



## Viral Dynamics of Delayed CTL-inclusive HIV-1 Infection Model With Both Virus-to-cell and Cell-to-cell Transmissions

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### Abstract

We consider a mathematical model that describes a viral infection of HIV-1 with both virus-to-cell and cell-to-cell transmission, CTL response immune and four distributed delays, describing intracellular delays and immune response delay. One of the main features of the model is that it includes a constant production rate of CTLs export from thymus, and an immune response delay. We derive the basic reproduction number and show that if the basic reproduction number is less than one, then the infection free equilibrium is globally asymptotically stable; whereas, if the basic reproduction number is greater than one, then there exist a chronic infection equilibrium, which is globally asymptotically stable in absence of immune response delay. Furthermore, for the special case with only immune response delay, we determine some conditions for stability switches of the chronic infection equilibrium. Numerical simulations indicate that the intracellular delays and immune response delay can stabilize and/or destabilize the chronic infection equilibrium.

**Keywords:** HIV-1 infection; Time delay; CTL immune response; Hopf bifurcation; Stability

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## 1. Introduction

Research on HIV/AIDS infection is performed in various domains including mathematical modelling. Mathematical modelling is about modelling the evolution of the disease using mathematical tools, mainly differential equations. Over the recent years, great efforts have been paid in mathematical modeling of within-host virus dynamics. Mathematical models have been developed to describe the *in vivo* infection process of many viruses such as human immunodeficiency virus type I (HIV-I), hepatitis C virus (HCV), hepatitis B virus (HBV), and human T-cell lymphotropic virus I (HTLV-I) (Perelson et al. (1993); Perelson et al. (1996); Nowak et al. (2018); Bonhoeffer et al. (1997); Wang et al. (2002); Katri and Ruan (2004); Herz et al. (1996)). These within-host models are useful for exploring possible mechanisms and outcomes of the viral infection process (Perelson et al. (1993); Perelson et al. (1996)), and for estimating key parameter values such as virion clearance rate, life span of infected cells, and average viral generation time *in vivo* (Bonhoeffer et al. (1997)).

Mathematical modelling is a useful tool to improve our understanding on the interactions between the population and its environment (Hugo and Simanjilo (2018); Mondal et al. (2018); Sarkar et al. (2017); Temgoua et al. (2018)). Mathematical models and their analysis are helpful in understanding the dynamical behavior of many human viruses such as HIV, HTLV-I and HBV (e.g., Elaiw et al. (2018); Lai and Zou (2014); Nkoa et al. (2013); Vargas-De-Leon (2014); Wang et al. (2016); Yuan et al. (2013)). Recently, it has been reported that the uninfected cells can also become infected because of direct contact with infected cells. The viral infection model with cell-to-cell transmission and distributed time delay have been proposed in Elaiw et al. (2018), Lai and Zou (2014), Wang et al. (2016), and Yang et al. (2015). They observed that the basic reproduction number of their model might be underevaluated if either cell-to-cell spread or virus-to-cell infection is neglected.

Note that the immune response after viral infection is common and is necessary for eliminating or controlling the disease. In most virus infections, cytotoxic T lymphocytes (CTLs) play a critical role in antiviral defense by attacking virus-infected cell. Many existing mathematical models for HIV infection with CTLs response are given by systems of ordinary differential equation (ODE) (e.g., Elaiw et al. (2018); Nkoa et al. (2013); Vargas-De-Leon (2014); Wang et al. (2016); Yuan et al. (2013)). However, time delays can not be ignored when modeling immune response, since antigenic stimulation generating CTLs may need a period of time, that is, the activation rate of CTL response at time  $t$  may depend on the population of antigen at a previous time (Yuan et al. (2013)). Moreover, all the aforementioned works do not take into account the constant production rate of CTLs exported from thymus. This consideration of export rate of new CTLs from thymus is considered in Nkoa et al. (2013), Tarfulea (2011), Tarfulea et al. (2011), and Vargas-De-Leon (2014) and is ignored by many authors.

Motivated by the works in Elaiw et al. (2018), Nkoa et al. (2013), Tarfulea (2011), and Yang et al. (2015), in the present paper we are concerned by the effect of both virus-to-cell and cell-to-cell transmissions with intracellular delays and immune response activation delay on the global dynamics of HIV-1 infection model. We consider a within-host viral infection model with both

virus-to-cell and cell-to-cell transmissions, immune response and four distributed delays, in which the first, second and fourth delay respectively describes the intracellular latency for virus-to-cell infection, the intracellular latency for the cell-to-cell infection and the time period that viruses penetrated into cells and infected cells release new virions (Yang et al. (2015)), and the third delay describes the activation delay of CTLs cells (Yuan et al. (2013)).

The rest of the paper is organized as follows. In Section 2, the mathematical model is constructed. Preliminaries including the positivity and boundedness of solutions are introduced in Section 3. In Section 4, the existence of infection-free equilibrium and its global stability are studied. Existence of a chronic infection equilibrium and its global stability with intracellular delays only are presented in Section 5. Furthermore, in this section, we find sufficient conditions for the occurrence of a Hopf bifurcation includes only the immune response delay. In Section 6, numerical simulations for several cases of the main model are presented. We further explore the delays and their effects on the stability of the chronic infection equilibrium. Section 7 concludes the paper.

## 2. The Model Formulation

The compartmental model includes the concentrations of healthy target cells  $T(t)$  which susceptible to infection, infected cells  $T_i(t)$  that produces viruses, cytotoxic T lymphocytes (CTLs) cells  $T_c(t)$  which are responsible of the destruction of infected cells and viruses  $V(t)$ . Let  $\beta_1$  be the virus-to-cell infection rate,  $\beta_2$  be the cell-to-cell infection rate,  $\delta$ ,  $\mu_1$ ,  $\alpha$  and  $c$  be death rates of healthy target cells, activated infected cells, cytotoxic CTLs cells and viruses, respectively. Let  $b$  be the production rate of healthy target cells,  $\lambda$  be the production rate of CTLs cells export from thymus,  $a$  be the proliferation rate of CTLs cells. Infected cells are eliminated by CTLs cells at a rate  $q$ , which represent the lytic activity of CTLs cells.  $e^{-\mu_1 s_1}$  is the survival rate of cells that are infected by viruses at time  $t$  and become activated  $s_1$  time later with a probability distribution  $f_1(s_1)$ . Then,  $\int_0^{\infty} \beta_1 T(t-s_1)V(t-s_1)f_1(s_1)e^{-\mu_1 s_1} ds_1$  describes the newly activated infected target cells which are infected by free viruses  $s_1$  time ago (Yang et al. (2015)).

Similarly,  $\int_0^{\infty} \beta_2 T(t-s_2)T_i(t-s_2)f_2(s_2)e^{-\mu_1 s_2} ds_2$  represents the newly activated infected target cells which are infected by infected cells  $s_2$  time ago (Yang et al. (2015)).  $e^{-\mu_2 s_3}$  is the survival rate of CTLs cells that are activated at time  $t$ , and become cytotoxic  $s_3$  time later with a probability distribution  $f_3(s_3)$ . Then,  $\int_0^{\infty} aT_i(t-s_3)T_c(t-s_3)f_3(s_3)e^{-\mu_2 s_3} ds_3$  represents the newly CTLs cells proliferated at time  $t$  (Yuan et al. (2013)). Let  $s_4$  be the random variable that is the time between viral RNA transcript and viral release and maturation with a probability distribution  $f_4(s_4)$ . Then,  $\int_0^{\infty} kT_i(t-s_4)f_4(s_4)e^{-\mu_3 s_4} ds_4$  describes the mature viral particles produced at time  $t$  (Yang et al. (2015)).  $k$  is the average number of viruses that bud out from an infected cell and  $e^{-\mu_3 s_4}$  is the survival rates of cells that start budding from activated infected cells at time  $t$  and become free mature viruses  $s_4$  time later. Note that  $s_1, s_2, s_3$  and  $s_4$  are all integration variables, without loss of generality; they all will be represented by  $s$ .

From the modeling perspective, the model (1) extends the basic model developed in Nkoa et al. (2013) by: **(i)** incorporating the cell-to-cell transmission, **(ii)** intracellular delays, and **(iii)** immune activation delay. Together with this latter improvement **(iii)**, the incorporation of a constant production rate of CTLs export from thymus in our model also extend the works in Elaiw et al. (2018), Wang et al. (2016), and Yuan et al. (2013). It is also noticeable that our model extends the models developed in Lai and Zou (2014), and Yang et al. (2015) by including CTL response immune delay.

The model is given as follows:

$$\left\{ \begin{array}{l} \frac{dT(t)}{dt} = b - \delta T - \beta_1 TV - \beta_2 TT_i, \\ \frac{dT_i(t)}{dt} = \int_0^\infty \beta_1 T(t-s)V(t-s)f_1(s)e^{-\mu_1 s} ds \\ \quad + \int_0^\infty \beta_2 T(t-s)T_i(t-s)f_2(s)e^{-\mu_1 s} ds - \mu_1 T_i - qT_i T_c, \\ \frac{dT_c(t)}{dt} = \lambda + a \int_0^\infty T_i(t-s)T_c(t-s)f_3(s)e^{-\mu_2 s} ds - \alpha T_c, \\ \frac{dV(t)}{dt} = k \int_0^\infty T_i(t-s)f_4(s)e^{-\mu_3 s} ds - cV, \end{array} \right. \quad (1)$$

$f_i(\nu) : [0, \infty) \rightarrow [0, \infty)$  are probability distributions with compact support,  $f_i(\nu) \geq 0$ , and  $\int_0^\infty f_i(\nu) d\nu = 1$ ,  $i = 1, \dots, 4$ .

