



Mathematical analysis of an HTLV-I infection model with the mitosis of $CD4^+$ T cells and delayed CTL immune response*

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Abstract. In this paper, we consider an improved Human T-lymphotropic virus type I (HTLV-I) infection model with the mitosis of $CD4^+$ T cells and delayed cytotoxic T-lymphocyte (CTL) immune response by analyzing the distributions of roots of the corresponding characteristic equations, the local stability of the infection-free equilibrium, the immunity-inactivated equilibrium, and the immunity-activated equilibrium when the CTL immune delay is zero is established. And we discuss the existence of Hopf bifurcation at the immunity-activated equilibrium. We define the immune-inactivated reproduction ratio R_0 and the immune-activated reproduction ratio R_1 . By using Lyapunov functionals and LaSalle's invariance principle, it is shown that if $R_0 < 1$, the infection-free equilibrium is globally asymptotically stable; if $R_1 < 1 < R_0$, the immunity-inactivated equilibrium is globally asymptotically stable; if $R_1 > 1$, the immunity-activated equilibrium is globally asymptotically stable when the CTL immune delay is zero. Besides, uniform persistence is obtained when $R_1 > 1$. Numerical simulations are carried out to illustrate the theoretical results.

Keywords: HTLV-I infection, the mitosis of $CD4^+$ T cells, delayed CTL immune response, the reproduction ratio, Lyapunov functionals, Hopf bifurcation.

1 Introduction

Human T-lymphotropic virus type I (HTLV-I) is a pathogenic retrovirus. About 10 million to 20 million people worldwide are infected [1, 13, 19]. It is closely linked to two main types of viral diseases: adult T cell leukaemia/lymphoma (ATL), an aggressive blood cancer; and HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP), a progressive neurological and inflammatory disease [8, 9, 20, 21]. However, there is no definite

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mechanism for the development of HTLV-I related diseases and no effective treatment. Besides, most of the infected persons are asymptomatic carriers, and only 0.1–4 % of the infected persons develop from long-term asymptomatic carriers to ATL or HAM/TSP [21].

Similar to Human Immunodeficiency Virus (HIV), the target cell of HTLV-I is CD4⁺ T cells. For the infected CD4⁺ T cells, a hypothesis was put forward by Asquith and Bangbam that only a small part of infected CD4⁺ cells express Tax [5]. Based on this, the infected CD4⁺ T cells were divided into actively infected CD4⁺ T cells and latently infected CD4⁺ T cells according to whether Tax is expressed or not [5]. And the hypothesis of dynamic interaction between CD4⁺ T cells without Tax expression and CD4⁺ T cells with Tax expression proposed by Asquith and Bangbam explains that HTLV-I infected individuals have a sustained activation of the specific immune response to HTLV-I, while the viral load increases [3]. Therefore, it is very important to distinguish latently infected CD4⁺ T cells from actively infected CD4⁺ T cells. For mitosis, it should be pointed out that although mitosis is a natural process that occurs in all CD4⁺ T cells, normal homeostatic mitosis occurs at a much slower rate than that of actively infected CD4⁺ T cells proliferation. To avoid unnecessarily complicating the mathematical analysis, the mitosis of the healthy and latently CD4⁺ T cells is ignored [15].

Based on the above discussion, in order to explore the dynamic interaction between latently infected CD4⁺ T cells and actively infected CD4⁺ T cells in HTLV-I infection, in [15], Lim and Li proposed the following mathematical model:

$$\begin{aligned}x'(t) &= \lambda - dx - \beta xy, \\u'(t) &= \delta\beta xy + \epsilon ry \left(1 - \frac{x+u}{k}\right) - (\mu + \sigma)u, \\y'(t) &= \sigma u - ay,\end{aligned}\tag{1}$$

where $x(t)$ denotes the concentration of healthy CD4⁺ T cells, which are produced at rate λ and die at rate d , $u(t)$ denotes the concentration of latently infected CD4⁺ T cells, and $y(t)$ denotes the concentration of actively infected CD4⁺ T cells; β is the transmission coefficient; a and μ represent the death rates of actively infected CD4⁺ T cells and latently infected CD4⁺ T cells, respectively; σ is the rate at which latently infected CD4⁺ T cells translate into actively infected CD4⁺ T cells. $\delta\beta xy$ and $\epsilon ry(1 - (x+u)/k)$ are used to describe the newly infected CD4⁺ T cells entering the latently infected CD4⁺ T cells compartment through infection and mitosis or vertical transmission, respectively.

In model (1), logistic growth term $ry(1 - (x+u)/k)$ is used to describe the mitosis of actively infected CD4⁺ T cells. However, the numerical results show that there is no qualitative difference between exponential growth term and logical growth term in the behaviour of trajectories [17]. Therefore, in order to avoid the complication of the model equation, it is reasonable to assume that $x(t)+u(t) \ll k$, the proliferation of actively infected CD4⁺ T cells follows an exponential growth term ry instead of logical growth term $ry(1 - (x+u)/k)$. The exponential growth term ry has been used by Lim and Maini [17].

In the process of HTLV-I infection, a strong cytotoxic T lymphocyte (CTL) immune response was established to fight infection [5, 12]. In the most virus infections, CTL

immune response can lower the proviral load and consequently lower the risk of disease [1]. However, experiments have shown that the cytotoxicity of CTL ultimately leads to demyelination of HAM/TSP central nervous system and the development of HAM/TSP disease [16]. It can be seen that the effect of CTL immune response on HTLV-I infection is much more complicated. Therefore, the consideration of CTL immune response in the HTLV-I infection model is of great significance to the study of the development and treatment of ATL or HAM/TSP.

Since antigenic stimulation to generate HTLV-I specific CTLs involves a series of events that require a time delay [7]. Therefore, it is necessary to consider the effect of time delay in the model, and the form of CTL immune function $f(y, z) = cy(t - \tau)$ has been used in [14]. Motivated by the works of Li and Shu [16], Lim and Maini [17], in this paper, we consider the following HTLV-I infection model with actively infected CD4⁺ T cells mitosis and delayed CTL immune response:

$$\begin{aligned} x'(t) &= \lambda - dx - \beta xy, \\ u'(t) &= \beta xy + ry - (\mu + \sigma)u, \\ y'(t) &= \sigma u - ay - pyz, \\ z'(t) &= cy(t - \tau)z(t - \tau) - bz, \end{aligned} \tag{2}$$

where $z(t)$ denotes the concentration of the specific CD8⁺ CTLs, b is the death rate of specific CD8⁺ CTLs; pyz describes actively infected CD4⁺ T cells being lysed by specific CD8⁺ CTLs, $cy(t - \tau)z(t - \tau)$ represents that the CTLs produced at time t depends on the concentration of CTLs and actively infected CD4⁺ T cells at time $t - \tau$ [16, 23]. Experiments have shown that the mitosis of actively CD4⁺ T cells is usually lower than the removal rate caused by natural death [17], hence, in the following, we assume that $a > r$.

The initial condition for system (2) takes the form

$$\begin{aligned} x(\theta) &= \phi_1(\theta), & u(\theta) &= \phi_2(\theta), & y(\theta) &= \phi_3(\theta), & z(\theta) &= \phi_4(\theta), \\ \phi_i(\theta) &\geq 0, & \theta &\in [-\tau, 0), & \phi_i(0) &> 0 & (i = 1, 2, 3, 4), \end{aligned} \tag{3}$$

where $(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)) \in C([-\tau, 0], \mathbb{R}_{+0}^4)$, here $\mathbb{R}_{+0}^4 = \{(x_1, x_2, x_3, x_4) : x_i \geq 0, i = 1, 2, 3, 4\}$.

