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Impact of Delay in Immune Response Activation on HIV Infection Dynamics

Mehdi Maziane[1*], El Mehdi Lotfi[1], Khalid Hattaf[1,2] and Noura Yousfi[1]

[1] *Department of Mathematics and Computer Science, Faculty of Sciences Ben M'sik, Hassan II University, P.O.Box 7955 Sidi Othman, Casablanca, Morocco.*
[2] *Centre Régional des Métiers de l'Education et de la Formation (CRMEF), 20340 Derb Ghalef, Casablanca, Morocco.*

Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Abstract

In this work, we propose an HIV infection model with cure of infected cells in eclipse stage and delay in the activation of immune response. The stability of the equilibria and the existence of the Hopf bifurcation are investigated. Moreover, numerical simulations are carried out to illustrate our theoretical results.

Keywords: HIV infection; CTL immune response; delay; hopf bifurcation.

**Corresponding author: E-mail: mehdimaziane@gmail.com;*

1 Introduction

Cytotoxic T Lymphocytes (CTL) cells are responsible of cellular immunity and they play a crucial role in antiviral defense by killing the productive infected cells. In addition, the activation of CTL immune response is not instantaneous. In reality, there is a delay in activation of CTL immune response. To model the impact of this delay on the dynamics of human immunodeficiency virus (VIH) infection, we propose the following model

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - \mu_T T(t) - f(T(t), V(t))V(t) + \rho E(t),\\
\frac{dE}{dt} &= f(T(t), V(t))V(t) - (\mu_E + \rho + \gamma)E(t),\\
\frac{dI}{dt} &= \gamma E(t) - \mu_I I(t) - pI(t)C(t),\\
\frac{dV}{dt} &= kI(t) - \mu_V V(t),\\
\frac{dC}{dt} &= aI(t-\tau)C(t-\tau) - \mu_C C(t),
\end{aligned} \tag{1.1}$$

where $T(t)$, $E(t)$, $I(t)$, $V(t)$ and $C(t)$ represent the concentrations of uninfected $CD4^+$ T cells, infected cells in the eclipse stage (unproductive infected cells), productive infected cells, free virus particles and CTL cells at time t, respectively. Further, λ is the production rate of the uninfected cells and $f(T, V)$ is the rate of uninfected cells to become infected by virus. The parameters μ_T, μ_E, μ_I, μ_V and μ_C are the death rate of uninfected $CD4^+$ T cells, infected cells in the eclipse stage, productive infected cells, free virus particles and CTL cells at time t, respectively. The γ, k and a are, respectively, the rates at which infected cells in the eclipse stage become productive infected cells, the production rate of virions by infected cells and the proliferation rate of CTL cells. The p represents the clearance of productive infected cells by CTL cells and ρ is the cure rate of the unproductive infected cells (i.e., the rate at which the unproductive infected cells return to the uninfected cells). Moreover, the infection transmission process is modeled by Hattaf's incidence rate [1] of the form $f(T, V) = \frac{\beta T}{1+\alpha_1 T+\alpha_2 V+\alpha_3 TV}$, where α_1, α_2, $\alpha_3 \geq 0$ are constants and $\beta > 0$ is the infection coefficient, and it includes the bilinear incidence rate, the saturated incidence rate, the Beddington-DeAngelis functional response [2, 3] and Crowley-Martin functional response [4]. Finally, τ represents the time needed for the activation of the CTL immune response.

On the other hand, the model governed by ordinary differential equations (ODEs) and presented by Maziane et al. in [5] is a special case of (1.1) when the delay in activation of CTL immune response is absent. It is important to note that the ODE model [5] is the generalization of the viral infection model in [6] and the improvement of the ODE models presented in [7–11].

The rest of this paper is structured as follows. In the next section, we first show the nonnegativity and boundedness of solutions, after, we discuss the existence of equilibria for system (1.1). The stability of the equilibria and the existence of Hopf bifurcation are investigated in section 3. Some numerical simulations are given in section 4 to illustrate our main results. Finally, the paper ends with a brief conclusion in section 5.

2 Basic Results

First, we establish the positivity and boundedness of solutions of model (1.1). The cell numbers should remain non-negative and bounded because this model describes the evolution of a cell population. Let $C = C([-\tau, 0]; \mathbb{R}^5)$ be the Banach space of continuous functions mapping from $[-\tau, 0]$ to $\mathbb{R}^5$ equipped with the sup-norm. Using the fundamental theory of differential equations [12], we can easily show that there exists a unique solution $(T(t), E(t), I(t), V(t), C(t))$ for system (1.1) with initial conditions $(T_0, E_0, I_0, V_0, C_0) \in C$. Moreover, and for biological reasons, we assume

that the initial conditions are non-negative

$$T_0(s) \geq 0, E_0(s) \geq 0, I_0(s) \geq 0, V_0(s) \geq 0, C_0(s) \geq 0, \qquad for \;\; s \in [-\tau; 0]. \tag{2.1}$$

Proposition 2.1. *The solution of system (1.1) satisfying condition (2.1) remains non-negative and bounded for all $t \geq 0$.*

Proof. It is easy to show the positivity of the solution of system (1.1) with initial conditions satisfying (2.1). Now, we show the boundedness of solution. Define

$$G(t) = T(t) + E(t) + I(t) + \frac{\mu_I}{2k} V(t) + \frac{p}{2a} C(t+\tau),$$

then

$$\begin{aligned} \frac{dG}{dt} &= \lambda - \mu_T T(t) - \mu_E E(t) - \frac{\mu_I}{2} I(t) - \frac{\mu_I \mu_V}{2k} V(t) - \frac{p\mu_C}{2a} C(t+\tau) - \frac{p}{2} I(t) C(t) \\ &\leq \lambda - \mu G(t), \end{aligned}$$

where $\mu = \min\left\{\mu_T, \mu_E, \frac{\mu_I}{2}, \mu_V, \mu_C\right\}$. Hence

$$G(t) \leq \max\left\{G(0), \frac{\lambda}{\mu}\right\}.$$

Therefore, $T(t)$, $E(t)$, $I(t)$, $V(t)$ and $C(t)$ are bounded. ■

Next, we discuss the existence of equilibria for system (1.1). Based on the results given in [5], we deduce that system (1.1) has an infection-free equilibrium of the form $Q_0\big(\frac{\lambda}{\mu_T}, 0, 0, 0, 0\big)$.
Hence, the basic reproduction number of (1.1) is given by

$$R_0 = \frac{\lambda \beta k \gamma}{\mu_I \mu_V (\lambda \alpha_1 + \mu_T)(\rho + \mu_E + \gamma)}. \tag{2.2}$$

We recall that R_0 represents the number of secondary infections produced by one productive infected cell during the period of infection when all cells are uninfected.