### 3. Preliminaries

Define the Banach space of fading memory type (see Lai and Zou (2014), and Yang et al. (2015))

$$\mathcal{C} = \{ \phi \in C((-\infty, 0] | \phi(\theta) e^{\mu\theta} \text{ is continuous for } \theta \in (-\infty, 0] \text{ and } \|\phi\| < \infty \}$$

where  $\mu$  is positive constant and the norm  $\|\phi\| = \sup_{\theta \leq 0} |\phi(\theta)| e^{\mu\theta}$ . The nonnegative cone of  $\mathcal{C}$  is defined by  $\mathcal{C}_+ = \mathcal{C}((-\infty, 0], \mathbb{R}_+)$ . For  $\phi \in \mathcal{C}$ , let  $\phi_t(\theta) = \phi(t + \theta)$ ,  $\theta \in (-\infty, 0]$ . We consider solutions  $(T, T_i, T_c, V)$  of system (1) with initial conditions

$$(T(0), T_i(0), T_c(0), V(0)) \in X := \mathcal{C}_+ \times \mathcal{C}_+ \times \mathcal{C}_+ \times \mathcal{C}_+. \quad (2)$$

By the standard theory of functional differential equations, we can obtain the existence of solutions for  $t > 0$ . Let

$$\eta_i = \int_0^\infty e^{-\mu_i s} f_i(s) ds, \quad i = 1, 2, \eta_3 = \int_0^\infty f_3(s) e^{-\mu_3 s} ds, \quad \eta_4 = \int_0^\infty f_4(s) e^{-\mu_4 s} ds.$$

#### Theorem 3.1.

Solutions of system (1) with initial conditions (2) are positive and ultimately uniformly bounded for  $t > 0$ .

**Proof:**

Let  $m(t) = \delta + \beta_1 V(t) + \beta_2 T_i(t)$  and  $d(t) = \mu_1 + qT_c(t)$ . Let  $r(t)$  be the sum of the two integral terms in the second equation of system (1) and  $n(t)$  be the integral term in the fourth equation of

system (1). From the first equation in (1), we have

$$T(t) = T(0)e^{-\int_0^t m(\xi)d\xi} + \int_0^t e^{-\int_\xi^t m(\theta)d\theta} b d\xi > 0, \quad \text{for } t \geq 0.$$

From the third equation in (1), it follows that  $\liminf_{t \rightarrow \infty} T_c(t) \geq \frac{\lambda}{\alpha} > 0$ . From the second and fourth equation in (1), we then have

$$T_i(t) = T_i(0)e^{-\int_0^t d(\xi)d\xi} + \int_0^t r(\xi)e^{-\int_\xi^t d(\theta)d\theta} d\xi \quad \text{and} \quad V(t) = \left[ V(0) + \int_0^t n(\xi)e^{c\xi} d\xi \right] e^{-ct},$$

which yield that  $T_i(t) > 0$ ,  $V(t) > 0$  for small  $t > 0$ . Now, we prove that  $T_i(t) > 0$  and  $V(t) > 0$  for all  $t > 0$ . Otherwise, there exists  $t_1 > 0$  such that  $\min\{T_i(t_1), V(t_1)\} = 0$ . If  $T_i(t_1) = 0$ ,  $T_i(t) > 0$  for  $0 \leq t < t_1$ , and  $V(t) > 0$  for  $0 \leq t < t_1$ , then we have  $\frac{dT_i(t_1)}{dt} > 0$ . This contradicts  $T_i(t_1) = 0$  and  $T_i(t) > 0$  for  $0 \leq t < t_1$ . If  $V(t_1) = 0$ ,  $V(t) > 0$  for  $0 \leq t < t_1$ , and  $T_i(t) > 0$  for  $0 \leq t < t_1$ , then, we obtain  $\frac{dV(t_1)}{dt} > 0$ , which is also a contradiction. Hence,  $T_i(t) > 0$  and  $V(t) > 0$  for all  $t > 0$ .

To prove boundedness, first by the positivity of solutions we have  $\frac{dT(t)}{dt} < b - \delta T(t)$ . It follows that  $\limsup_{t \rightarrow \infty} T(t) \leq \frac{b}{\delta}$ , implying  $T_s(t)$  is bounded. Let

$$G_1(t) = \int_0^\infty f_1(s)e^{-\mu_1 s} T(t-s) ds + \int_0^\infty f_2(s)e^{-\mu_1 s} T(t-s) ds + T_i(t).$$

Since  $T(t)$  is bounded and  $\int_0^\infty f(u)du$  is convergent, the integral in  $G(t)$  is well defined and differentiable with respect to  $t$ . Moreover, when taking the time derivative of  $G(t)$ , the order of the differentiation and integration can be switched. Thus, we have

$$\begin{aligned} \dot{G}_1(t) &= b(\eta_1 + \eta_2) - \delta \int_0^\infty f_1(s)e^{-\mu_1 s} T(t-s) ds - \delta \int_0^\infty f_2(s)e^{-\mu_1 s} T(t-s) ds \\ &\quad - \mu_1 T_i - q T_i T_c \\ &\leq b(\eta_1 + \eta_2) - \delta \int_0^\infty f_1(s)e^{-\mu_1 s} T(t-s) ds - \delta \int_0^\infty f_2(s)e^{-\mu_1 s} T(t-s) ds \\ &\quad - \left( \mu_1 + \frac{q\lambda}{\alpha} \right) T_i(t) \leq b(\eta_1 + \eta_2) - d_1 G_1(t), \end{aligned}$$

where  $d_1 = \min\{\delta, \mu_1 + \frac{q\lambda}{\alpha}\}$ . Therefore,  $\limsup_{t \rightarrow \infty} G_1(t) \leq \frac{b(\eta_1 + \eta_2)}{d_1} := M_1$ , implying that  $\limsup_{t \rightarrow \infty} T_i(t) \leq M_1$ . Then, from the fourth equation of system (1), we have

$$\dot{V}(t) = k \int_0^\infty e^{-\mu_4 s} f_4(s) T_i(t-s) ds - cV \leq kM_1\eta_4 - cV.$$

Thus,  $\limsup_{t \rightarrow \infty} V(t) \leq \frac{kM_1\eta_4}{c} := M_2$ . Now determine the upper bound of  $T_c(t)$ . Let

$$G_2(t) = \int_0^\infty f_3(s)e^{-\mu_3 s} T_i(t-s) ds + \frac{q}{a} T_c(t).$$

Thus, we have

$$\begin{aligned} \dot{G}_2(t) &= \int_0^\infty f_3(s)e^{-\mu_3 s}r(t-s)ds - \mu_1 \int_0^\infty f_3(s)e^{-\mu_3 s}T_i(t-s)ds + \frac{q\lambda}{a} - \alpha \frac{q}{a}T_c(t) \\ &\leq \frac{b\eta_3}{\delta}(\beta_1\eta_1M_2 + \beta_2\eta_2M_1) + \frac{q\lambda}{a} - \mu_1 \int_0^\infty f_3(s)e^{-\mu_3 s}T_i(t-s)ds - \alpha \frac{q}{a}T_c(t) \\ &\leq d_2 - d_3G_2(t), \end{aligned}$$

where

$$d_2 = \frac{b\eta_3}{\delta}(\beta_1\eta_1M_2 + \beta_2\eta_2M_1) + \frac{q\lambda}{a} \quad \text{and} \quad d_3 = \{\alpha, \mu_1\}.$$

Hence,  $\limsup_{t \rightarrow \infty} G_2(t) \leq \frac{d_2}{d_3} := M_3$ , implying that  $\limsup_{t \rightarrow \infty} T_c(t) \leq \frac{a}{q}M_3$ . Thus,  $T(t)$ ,  $T_i(t)$ ,  $T_c(t)$  and  $V(t)$  are uniformly bounded. ■

Theorem 3.1 implies that omega limit sets of system (1) are contained in the following bounded feasible region:

$$\Omega = \left\{ (T, T_i, T_c, V) \in \mathcal{C}_+^4 : \|T_s\| \leq \frac{b}{\delta}, \|T_i\| \leq M_1, \frac{\lambda}{\alpha} \leq T_c \leq \frac{a}{q}M_3, \|V\| \leq M_2 \right\}.$$

It can be verified that the region  $\Omega$  is positively invariant with respect (1) and the system is well posed.

#### 4. The infection-free equilibrium and its stability

System (1) has an infection-free equilibrium  $E_0 = (\frac{b}{\delta}, 0, \frac{\lambda}{\alpha}, 0)$ . We defined the basic reproduction number as follows:

$$\mathcal{R}_0 = \mathcal{R}_{01} + \mathcal{R}_{02} = \frac{k \beta_1 b \eta_1 \eta_4}{c\delta (\mu_1 + \frac{q\lambda}{\alpha})} + \frac{\beta_2 b \eta_2}{\delta (\mu_1 + \frac{q\lambda}{\alpha})},$$

which represents the average number of secondary infections. In fact,  $\frac{k \beta_1 b \eta_1 \eta_4}{c\delta (\mu_1 + \frac{q\lambda}{\alpha})}$  is the average number of secondary viruses caused by a virus, that is the basic reproduction number corresponding to virus-to-cell infection mode, while  $\frac{\beta_2 b \eta_2}{\delta (\mu_1 + \frac{q\lambda}{\alpha})}$  is the average number of secondary infected cells that caused by an infected cell, that is the basic reproduction number corresponding to cell-to-cell infection mode. The factors have the biological interpretations as follows:

- $\frac{b\beta_1\eta_1}{\delta}$  is the number of new infections caused by a virus in target susceptible cells,
- $\frac{q\lambda}{\alpha}$  is the rate at which infected cells are eliminated by the CTLs response,
- $\frac{1}{\mu_1 + \frac{q\lambda}{\alpha}}$  is the average time that an infectious cell survives,

- $k\eta_4$  is the rate at which infected cells bud into viruses,
- $\frac{1}{c}$  is gives the average life-span of a virus,
- $\frac{b\beta_2\eta_2}{\mu_1 + \frac{q\lambda}{\alpha}}$  represents the number of new infections caused by an infected cell in target susceptible cells.

The result below that follows is straightforward.

**Theorem 4.1.**

The infection-free equilibrium  $E_0$  of system (1) is locally asymptotically stable in the feasible region  $\Omega$  whenever  $\mathcal{R}_0 < 1$  and unstable otherwise.