This paper is organized as follows. In Section 2, we show the positivity and boundedness of solutions to system (2). In Section 3, the existence of feasible equilibria, the local stability of the infection-free equilibrium, the immunity-inactivated equilibrium, and the immunity-activated equilibrium (when $\tau = 0$) is established. And we discuss the existence of Hopf bifurcation at the immunity-activated equilibrium. In Section 4, by constructing suitable Lyapunov functionals and using LaSalle's invariance principle, the global stability of the infection-free equilibrium, the immune-inactivated equilibrium, and the immune-activated equilibrium (when $\tau = 0$) is established. In Section 5, we analyze the uniform persistence of system (2) when the immune-activated reproduction ratio is greater than one. In Section 6, we give some numerical simulations to illustrate the theoretical results. Finally, a brief remark is given in Section 7 to conclude this work.

2 The positivity and boundedness of solutions

Theorem 1. Any solution of system (2) with the initial condition (3) is defined on $[0, +\infty)$ and remains positive for all $t > 0$.

Proof. Let $(x(t), u(t), y(t), z(t))$ be any solution of system (2) with the initial condition (3). First, by the first equation of system (2) we have $\dot{x}|_{x=0} = \lambda > 0$. This implies that $x(t) > 0$ for all $t > 0$ as long as $x(0) = \phi_1(0) > 0$.

Next, we show that $u(t) > 0$ for all $t > 0$. Notice that $u_0 = \phi_2(0) > 0$ if there exists a t_0 such that $u(t_0) = 0$, then $t_0 > 0$. Assume that t_0 is the first time such that $u(t) = 0$, that is, $t_0 = \inf\{t > 0: u(t_0) = 0\}$. Then $\dot{u}(t_0) = (\beta x(t_0) + r)y(t_0) \leq 0$. Hence, $y(t_0) \leq 0$. By the third equation of system (2) we have

$$y(t) = \left(\phi_3(0) + \sigma \int_0^t u(s) e^{\int_0^s (a+pz(v)) dv} ds \right) e^{-\int_0^s (a+pz(s)) ds}.$$

Thus, we have $y(t_0) > 0$. The contradiction shows that $u(t) > 0$ for all $t > 0$. Similarly, we can obtain $y(t) > 0$ for all $t > 0$.

Furthermore, by the fourth equation of system (2) we have

$$z(t) = \left(\phi_4(0) + c \int_0^t y(s - \tau) z(s - \tau) e^{bs} ds \right) e^{-bt}.$$

When $t \in [0, \tau)$, we have $z(t - \tau) = \phi_4(t - \tau) > 0$. Hence, according to (2), we have $z(t) > 0$ for $t \in [0, \tau)$. Similarly, when $t \in [\tau, 2\tau)$, we can obtain that $z(t) > 0$. By using mathematical induction method we have $z(t) > 0$ for all $t > 0$. This completes the proof. \square

Theorem 2. There is a positive constant M such that for any positive solution $(x(t), u(t), y(t), z(t))$ of system (2) with the initial condition (3),

$$\begin{aligned} \limsup_{t \rightarrow +\infty} x(t) &< M, & \limsup_{t \rightarrow +\infty} u(t) &< M, \\ \limsup_{t \rightarrow +\infty} y(t) &< M, & \limsup_{t \rightarrow +\infty} z(t) &< M. \end{aligned}$$

Proof. Let $(x(t), u(t), y(t), z(t))$ be any positive solution of system (2) with the initial condition (3). Define

$$N(t) = x(t) + u(t) + y(t) + \frac{p}{c} z(t + \tau).$$

Calculating the derivative of $N(t)$ along positive solution of system (2), it follows that

$$\begin{aligned} \dot{N}(t) &= \lambda - dx(t) - \mu u(t) - (a - r)y(t) - \frac{bp}{c} z(t + \tau) \\ &\leq \lambda - mN(t), \end{aligned}$$

yielding $\limsup_{t \rightarrow +\infty} N(t) \leq \lambda/m$, where $m = \min\{d, \mu, a - r, b\}$.

Therefore, the following set is positively invariant for system (2):

$$\Omega = \left\{ (x, u, y, z) \in \mathbb{R}_+^4 : 0 \leq x(t) + u(t) + y(t) + \frac{p}{c}z(t + \tau) \leq \frac{\lambda}{m} \right\}.$$

If we choose $M = (\lambda/m) \min\{1, c/p\}$, then Theorem 2 follows. □

3 Equilibria, local stability, and Hopf bifurcation

In this section, we study the existence of feasible equilibria, the local stability of the infection-free equilibrium, the immunity-inactivated equilibrium, and the immunity-activated equilibrium (when $\tau = 0$) of system (2) by analyzing the distributions of roots of the corresponding characteristic equations, and we show the existence of Hopf bifurcation at the immunity-activated equilibrium.

System (2) always has an infection-free equilibrium $E_0(\lambda/d, 0, 0, 0)$. We can obtain the immune-inactivated reproduction ratio by using the method of the next generation matrix [24]:

$$R_0 = \rho(FV^{-1}) = \frac{(\beta\lambda + rd)\sigma}{ad(\mu + \sigma)},$$

where $\rho(FV^{-1})$ is the spectrum radius of FV^{-1} . R_0 represents the expected number of newly infected cells generated by a single infected cell in its life span. If $R_0 > 1$, in addition to the infection-free equilibrium, system (2) has an immunity-inactivated equilibrium $E_1(x_1, u_1, y_1, 0)$, where

$$\begin{aligned} x_1 &= \frac{a(\mu + \sigma) - r\sigma}{\beta\sigma}, & u_1 &= \frac{a^2d(\mu + \sigma)(R_0 - 1)}{\beta\sigma[a(\mu + \sigma) - r\sigma]}, \\ y_1 &= \frac{ad(\mu + \sigma)}{\beta[a(\mu + \sigma) - r\sigma]}(R_0 - 1). \end{aligned}$$

Further, by calculation we obtain the immune-activated reproduction ratio

$$R_1 = \frac{\sigma[\beta\lambda c + r(\beta b + cd)]}{a(\mu + \sigma)(\beta b + cd)}.$$

If $R_1 > 1$, in addition to E_0 and E_1 , system (2) has an immunity-activated equilibrium $E^*(x^*, u^*, y^*, z^*)$, where

$$x^* = \frac{\lambda c}{\beta b + cd}, \quad u^* = \frac{ab}{\sigma c}R_1, \quad y^* = \frac{b}{c}, \quad z^* = \frac{a}{p}(R_1 - 1).$$

Theorem 3. *If $R_0 < 1$, the infection-free equilibrium E_0 of system (2) is locally asymptotically stable; if $R_0 > 1$, E_0 is unstable.*

Proof. The characteristic equation of system (2) at the equilibrium E_0 is

$$(s + b)(s + d)[s^2 + (a + \mu + \sigma)s + (1 - R_0)] = 0. \tag{4}$$

Clearly, (4) has negative real roots $s_1 = -b$, $s_2 = -d$, and other roots of (4) are determined by the following equation:

$$f(s) := s^2 + (a + \mu + \sigma)s + (1 - R_0) = 0. \quad (5)$$

If $R_0 < 1$, it is easy to show that all roots of (5) have only negative real parts. Therefore, the equilibrium E_0 is locally asymptotically stable.