If $R_0 > 1$, there exists an other biological equilibrium $Q_1(T_1, E_1, I_1, V_1, 0)$ with $T_1 \in \big(0, \frac{\lambda}{\mu_T}\big)$, $E_1 = \frac{\lambda - \mu_T T_1}{\mu_E + \gamma}$, $I_1 = \frac{\gamma(\lambda - \mu_T T_1)}{\mu_I(\mu_E + \gamma)}$ and $V_1 = \frac{k\gamma(\lambda - \mu_T T_1)}{\mu_I \mu_V (\mu_E + \gamma)}$. This equilibrium correspond to positive levels of healthy cells, unproductive infected cells, productive infected cells and virus, but no CTL immune response.

In addition to R_0, we define the CTL immune response reproduction number R_1 of our ODE model by

$$R_1 = \frac{aI_1}{\mu_C}, \tag{2.3}$$

where $\frac{1}{\mu_C}$ represents the average life expectancy of CTL cells, and I_1 is the number of productive infected cells at Q_1. Hence, R_1 represents the average number of CTL cells activated by the productive infected cells when viral infection is successful.

If $R_1 > 1$, there exists an infection equilibrium $Q_2(T_2, E_2, I_2, V_2, C_2)$ with $T_2 \in \big(0, \frac{\lambda}{\mu_T} - \frac{\mu_I \mu_C (\mu_E + \gamma)}{a\gamma\mu_T}\big)$, $E_2 = \frac{\lambda - \mu_T T_2}{\mu_E + \gamma}$, $I_2 = \frac{\mu_C}{a}$, $V_2 = \frac{k\mu_C}{a\mu_V}$ and $C_2 = \frac{a\gamma(\lambda - \mu_T T_2) - \mu_I \mu_C (\mu_E + \gamma)}{p\mu_C(\mu_E + \gamma)}$. This equilibrium denotes the state in which both the virus and the CTL immune response are present.

Theorem 2.1.

(i) *When $R_0 \leq 1$, the system (1.1) has always an infection-free equilibrium of the form* $Q_0\big(\frac{\lambda}{\mu_T}, 0, 0, 0, 0\big)$.

(ii) *When $R_0 > 1$, the system (1.1) has an immune-free infection equilibrium of the form* $Q_1(T_1, E_1, I_1, V_1, 0)$ *with* $T_1 \in \big(0, \frac{\lambda}{\mu_T}\big)$, $E_1 = \frac{\lambda - \mu_T T}{\mu_E + \gamma}$, $I_1 = \frac{\gamma(\lambda - \mu_T T)}{\mu_I(\mu_E + \gamma)}$ *and* $V_1 = \frac{k\gamma(\lambda - \mu_T T)}{\mu_I \mu_V(\mu_E + \gamma)}$.

(iii) *When $R_1 > 1$, the system (1.1) has an infection equilibrium of the form* $Q_2(T_2, E_2, I_2, V_2, C_2)$ *with* $T_2 \in \big(0, \frac{\lambda}{\mu_T} - \frac{\mu_I \mu_C(\mu_E + \gamma)}{a\gamma\mu_T}\big)$, $E_2 = \frac{\lambda - \mu_T T_2}{\mu_E + \gamma}$, $I_2 = \frac{\mu_C}{a}$, $V_2 = \frac{k\mu_C}{a\mu_V}$ *and* $C_2 = \frac{a\gamma(\lambda - \mu_T T_2) - \mu_I \mu_C(\mu_E + \gamma)}{p\mu_C(\mu_E + \gamma)}$.

3 Stability Analysis

Now, we focus on the global stability of the infection-free equilibrium Q_0 and the immune-free equilibrium Q_1. At first, let $\Phi(x) = x - 1 - \ln(x)$. Note that Φ has a global minimum at 1 and $\Phi(1) = 0$. To simplify, we will use the notation: $\psi(t) = \psi$ and $\psi(t - \tau) = \psi_\tau$, for any $\psi \in \{T, E, I, V, C\}$.

Theorem 3.1. *If $R_0 \leq 1$, then the infection-free equilibrium Q_0 is globally asymptotically stable.*

Proof. Consider the following Lyapunov functional

$$\begin{aligned} W_0(T, E, I, V, C) &= T - T_0 - \int_{T_0}^{T} \frac{f(T_0, 0)}{f(S, 0)} dS + \frac{\rho(T - T_0 + E)^2}{2(1 + \alpha_1 T_0)(\mu_T + \mu_E + \gamma)T_0} \\ &\quad + \frac{\rho + \mu_E + \gamma}{\gamma} I + E + \frac{\mu_I(\rho + \mu_E + \gamma)}{k\gamma} V + \frac{p(\rho + \mu_E + \gamma)}{a\gamma} C \\ &\quad + \frac{p(\rho + \mu_E + \gamma)}{\gamma} \int_{t-\tau}^{t} IC d\theta, \end{aligned}$$

where $T_0 = \frac{\lambda}{\mu_T}$.

Calculating the time derivative of W_0 along the positive solutions of system (1.1), we obtain

$$\begin{aligned} \frac{dW_0}{dt} &= \left(1 - \frac{f(T_0, 0)}{f(T, 0)}\right) \frac{dT}{dt} + \frac{\rho(T - T_0 + E)(\frac{dT}{dt} + \frac{dE}{dt})}{(1 + \alpha_1 T_0)(\mu_T + \mu_E + \gamma)T_0} \\ &\quad + \frac{\rho + \mu_E + \gamma}{\gamma} \frac{dI}{dt} + \dot{E} + \frac{\mu_I(\rho + \mu_E + \gamma)}{k\gamma} \frac{dV}{dt} + \frac{p(\rho + \mu_E + \gamma)}{a\gamma} \frac{dC}{dt} \\ &\quad + \frac{p(\rho + \mu_E + \gamma)}{\gamma} \frac{d}{dt} \int_{t-\tau}^{t} IC d\theta. \end{aligned}$$