**Proof:**

The characteristic equation of system (1) at the equilibrium  $E_0$  is

$$(\nu + \delta)(\nu + \alpha) \left[ (\nu + c) \left( \nu + \mu_1 + \frac{q\lambda}{\alpha} - \frac{b\beta_2\bar{\eta}_2}{\delta} \right) - \frac{kb\beta_1}{\delta} \bar{\eta}_1 \bar{\eta}_4 \right] = 0, \quad (3)$$

where  $\bar{\eta}_i = \int_0^\infty e^{-(\mu_i + \nu)s} f_i(s) ds$ ,  $i = 1, 2$ ,  $\bar{\eta}_3 = \int_0^\infty e^{-(\mu_2 + \nu)s} f_3(s) ds$  and  $\bar{\eta}_4 = \int_0^\infty e^{-(\mu_3 + \nu)s} f_4(s) ds$ . We see that (3) has eigenvalues  $\nu_1 = -\delta$ ,  $\nu_2 = -\alpha$  and other eigenvalues are determined by

$$(\nu + c) \left( \nu + \mu_1 + \frac{q\lambda}{\alpha} - \frac{b\beta_2\bar{\eta}_2}{\delta} \right) - \frac{kb\beta_1}{\delta} \bar{\eta}_1 \bar{\eta}_4 = 0,$$

which are equivalent to

$$\Psi(\nu) := \left( \frac{\nu}{\mu_1 + \frac{q\lambda}{\alpha}} + 1 \right) (\nu + c) - \mathcal{R}_0 \left( \frac{\bar{\eta}_2 \mathcal{R}_{02}}{\eta_2 \mathcal{R}_0} \nu + c \frac{\bar{\eta}_2 \mathcal{R}_{02}}{\eta_2 \mathcal{R}_0} + c \frac{\bar{\eta}_1 \bar{\eta}_4 \mathcal{R}_{01}}{\eta_1 \eta_4 \mathcal{R}_0} \right) = 0. \quad (4)$$

Thus,  $\Psi(0) = c(1 - \mathcal{R}_0) < 0$  when  $\mathcal{R}_0 > 1$ . Note that

$$\bar{\eta}_1 \leq \int_0^\infty f_1(s) ds = 1, i = 1, 2, 3, 4.$$

Then, we have

$$\Psi(\nu) \geq \left( \frac{\nu}{\mu_1 + \frac{q\lambda}{\alpha}} + 1 \right) (\nu + c) - \mathcal{R}_0 \left( \frac{\mathcal{R}_{02}}{\eta_2 \mathcal{R}_0} \nu + c \frac{\mathcal{R}_{02}}{\eta_2 \mathcal{R}_0} + c \frac{\mathcal{R}_{01}}{\eta_1 \eta_4 \mathcal{R}_0} \right) \rightarrow +\infty,$$

as  $\nu \rightarrow +\infty$ . This yields that Equation (4) has at least one positive root. Therefore, the infection-free equilibrium  $E_0$  is unstable if  $\mathcal{R}_0 > 1$ . ■

Biologically speaking, Theorem 4.1 implies that infection can be eliminated if the initial sizes of cells are in the basin of attraction of the infection-free equilibrium. Thus, the infection can be effectively controlled if  $\mathcal{R}_0 < 1$ . One can remark that  $\mathcal{R}_0$  depends on  $\lambda$  and is a decreasing function of this rate. Hence, the constant rate  $\lambda$  could be an important control parameter in order to reduce

$\mathcal{R}_0$  to a value less than unity. To ensure that the effective control of the infection is independent of the initial size of the cells, a global stability result must be established for the infection-free equilibrium.

**Theorem 4.2.**

If  $\mathcal{R}_0 \leq 1$ , then the infection-free equilibrium  $E_0$  of system (1) is globally asymptotically stable in  $\Omega$ .

**Proof:**

We define a Lyapunov function as follows:

$$L(t) = T_i + \frac{b\beta_1\eta_1}{c\delta}V + \int_0^\infty f_1(s)e^{-\mu_1s} \int_{t-s}^t \beta_1T(\tau)V(\tau)d\tau ds + \int_0^\infty f_2(s)e^{-\mu_1s} \int_{t-s}^t \beta_2T(\tau)T_i(\tau)d\tau ds + \frac{b\beta_1\eta_1}{c\delta} \int_0^\infty f_4(s)e^{-\mu_3s} \int_{t-s}^t kT_i(\tau)d\tau ds.$$

Then, the time derivative of  $L(t)$  along solutions of system (1) satisfies

$$\frac{dL(t)}{dt} = \beta_1\eta_1TV + \beta_2\eta_2TT_i + \frac{kb\beta_1\eta_1\eta_4}{c\delta}T_i - \mu_1T_i - qT_iT_c - \frac{b\beta_1\eta_1}{\delta}V.$$

Since  $T \leq \frac{b}{\delta}$  and  $T_c \geq \frac{\lambda}{\alpha}$ , we have

$$\frac{dL(t)}{dt} \leq \left[ \frac{b\beta_2\eta_2}{\delta} + \frac{kb\beta_1\eta_1\eta_4}{c\delta} - \left( \mu_1 + \frac{q\lambda}{\alpha} \right) \right] T_i = \left( \mu_1 + \frac{q\lambda}{\alpha} \right) (\mathcal{R}_0 - 1)T_i.$$

$\frac{dL(t)}{dt} \leq 0$  whenever  $\mathcal{R}_0 \leq 1$ . Moreover,  $\frac{dL(t)}{dt} = 0 \Leftrightarrow T_i = V = 0$  or  $T = \frac{b}{\delta}$ ,  $T_c = \frac{\lambda}{\alpha}$  and  $\mathcal{R}_0 = 1$ . Thus, the largest invariant set  $\mathcal{H}$  such as  $\mathcal{H} \subset \left\{ (T, T_i, T_c, V) \in \mathbb{R}_+^4 / \frac{dL(t)}{dt} = 0 \right\}$  is the singleton  $\{E_0\}$ . By LaSalle’s Principle,  $E_0$  is globally asymptotically stable in  $\Omega$ , completing the proof. ■

## 5. The chronic infection equilibrium and its stability

### 5.1. Existence and uniqueness

The existence of a chronic infection equilibrium of the model (1) is addressed when  $\mathcal{R}_0 > 1$ . The infection is endemic if the infected cells persist above a certain positive level. We have the following result.

**Theorem 5.1.**

System (1) always has a infection-free equilibrium  $E_0$ , and

- (i) if  $\mathcal{R}_0 < 1$ , system (1) has no positive chronic infection equilibrium,
- (ii) if  $\mathcal{R}_0 > 1$ , system (1) has a unique positive chronic infection equilibrium  $E^*$ .



**Proof:**

Denote by  $E^* = (T^*, T_i^*, T_c^*, V^*)$  the chronic infection equilibrium of system (1). At this point, the system (1) satisfies the following relations:

$$\begin{cases} b = \delta T^* + \beta_1 T^* V^* + \beta_2 T^* T_i^*, \\ \beta_1 \eta_1 T^* V^* + \beta_2 \eta_2 T^* T_i^* = \mu_1 T_i^* + q T_i^* T_c^*, \\ \lambda + a \eta_3 T_i^* T_c^* = \alpha T_c^*, \\ k \eta_4 T_i^* = c V^*. \end{cases} \quad (5)$$

Solving (5) yields

$$\begin{cases} T^* = \frac{b}{\delta + (\beta_1 + \frac{\beta_2 c}{k \eta_4}) V^*}, \\ T_c^* = \frac{k b \beta_1 \eta_1 \eta_4 + b \beta_2 \eta_2 c - c \mu_1 \delta - c \mu_1 (\beta_1 + \frac{\beta_2 c}{k \eta_4}) V^*}{q c (\delta + \beta_1 V^* + \frac{\beta_2 c}{k \eta_4} V^*)}, \\ T_i^* = \frac{c V^*}{k \eta_4}, \end{cases}$$

where  $V^*$  is a positive root of

$$\lambda + a \eta_3 T_i^* T_c^* - \alpha T_c^* = 0. \quad (6)$$

After expansion and substitution of  $T^*$ ,  $T_i^*$ ,  $T_c^*$  by their expressions, Equation (6) is equivalent to polynomial

$$P(V) = a_2 V^2 + a_1 V + a_0 = 0, \quad (7)$$

with the coefficients  $a_2$ ,  $a_1$  and  $a_0$  given by

$$\begin{aligned} a_2 &= \frac{a \eta_3 c^2 \mu_1}{k \eta_4} \left( \beta_1 + \frac{\beta_2 c}{k \eta_4} \right), \\ a_1 &= \frac{a \eta_3 c^2 \mu_1 \delta}{k \eta_4} - a \eta_3 b c \left( \beta_1 \eta_1 + \frac{\beta_2 \eta_2 c}{k \eta_4} \right) - \left( \beta_1 + \frac{\beta_2 c}{k \eta_4} \right) (\mu_1 c \alpha + q \lambda c), \\ a_0 &= c \delta \alpha \left( \mu_1 + \frac{q \lambda}{\alpha} \right) (\mathcal{R}_0 - 1). \end{aligned} \quad (8)$$

Using  $T_c \geq 0$  one shows that  $V \leq V_{max}$ , where

$$V_{max} = \frac{k b \beta_1 \eta_1 \eta_4 + b \beta_2 \eta_2 c - c \mu_1 \delta}{c \mu_1 \left( \beta_1 + \frac{\beta_2 c}{k \eta_4} \right)} = \frac{c \mu_1 \delta (\mathcal{R}_0 - 1) + \mathcal{R}_0 \frac{c \delta q \lambda}{\alpha}}{c \mu_1 \left( \beta_1 + \frac{\beta_2 c}{k \eta_4} \right)} > 0.$$

Furthermore, some calculations give

$$P(0) = a_0, \quad P(V_{max}) = -\frac{a_0 b \lambda q (k \beta_1 \eta_1 \eta_4 + \beta_2 \eta_2 c)}{\mu_1} < 0, \quad \text{and} \quad \lim_{V \rightarrow +\infty} P(V) = +\infty.$$

• If  $\mathcal{R}_0 \leq 1$ , then,  $P(0) = a_0 \leq 0$  and the equation  $P(V) = 0$  has a unique positive root on  $]V_{max}; +\infty[$ . Since for all  $V \geq V_{max}$ ,  $T_c^* \leq 0$ , it follows that system (1) has no positive chronic

infection equilibrium in this case.

- If  $\mathcal{R}_0 > 1$ , then,  $P(0) = a_0 > 0$  and the equation  $P(V) = 0$  has two positive roots: one solution on interval  $]0; V_{max}[$  and another solution on  $]V_{max}; +\infty[$ .

Since  $T_c^*$  is positive for  $0 < V < V_{max}$  and negative for  $V > V_{max}$ , it follows that system (1) has a unique positive chronic infection equilibrium when  $\mathcal{R}_0 > 1$ . ■

### 5.2. Stability analysis of chronic infection equilibrium

On the stability analysis of the chronic infection equilibrium, we only discuss the following special cases: **(i)**  $\tau_i \geq 0, i = 1, 2, 4, \tau_3 = 0$  and **(ii)**  $\tau_i = 0, i = 1, 2, 4, \tau_3 > 0$ . However, aiming at the case  $\tau_i > 0, i = 1, 2, 3, 4$ , the theoretical analysis is very complicated. We will give numerical analysis for this case in the next section.