If $R_0 > 1$, we have $f(0) < 0$, $f(s) \rightarrow +\infty$ ($s \rightarrow +\infty$). Hence, (5) has at least one positive real root. Accordingly, E_0 is unstable. \square

Theorem 4. *If $R_1 < 1 < R_0$, the immunity-inactivated equilibrium E_1 of system (2) is locally asymptotically stable; if $R_1 > 1$, E_1 is unstable.*

Proof. The characteristic equation of system (2) at the equilibrium E_1 is

$$g(s)h(s) = 0, \quad (6)$$

where

$$\begin{aligned} g(s) &= s + b - cy_1 e^{-s\tau}, \\ h(s) &= (s + d + \beta y_1) \left(\frac{s}{\mu + \sigma} + 1 \right) \left(\frac{s}{a} + 1 \right) \\ &\quad + \beta y_1 - (s + d + \beta y_1) - \frac{\beta y_1 r \sigma}{a(\mu + \sigma)}. \end{aligned}$$

We first claim that all roots of the following transcendental equation

$$s + b - cy_1 e^{-s\tau} = 0 \quad (7)$$

have negative real parts. Otherwise, there exists a root $s_1 = a_1 + ib_1$ with $a_1 \geq 0$. If $R_1 < 1 < R_0$, we have

$$|s_1 + b| \geq b, \quad |cy_1 e^{-s_1\tau}| \leq |cy_1| < b.$$

It follows that

$$|s_1 + b| > |cy_1 e^{-s_1\tau}|,$$

which contradicts (7). Hence, all roots of (7) have negative real parts, and other roots of (6) are determined by the following equation:

$$\begin{aligned} &(s + d + \beta y_1) \left(\frac{s}{\mu + \sigma} + 1 \right) \left(\frac{s}{a} + 1 \right) + \beta y_1 \\ &= (s + d + \beta y_1) + \frac{\beta y_1 r \sigma}{a(\mu + \sigma)}. \end{aligned} \quad (8)$$

Now, we claim that all roots of (8) have negative real parts. Otherwise, there exists a root $s_2 = a_2 + ib_2$ with $a_2 \geq 0$. In this case, we have

$$\left| \frac{s_2}{\mu + \sigma} + 1 \right| > 1, \quad \left| \frac{s_2}{a} + 1 \right| > 1, \quad \left| \beta y_1 \right| > \left| \beta y_1 \frac{r\sigma}{a(\mu + \sigma)} \right|.$$

It follows that

$$\begin{aligned} & \left| (s_2 + d + \beta y_1) \left(\frac{s_2}{\mu + \sigma} + 1 \right) \left(\frac{s_2}{a} + 1 \right) + \beta y_1 \right| \\ & > \left| (s_2 + d + \beta y_1) + \frac{\beta y_1 r \sigma}{a(\mu + \sigma)} \right|, \end{aligned}$$

which contradicts (8). Therefore, if $R_1 < 1 < R_0$, all roots of (8) have negative real parts. Further, all roots of (6) have negative real parts. Accordingly, E_1 is locally asymptotically stable.

If $R_1 > 1$, it only needs to consider (7), it is clear that $g(0) = b - cy_1 < 0$, $g(s) = s + b - cy_1 e^{-s\tau} \rightarrow +\infty$ ($s \rightarrow +\infty$). Therefore, (6) has at least one positive real root. Accordingly, E_1 is unstable. \square

The characteristic equation of system (2) at the immunity-activated equilibrium E^* is

$$s^4 + p_3 s^3 + p_2 s^2 + p_1 s + p_0 + (q_3 s^3 + q_2 s^2 + q_1 s + q_0) e^{-s\tau} = 0, \tag{9}$$

where

$$\begin{aligned} p_0 &= \beta^2 x^* y^* b \sigma, \\ p_1 &= b(d + \beta y^*)(a + pz^* + \mu + \sigma) + \beta^2 x^* y^* \sigma, \\ p_2 &= (d + \beta y^*)(a + pz^* + b + \mu + \sigma) + b(a + pz^* + \mu + \sigma), \\ p_3 &= a + pz^* + d + \beta y^* + b + \mu + \sigma, \\ q_0 &= -b[\beta^2 x^* y^* \sigma - (d + \beta y^*)(\mu + \sigma)pz^*], \\ q_1 &= -b[(\mu + \sigma)(d + \beta y^*) + (a + pz^*)(d + \beta y^*) - pz^*(\mu + \sigma + d + \beta y^*)], \\ q_2 &= -b(a + d + \beta y^* + \mu + \sigma), \\ q_3 &= -b. \end{aligned}$$

When $\tau = 0$, (9) reduces to

$$\begin{aligned} & s(s + d + \beta y^*)(s + \mu + \sigma)(s + a + pz^*) + s\beta^2 x^* y^* \sigma \\ & \quad + (s + d + \beta y^*)(s + \mu + \sigma)pbz^* \\ & = s(s + d + \beta y^*)(a + pz^*)(\mu + \sigma). \end{aligned} \tag{10}$$

Now, we claim that all roots of (10) have negative real parts. Otherwise, (10) has at least one root $s_1 = x_1 + iy_1$ with $x_1 \geq 0$. Noting that

$$\begin{aligned} & \left| s_1(s_1 + d + \beta y^*)(s_1 + \mu + \sigma)(s_1 + a + pz^*) + s_1\beta^2 x^* y^* \sigma \right. \\ & \quad \left. + (s_1 + d + \beta y^*)(s_1 + \mu + \sigma)pbz^* \right| \\ & > \left| s_1(s_1 + d + \beta y^*)(a + pz^*)(\mu + \sigma) \right|, \end{aligned}$$

which contradicts (10). Thus, all roots of (10) have negative real parts. Hence, when $\tau = 0$, the equilibrium E^* is locally asymptotically stable.

When $\tau > 0$, substituting $s = i\omega$ ($\omega > 0$) into (9) and separating real and imaginary parts, we have

$$\begin{aligned} \omega^4 - p_2\omega^2 + p_0 &= (q_3\omega^3 - q_1\omega) \sin \omega\tau + (q_2\omega^2 - q_0) \cos \omega\tau, \\ p_3\omega^3 - p_1\omega &= (q_2\omega^2 - q_0) \sin \omega\tau - (q_3\omega^3 - q_1\omega) \cos \omega\tau. \end{aligned} \quad (11)$$

Squaring and adding the two equations of (11), it follows that

$$\omega^8 + C_3\omega^6 + C_2\omega^4 + C_1\omega^2 + C_0 = 0, \quad (12)$$

where

$$\begin{aligned} C_0 &= p_0^2 - q_0^2, & C_1 &= p_1^2 - 2p_0p_2 - q_1^2 + 2q_0q_2, \\ C_2 &= p_2^2 + 2p_0 - 2p_1p_3 + 2q_1q_3 - q_2^2, & C_3 &= p_3^2 - 2p_2 - q_3^2. \end{aligned}$$

Let $z = \omega^2$. Equation (12) becomes

$$h(z) := z^4 + C_3z^3 + C_2z^2 + C_1z + C_0 = 0. \quad (13)$$

Clearly, if $C_0 < 0$, we have $h(0) = C_0 < 0$, $\lim_{z \rightarrow +\infty} h(z) = +\infty$.