Noting that $\lambda = \mu_T T_0$, we get

$$\begin{aligned}
\frac{dW_0}{dt} &= \Big(1-\frac{f(T_0,0)}{f(T,0)}\Big)\mu_T(T_0-T)+\frac{f(T_0,0)f(T,V)}{f(T,0)}V+\rho\Big(1-\frac{f(T_0,0)}{f(T,0)}\Big)E\\
&\quad -\frac{\rho\mu_T(T-T_0)^2}{(1+\alpha_1T_0)(\mu_T+\mu_E+\gamma)T_0}-\frac{\rho(\mu_E+\gamma)E^2}{(1+\alpha_1T_0)(\mu_T+\mu_E+\gamma)T_0}\\
&\quad +\frac{\rho E}{(1+\alpha_1T_0)T_0}\big(T_0-T\big)-\frac{p(\rho+\mu_E+\gamma)}{\gamma}IC-\frac{\mu_I\mu_V(\rho+\mu_E+\gamma)}{k\gamma}V\\
&\quad +\frac{p(\rho+\mu_E+\gamma)}{\gamma}I_\tau C_\tau-\frac{\mu_C p(\rho+\mu_E+\gamma)}{a\gamma}C+\frac{p(\rho+\mu_E+\gamma)}{\gamma}\big[IC-I_\tau C_\tau\big]\\
&= -\Big(\frac{1}{T}+\frac{\rho}{(\mu_T+\mu_E+\gamma)T_0}\Big)\frac{\mu_T(T-T_0)^2}{1+\alpha_1T_0}-\frac{\rho(\mu_E+\gamma)E^2}{(1+\alpha_1T_0)(\mu_T+\mu_E+\gamma)T_0}\\
&\quad -\frac{\rho(T-T_0)^2E}{(1+\alpha_1T_0)TT_0}+\frac{\mu_I\mu_V(\rho+\mu_E+\gamma)}{k\gamma}(R_0-1)V\\
&\quad -\frac{(\alpha_2+\alpha_3T)V^2}{1+\alpha_1T+\alpha_2V+\alpha_3TV}f(T_0,0)-\frac{\mu_C p(\rho+\mu_E+\gamma)}{a\gamma}C.
\end{aligned}$$

Therefore, $\frac{dW_0}{dt}\le 0$ if $R_0\le 1$. Further, $\frac{dW_0}{dt}=0$ if and only if $T=\frac{\lambda}{\mu_T}$, $E=0$, $I=0$, $V=0$ and $C=0$. Hence, the largest compact invariant set in $\{(T,E,I,V,C)|\frac{dW_0}{dt}=0\}$ is just the singleton $\{Q_0\}$. Thus, the global stability of the infection-free equilibrium Q_0 follows from LaSalle's invariance principle [13]. ■

Theorem 3.2. *The immune-free infection equilibrium Q_1 of system (1.1) is globally asymptotically stable if $R_1\le 1<R_0$ and*

$$R_0\le 1+\frac{[\mu_T\mu_I\mu_V(\mu_E+\gamma)+\alpha_2\mu_T\lambda k\gamma](\mu_E+\rho+\gamma)+\rho\alpha_3k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E+\rho+\gamma)(\mu_T+\alpha_1\lambda)}. \tag{3.1}$$

Proof. Constructing a Lyapunov functional W_1 as follows

$$\begin{aligned}
W_1(T,E,I,V,C) &= T-T_1-\int_{T_1}^{T}\frac{f(T_1,V_1)}{f(S,V_1)}dS\\
&\quad +\frac{\rho(1+\alpha_2V_1)(T-T_1+E-E_1)^2}{2(1+\alpha_1T_1+\alpha_2V_1+\alpha_3T_1V_1)(\mu_T+\mu_E+\gamma)T_1}\\
&\quad +\frac{f(T_1,V_1)V_1}{\gamma E_1}I_1\Phi(\frac{I}{I_1})+E_1\Phi(\frac{E}{E_1})+\frac{\mu_If(T_1,V_1)V_1}{k\gamma E_1}V_1\Phi(\frac{V}{V_1})\\
&\quad +\frac{pf(T_1,V_1)V_1}{a\gamma E_1}C+\frac{pf(T_1,V_1)V_1}{\gamma E_1}\int_{t-\tau}^{t}ICd\theta.
\end{aligned}$$

The time derivative of W_1 along the positive solutions of system (1.1) satisfies

$$\begin{aligned}
\frac{dW_1}{dt} &= \Big(1-\frac{f(T_1,V_1)}{f(T,V_1)}\Big)\frac{dT}{dt}+\frac{\rho(1+\alpha_2V_1)(T-T_1+E-E_1)(\frac{dT}{dt}+\frac{dE}{dt})}{(1+\alpha_1T_1+\alpha_2V_1+\alpha_3T_1V_1)(\mu_T+\mu_E+\gamma)T_1}\\
&\quad +\frac{f(T_1,V_1)V_1}{\gamma E_1}\Big(1-\frac{I_1}{I}\Big)\frac{dI}{dt}+\Big(1-\frac{E_1}{E}\Big)\frac{dE}{dt}+\frac{\mu_If(T_1,V_1)V_1}{k\gamma E_1}\Big(1-\frac{V_1}{V}\Big)\frac{dV}{dt}\\
&\quad \frac{pf(T_1,V_1)V_1}{a\gamma E_1}\frac{dC}{dt}+\frac{pf(T_1,V_1)V_1}{\gamma E_1}\frac{d}{dt}\int_{t-\tau}^{t}ICd\theta.
\end{aligned}$$

Using $\lambda = \mu_T T_1 + f(T_1, V_1)V_1 - \rho E_1$, we get

$$\begin{aligned}
\frac{dW_1}{dt} &= \left(1 - \frac{f(T_1,V_1)}{f(T,V_1)}\right)\mu_T(T_1 - T) + \frac{f(T_1,V_1)f(T,V)}{f(T,V_1)}V + \rho\left(1 - \frac{f(T_1,V_1)}{f(T,V_1)}\right)E \\
&\quad - \frac{\mu_T\rho(1+\alpha_2V_1)}{(1+\alpha_1T_1+\alpha_2V_1+\alpha_3T_1V_1)(\mu_T+\mu_E+\gamma)T_1}(T-T_1)^2 \\
&\quad - \frac{\rho(1+\alpha_2V_1)(\mu_E+\gamma)}{(1+\alpha_1T_1+\alpha_2V_1+\alpha_3T_1V_1)(\mu_T+\mu_E+\gamma)T_1}(E-E_1)^2 \\
&\quad - \frac{\rho(1+\alpha_2V_1)(E-E_1)(T-T_1)^2}{(1+\alpha_1T_1+\alpha_2V_1+\alpha_3T_1V_1)T_1T} - \frac{(f(T_1,V_1))^2}{f(T,V_1)}V_1 + 4f(T_1,V_1)V_1 \\
&\quad - f(T_1,V_1)V - f(T_1,V_1)V_1\frac{I_1E}{IE_1} - f(T,V)V\frac{E_1}{E} - f(T_1,V_1)V_1\frac{V_1I}{I_1V} \\
&\quad + \frac{pf(T_1,V_1)V_1}{\gamma E_1}(I_1 - \frac{\mu_C}{a})C \\
&= - \frac{(1+\alpha_2V_1)(T-T_1)^2}{TT_1(1+\alpha_1T_1+\alpha_2V_1+\alpha_3T_1V_1)}\left((\mu_TT_1 - \rho E_1) + \frac{\rho\mu_TT}{\mu_T+\mu_E+\gamma} + \rho E\right) \\
&\quad - \frac{\rho(E-E_1)^2(1+\alpha_2V_1)(\mu_E+\gamma)}{T_1(1+\alpha_1T_1+\alpha_2V_1+\alpha_3T_1V_1)(\mu_T+\mu_E+\gamma)} \\
&\quad + f(T_1,V_1)V_1\left(5 - \frac{f(T_1,V_1)}{f(T,V_1)} - \frac{I_1E}{E_1I} - \frac{f(T,V)}{f(T_1,V_1)}\frac{VE_1}{V_1E} - \frac{V_1I}{VI_1} - \frac{f(T,V_1)}{f(T,V)}\right) \\
&\quad - \frac{f(T_1,V_1)(1+\alpha_1T)(\alpha_2+\alpha_3T)(V-V_1)^2}{(1+\alpha_1T+\alpha_2V_1+\alpha_3TV_1)(1+\alpha_1T+\alpha_2V+\alpha_3TV)} \\
&\quad + \frac{p\mu_Cf(T_1,V_1)V_1}{a\gamma E_1}(R_1 - 1)C.
\end{aligned}$$