#### 5.2.1. Global stability of chronic infection equilibrium when $\tau_i \geq 0, i = 1, 2, 4$ and $\tau_3 = 0$ .

Here, we will prove the global stability of the chronic infection equilibrium of system (1) with  $\tau_3 = 0$  by the Lyapunov direct method.

#### Theorem 5.2.

Consider system (1) with  $f_1(s) = f_2(s), \tau_i \geq 0, i = 1, 2, 4$  and  $\tau_3 = 0$ . If  $\mathcal{R}_0 > 1$ , then, the chronic infection equilibrium  $E^*$  is globally asymptotically stable.

#### Proof:

Consider system (1) with  $\tau_i \leq 0, i = 1, 2, 4$  and  $\tau_3 = 0$ . Suppose  $\mathcal{R}_0 > 1$  and  $f_1(s) = f_2(s)$ . For convenience of notation, we denote  $g(x) = x - 1 - \ln x$ . It is easy to see that  $g(x) \geq 0$  for  $x > 0$  and  $g'(x) = 1 - \frac{1}{x}$ . Furthermore,  $g$  has a global minimum at 1 and satisfies  $g(1) = 0$ . We define a Lyapunov functions as follows:

$$U(t) = U_1(t) + U_2(t) + U_3(t),$$

where

$$U_1 = T(t) - T^* \ln \frac{T(t)}{T^*} + \frac{1}{\eta_1} \left( T_i(t) - T_i^* \ln \frac{T_i(t)}{T_i^*} \right) + \frac{q}{a\eta_1} \left( T_c(t) - T_c^* \ln \frac{T_c(t)}{T_c^*} \right) + \frac{\beta_1 T^*}{c} \left( V(t) - V^* \ln \frac{V(t)}{V^*} \right),$$

$$U_2(t) = \frac{\beta_1 T^* V^*}{\eta_1} \int_0^\infty f_1(s) e^{-\mu_1 s} \int_{-s}^0 g \left( \frac{T(t+\tau)V(t+\tau)}{T^*V^*} \right) d\tau ds + \frac{\beta_2 T^* T_i^*}{\eta_1} \int_0^\infty f_1(s) e^{-\mu_1 s} \int_{-s}^0 g \left( \frac{T(t+\tau)T_i(t+\tau)}{T^*T_i^*} \right) d\tau ds,$$

and

$$U_3(t) = \frac{\beta_1 T^* V^*}{\eta_4} \int_0^\infty f_4(s) e^{-\mu_3 s} \int_{-s}^0 g\left(\frac{T(t+\tau)T_i(t+\tau)}{T_i^*}\right) d\tau ds.$$

Calculating the time derivative of  $U_1, U_2$  and  $U_3$  along the solutions of system (1), we have

$$\begin{aligned} \frac{dU_1}{dt} &= \left(1 - \frac{T^*}{T}\right) [b - \delta T - \beta_1 TV - \beta_2 TT_i] \\ &+ \frac{1}{\eta_1} \left(1 - \frac{T_i^*}{T_i}\right) \left(\int_0^\infty f_1(s) e^{-\mu_1 s} \beta_1 T(t-s) V(t-s) ds \right. \\ &+ \left. \int_0^\infty f_1(s) e^{-\mu_1 s} \beta_2 T(t-s) T_i(t-s) ds - \mu_1 T_i - q T_i T_c\right) \\ &+ \frac{q}{a\eta_1} \left(1 - \frac{T_c^*}{T_c}\right) [\lambda + a T_i T_c - \alpha T_c] \\ &+ \frac{\beta_1 T^*}{c} \left(1 - \frac{V^*}{V}\right) \left(\int_0^\infty k T_i(t-s) f_4(s) e^{-\mu_3 s} ds - cV\right), \\ &= b - \delta T - \beta_1 TV - \beta_2 TT_i - b \frac{T^*}{T} + \delta T^* + \beta_1 VT^* + \beta_2 T_i T^* \\ &+ \frac{1}{\eta_1} \int_0^\infty \beta_1 T(t-s) V(t-s) f_1(s) e^{-\mu_1 s} ds + \frac{1}{\eta_1} \int_0^\infty \beta_2 T(t-s) T_i(t-s) f_1(s) e^{-\mu_1 s} ds \\ &- \frac{\mu_1}{\eta_1} T_i - \frac{q}{\eta_1} T_i T_c - \frac{1}{\eta_1} \frac{T_i^*}{T_i} \int_0^\infty f_1(s) e^{-\mu_1 s} \beta_1 T(t-s) V(t-s) ds \\ &- \frac{1}{\eta_1} \frac{T_i^*}{T_i} \int_0^\infty f_1(s) e^{-\mu_1 s} \beta_2 T(t-s) T_i(t-s) ds + \frac{\mu_1}{\eta_1} T_i^* + \frac{q T_i^* T_c}{\eta_1} \\ &+ \frac{q}{a\eta_1} \left(\lambda + a T_i T_c - \alpha T_c - \lambda \frac{T_c^*}{T_c} - a T_i T_c^* + \alpha T_c^*\right) \\ &+ \frac{k\beta_1 T^*}{c} \int_0^\infty T_i(t-s) f_4(s) e^{-\mu_3 s} ds - \beta_1 T^* V + \beta_1 T^* V^* \\ &- \frac{k\beta_1 T^* V^*}{c} \int_0^\infty T_i(t-s) f_4(s) e^{-\mu_3 s} ds, \end{aligned}$$

and

$$\begin{aligned} \frac{dU_2}{dt} &= \beta_1 TV + \beta_2 TT_i - \frac{1}{\eta_1} \int_0^\infty \beta_1 T(t-s) V(t-s) f_1(s) e^{-\mu_1 s} ds \\ &- \frac{1}{\eta_1} \int_0^\infty \beta_2 T(t-s) T_i(t-s) f_1(s) e^{-\mu_1 s} ds \\ &+ \frac{\beta_1 T^* V^*}{\eta_1} \int_0^\infty f_1(s) e^{-\mu_1 s} \ln \frac{T(t-s) V(t-s)}{TV} ds \\ &+ \frac{\beta_2 T^* T_i^*}{\eta_1} \int_0^\infty f_1(s) e^{-\mu_1 s} \ln \frac{T(t-s) T_i(t-s)}{TT_i} ds, \end{aligned}$$

and

$$\begin{aligned} \frac{dU_3}{dt} &= \beta_1 T^* V^* \frac{T_i}{T_i^*} - \frac{\beta_1 T^* V^*}{\eta_4 T_i^*} \int_0^\infty T_i(t-s) f_4(s) e^{-\mu_3 s} ds \\ &\quad + \frac{\beta_1 T^* V^*}{\eta_4} \int_0^\infty f_4(s) e^{-\mu_3 s} \ln \frac{T_i(t-s)}{T_i} ds. \end{aligned}$$

Taking the derivative of  $U(t)$  and making use of the equations (5) defining the positive equilibrium  $E^*$ , we obtain after simplifications:

$$\begin{aligned} \frac{dU}{dt} &= \delta T^* \left( 2 - \frac{T}{T^*} - \frac{T^*}{T} \right) + \frac{q\lambda}{a\eta_1} \left( 2 - \frac{T_c}{T_c^*} - \frac{T_c^*}{T_c} \right) + 2\beta_1 T^* V^* + \beta_2 T^* T_i^* + \frac{\mu_1}{\eta_1} T_i^* \\ &\quad + \frac{q}{\eta_1} T_i^* T_c^* - \beta_1 T^* V^* \frac{T^*}{T} - \beta_2 T^* T_i^* \frac{T^*}{T} - \frac{1}{\eta_1} \frac{T_i^*}{T_i} \int_0^\infty f_1(s) e^{-\mu_1 s} \beta_1 T(t-s) V(t-s) ds \\ &\quad - \frac{1}{\eta_1} \frac{T_i^*}{T_i} \int_0^\infty \beta_2 T(t-s) T_i(t-s) f_1(s) e^{-\mu_1 s} ds - \frac{\beta_1 T^* V^*}{\eta_4 T_i^*} \frac{V^*}{V} \int_0^\infty T_i(t-s) f_4(s) e^{-\mu_3 s} ds \\ &\quad + \frac{\beta_1 T^* V^*}{\eta_1} \int_0^\infty f_1(s) e^{-\mu_1 s} \ln \frac{T(t-s) V(t-s)}{TV} ds + \frac{\beta_1 T^* V^*}{\eta_4} \int_0^\infty f_4(s) e^{-\mu_3 s} \ln \frac{T_i(t-s)}{T_i} ds \\ &\quad + \frac{\beta_2 T^* T_i^*}{\eta_1} \int_0^\infty f_1(s) e^{-\mu_1 s} \ln \frac{T(t-s) T_i(t-s)}{TT_i} ds, \\ &= \delta T^* \left( 2 - \frac{T}{T^*} - \frac{T^*}{T} \right) + \frac{q\lambda}{a\eta_1} \left( 2 - \frac{T_c}{T_c^*} - \frac{T_c^*}{T_c} \right) + \beta_1 T^* V^* + \beta_2 T^* T_i^* \\ &\quad - \beta_1 T^* V^* \frac{T^*}{T} - \beta_2 T^* T_i^* \frac{T^*}{T} + \beta_1 T^* V^* \ln \frac{T^* V^* T_i}{TV T_i^*} \\ &\quad + \frac{\beta_1 T^* V^*}{\eta_1} \int_0^\infty f_1(s) e^{-\mu_1 s} \left[ 1 - \frac{T(t-s) V(t-s) T_i^*}{T^* V^* T_i} + \ln \frac{T(t-s) V(t-s) T_i^*}{T^* V^* T_i} \right] ds \\ &\quad + \frac{\beta_2 T^* T_i^*}{\eta_1} \int_0^\infty f_1(s) e^{-\mu_1 s} \left[ 1 - \frac{T(t-s) T_i(t-s)}{T^* T_i} + \ln \frac{T(t-s) T_i(t-s)}{T^* T_i} \right] ds \\ &\quad + \frac{\beta_1 T^* V^*}{\eta_4} \int_0^\infty f_4(s) e^{-\mu_3 s} \left[ 1 - \frac{T_i(t-s) V^*}{T_i^* V} + \ln \frac{T_i(t-s) V^*}{T_i^* V} \right] ds \\ &\quad + \beta_1 T^* V^* \ln \frac{T_i^* V}{T_i V^*} + \beta_2 T^* T_i^* \ln \frac{T^*}{T}, \\ &= \delta T^* \left( 2 - \frac{T}{T^*} - \frac{T^*}{T} \right) + \frac{q\lambda}{a\eta_1} \left( 2 - \frac{T_c}{T_c^*} - \frac{T_c^*}{T_c} \right) - [\beta_1 T^* V^* + \beta_2 T^* T_i^*] g \left( \frac{T^*}{T} \right) \\ &\quad - \frac{\beta_1 T^* V^*}{\eta_1} \int_0^\infty f_1(s) e^{-\mu_1 s} g \left( \frac{T(t-s) V(t-s) T_i^*}{T^* V^* T_i} \right) ds \\ &\quad - \frac{\beta_2 T^* T_i^*}{\eta_1} \int_0^\infty f_1(s) e^{-\mu_1 s} g \left( \frac{T(t-s) T_i(t-s)}{T^* T_i} \right) ds \\ &\quad - \frac{\beta_1 T^* V^*}{\eta_4} \int_0^\infty f_4(s) e^{-\mu_3 s} g \left( \frac{T_i(t-s) V^*}{T_i^* V} \right) ds. \end{aligned}$$