Therefore, (13) has at least one positive root. From (13) we have

$$h'(z) = 4z^3 + 3C_3z^2 + 2C_2z + C_1.$$

Denote

$$P = \frac{8C_2 - 3C_3^2}{16}, \quad Q = \frac{C_3^3 - 4C_3C_2 + 8C_1}{32}, \quad D_0 = \frac{Q^2}{4} + \frac{P^3}{27},$$

and

$$\begin{aligned} z_1^* &= -\frac{C_1}{4} + \sqrt[3]{-\frac{Q}{2} + \sqrt{D_0}} + \sqrt[3]{-\frac{Q}{2} - \sqrt{D_0}} \quad \text{if } D_0 > 0, \\ z_2^* &= \max \left\{ -\frac{C_1}{4} - 2\sqrt[3]{\frac{Q}{2}}, -\frac{C_1}{4} + \sqrt[3]{\frac{Q}{2}} \right\} \quad \text{if } D_0 = 0, \\ z_3^* &= \max \left\{ -\frac{C_1}{4} + 2 \operatorname{Re}\{\alpha\}, -\frac{C_1}{4} + 2 \operatorname{Re}\{\alpha\varepsilon\}, -\frac{C_1}{4} + 2 \operatorname{Re}\{\alpha\bar{\varepsilon}\} \right\} \quad \text{if } D_0 < 0, \end{aligned}$$

where α is one of cubic roots of the complex number $Q/2 + \sqrt{D_0}$, and $\varepsilon = -1/2 + \sqrt{3}/2i$. By [27] we have the following result.

Lemma 1. (See [27].)

- (i) If $C_0 < 0$, then (13) has at least one positive root.
- (ii) Assume that $C_0 \geq 0$, then (13) has no positive roots if one of the following conditions holds:
 - (a) $D_0 > 0$ and $z_1^* < 0$;
 - (b) $D_0 = 0$ and $z_2^* < 0$;
 - (c) $D_0 < 0$ and $z_3^* < 0$.

(iii) Assume that $C_0 \geq 0$, then (13) has at least one positive root if one of the following conditions holds:

- (a) $D_0 > 0$, $z_1^* > 0$, and $h(z_1^*) < 0$;
- (b) $D_0 = 0$, $z_2^* > 0$, and $h(z_2^*) < 0$;
- (c) $D_0 < 0$, $z_3^* > 0$, and $h(z_3^*) < 0$.

Without loss of generality, we assume that (13) has positive real roots z_k ($k = 1, 2, \dots, \bar{k}$), where $1 \leq \bar{k} \leq 4$. Then (12) has positive roots $\omega_k = \sqrt{z_k}$ ($k = 1, 2, \dots, \bar{k}$). From (11) we have

$$\tau_k^{(j)} = \frac{1}{\omega_k} \arccos \left[\frac{(\omega_k^4 - p_2\omega_k^2 + p_0)(q_2\omega_k^2 - q_0) - (p_3\omega_k^3 - p_1\omega_k)(q_3\omega_k^3 - q_1\omega_k)}{(q_3\omega_k^3 - q_1\omega_k)^2 + (q_2\omega_k^2 - q_0)^2} + 2\pi j \right],$$

where $k = 1, 2, \dots, \bar{k}$, $j = 1, 2, \dots$. Then $\pm\omega_k$ is a pair of purely imaginary roots of (12) with $\tau = \tau_k^{(j)}$.

Denote $\tau_0 = \min_{k \in \{1, 2, \dots, \bar{k}\}} \{\tau_k^{(0)}\}$, $\omega_0 = \omega_{k_0}$. Let $s(\tau) = \psi(\tau) + i\omega(\tau)$ be a root of (9) satisfying $\psi(\tau_k^{(j)}) = 0$, $\omega(\tau_k^{(j)}) = \omega_k$. Differentiating (9) with respect τ , we have

$$\begin{aligned} \left(\frac{ds}{d\tau} \right)^{-1} &= -\frac{4s^3 + 3s^2p_3 + 2sp_2 + p_1}{s(s^4 + p_3s^3 + p_2s^2 + p_1s + p_0)} \\ &\quad + \frac{3q_3s^2 + 2q_2s + q_1}{s(q_3s^3 + q_2s^2 + q_1s + q_0)} - \frac{\tau}{s}. \end{aligned} \tag{14}$$

Therefore, we obtain from (11) and (14) that

$$\text{sign} \left\{ \frac{d(\text{Re } s)}{d\tau} \right\}_{\tau=\tau_0} = \text{sign} \frac{h'(\omega_0^2)}{(q_3\omega_0^2 - q_1)^2 + (q_0 - q_2\omega_0^2)^2}.$$

From what has been discussed above we have the following result [22, 26].

Theorem 5. For system (2), we have

- (i) If Eq. (13) has no positive roots, then the equilibrium E^* is locally asymptotically stable.
- (ii) If Eq. (13) has at least one positive root, and $h'(\omega_0^2) \neq 0$, then the equilibrium E^* is locally asymptotically stable for $\tau \in [0, \tau_0)$ and unstable for $\tau > \tau_0$. Further, system (2) undergoes a Hopf bifurcation at E^* when $\tau = \tau_0$.

4 Global stability

In this section, we study the global stability of the infection-free equilibrium, the immune-inactivated equilibrium, and the immune-activated equilibrium (when $\tau = 0$) of system (2) by using Lyapunov functionals and LaSalle’s invariance principle.

Theorem 6. If $R_0 < 1$, the infection-free equilibrium $E_0(x_0, 0, 0, 0)$ of system (2) is globally asymptotically stable.

Proof. Let $(x(t), u(t), y(t), z(t))$ be any positive solution of system (2) with the initial condition (3). Define

$$W_0(t) = x(t) - x_0 - x_0 \ln \frac{x(t)}{x_0} + u(t) + \frac{\mu + \sigma}{\sigma} y(t) \\ + \frac{p(\mu + \sigma)}{c\sigma} z(t) + \frac{p(\mu + \sigma)}{\sigma} \int_{t-\tau}^t y(s)z(s) ds,$$

where $x_0 = \lambda/d$. Calculating the derivative of $W_0(t)$ along positive solution of system (2) yields

$$\dot{W}_0(t) = \left(1 - \frac{x_0}{x}\right)(\lambda - dx) + \beta x_0 y + r y - \frac{\mu + \sigma}{\sigma} a y - \frac{p(\mu + \sigma)}{c\sigma} b z \\ = -\frac{d(x - x_0)^2}{x} + \left(\frac{\beta\lambda}{d} + r - \frac{a(\mu + \sigma)}{\sigma}\right) y - \frac{p(\mu + \sigma)}{c\sigma} b z \\ = -\frac{d(x - x_0)^2}{x} + \frac{a(\mu + \sigma)}{\sigma} (R_0 - 1) y - \frac{p(\mu + \sigma)}{c\sigma} b z.$$

It follows that $\dot{W}_0(t) \leq 0$, $\dot{W}_0(t) = 0$ if and only if $x = x_0$, $u = 0$, $y = 0$, $z = 0$. The maximal variant set in $\{(x(t), u(t), y(t), z(t)) \in \Omega: \dot{W}_0(t) = 0\}$ is the singleton $\{E_0\}$. From Theorem 3, E_0 is locally asymptotically stable. Accordingly, the global stability of E_0 follows from LaSalle's invariance principle. \square