Using the arithmetic-geometric inequality, we get

$$5 - \frac{f(T_1,V_1)}{f(T,V_1)} - \frac{I_1E}{E_1I} - \frac{f(T,V)}{f(T_1,V_1)}\frac{VE_1}{V_1E} - \frac{V_1I}{VI_1} - \frac{f(T,V_1)}{f(T,V)} \leq 0. \tag{3.2}$$

Therefore, $\frac{dW_1}{dt} \leq 0$ if $R_1 \leq 1$ and $\rho E_1 \leqslant \mu_T T_1$.

Obviously, the condition $\rho E_1 \leqslant \mu_T T_1$ is equivalent to

$$R_0 \leq 1 + \frac{[\mu_T\mu_I\mu_V(\mu_E+\gamma) + \alpha_2\mu_T\lambda k\gamma](\mu_E+\rho+\gamma) + \rho\alpha_3k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E+\rho+\gamma)(\mu_T+\alpha_1\lambda)}.$$

In addition, $\frac{dW_1}{dt} = 0$ if and only if $T = T_1$, $E = E_1$, $I = I_1$, $V = V_1$ and $C = 0$. Hence, the largest compact invariant set in $\{(T,E,I,V,C)|\frac{dW_1}{dt} = 0\}$ is the singleton $\{Q_1\}$. This prove the global stability of Q_1 by using LaSalle's invariance principle [13]. ■

For the global stability of the chronic infection equilibrium, we give the following result without any proof, since the proof is similar to that presented by Maziane et al. in [5].

Theorem 3.3. *When $\tau = 0$, the chronic infection equilibrium with immune response Q_2 is globally asymptotically stable if $R_1 > 1$ and*

$$k\beta\mu_C\rho \leq \alpha_1\lambda\rho a\mu_V + \mu_T(\rho+\mu_E+\gamma)(\alpha_2k\mu_C + a\mu_V) + \alpha_3\rho\lambda k\mu_C. \tag{3.3}$$

Next, we investigate the local stability of the chronic infection equilibrium $Q_2(T_2, E_2, I_2, V_2, C_2)$.

The associated characteristic equation of system (1.1) is given by

$$\lambda^5 + a_1\lambda^4 + a_2\lambda^3 + a_3\lambda^2 + a_4\lambda + a_5 + e^{-\lambda\tau}\big(b_1\lambda^4 + b_2\lambda^3 + b_3\lambda^2 + b_4\lambda + b_5\big) = 0, \tag{3.4}$$

where,

$$\begin{aligned}
a_1 = \;& \frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T + \mu_I + \mu_V + \mu_C + pC_2 + \mu_E + \rho + \gamma,\\
a_2 = \;& \Big(\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T\Big)\Big[(\mu_E+\rho+\gamma) + \mu_V + \mu_I + \mu_C + pC_2\Big]\\
& +(\mu_E+\rho+\gamma)(\mu_V+\mu_I+\mu_C+pC_2) + (\mu_I+pC_2)(\mu_V+\mu_C) + \mu_V\mu_C + \mu_T\rho,\\
a_3 = \;& \Big(\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T\Big)\Big[(\mu_V+\mu_C)(\mu_I+pC_2) + \mu_V\mu_C\Big]\\
& +\Big(\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T\Big)(\mu_E+\gamma)(\mu_I+\mu_V+\mu_C+pC_2) + \mu_C\mu_V(\mu_I+pC_2+\mu_E+\rho+\gamma)\\
& -k\gamma\frac{\partial f(T_2,V_2)}{\partial V}V_2 + \mu_T\rho(\mu_V+\mu_I+\mu_C+pC_2),\\
a_4 = \;& \Big(\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T\Big)\Big[\mu_V\mu_C(\mu_I+pC_2) + (\mu_E+\gamma)(\mu_V+\mu_I+pC_2)\mu_C\\
& -k\gamma\frac{\partial f(T_2,V_2)}{\partial V}V_2\Big] - k\gamma\mu_C\frac{\partial f(T_2,V_2)}{\partial V}V_2 + \rho\mu_T\Big((\mu_I+pC_2)(\mu_C+\mu_V) + \mu_V\mu_C\Big)\\
& +\frac{\partial f(T_2,V_2)}{\partial T}V_2\Big[k\gamma\frac{\partial f(T_2,V_2)}{\partial V}V_2 + \mu_V(\mu_E+\gamma)(\mu_I+pC_2)\Big],\\
a_5 = \;& -\Big(\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T\Big)k\gamma\frac{\partial f(T_2,V_2)}{\partial V}V_2\mu_C + \frac{\partial f(T_2,V_2)}{\partial T}V_2\mu_C\big(\frac{\partial f(T_2,V_2)}{\partial V}V_2 + f(T_2,V_2)\big)\\
& -k\gamma\mu_T\mu_V\frac{\partial f(T_2,V_2)}{\partial V}V_2,\\
b_1 = \;& -\mu_C,\\
b_2 = \;& -\mu_C\Big[\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T + \mu_I + \mu_V + \mu_E + \rho + \gamma\Big],\\
b_3 = \;& -\mu_C\Big[\Big(\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T\Big)\big(\mu_I+\mu_V+\mu_E+\gamma\big) + \mu_I\mu_V + (\mu_I+\mu_V)(\mu_E+\rho+\gamma) + \rho\mu_T\Big],\\
b_4 = \;& -\mu_C\Big[\Big(\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T\Big)\Big(\mu_I\mu_V + (\mu_E+\gamma)(\mu_I+\mu_V)\Big) - k\gamma\Big(\frac{\partial f(T_2,V_2)}{\partial V}V_2 + f(T_2,V_2)\Big)\\
& +\mu_T\rho(\mu_I+\mu_V)\Big],\\
b_5 = \;& -\mu_C\Big[\Big(\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T\Big)\mu_I\mu_V(\mu_E+\gamma) - k\gamma\mu_T\Big(\frac{\partial f(T_2,V_2)}{\partial V}V_2 + f(T_2,V_2)\Big) + \rho\mu_T\mu_I\mu_V\Big].
\end{aligned}$$