According to the property of  $g$ , we obtain that  $\frac{dU(t)}{dt} \leq 0$ . It can be verified that  $\frac{dU(t)}{dt} = 0$  if and only if

$$\frac{T}{T^*} = \frac{T_c}{T_c^*} = \frac{T(t-s)V(t-s)T_i^*}{T^*V^*T_i} = \frac{T(t-s)t_i(t-s)}{T^*T_i} = \frac{T_i(t-s)V^*}{T_i^*V} = 1.$$

It means that the largest invariant set  $\mathcal{M}_0 \subseteq \mathcal{M} = \left\{ (T, T_i, T_c, V) : \frac{dU}{dt} = 0 \right\}$  is the singleton  $\left\{ E^* \right\}$ . Again by the Lyapunov-LaSalle invariance principle, the chronic infection equilibrium  $E^*$  of system (1) is globally asymptotically stable. ■

### 5.2.2. Local stability and Hopf bifurcation when $\tau_i = 0$ , $i = 1, 2, 4$ , $\tau_3 \geq 0$ .

In this subsection, we consider model (1) with particular distribution functions  $f_i(s)$ ,  $i = 1, 2, 3, 4$  as :  $f_1(s) = f_2(s) = \delta(s - \tau_1)$ ,  $f_3(s) = \delta(s - \tau_3)$  and  $f_4(s) = \delta(s - \tau_4)$ , where  $\delta(\cdot)$  is the dirac delta function. We consider the special case where  $\tau_1 = \tau_2 = \tau_4 = 0$  and  $\tau_3 \geq 0$ . Then, we obtain that  $\eta_1 = \eta_2 = \eta_4 = 1$  and  $\eta_3 = e^{-\mu_2\tau_3}$ . In this case, the characteristic equation at the equilibrium  $E^*$  is

$$\nu^4 + A_3\nu^3 + A_2\nu^2 + A_1\nu + A_0 + [B_3(\tau_3)\nu^3 + B_2(\tau_3)\nu^2 + B_1(\tau_3)\nu + B_0(\tau_3)] e^{-\tau_3\nu} = 0, \quad (9)$$

where

$$\begin{aligned} A_3 &= \frac{b}{T^*} + c + \alpha + \frac{k\beta_1 T^*}{c}, \\ A_2 &= \frac{b}{T^*} \left( c + \alpha + \frac{k\beta_1 T^*}{c} \right) + \beta_2 T^* (\beta_1 V^* + \beta_2 T_i^*) + c\alpha + \frac{\alpha k\beta_1 T^*}{c}, \\ A_1 &= \frac{\alpha b}{T^*} \left( c + \frac{k\beta_1 T^*}{c} \right) + [k\beta_1 + \beta_2(c + \alpha)] T^* (\beta_1 V^* + \beta_2 T_i^*), \\ A_0 &= \alpha T^* (\beta_1 V^* + \beta_2 T_i^*) (k\beta_1 + c\beta_2), \\ B_3(\tau_3) &= -aT_i^* e^{-\mu_2\tau_3}, \\ B_2(\tau_3) &= -aT_i^* e^{-\mu_2\tau_3} \left( \frac{b}{T^*} + \frac{k\beta_1 T^*}{c} + c \right) + aqT_i^* T_c^* e^{-\mu_2\tau_3}, \\ B_1(\tau_3) &= aT_i^* e^{-\mu_2\tau_3} \left[ qT_c^* \left( c + \frac{b}{T^*} \right) - \frac{b}{T^*} \left( c + \frac{k\beta_1 T^*}{c} \right) - \beta_2 T^* (\beta_1 V^* + \beta_2 T_i^*) \right], \\ B_0(\tau_3) &= aT_i^* e^{-\mu_2\tau_3} \left[ cqT_c^* \frac{b}{T^*} - T^* (k\beta_1 + c\beta_2) (\beta_1 V^* + \beta_2 T_i^*) \right]. \end{aligned}$$

When  $\tau_3 = 0$ , the stability is given by the following theorem.

#### Theorem 5.3.

Consider system (1) with  $\tau_i = 0$ ,  $i = 1, 2, 3, 4$ . If  $\mathcal{R}_0 > 1$ , then, the chronic infection equilibrium  $E^*$  is locally asymptotically stable provided that (11) holds.

**Proof:**

For  $\tau_3 = 0$ , equation (9) becomes

$$\nu^4 + (A_3 + B_3(0))\nu^3 + (A_2 + B_2(0))\nu^2 + (A_1 + B_1(0))\nu + A_0 + B_0(0). \tag{10}$$

Using the Routh-Hurwitz criterion on (10), we investigate the local stability of  $E^*$ . The relevant Routh-Hurwitz determinants are:

$$\begin{cases} \Delta_1 = A_3 + B_3(0) > 0, \\ \Delta_2 = (A_3 + B_3(0))(A_2 + B_2(0)) - (A_1 + B_1(0)) > 0, \\ \Delta_3 = (A_1 + B_1(0))\Delta_2 - (A_3 + B_3(0))^2(A_0 + B_0(0)) > 0, \\ \Delta_4 = (A_0 + B_0(0))\Delta_3 > 0. \end{cases}$$

Since all the parameters of model (1) are positive, it follows that

$$\Delta_1 = \frac{b}{T^*} + c + \frac{k\beta_1 T^*}{c} + \alpha - aT_i^* = \frac{b}{T^*} + c + \frac{k\beta_1 T^*}{c} + \frac{\lambda}{T_c^*} > 0.$$

Furthermore, by straightforward computations, we show that

$$\begin{aligned} \Delta_2 &= \left( \frac{b}{T^*} + c + \frac{k\beta_1 T^*}{c} + \frac{\lambda}{T_c^*} \right) [aqT_i^* T_c^* + \beta_2 T^* (\beta_1 V^* + \beta_2 T_i^*) \\ &\quad + \frac{b}{T^*} \left( c + \frac{k\beta_1 T^*}{c} \right) + \frac{\lambda}{T_c^*} \left( \frac{b}{T^*} + c + \frac{k\beta_1 T^*}{c} \right)] - aqT_i^* T_c^* \left( c + \frac{b}{T^*} \right) \\ &\quad - \frac{b}{T^*} \frac{\lambda}{T_c^*} \left( c + \frac{k\beta_1 T^*}{c} \right) - T^* (\beta_1 V^* + \beta_2 T_i^*) \left( k\beta_1 + \beta_2 c + \beta_2 \frac{\lambda}{T_c^*} \right), \\ &= aqT_i^* T_c^* \left( \frac{k\beta_1 T^*}{c} + \frac{\lambda}{T_c^*} \right) + \frac{b}{T^*} \left( c + \frac{k\beta_1 T^*}{c} \right) \left( \frac{b}{T^*} + c + \frac{k\beta_1 T^*}{c} \right) \\ &\quad + \frac{\lambda}{T_c^*} \left( \frac{b}{T^*} + c + \frac{k\beta_1 T^*}{c} \right) \left( \frac{b}{T^*} + c + \frac{k\beta_1 T^*}{c} + \frac{\lambda}{T_c^*} \right) \\ &\quad + T^* (\beta_1 V^* + \beta_2 T_i^*) \left[ \beta_2 \left( \frac{b}{T^*} + \frac{k\beta_1 T^*}{c} \right) - k\beta_1 \right] > 0. \end{aligned}$$

Thus, all solutions of (10) have negative real parts if and only if

$$\Delta_3 = (A_1 + B_1(0))\Delta_2 - (A_3 + B_3(0))^2(A_0 + B_0(0)) > 0. \tag{11}$$

■

The root of (9) depends on  $\tau_3$  continuously. A root of (9) may pass through the imaginary axis and enter the right side when  $\tau_3$  increases. Let us consider  $\nu = \mu(\tau_3) + i\omega(\tau_3)$  a root of equation (9). We are interested in the change of stability of chronic infection equilibrium  $E^*$ , which will occur at the values of  $\tau_3$  for which  $\mu(\tau_3) = 0$  and  $\omega(\tau_3) > 0$ .  $\nu = i\omega$  is the critical case since a root may enter the right side or the left side under small perturbation when it locates on the imaginary axis. After substituting  $\nu = i\omega$  into (9) and separating the real and the imaginary parts, we obtain that

$$\begin{aligned} M(\omega) \cos \omega\tau_3 + N(\omega) \sin \omega\tau_3 &= E(\omega), \\ N(\omega) \cos \omega\tau_3 - M(\omega) \sin \omega\tau_3 &= F(\omega), \end{aligned} \tag{12}$$

where

$$M(\omega) = B_2(\tau_3)\omega^2 - B_0(\tau_3), \quad N(\omega) = B_3(\tau_3)\omega^3 - B_1(\tau_3)\omega,$$

$$E(\omega) = \omega^4 + A_0 - A_2\omega^2, \quad F(\omega) = -A_3\omega^3 + A_1\omega.$$

From (12), we can get

$$\cos \omega\tau_3 = \frac{M(\omega)E(\omega) + N(\omega)F(\omega)}{M(\omega)^2 + N(\omega)^2} \quad \text{and} \quad \sin \omega\tau_3 = \frac{N(\omega)E(\omega) - M(\omega)F(\omega)}{M(\omega)^2 + N(\omega)^2}. \quad (13)$$