Theorem 7. *If $R_1 < 1 < R_0$, the immunity-inactivated equilibrium $E_1(x_1, u_1, y_1, 0)$ of system (2) is globally asymptotically stable.*

Proof. Let $(x(t), u(t), y(t), z(t))$ be any positive solutions of system (2) with the initial condition (3). Define

$$W_1(t) = x(t) - x_1 - x_1 \ln \frac{x(t)}{x_1} + u(t) - u_1 - u_1 \ln \frac{u(t)}{u_1} + \frac{p(\mu + \sigma)}{c\sigma} z(t) \\ + \frac{\mu + \sigma}{\sigma} \left(y(t) - y_1 - y_1 \ln \frac{y(t)}{y_1} \right) + \frac{p(\mu + \sigma)}{\sigma} \int_{t-\tau}^t y(s)z(s) ds.$$

Calculating the derivative of $W_1(t)$ along positive solution of system (2), it follows that

$$\dot{W}_1(t) = \lambda \left(1 - \frac{x_1}{x}\right) - dx + dx_1 + \beta x_1 y + r y - (\beta x y + r y) \frac{u_1}{u} \\ + (\mu + \sigma) u_1 - \frac{a(\mu + \sigma)}{\sigma} y - (\mu + \sigma) u \frac{y_1}{y} + \frac{\mu + \sigma}{\sigma} a y_1 \\ + p y_1 z \frac{\mu + \sigma}{\sigma} - \frac{p(\mu + \sigma)}{c\sigma} b z. \quad (15)$$

On substituting

$$\lambda = dx_1 + \beta x_1 y_1, \quad \beta x_1 y_1 + r y_1 = (\mu + \sigma) u_1, \quad \sigma u_1 = a y_1$$

into (15), we obtain

$$\begin{aligned} \dot{W}_1(t) &= dx_1 \left(2 - \frac{x_1}{x} - \frac{x}{x_1} \right) + \beta x_1 y_1 - \beta x_1 y_1 \frac{x_1}{x} - \beta x_1 y_1 \frac{x y u_1}{x_1 y_1 u} + \beta x_1 y_1 + r y_1 \\ &\quad + \beta x_1 y_1 + r y_1 - r y_1 \frac{y u_1}{y_1 u} + p y_1 z \frac{\mu + \sigma}{\sigma} - \frac{p(\mu + \sigma)}{c \sigma} b z - (\beta x_1 y_1 + r y_1) \frac{u y_1}{u_1 y} \\ &= dx_1 \left(2 - \frac{x_1}{x} - \frac{x}{x_1} \right) + \beta x_1 y_1 \left(3 - \frac{x_1}{x} - \frac{x y u_1}{x_1 y_1 u} - \frac{u y_1}{u_1 y} \right) \\ &\quad + r y_1 \left(2 - \frac{y u_1}{y_1 u} - \frac{u y_1}{u_1 y} \right) + \frac{p(\mu + \sigma)^2 (\beta b + a d)}{\beta \sigma c [a(\mu + \sigma) - r \sigma]} (R_1 - 1) z. \end{aligned}$$

It follows that $\dot{W}_1(t) \leq 0$. Clearly, we obtain that $\dot{W}_1(t) = 0$ if and only if $x = x_1$, $z = 0$,

$$3 - \frac{x_1}{x} - \frac{x y u_1}{x_1 y_1 u} - \frac{u y_1}{u_1 y} = 0, \quad 2 - \frac{y u_1}{y_1 u} - \frac{u y_1}{u_1 y} = 0.$$

It follows from $x(t) = x_1$ that $\dot{x}(t) = 0$. According to the first equation of system (2), we have

$$0 = \dot{x}(t) = \lambda - dx_1 - \beta x_1 y(t),$$

which yields $y(t) = y_1$. In addition, according to (4), we have $u(t) = u_1$. Hence, $\dot{W}_1(t) = 0$ if and only if $x = x_1$, $u = u_1$, $y = y_1$, $z = 0$. Hence, the maximal variant set in $\{(x(t), u(t), y(t), z(t)) \in \Omega : \dot{W}_1(t) = 0\}$ is the singleton $\{E_1\}$. Note that E_1 is locally asymptotically stable. From LaSalle’s invariance principle we conclude that E_1 is globally asymptotically stable. \square

Theorem 8. *If $R_1 > 1$, the immunity-activated equilibrium $E^*(x^*, u^*, y^*, z^*)$ of system (2) is globally asymptotically stable when $\tau = 0$.*

Proof. Let $(x(t), u(t), y(t), z(t))$ be any positive solution of system (2) with the initial condition (3). Define

$$\begin{aligned} W_2(t) &= x(t) - x^* - x^* \ln \frac{x(t)}{x^*} + u(t) - u^* - u^* \ln \frac{u(t)}{u^*} \\ &\quad + \frac{\mu + \sigma}{\sigma} \left(y(t) - y^* - y^* \ln \frac{y(t)}{y^*} \right) + \frac{p(\mu + \sigma)}{c \sigma} \left(z(t) - z^* - z^* \ln \frac{z(t)}{z^*} \right). \end{aligned}$$

Calculating the derivative of $W_2(t)$ along positive solution of system (2), it follows that

$$\begin{aligned} \dot{W}_2(t) &= \left(1 - \frac{x^*}{x} \right) (\lambda - dx - \beta xy) + \left(1 - \frac{u^*}{u} \right) [\beta xy + ry - (\mu + \sigma)u] \\ &\quad + \frac{\mu + \sigma}{\sigma} \left(1 - \frac{y^*}{y} \right) (\sigma u - ay - pyz) + \frac{p(\mu + \sigma)}{c \sigma} \left(1 - \frac{z^*}{z} \right) (cyz - bz). \quad (16) \end{aligned}$$

On substituting

$$\begin{aligned}\lambda &= dx^* + \beta x^* y^*, & \beta x^* y^* + ry^* &= (\mu + \sigma)u^*, \\ \sigma u^* &= ay^* - py^* z^*, & cy^* &= b\end{aligned}$$

into (16), we obtain

$$\begin{aligned}\dot{W}_2(t) &= \left(1 - \frac{x^*}{x}\right)(\lambda - dx - \beta xy) + \left(1 - \frac{u^*}{u}\right)[\beta xy + ry - (\mu + \sigma)u] \\ &+ \frac{\mu + \sigma}{\sigma} \left(1 - \frac{y^*}{y}\right)(pyz^* - pyz) + \frac{p(\mu + \sigma)}{c\sigma} \left(1 - \frac{z^*}{z}\right)(cyz - bz) \\ &+ \frac{\beta x^* y^* + ry^*}{\sigma u^*} \left(1 - \frac{y^*}{y}\right) \left(\sigma u - \sigma u^* \frac{y^*}{y}\right) \\ &= dx^* \left(2 - \frac{x^*}{x} - \frac{x}{x^*}\right) + \beta x^* y^* \left(3 - \frac{x^*}{x} - \frac{xyu^*}{x^* y^* u} - \frac{uy^*}{u^* y}\right) \\ &+ ry^* \left(2 - \frac{yu^*}{y^* u} - \frac{uy^*}{u^* y}\right).\end{aligned}$$

It follows that $\dot{W}_2(t) \leq 0$. Clearly, we obtain that $\dot{W}_2(t) = 0$ if and only if $x = x^*$,

$$3 - \frac{x^*}{x} - \frac{xyu^*}{x^* y^* u} - \frac{uy^*}{u^* y} = 0, \quad 2 - \frac{yu^*}{y^* u} - \frac{uy^*}{u^* y} = 0.$$

It follows from $x(t) = x^*$ that $\dot{x}(t) = 0$. According to the first equation of system (2), we have

$$0 = \dot{x}(t) = \lambda - dx^* - \beta x^* y(t),$$

which yields $y(t) = y^*$. In addition, according to (4), we have $u(t) = u^*$. Furthermore, we have $z(t) = z^*$. Hence, we have $\dot{W}_2(t) = 0$ if and only if $x = x^*$, $u = u^*$, $y = y^*$, $z = z^*$. Hence, the maximal variant set in $\{(x(t), u(t), y(t), z(t)) \in \Omega: \dot{W}_2(t) = 0\}$ is the singleton $\{E^*\}$. Noting that E^* is locally asymptotically stable. From LaSalle's invariance principle we see that E^* is globally asymptotically stable when $\tau = 0$. \square

5 Uniform persistence

In this section, we verify the uniform persistence of system (2) when $R_1 > 1$.

