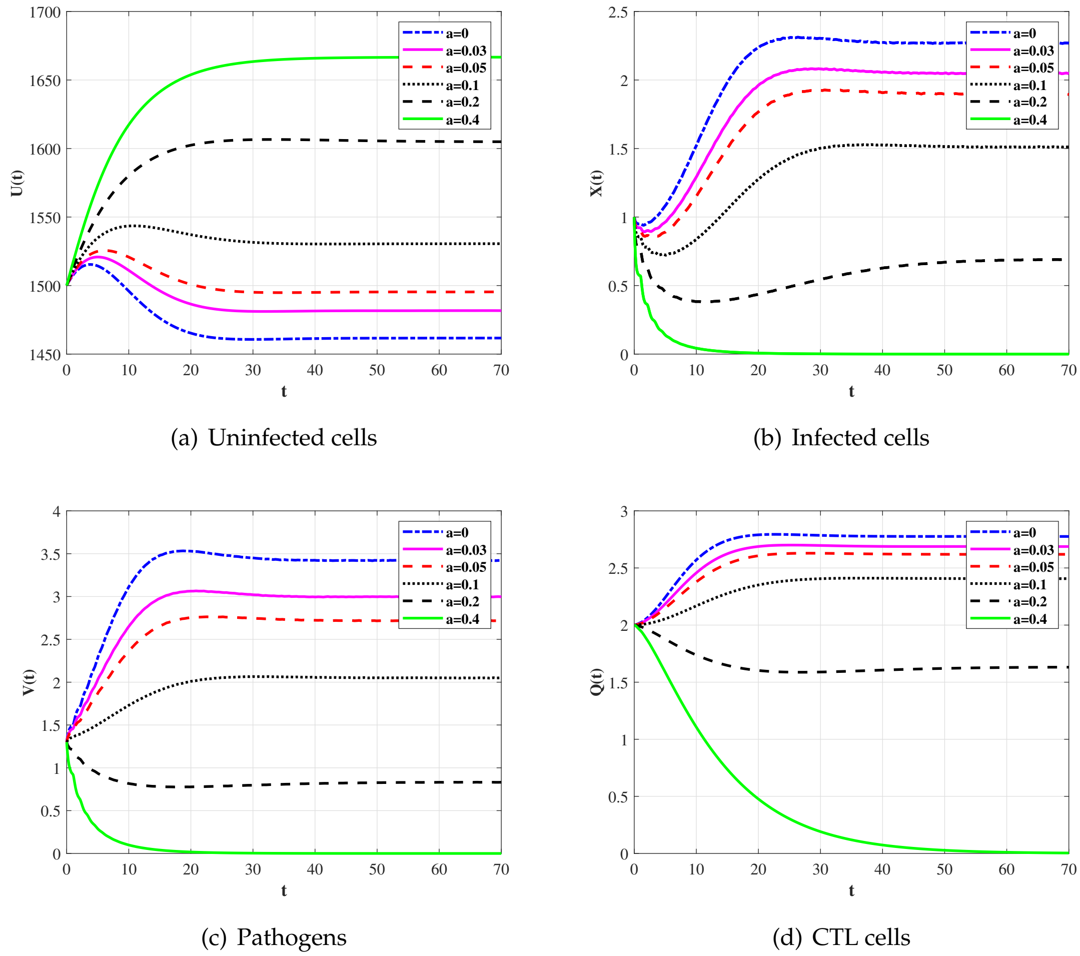
Figure 1. The trajectories simulations of model (4.1)-(4.4) with IC1-IC3.



(a) Uninfected cells (b) Infected cells

(c) Pathogens (d) CTL cells

Figure 2. The trajectories simulations of model (4.1)-(4.4) with different values of α.