Squaring and adding (13), we obtain

$$F(\omega, \tau_3) := \omega^8 + C_6(\tau_3)\omega^6 + C_4(\tau_3)\omega^4 + C_2(\tau_3)\omega^2 + C_0(\tau_3) = 0, \quad (14)$$

where

$$C_6(\tau_3) = A_3^2 - 2A_2 - B_3(\tau_3)^2,$$

$$C_4(\tau_3) = A_2^2 - 2A_3A_1 + 2A_0 - B_2(\tau_3)^2 + 2B_3(\tau_3)B_1(\tau_3),$$

$$C_2(\tau_3) = A_1^2 - 2A_2A_0 - B_1(\tau_3)^2 + 2B_2(\tau_3)B_0(\tau_3),$$

$$C_0(\tau_3) = A_0^2 - B_0(\tau_3)^2.$$

Denote

$$I = \left\{ \omega(\tau_3) > 0 : F(\omega, \tau_3) = 0 \right\},$$

which is a finite set. If  $I \neq \emptyset$ , then  $E^*$  is stable for  $\tau_3 \geq 0$ . Note that

$$F(0, \tau_3) = A_0^2 - B_0(\tau_3)^2, \quad \lim_{\omega \rightarrow +\infty} F(\omega, \tau_3) = +\infty.$$

In addition, we have

$$\begin{aligned} A_0 + B_0(\tau_3) &= T^*(\beta_1V^* + \beta_2T_i^*)(k\beta_1 + c\beta_2)(\alpha - aT_i^*e^{-\mu_2\tau_3}) + aT_i^*cqT_c^* \frac{b}{T^*} e^{-\mu_2\tau_3} \\ &= \frac{\lambda}{T_c^*} T^*(\beta_1V^* + \beta_2T_i^*)(k\beta_1 + c\beta_2) + aT_i^*cqT_c^* \frac{b}{T^*} e^{-\mu_2\tau_3} > 0. \end{aligned}$$

Therefore, if

$$(\mathcal{H}_1) \quad A_0 < B_0(\tau_3),$$

holds, then,  $I \neq \emptyset$  and  $F(\omega, \tau_3) = 0$  has at least one positive solution.

Assume  $I = \{\omega_1, \omega_2, \dots, \omega_{j_0}\}$ . For  $j \in \{1, 2, \dots, j_0\}$ , choose the unique angle  $\theta_j(\tau_{3j}) \in [0, 2\pi)$  such that

$$\begin{aligned} \cos \theta_j(\tau_{3j}) &= \frac{M(\omega_j)E(\omega_j) + N(\omega_j)F(\omega_j)}{M(\omega_j)^2 + N(\omega_j)^2}, \\ \sin \theta_j(\tau_{3j}) &= \frac{N(\omega_j)E(\omega_j) - M(\omega_j)F(\omega_j)}{M(\omega_j)^2 + N(\omega_j)^2}. \end{aligned} \quad (15)$$

Now, define the function as follows

$$S_n(\tau_{3j}) = \tau_{3j} - \frac{\theta_j(\tau_{3j}) + 2n\pi}{\omega_j(\tau_{3j})}, \quad n \in \{0, 1, 2, \dots\}.$$

Then, the characteristic equation (9) has a purely imaginary root  $\nu = i\omega_j(\tau_{3j}^*)$  at delay  $\tau_3 = \tau_{3j}^*$  with  $\omega_j(\tau_{3j}^*) > 0$  if and only if  $\tau_{3j}^*$  is a root of function  $S_n(\tau_{3j}) = 0$  for some  $n \in \mathbb{N}$  and

$j \in \{1, 2, \dots, j_0\}$ . Thus, the following remark comes from Theorem 2.2 in Beretta and Kuang (2002).

**Remark 5.4.**

The characteristic equation (9) admits a pair of simple and conjugate roots  $\nu(\tau_{3j}^*) = \pm i\omega_j(\tau_{3j}^*)$ ,  $\omega_j(\tau_{3j}^*) > 0$  at  $\tau_{3j}^*$  if  $S_n(\tau_{3j}^*) = 0$  for some  $n \in \mathbb{N}$  and  $j \in \{1, 2, \dots, j_0\}$ . This pair of simple conjugate pure imaginary roots crosses the imaginary axis from left to right  $\delta(\tau_{3j}^*) > 0$  and crosses the imaginary axis from right to left if  $\delta(\tau_{3j}^*) < 0$ , where

$$\delta(\tau_{3j}^*) = \text{sign} \left\{ \frac{d\text{Re}\nu}{d\tau_3} \Big|_{\nu=i\omega(\tau_{3j}^*)} \right\} = \text{sign} \left\{ \frac{dS_n(\tau_3)}{d\tau_3} \Big|_{\tau_3=\tau_{3j}^*} \right\} = \text{sign}\{F'_\omega(\omega_j, \tau_{3j}^*)\}.$$

Based on the above analysis, we obtain the following remark by Theorem 5.4 and the Hopf bifurcation theorem in Beretta and Kuang (2002).

**Remark 5.5.**

Consider system (1) with  $\tau_i = 0$ ,  $i = 1, 2, 4$  and the special form  $f_3(s) = \delta(s - \tau_3)$ . Assume that  $\mathcal{R}_0 > 1$  and  $(\mathcal{H}_1)$  holds. Then, there exists a  $\tau_3^*$  such that the chronic infection equilibrium  $E^*$  is locally asymptotically stable when  $0 \leq \tau_3 < \tau_3^*$ , and becomes unstable when  $\tau_3$  staying in some right neighborhood of  $\tau_3^*$ . Furthermore, a Hopf bifurcation occurs at  $\tau_3 = \tau_3^*$ .

## 6. Numerical simulations

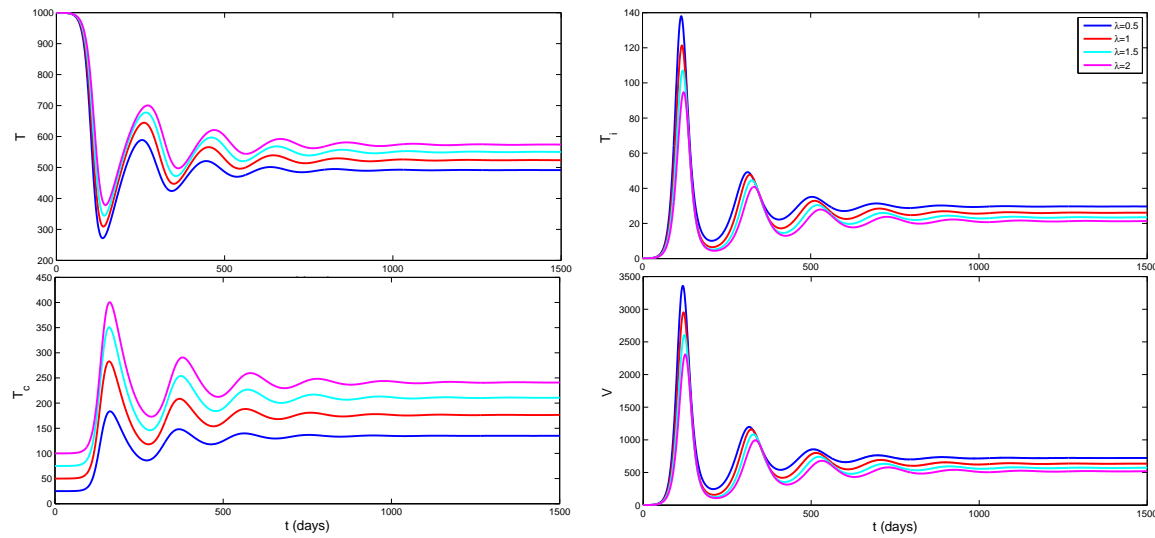
In this section, we perform numerical simulations for the model (1) with particular distribution functions  $f_i(s)$ ,  $i = 1, 2, 3, 4$  as :  $f_1(s) = f_2(s) = \delta(s - \tau_1)$ ,  $f_3(s) = \delta(s - \tau_3)$  and  $f_4(s) = \delta(s - \tau_4)$ , where  $\delta(\cdot)$  is the dirac delta function,  $s_i$ ,  $i = 1, 2, 3, 4$  are positive constants. Then, we can see that  $\eta_1 = \eta_2 = e^{-\mu_1\tau_1}$ ,  $\eta_3 = e^{-\mu_2\tau_3}$  and  $\eta_4 = e^{-\mu_3\tau_4}$ . We examine the behavior of the infected steady state  $E^*$  using data sets that are commonly used in the literature (Nkoa et al. (2013); Wang et al. (2016); Yang et al. (2015)). Values of parameters are defined as:  $b = 10$ ,  $\delta = 0.01$ ,  $\beta_1 = 2.5e - 4$ ,  $\beta_2 = 6.5e - 4$ ,  $\mu_1 = 0.1$ ,  $a = 3e - 2$ ,  $q = 4e - 2$ ,  $k = 100$ ,  $\alpha = 0.15$ ,  $c = 3$ ,  $\lambda = 1$ ,  $\mu_2 = 0.3$  and  $\mu_3 = 0.1$ . By simple computing when  $\mathcal{R}_0 > 1$ , the global stability of the chronic infection equilibrium  $E^*$  as demonstrated in Theorem 5.2 is numerically shown on Figure 1 for fixed delays  $\tau_1 = \tau_2 = 8$ ,  $\tau_3 = 0$  and  $\tau_4 = 2.5$ .

### 6.1. Effect of CTLs constant production rate

In order to investigate the effect of CTLs production rate, we carry out some numerical simulations to show the contribution of CTLs constant production rate during the whole infection. We set the production rate  $\lambda$  as 0.5, 1, 1.5, 2. We choose  $\tau_1 = \tau_2 = 3$ ,  $\tau_3 = 0$  and  $\tau_4 = 2.5$ . From the four figures of Figure 1, we can observe that uninfected and CTLs cells reach a higher peak level as  $\lambda$  increases while the peak level of infected cells and viruses decreases as  $\lambda$  increases. If we interpret the constant rate  $\lambda > 0$  as an inflow of antiviral drugs, one can observe from Figure 1 that the entry



of antiviral drugs into the host is important as a control parameter in order to reduce the viral load.