Assume that $T(t)$ is a C_0 semigroup of X satisfying

$$T(t) : X^0 \rightarrow X^0, \quad X_0 \rightarrow X_0. \quad (17)$$

Let $T_\partial(t) = T(t)|_{X_0}$, A_∂ be the global attractor for $T_\partial(t)$. The following results was developed in [10].

Lemma 2. (See [10].) *Suppose that $T(t)$ satisfies (17) and that the following conditions are valid:*

- (i) There is a $t_0 \geq 0$ such that $T(t)$ is compact for $t > t_0$.
- (ii) $T(t)$ is point dissipative in X .
- (iii) $\tilde{A}_\partial = \cup \omega(x)$ ($x \in A_\partial$) is isolated and has an acyclic covering \tilde{M} , where $\tilde{M} = \{M_1, M_2, \dots, M_n\}$.
- (iv) $W^s(M_i) \cap X^0 = \emptyset$, $i = 1, 2, \dots, n$.

Then $T(t)$ is uniformly persistent in the sense that there is an $\varepsilon > 0$ such that, for any $x \in X^0$,

$$\liminf_{t \rightarrow +\infty} d(T(t)x, X_0) \geq \varepsilon,$$

where d is the distance of $T(t)x$ from X_0 .

Theorem 9. If $R_1 > 1$, system (2) is uniformly persistent.

Proof. Let $X = \mathbb{R}_+^4$, $X_0 = U_1 \cup U_2$, where $U_1 = \{(x, u, y, z) \in \mathbb{R}_+^4 : u \equiv 0, y \equiv 0\}$, $U_2 = \{(x, u, y, z) \in \mathbb{R}_+^4 : z \equiv 0\}$. Let $X^0 = X \setminus X_0$, where X_0 is a positive invariant set for system (2), X^0 is a positive invariant set for system (2) when any initial component is zero. Therefore, X satisfies (17). Denote

$$\begin{aligned} \phi_0 &= (\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)), \\ T(t)_{\phi_0} &:= (x(t), u(t), y(t), z(t)) \quad (t \geq 0), \end{aligned}$$

where $(x(t), u(t), y(t), z(t))$ is a positive solution of system (2) with the initial condition (3). Then $\{T(t)\}_{t \geq 0}$ is a C_0 semigroup generated by (2). It is easy to prove that conditions (i)–(iv) of Lemma 2 is satisfied when $R_1 > 1$. Therefore, all solutions of system (2) in X^0 are uniform repellers with respect to X_0 [25]. In other words, there is an $\varepsilon_0 > 0$ such that for any solution $\Phi(t) := (x(t), u(t), y(t), z(t))$ of system (2) with initial condition in X^0 , we have

$$\liminf_{t \rightarrow +\infty} d(\Phi(t), X_0) \geq \varepsilon_0,$$

where d is the distance of $\Phi(t)$ from X_0 . Thus, there exists an $\varepsilon_1 > 0$ such that

$$\liminf_{t \rightarrow +\infty} (y(t) + u(t)) \geq \varepsilon_1, \quad \liminf_{t \rightarrow +\infty} z(t) \geq \varepsilon_1$$

for any solution of system (2) with the initial condition in X^0 . We obtain from the first equation of system (2) that

$$x' = \lambda - dx - \beta xy \geq \lambda - (d + \beta M)x.$$

By comparison we have $x(t) > \lambda/2(d + \beta M)$ for sufficiently large t , for any solution of system (2) with initial condition in X^0 .

Let $y_\infty = \liminf_{t \rightarrow +\infty} y(t)$, $u_\infty = \liminf_{t \rightarrow +\infty} u(t)$. By the fluctuations lemma in [11] there exists a sequence $\tau_n \rightarrow \infty$, $y(\tau_n) \rightarrow y_\infty$ and $y'(\tau_n) = 0$. By the third equation of system (2) we have

$$0 = \sigma \lim_{n \rightarrow \infty} u(\tau_n) - ay_\infty - py_\infty \lim_{n \rightarrow \infty} z(\tau_n),$$

and hence

$$\frac{a + pM}{\sigma}y_\infty + y_\infty \geq u_\infty + y_\infty \geq \varepsilon_1.$$

Therefore, $y_\infty \geq \varepsilon_1\sigma/(a + pM + \sigma)$. Similarly, there exists a sequence $\tau_n \rightarrow \infty$, $u(\tau_n) \rightarrow u_\infty$ and $u'(\tau_n) = 0$. Then by the second equation of system (2) we have

$$\begin{aligned} (\mu + \sigma)u_\infty &= \beta \lim_{n \rightarrow \infty} x(\tau_n)y(\tau_n) + r \lim_{n \rightarrow \infty} y(\tau_n) \\ &\geq \left(\frac{\beta\lambda}{2(d + \beta M)} + r \right) y_\infty. \end{aligned}$$

Hence,

$$u_\infty \geq \frac{[\beta\lambda + 2r(d + \beta M)]\varepsilon_1\sigma}{2(d + \beta M)(a + pM + \sigma)(\mu + \sigma)} := \varepsilon_2.$$

Let $\varepsilon = \min\{\lambda/(d + \beta M), \varepsilon_2, \varepsilon_1\sigma/(a + pM + \sigma), \varepsilon_1\}$. We have

$$\begin{aligned} \liminf_{t \rightarrow +\infty} x(t) &\geq \varepsilon, & \liminf_{t \rightarrow +\infty} u(t) &\geq \varepsilon, \\ \liminf_{t \rightarrow +\infty} y(t) &\geq \varepsilon, & \liminf_{t \rightarrow +\infty} z(t) &\geq \varepsilon, \end{aligned}$$

for any solution of system (2) with the initial condition in X^0 . Hence, system (2) is uniformly persistent. □

6 Numerical simulation

In this section, we carry out numerical simulations to illustrate our analytical results. The relevant parameters are listed in Table 1. Here, we choose the initial condition as $(850, 1, 0.5, 1)$ [6].

We choose $\lambda = 1, \beta = 0.001, r = 0.02, \sigma = 0.003, p = 0.029, a = \mu = d = 0.03, c = 0.036, b = 0.04$. By calculation we obtain that $R_0 = 10/93 < 1$. System (2) has an infection-free equilibrium $E_0(100/3, 0, 0, 0)$. From Theorem 3 the equilibrium E_0 is locally asymptotically stable (see Fig. 1).