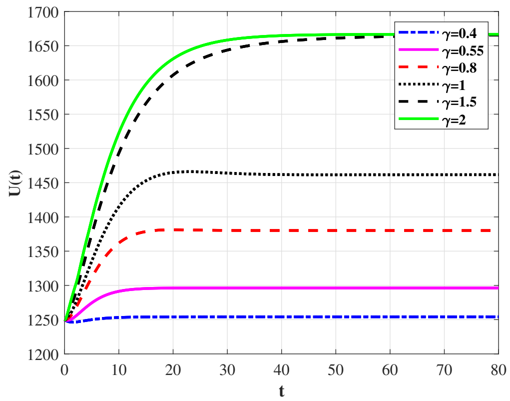
(a) Uninfected cells

(b) Infected cells

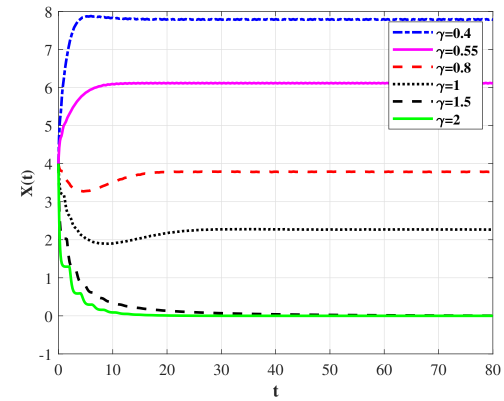
(c) Pathogens

(d) CTL cells

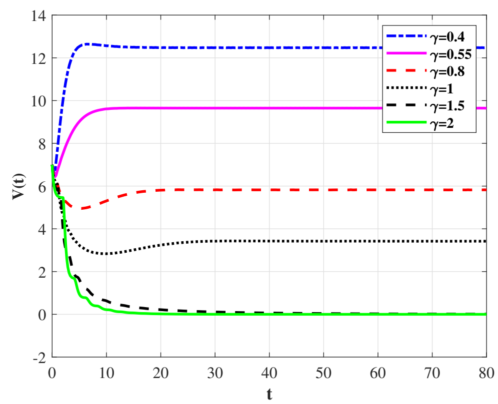
Figure 3. The trajectories simulations of model (4.1)-(4.4) with different values of a.



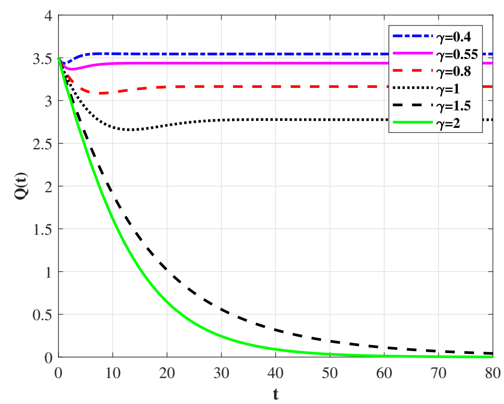
(a) Uninfected cells



(b) Infected cells

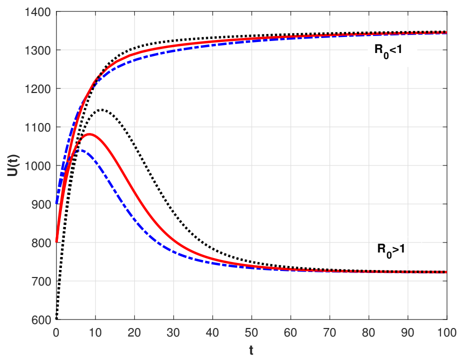


(c) Pathogens

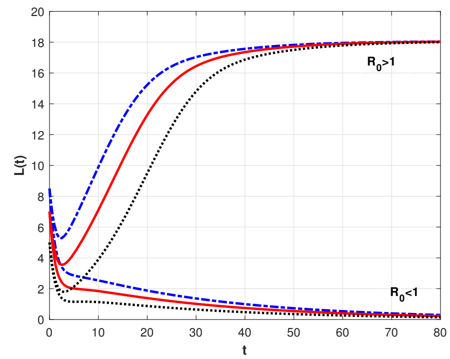


(d) CTL cells

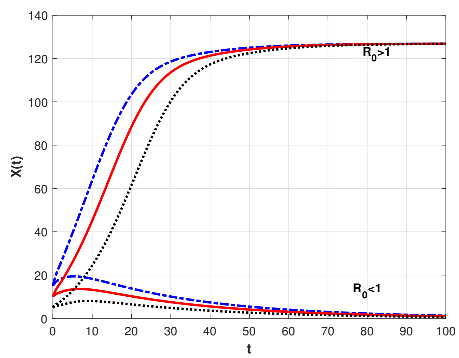
Figure 4. The trajectories simulations of model (4.1)-(4.4) with different values of γ.



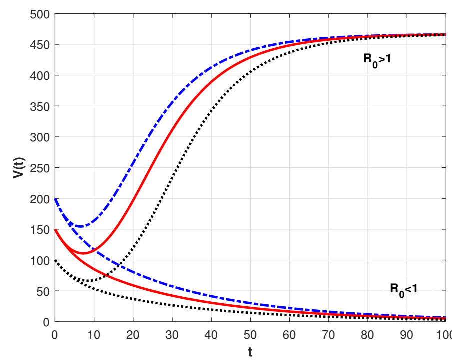
(a) Uninfected cells



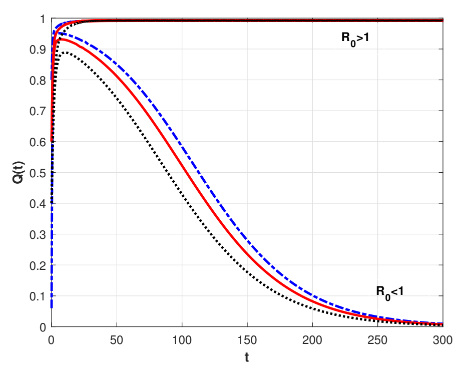
(b) Latently Infected cells



(c) Productively infected cells



(d) Pathogens



(e) CTL cells

Figure 5. The trajectories simulation of model (3.1)-(3.5) with IC1-IC3.

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