**Figure 1.** Simulation results showing the effect of  $\lambda$  on the dynamics of the model with  $\tau_1 = \tau_2 = 3$ ,  $\tau_3 = 0$  and  $\tau_4 = 2.5$

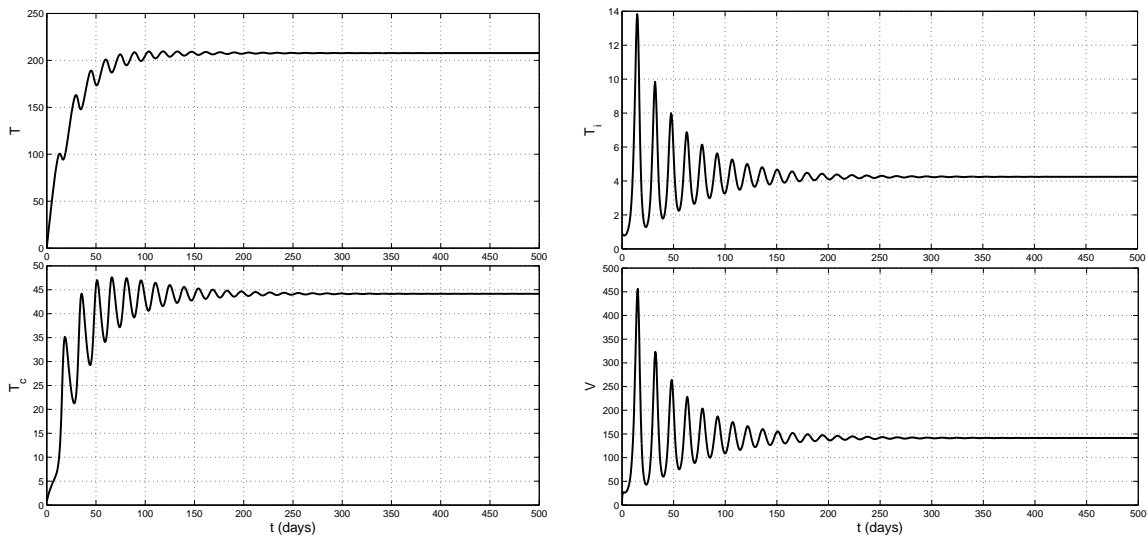
## 6.2. Effect of immune response delay

In order to illustrate our theoretical findings obtained in Theorem 5.5, we simulate model (1) with  $\tau_1 = \tau_2 = \tau_4 = 0$  and the special form  $f_3(s) = \delta(s - \tau_3)$  with  $\tau_3 \geq 0$ . First, we set  $\tau_3 = 0$  and keep others parameters. We get  $E^* = (207.7479, 4.2451, 44.1567, 141.5038)$ ,  $\mathcal{R}_0 = 24.5000$  and  $\Delta_3 = 6.0670 > 0$ , i.e., condition (11) holds. Then, the local stability of the chronic infection equilibrium  $E^*$  as established in Theorem 5.3 is numerically shown on Figure 2.

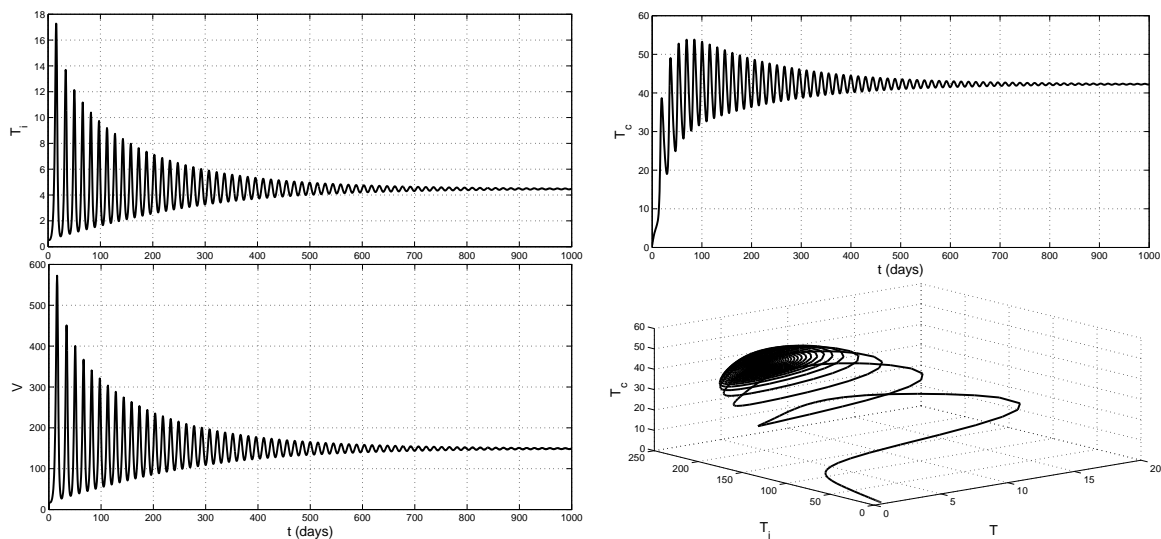
Now, we vary the value of  $\tau_3$  more than zero to see the effect of immune response delay. Through numerical calculations, we get two critical values of delay  $\tau_3$ , denoted by  $\tau_3^* = 0.2683$  and  $\tau_3^{**} = 5.5527$ . Figure 3 illustrates the local asymptotic stability of  $E^*$  for  $\tau_3 = 0.2 < \tau_3^*$  as established in Remark 5.5.

When we increase the value of immune response delay to  $\tau_3 = 0.3 \in (\tau_3^*, \tau_3^{**})$ , Figure 4 shows that  $E^*$  becomes unstable and system undergoes Hopf bifurcation at  $\tau_3 = \tau_3^*$ . This latter case is also illustrated on Figure 5 for  $\tau_3 = 5.4 \in (\tau_3^*, \tau_3^{**})$ .

Now, we increase again the value of immune response delay to  $\tau_3 = 5.7 > \tau_3^{**}$ . We see from Figure 6 that the chronic infection equilibrium  $E^*$  regain its stability for  $\tau_3 > \tau_3^{**}$  and Hopf bifurcation occurs at  $\tau_3 = \tau_3^{**}$ .



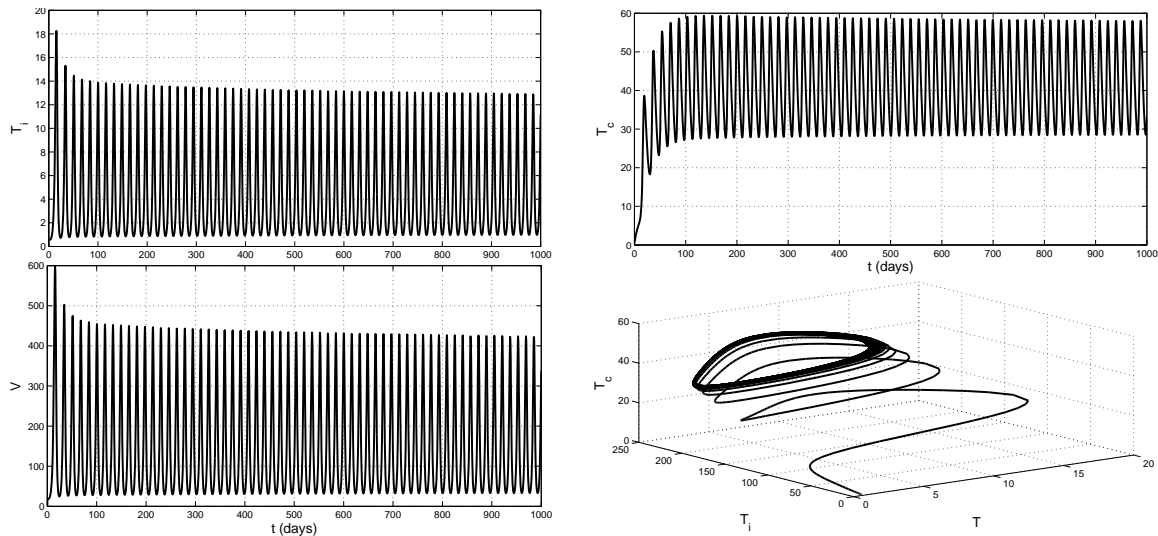
**Figure 2.** The time series of model (1) for  $\tau_i = 0, i = 1, 2, 3, 4$ . The chronic infection equilibrium  $E^*$  is asymptotically stable



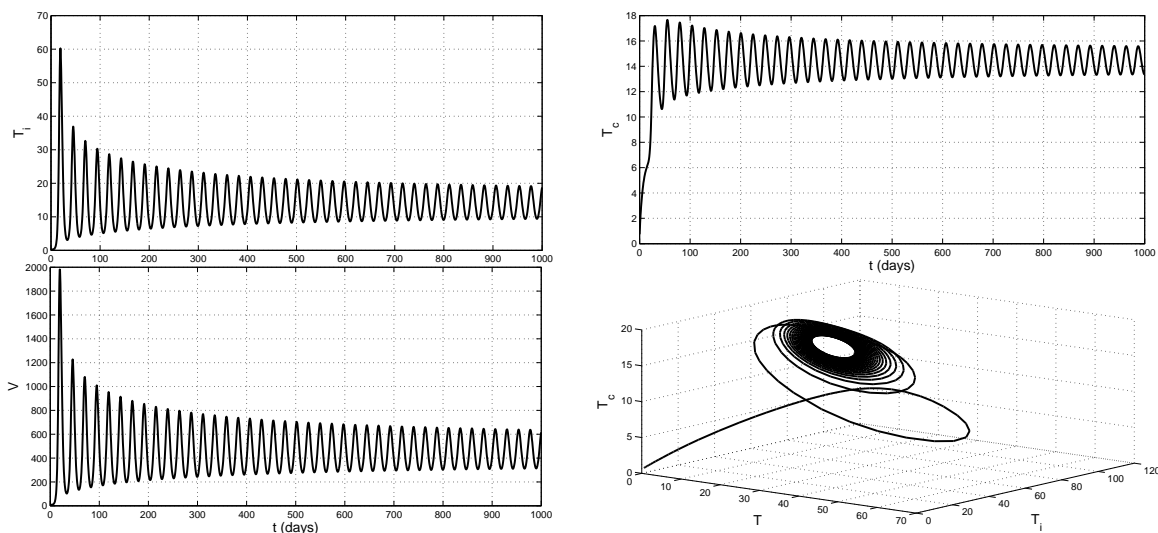
**Figure 3.** The time series of model (1) for  $\tau_i = 0, i = 1, 2, 4$ , and  $\tau_3 = 0.2$ . The chronic infection equilibrium  $E^*$  is asymptotically stable when  $\tau_3 < \tau_3^* = 0.2683$