For $\tau \neq 0$, we assume that $\lambda = i\omega$ with $\omega > 0$ is a purely imaginary root of (3.4). substituting $\lambda = i\omega$ in (3.4) and equating real parts and imaginary parts, we have

$$\begin{aligned}
w^5 - a_2w^3 + a_4w &= (b_1w^4 - b_3w^2 + b_5)\sin\omega\tau + (b_2w^3 - b_4w)\cos\omega\tau,\\
a_1w^4 - a_3w^2 + a_5 &= -(b_1w^4 - b_3w^2 + b_5)\cos\omega\tau + (b_2w^3 - b_4w)\sin\omega\tau.
\end{aligned} \tag{3.5}$$

Squaring and adding both equations of (3.5), we obtain

$$\omega^{10} + c_1\omega^8 + c_2\omega^6 + c_3\omega^4 + c_4\omega^2 + c_5 = 0, \tag{3.6}$$

where

$$\begin{aligned} c_1 = &\quad a_1^2 - 2a_2 - b_1^2, \\ c_2 = &\quad a_2^2 + 2a_4 - 2a_1a_3 + 2b_1b_3 - b_2^2, \\ c_3 = &\quad a_3^2 - 2a_2a_4 - b_3^2 + 2b_2b_4 + 2a_1a_5 - 2b_1b_5, \\ c_4 = &\quad a_4^2 - b_4^2 - 2a_3a_5 + 2b_3b_5, \\ c_5 = &\quad a_5^2 - b_5^2. \end{aligned}$$

Letting $z = \omega^2$ yields

$$h(z) = z^5 + c_1z^4 + c_2z^3 + c_3z^2 + c_4z + c_5 = 0. \tag{3.7}$$

Lemma 3.4. *If $c_5 < 0$, then Eq. (3.7) has at least one positive root.*

Proof. Since $\lim_{z\to+\infty} h(z) = +\infty$ and $h(0) = c_5 < 0$, then there exists a $z_0 \in (0, +\infty)$ such that $h(z_0) = 0$. ■

For the case of $c_5 \geq 0$, we consider the following equation

$$h'(z) = 5z^4 + 4c_1z^3 + 3c_2z^2 + 2c_3z + c_4 = 0. \tag{3.8}$$

Let $z = y - \frac{1}{5}c_1$, then equation (3.8) becomes

$$y^4 + p_1y^2 + q_1y + r_1 = 0, \tag{3.9}$$

where

$$\begin{aligned} p_1 = &\quad -\frac{6}{25}c_1^2 + \frac{3}{5}c_2, \\ q_1 = &\quad \frac{8}{125}c_1^3 + \frac{6}{25}c_1c_2 + \frac{2}{5}c_3, \\ r_1 = &\quad -\frac{3}{625}c_1^4 + \frac{3}{125}c_1^2c_2 - \frac{2}{25}c_1c_3 + \frac{1}{5}c_4. \end{aligned}$$

If $q_1 = 0$, then the solutions of (3.9) are

$$y_1 = \sqrt{\frac{-p_1 + \sqrt{\Delta_0}}{2}}, \qquad y_2 = -\sqrt{\frac{-p_1 + \sqrt{\Delta_0}}{2}},$$

$$y_3 = \sqrt{\frac{-p_1 - \sqrt{\Delta_0}}{2}}, \qquad y_4 = -\sqrt{\frac{-p_1 - \sqrt{\Delta_0}}{2}},$$

where $\Delta_0 = p_1^2 - 4r_1$. Then $z_i = y_i - \frac{1}{5}c_1$, $i = 1, 2, 3, 4$ are the roots of (3.8). From [14], we have the following result.

Lemma 3.5. *Suppose that $c_5 \geq 0$ and $q_1 = 0$.*

(i) *If $\Delta_0 < 0$, then (3.7) has no positive real roots.*

(ii) *If $\Delta_0 \geq 0$, $p_1 \geq 0$ and $r_1 > 0$, then (3.7) has no positive real roots.*

(iii) *If (i) and (ii) are not satisfied, then (3.7) has positive real roots if and only if there exists at least one $z^* \in \{z_1, z_2, z_3, z_4\}$ such that $z^* > 0$ and $h(z^*) \leq 0$.*

Next, we assume that $q_1 \neq 0$. Denote

$$\begin{aligned}
p_2 = &\quad -\frac{1}{3}p_1^2 - 4r_1,\\
q_2 = &\quad -\frac{2}{27}p_1^3 + \frac{8}{3}p_1 r_2 - q_1^2,\\
\Delta_1 = &\quad \frac{1}{27}p_2^3 + \frac{1}{4}q_2^2,\\
s_* = &\quad \sqrt[3]{-\frac{q_2}{2} + \sqrt{\Delta_1}} + \sqrt[3]{-\frac{q_2}{2} - \sqrt{\Delta_1}} + \frac{1}{3}p_1,\\
\Delta_2 = &\quad -s_* - p_1 + \frac{2q_1}{\sqrt{s_* - p_1}},\\
\Delta_3 = &\quad -s_* - p_1 - \frac{2q_1}{\sqrt{s_* - p_1}}.\\
\bar{z} = &\quad \frac{q_1}{2(p_1 - s_*)} - \frac{1}{5}p.
\end{aligned}$$

Similarly to [14], we get the following results.

Lemma 3.6. *Suppose that $c_5 \geq 0$, $q_1 \neq 0$ and $s_* > p_1$.*

(i) *If $\Delta_2 < 0$ and $\Delta_3 < 0$, then (3.7) has no positive real roots.*

(ii) *If (i) is not satisfied, then (3.7) has positive real roots if and only if there exists at least one $z^* \in \{z_1, z_2, z_3, z_4\}$ such that $z^* > 0$ and $h(z^*) \leq 0$.*

Lemma 3.7. *If $c_5 \geq 0$, $q_1 \neq 0$ and $s_* < p_1$, then (3.7) has positive real roots if and only if $\frac{q_1^2}{4(p_1 - s_*)^2} + \frac{1}{2}s_* = 0$, $\bar{z} > 0$ and $h(\bar{z}) \leq 0$.*

Suppose that (3.7) has positive roots z_k, $k = 1, 2, 3, 4, 5$, where $w_k = \sqrt{z_k}$. From (3.5), we have

$$\begin{aligned}
\cos \omega_k \tau &= \frac{(w^5 - a_2 w^3 + a_4 w)(b_2 w^3 - b_4 w) - (a_1 w^4 - a_3 w^2 + a_5)(b_1 w^4 - b_3 w^2 + b_5)}{(b_2 w^3 - b_4 w)^2 + (b_1 w^4 - b_3 w^2 + b_5)^2}\\
&= L(\omega_k).
\end{aligned}$$

Let

$$\tau_j^k = \frac{1}{\omega_k}\Big[\arccos L(\omega_k) + 2j\pi\Big], \qquad k = 1, 2, 3, 4, 5, \quad j = 0, 1, 2, \ldots .$$

Then $\pm i w_k$ is a pair of purely imaginary roots of (3.4) with $\tau = \tau_j^k$.
Define

$$\tau_0 = \tau_{j_0}^{k_0} = \min_{1 \leq k \leq 5, j \geq 1}\{\tau_j^k\}, \qquad w_0 = w_{k_0}.$$

From Theorem 3.3 and Lemmas 3.4-3.7, we have the following result.