Table 1. Table of biologically relevant parameter ranges (values).

Parameter	Value	Biological meaning	Ref.
λ	1–10	Rate of production of healthy cells	[14]
β	0.001	Infectious transmissibility coefficient	[14]
d	0.01–0.11	Natural death rate of healthy cells	[14]
r	0.01–0.045	Proliferation rate of actively infected cells	[4]
μ	0.01–0.11	Natural death rate of latently infected cells	[14]
σ	0.0003–0.03	Rate of spontaneous Tax expression	[15]
a	0.01–0.11	Natural death rate of actively infected cells	[14]
p	0.007–0.220	Rate of CTL lysis of actively infected cells	[4]
c	0.009–0.16	Proliferation rate of CTLs	[2]
b	0.03–0.05	Natural death rate of virus-specific CTLs	[14]

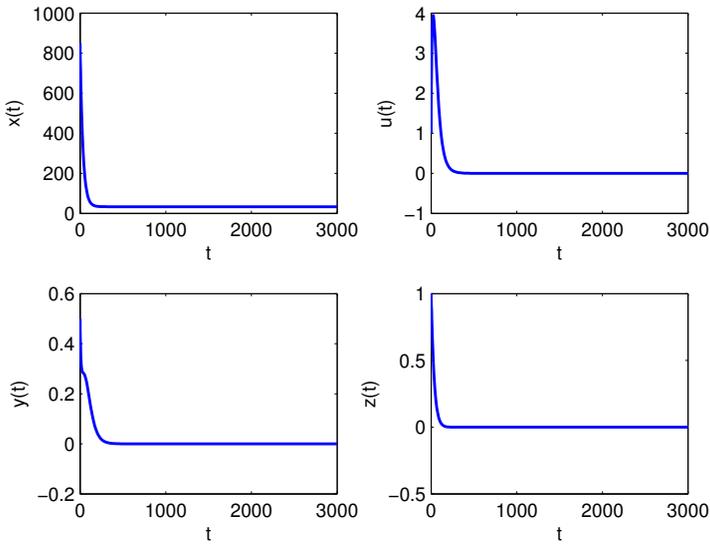


Figure 1. When $R_0 < 1$, $E_0(100/3, 0, 0, 0)$ is locally asymptotically stable.

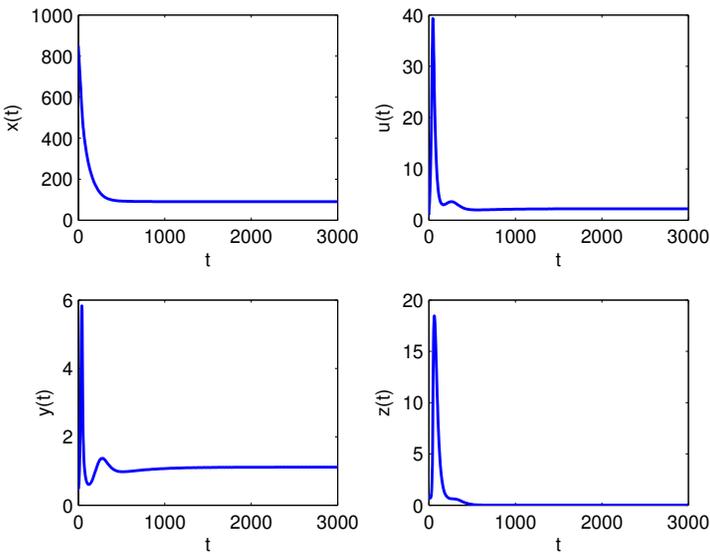


Figure 2. When $R_1 < 1 < R_0$, $E_1(30, 40/3, 40/3, 0)$ is locally asymptotically stable.

We choose $\lambda = 1$, $d = 0.01$, $\beta = 0.001$, $r = 0.03$, $\mu = \sigma = 0.03$, $a = 0.06$, $p = 0.029$, $c = 0.036$, $b = 0.05$. It is easy to show $R_1 = 161/164 < 1 < 10/9 = R_0$. System (2) has an immunity-inactivated equilibrium $E_1(90, 20/9, 10/9, 0)$. From Theorem 4 the equilibrium E_1 is locally asymptotically stable. Numerical simulation illustrates this fact (see Fig. 2).

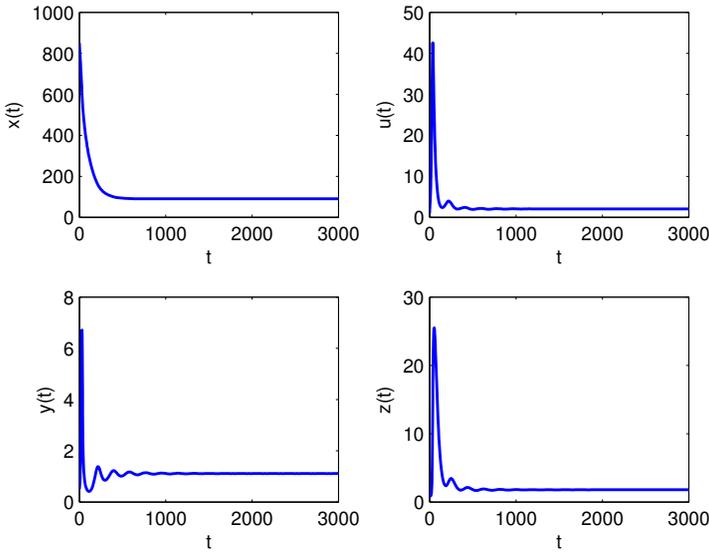


Figure 3. When $R_1 > 1$, $\tau = 0.2 < \tau_0$, $E^*(90, 110/54, 10/9, 25/29)$ is locally asymptotically stable.

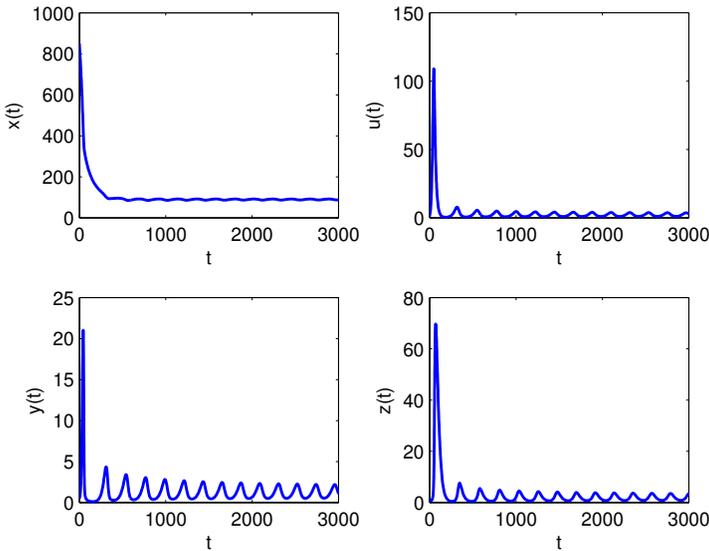


Figure 4. When $R_1 > 1$, $\tau = 8.5 > \tau_0$, $E^*(90, 110/54, 10/9, 25/29)$ is unstable.