### 6.3. Effect of intracellular delays and immune response delay on the dynamics of model (1)

It is challenging to analyze model (1) for the joint effect of four delays theoretically. So, we use numerical simulations to further investigate the effect of intracellular delays and immune response delay on the dynamics of model when  $\tau_i > 0, i = 1, 2, 3, 4$ . To this end, we choose  $\tau_4 = 2.5$  and  $\tau_1 = \tau_2$ . Figure 7 plots the chronic infection equilibrium  $E^*$  when  $\tau_1$  varies and  $\tau_3 = 5$  is fixed. From this figure, we see that for fixed immune response delay, when we increase the intracellular delay for both virus-to-cell and cell-to-cell infections, the trajectories of model (1) evolve from unstable to stable state. A similar result is observed in Figure 8 when we fix intracellular delay



**Figure 4.** The time series of model (1) for  $\tau_i = 0$ ,  $i = 1, 2, 4$ , and  $\tau_3 = 0.3$ . The chronic infection equilibrium  $E^*$  becomes unstable and a Hopf bifurcation occurs when  $\tau_3 \in (\tau_3^*, \tau_3^{**})$ . Here,  $\tau_3^{**} = 5.5527$

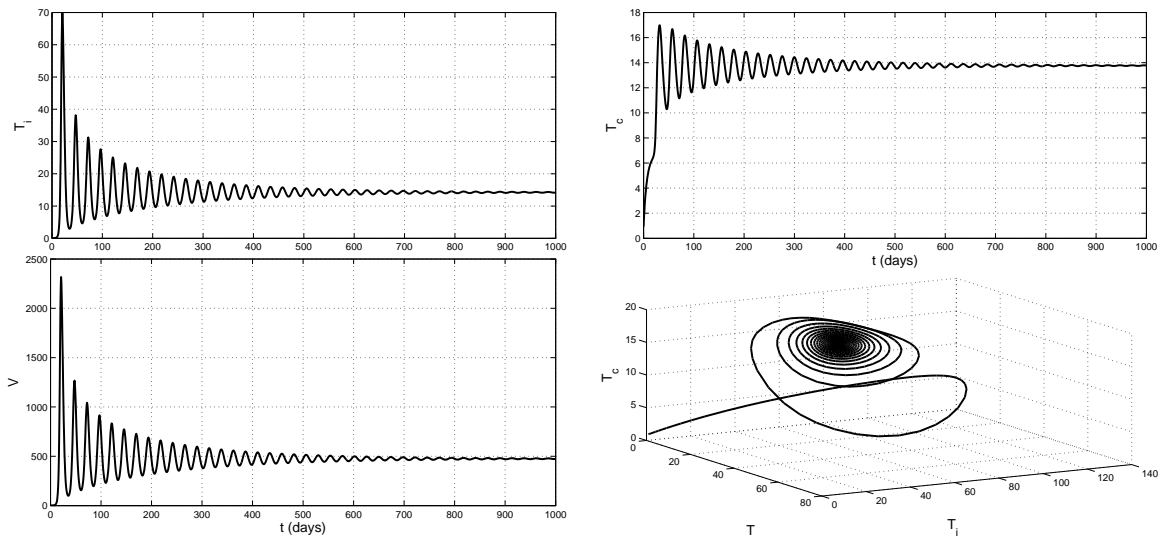


**Figure 5.** The time series of model (1) for  $\tau_i = 0$ ,  $i = 1, 2, 4$ , and  $\tau_3 = 5.4$ . The chronic infection equilibrium  $E^*$  becomes unstable and a Hopf bifurcation occurs at  $\tau_3 = \tau_3^*$

( $\tau_1 = 3$ ) and vary immune response delay  $\tau_3$ . These figures demonstrate that the chronic infection equilibrium  $E^*$  destabilizes as  $\tau_1$  and  $\tau_3$  decreases. Therefore, an increase in the intracellular delay or the immune response delay can stabilize the infected steady state  $E^*$ .

## 7. Conclusion

In this paper, we have investigated the dynamical properties of a delayed HIV-1 infection model with both virus-to-cell and cell-to-cell transmissions, and CTL immune response delay. This model extends some previous models and also take into account of a rate of CTLs cells exported from thymus. We have derived the basic reproductive number,  $\mathcal{R}_0$  and we have established that when



**Figure 6.** The time series of model (1) for  $\tau_i = 0, i = 1, 2, 4,$  and  $\tau_3 = 5.7$ . The chronic infection equilibrium  $E^*$  becomes stable when  $\tau_3 > \tau_3^{**} = 5.5527$

the basic reproductive number  $\mathcal{R}_0$  is less than unity, there is a disease free equilibrium  $E_0$  which is globally asymptotically stable; while when the basic reproductive number  $\mathcal{R}_0$  is greater than unity, there exists an unique chronic infection equilibrium  $E^*$  which is globally asymptotically stable in absence of immune response delay. Furthermore, we have explored the local stability of the chronic infection equilibrium for the special case with only immune response delay.

We have determined some conditions leading to the occurrence of Hopf bifurcation and found that when immune response delay increase, there are stability switches of the chronic infection equilibrium. Numerical simulations were used to further investigate the infected steady state and the existence of the Hopf bifurcation with positive delays. We have observed that for fixed immune response delay, when intracellular delay increase, there is also stability switches of the chronic infection equilibrium. These analysis reveal that the sustained oscillations occur when the intracellular delays and immune delay are incorporated simultaneously in the model.

It is challenging to study stability and Hopf bifurcation of the chronic infection equilibrium for the joint effect of four delays theoretically. As far as future investigations are concerned, we are planning to study local stability and Hopf bifurcation of the chronic infection equilibrium in a general case with all delays being positive. This possible extension on which we are already working will be studied on a separate paper.

**Acknowledgment:**

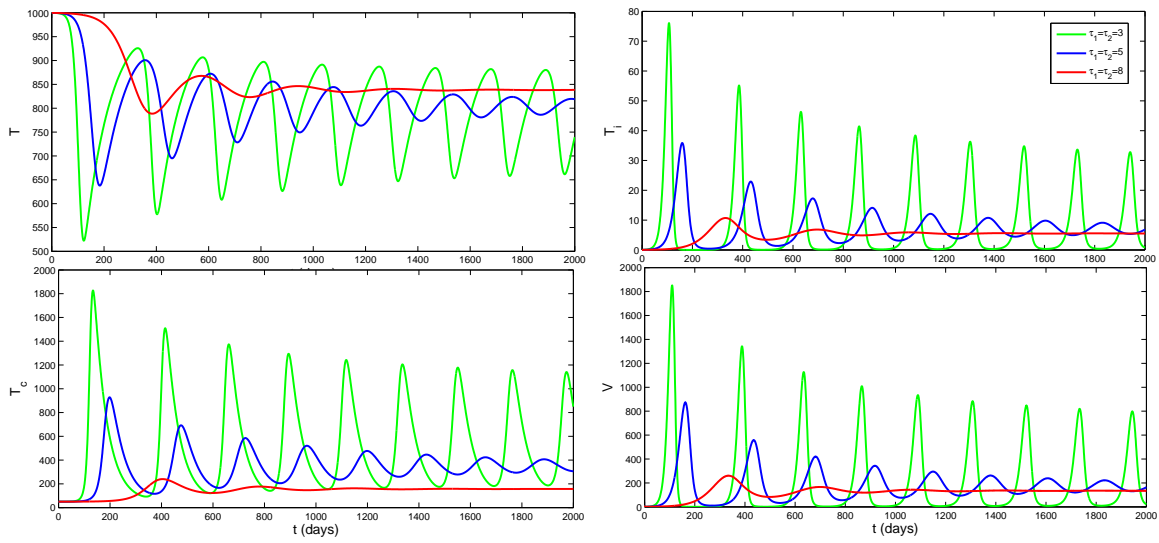
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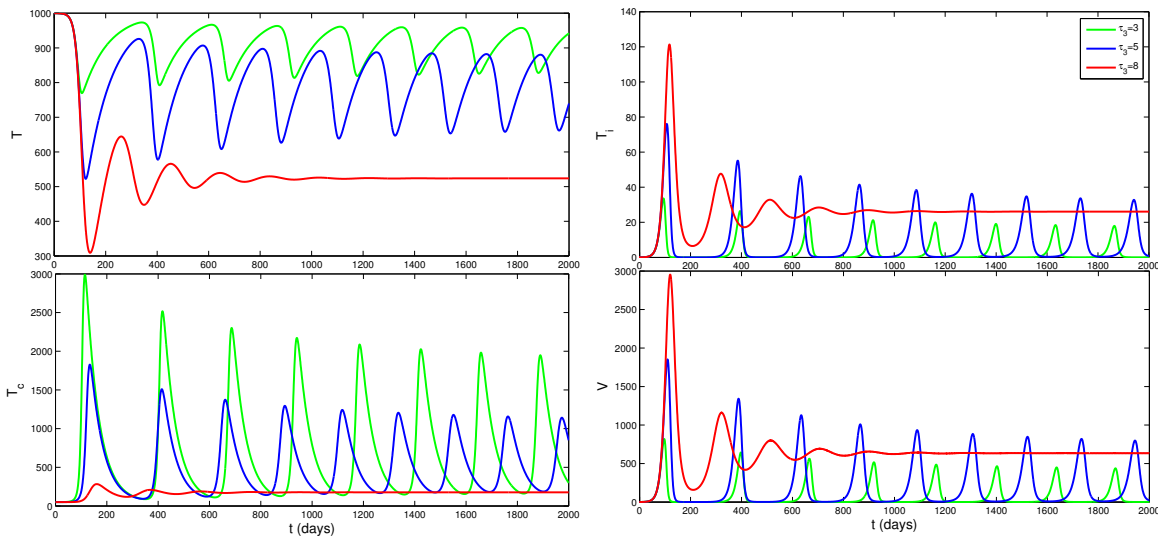
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**Appendix**



**Figure 7.** Simulation results showing the effect of intracellular delay  $\tau_1$  when immune response delay is fixed ( $\tau_3 = 5$ )



**Figure 8.** Simulation results showing the effect of immune response delay  $\tau_3$  when intracellular delay  $\tau_1$  is fixed ( $\tau_1 = 3$ )