Lemma 3.8. *Suppose that $R_1 > 1$ and (3.3) hold.*

(i) *If one of the following holds: (a) $c_5 < 0$; (b) $c_5 \geq 0$, $q_1 = 0$, $\Delta_0 \geq 0$ and $p_1 < 0$ or $r_1 \leq 0$ and there exist $z^* \in \{z_1, z_2, z_3, z_4\}$ such that $z^* > 0$ and $h(z^*) \leq 0$; (c) $c_5 \geq 0$, $q_1 \neq 0$, $s_* > p_1$, $\Delta_2 \geq 0$ or $\Delta_3 \geq 0$ and there exist $z^* \in \{z_1, z_2, z_3, z_4\}$ such that $z^* > 0$ and $h(z^*) \leq 0$; (d) $c_5 \geq 0$, $q_1 \neq 0$, $s_* < p_1$, $\frac{q_1^2}{4(p_1 - s^*)^2} + \frac{1}{2}s_* = 0$, $\bar{z} > 0$ and $h(\bar{z}) \leq 0$, then all the roots of (3.4) have negative real parts when $\tau \in [0, \tau_0)$.*

(ii) *If all the conditions $(a) - (d)$ of (i) are not satisfied, then all roots of (3.4) have negative real parts for all $\tau \geq 0$.*

Let $\lambda(\tau) = \xi(\tau) + i\omega(\tau)$ be a root of (3.4) satisfying $\xi(\tau) = 0$ and $\omega(\tau) = \omega_0$. Differentiating the two sides of (3.4) with respect to τ and noticing that λ is a function of τ, it follows that

$$\begin{aligned}\left(\frac{d\lambda}{d\tau}\right)^{-1} = & -\frac{5\lambda^4 + 4a_1\lambda^3 + 3a_2\lambda^2 + 2a_3\lambda + a_4}{\lambda(\lambda^5 + a_1\lambda^4 + a_2\lambda^3 + a_3\lambda^2 + a_4\lambda + a_5)} \\ & + \frac{4b_1\lambda^3 + 3b_2\lambda^2 + 2b_3\lambda^1 + b_4}{\lambda(b_1\lambda^4 + b_2\lambda^3 + b_3\lambda^2 + b_4\lambda + b_5)} - \frac{\tau}{\lambda}.\end{aligned}$$

By (3.5) we get

$$\begin{aligned}\left[\frac{dRe(\lambda(\tau))}{d\tau}\right]^{-1}_{\tau=\tau_k^j} = & -\frac{(5\omega_k^4 - 3a_2\omega_k^2 + a_4)(-\omega_k^6 + a_2\omega_k^4 - a_4\omega_k^2)}{(-\omega_k^6 + a_2\omega_k^4 - a_4\omega_k^2)^2 + (a_1\omega_k^5 - a_3\omega_k^3 + a_5\omega_k)^2} \\ & + \frac{(4a_1\omega_k^3 - 2a_3\omega_k)(a_1\omega_k^5 - a_3\omega_k^3 + a_5\omega_k)}{(-\omega_k^6 + a_2\omega_k^4 - a_4\omega_k^2)^2 + (a_1\omega_k^5 - a_3\omega_k^3 + a_5\omega_k)^2} \\ & + \frac{(-3b_2\omega_k^2 + b_4)(b_2\omega_k^4 - b_4\omega_k^2)}{(b_2\omega_k^4 - b_4\omega_k^2)^2 + (b_1\omega_k^5 - b_3\omega_k^3 + b_5\omega_k)^2} \\ & + \frac{(-4b_1\omega_k^3 + 2b_3\omega_k)(b_1\omega_k^5 - b_3\omega_k^3 + b_5\omega_k)}{(b_2\omega_k^4 - b_4\omega_k^2)^2 + (b_1\omega_k^5 - b_3\omega_k^3 + b_5\omega_k)^2}.\end{aligned}$$

From (3.4) we obtain

$$(\omega^5 - a_2\omega^3 + a_4\omega)^2 + (a_1\omega^4 - a_3\omega^2 + a_5)^2 = (b_2\omega^3 - b_4\omega)^2 + (b_1\omega^4 - b_3\omega^2 + b_5).$$

Then

$$\begin{aligned}\left[\frac{dRe(\lambda(\tau))}{d\tau}\right]^{-1}_{\tau=\tau_k^j} = & \frac{5z_k^4 + 4c_1z_k^3 + 3c_2z_k^2 + 2c_3z_k + a_4}{(b_1\omega_k^4 - b_3\omega_k^2 + b_5)^2 + (b_2\omega_k^2 - b_4)^2} \\ = & \frac{h'(z_k)}{(b_1\omega_k^4 - b_3\omega_k^2 + b_5)^2 + (b_2\omega_k^2 - b_4)^2}.\end{aligned}$$

Therefore, it follows that

$$sign\left[\frac{dRe(\lambda(\tau))}{d\tau}\right]_{\tau=\tau_k^j} = sign\left[\frac{dRe(\lambda(\tau))}{d\tau}\right]^{-1}_{\tau=\tau_k^j} = sign\Big[h'(z_k)\Big].$$

Since $z_k > 0$, then $Re\left[\frac{d\lambda_k(\tau)}{d\tau}\right]_{\tau=\tau_k^j}$ and $h'(z_k)$ have the same sign.

Summarizing the above analysis in the following result.