We choose $\lambda = 1$, $\beta = 0.001$, $r = 0.02$, $d = 0.01$, $p = 0.029$, $a = \sigma = \mu = 0.03$, $c = 0.036$, $b = 0.04$. It is easy to show $R_1 = 11/6 > 1$. System (2) has an immunity-activated equilibrium $E^*(90, 110/54, 10/9, 25/29)$. From Theorem 5 the equilibrium E^* is locally asymptotically stable when $\tau < \tau_0$, E^* is unstable when $\tau > \tau_0$. Numerical simulation illustrates this fact (see Figs. 3 and 4).

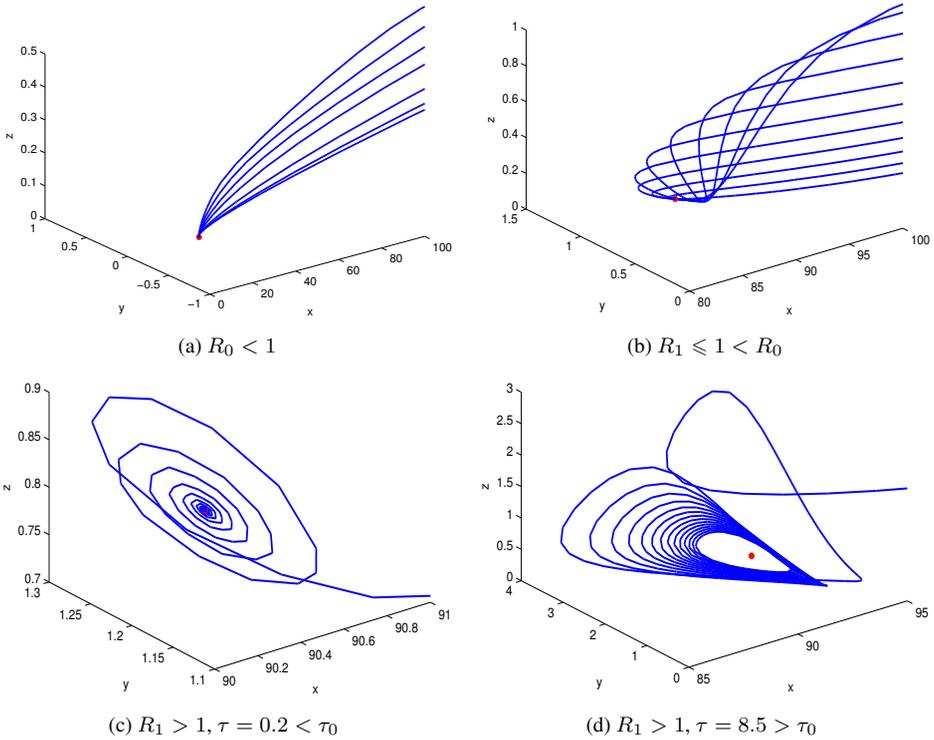


Figure 5. Phase trajectory of the feasible equilibria of system (2).

In order to see the behavior of the solution of system (2), we obtain the phase trajectory of the feasible equilibria of system (2) (see Fig. 5). From Figs. 5(a) and 5(b) we see that the infection-free equilibrium E_0 and the immunity-inactivated equilibrium E_1 are locally asymptotically stable for any $\tau \geq 0$. Besides, the immunity-activated equilibrium E^* is locally asymptotically stable when $\tau < \tau_0$, a periodic oscillation exists when $\tau > \tau_0$ (see Figs. 5(c) and 5(d)). Besides, we obtain the bifurcation diagram of system (2) (see Fig. 6).

LHS allows an un-biased estimate for each parameter of R_0 and R_1 , a probability density function is defined and divided into N equal probability intervals. N represents the sample size. The choice for N should be at least $k + 1$, where k is the parameters varied, but usually much larger to ensure accuracy. A single value is then selected randomly from every interval [18]. In this way, an input value from each sampling interval is used only once in the analysis, but the entire parameter space is equitably sampled in an efficient manner.

Through analysis of the sample derived from LHS, we can obtain large efficient data in respect to different parameters of R_0 and R_1 . Figure 7 shows that r, σ are both positive correlative variables with R_0 and R_1 . It is clear that σ contributes more to R_0 and R_1 than r , hence, σ is a more important factor.

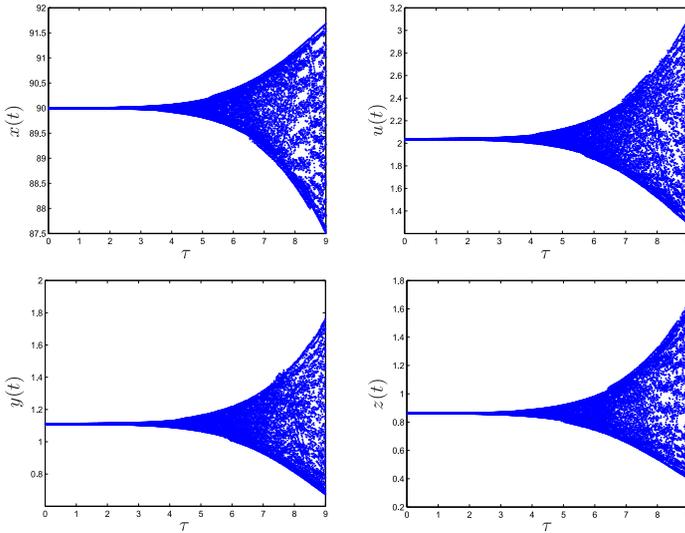


Figure 6. The bifurcation diagram of system (2) plotted for increasing values of the time delay.

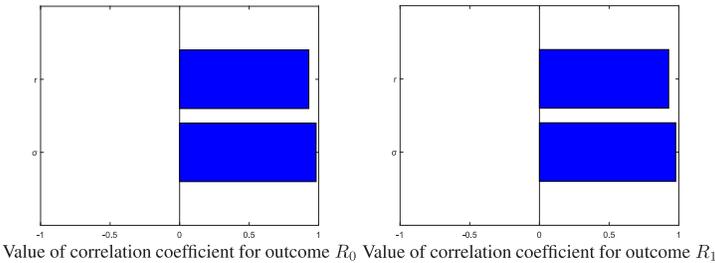


Figure 7. Tornado plot of partial rank correlation coefficients in respect to R_0, R_1 .

7 Conclusions

In this paper, we considered an improved HTLV-I infection model with $CD4^+$ T cells mitosis and delayed cytotoxic T-lymphocyte (CTL) immune response. Through a rigorous mathematical analysis, the threshold dynamical of the model was established, and it can be determined by the immune-inactivated reproduction ratio R_0 and the immune-activated reproduction ratio R_1 . If $R_0 < 1$, the infection-free equilibrium is globally asymptotically stable; if $R_1 < 1 < R_0$, the immunity-inactivated equilibrium is globally asymptotically stable; if $R_1 > 1$, the immunity-activated equilibrium is globally asymptotically stable when $\tau = 0$. Besides, we established the existence of Hopf bifurcation at the immunity-activated equilibrium. By Theorem 5 we found that when the delay varies, the immunity-activated steady state loses its stability and Hopf bifurcation occurs. That is to say, the time delay can destabilize the immunity-activated equilibrium and lead to periodic oscillation through Hopf bifurcation. Numerical simulations showed the occurrence of

bifurcating periodic oscillation when the delay passes the critical value. Sensitivity analysis showed that σ has a great influence on the threshold parameter R_0 and R_1 , which can provide some suggestions for clinical treatment of HTLV-I related diseases.

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