Theorem 3.9. *Suppose that $R_1 > 1$ and (3.3) hold.*

(i) *If the conditions $(a) - (d)$ of Lemma 3.8 are all not satisfied, then the chronic infection equilibrium Q_2 is locally asymptotically stable for all time delay $\tau \geq 0$.*

(ii) *If one of the conditions $(a)-(d)$ of Lemma 3.8 is satisfied, then the chronic infection equilibrium Q_2 is locally asymptotically stable for $\tau \in [0, \tau_0)$.*

(iii) *If the condition of (ii) is satisfied and $h'(z_k) \neq 0$, then system (1.1) undergoes a Hopf bifurcation at Q_2 when $\tau = \tau_0$.*

4 Numerical Simulations

We choose the following data set of system (1.1): $\Lambda = 10$, $\mu_T = 0.0139$, $\beta = 2.4 \times 10^{-5}$, $\alpha_1 = 0.1$, $\alpha_2 = 0.01$, $\alpha_3 = 0.00001$, $\rho = 0.01$, $\gamma = 0.01$, $\mu_I = 0.27$, $\mu_E = 0.0347$, $p = 0.001$, $k = 1200$, $\mu_V = 3$, $a = 0.002$ and $\mu_C = 0.1$. By calculation we have $R_0 = 0.1141 < 1$. In this case, system (1.1) has an infection-free equilibrium $Q_f(719, 4245, 0, 0, 0, 0)$. Hence, by Theorem 3.2, Q_f is globally asymptotically stable. (See fig 1).

In fig 2, we choose $\beta = 0.0012$ and keep all other parameter values. By calculation, we have $R_0 = 3.2055$ and $R_1 = 0.8183$ and $\frac{[\mu_T\mu_I\mu_V(\mu_E+\gamma)+\alpha_2\mu_T\lambda k\gamma](\mu_E+\rho+\gamma)+\rho\alpha_3 k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E+\rho+\gamma)(\mu_T+\alpha_1\lambda)} = 3.3465$. In this case, system (1.1) has an immune-free equilibrium $Q_1(139.7195, 180.2658, 6.6765, 2671.8, 0)$. By Theorem 3.3, Q_1 is globally asymptotically stable. In the absence of CTL cells, the $CD4^+T$ cells decrease to the value 139.7195, which means that the patient enters in the phase AIDS, (< 200 cell mm^{-3}).

Now, we change one parameter, which is $a = 0.065$, then, we have $R_1 = 3.8292 > 1$, condition (3.3) holds and (3.4) have no positive root. Then, the system (1.1) have a chronic infection equilibrium $Q_2(341.6990, 129.5433, 1.9973, 798.8222, 380.0478)$. From the Theorem 3.9($i$), we get that Q_2 is locally asymptotically stable for any time delay $\tau \geq 0$. (See fig 3).

Next, we choose $k = 1500$, then we get that $R_1 = 4.1492 > 1$, condition (3.3) holds and (3.4) have two positive roots. By calculation, we have $\tau_0 = 45, 1203$. From Theorem 3.9 (ii), $Q_2(319.4270, 122.1529, 1.4771, 738.3008, 557.2327)$ is locally asymptotically stable for if $0 < \tau < \tau_0$. (See Fig. 4).

Finally, Fig 5 shows the occurrence of Hopf bifurcations in the case of $\tau = 67 > \tau_0$.

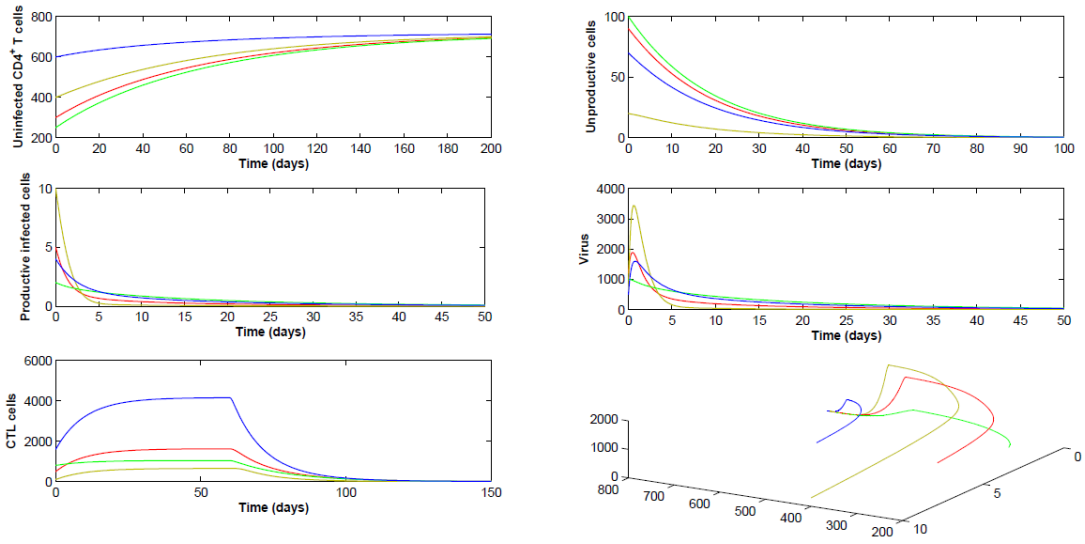

Fig. 1. Stability of the infection-free equilibrium Q_0 of system (1.1) for different initial conditions, when $R_0 \leq 1$, for all $\tau \geq 0$

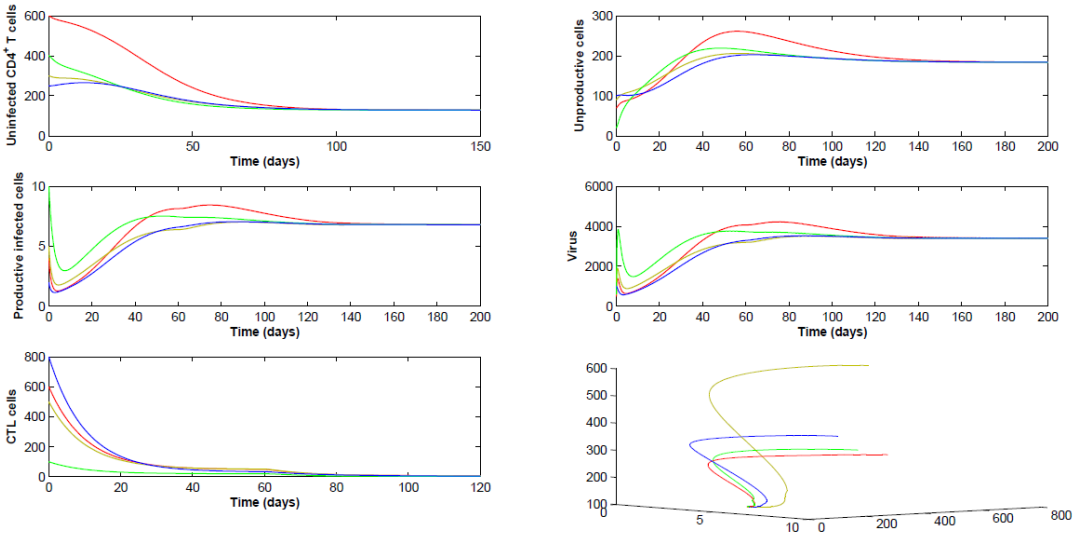

Fig. 2. Stability of the immune-free infection equilibrium Q_1 of system (1.1) for different initial conditions, when $R_0 > 1 \geq R_1$ and condition (3.1) holds, for all $\tau \geq 0$

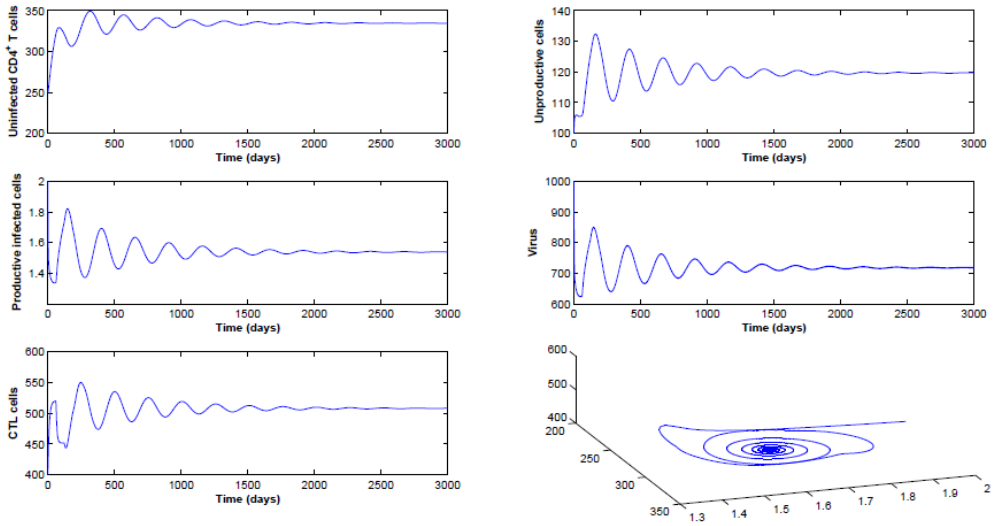

Fig. 3. Stability of the chronic infection-equilibrium Q_2 of system (1.1) when $R_1 > 1$ and condition (3.3) holds, for all $\tau \geq 0$

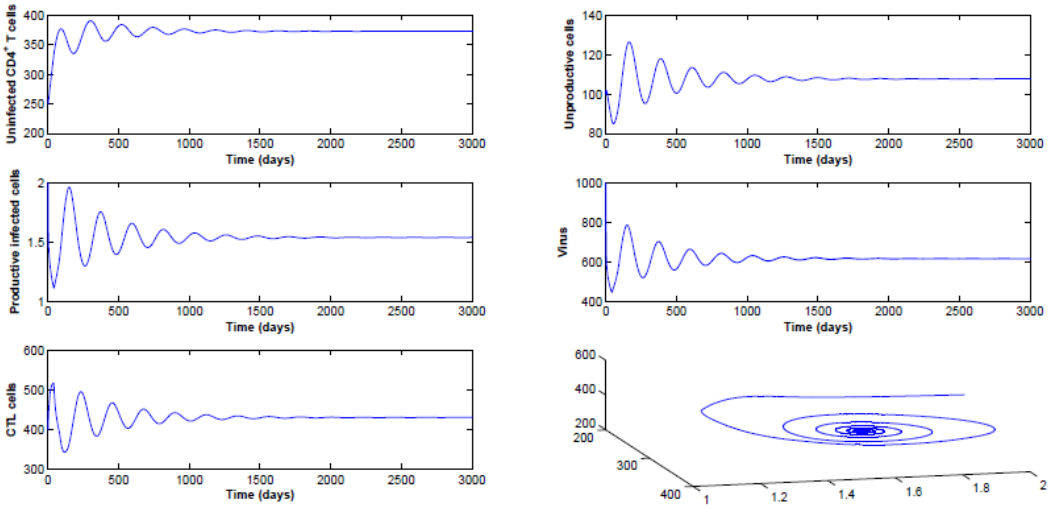

Fig. 4. Stability of the chronic infection equilibrium Q_2 of system (1.1) when $R_1 > 1$, condition (3.3) holds and $\tau = 40$

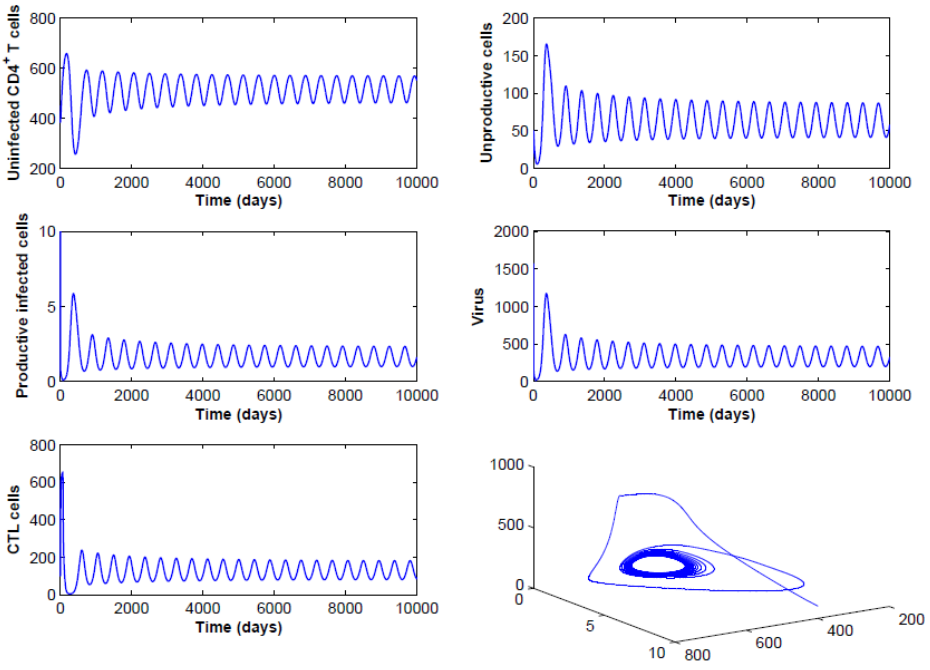

Fig. 5. A periodic solutions appear when $R_1 > 1$, condition (3.3) holds and $\tau = 67$

5 Conclusion

In this paper, we have proposed a delayed HIV infection model with cure of infected cells in eclipse stage. The delay represents the time needed for the activation of the CTL immune response. In addition, the infection transmission process in the proposed model is modeled by Hattaf's incidence rate that includes the traditional bilinear incidence rate, the saturated incidence rate, the Beddington-DeAngelis functional response and Crowley-Martin functional response. We have proved that the delay has no effect on the dynamics of the model when $R_0 \leq 1$ or $R_1 \leq 1 \leq R_0$. However, when $R_1 > 1$, the model loses its stability when the time delay is large.

Competing Interests

Authors have declared that no competing interests exist.

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