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*Research Article*

# Global Dynamics of an HTLV-1 Model with Cell-to-Cell Infection and Mitosis

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A mathematical model of human T-cell lymphotropic virus type 1 in vivo with cell-to-cell infection and mitosis is formulated and studied. The basic reproductive number $R_0$ is derived. It is proved that the dynamics of the model can be determined completely by the magnitude of $R_0$. The infection-free equilibrium is globally asymptotically stable (unstable) if $R_0 < 1$ ($R_0 > 1$). There exists a chronic infection equilibrium and it is globally asymptotically stable if $R_0 > 1$.

## 1. Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1) is a pathogenic retrovirus and persists indefinitely in the infected hosts [1–4]. There are approximately 10–20 million infected people worldwide [5, 6]. HTLV-1 is associated causatively with a large number of pathologies. A slowly progressive neurologic disease HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) [7] and adult T-cell leukemia (ATL) are two most common forms of the disease [8]. The majority of HTLV-1 infected individuals remain lifelong asymptomatic carriers (ACs). The remaining 0.25–3% of infected individuals develop into HAM/TSP [9]. The virus can be transmitted from mother to child, through sexual contact, and by needle sharing and contaminated blood products [5, 9].

In HTLV-1 infection, the initial infection is subclinical. The virus preferentially integrates into the genome of host T lymphocytes. Since the virions are almost undetectable from extracellular matrix, the viral burden is quantified as the proportion of peripheral blood mononuclear cells that carry an integrated HTLV-1 provirus. About 90–95% of the proviral load in chronic HTLV-1 infection is carried by $CD4^+$ T cells and 5–10% by $CD8^+$ T cells [10–13].

To persist within the host, HTLV-1 requires two routes: (i) infectious spread to uninfected cells via cell-to-cell contact known as the virological synapse, cellular conduits, extracellular viral assemblies, and transinfection via dendritic cells [9] and (ii) clonal expansion, which would actively promote mitotic proliferation of infected cells, and pass on the provirus to daughter cells. It is assumed that infection of an individual with HTLV-1 occurs in two stages; the virus is thought to initially spread from T cells to T cells, primarily $CD4^+$ T cells, and later to persist by clonal expansion of infected cells [12].

It has been observed that HTLV-1 infection has a lower rate of proviral genetic variation than HIV infection, which suggests that the vertical transmission through mitotic division rather than horizontal transmission through cell-to-cell contact plays an important role [14, 15]. HTLV-1 succeeds in causing a persistent infection with a high proviral load and remains approximately stable in one individual over years. In order to identify the underlying mechanism of HTLV-1 persistence in vivo and the key factors determining the HTLV-1 provirus load and the disease risk, Asquith and Bangham [1] have used a combination of mathematical and experimental techniques to propose a model of HTLV-1 persistence. Mitosis is the main route of viral replication, and the expression of HTLV-1 proteins, particularly Tax, is required to promote the

selective expansion of cells that harbour a provirus [5, 16–18], though the majority of infected cells are not expressing viral protein. Although the Tax expressing is silenced in the majority of surviving cells and a small proportion (0.03%–3%) of infected cells can express Tax, the cells with Tax expression proliferate more rapidly than silently infected and uninfected cells, leading to the selective expansion of infected cells and an increase in proviral load [1]. The small proportion of infected cells that express viral proteins play a crucial role, and the very high provirus load in HTLV-1 infection is maintained by proliferation of infected T cells, induced by the Tax protein of HTLV-1 [19].

It has been observed that the $CD4^+$ T cells population from HAM/TSP patients express higher levels of *tax* mRNA than $CD4^+$ T cells from ACs. Tax expression at any given proviral load is significantly higher in the HAM/TSP patients than that in the ACs [20]; thus a high rate of viral protein expression is associated with a large increase in the prevalence of HAM/TSP, and Tax expression is a significant predictor of the disease [1].

Most of the existing models have considered the persistence and pathogenesis for HTLV-1 infection of $CD4^+$ T cells. Mathematical models that take into account both infectious and mitotic routes have also been developed to describe the interaction in vivo among HTLV-1 [14, 20–22]. Motivated by the new hypothesis of HTLV-1 infection by Asquith and Bangham, we construct a model with three compartments, healthy $CD4^+$ T cells $x$, resting infected $CD4^+$ T cells $u$, and Tax-expressing infected $CD4^+$ T cells $y$, to investigate the dynamics of the HTLV-1 infection. The model is formulated and the required conditions are given in Section 2. The stability of equilibria is presented in Section 3. The simulations are done in Section 4. The concluding remarks are given in Section 5.

## 2. Model Formulation

In this section, we construct a mathematical model including the spontaneous HTLV-1 antigen Tax expression, cell-to-cell contact, and mitotic infectious routes to describe the viral dynamics. Let $x(t)$ be the number of healthy $CD4^+$ T cells at time $t$, let $u(t)$ be the number of the resting infected $CD4^+$ T cells at time $t$, and let $y(t)$ be the number of Tax-expressing infected $CD4^+$ T cells at time $t$. We consider only HAM/TSP among nonmalignant HTLV-1 infection diseases; the dynamics of ATL and other aggressive malignancies may be very different. Although mitosis occurs in all $CD4^+$ T cells as a natural process, normal homeostatic proliferation occurs at a very slower rate than that of selective mitotic division in Tax-expressing infected cells. We ignore the effects of passive homeostatic proliferation of the healthy and resting infected $CD4^+$ T cells to simplify the model.

Healthy $CD4^+$ T cells are produced in bone marrow at a constant rate $\lambda$ [23, 24]; we assume that the new cells generated in the bone marrow are uninfected. The infected $CD4^+$ T cells can make the healthy $CD4^+$ T cells get infected through cell-to-cell contact. The infectious incidence is described by a bilinear term $\beta xy$, where $\beta$ is the transmission

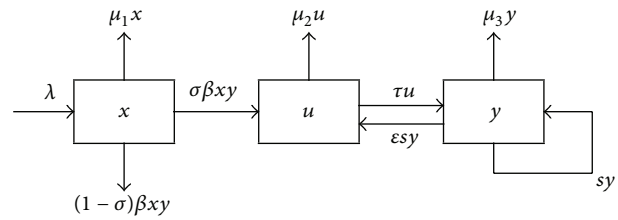


Figure 1: The schematic diagram of the HTLV-1 infection in vivo.

coefficient among $CD4^+$ T cells [25]. The newly infected cells experience an irreparable destruction by the strong adaptive immune responses. As a result, a small fraction $\sigma\beta xy$, $\sigma \in (0,1)$, survives after the immune attack and becomes the resting infected cells [14, 22]. Every day, a small proportion $\tau$ of resting infected cells express Tax with $\tau \in (0.3\%, 3\%)$ [26]. The mitotic transmission of HTLV-1 involving selective clonal expansion of these Tax-expressing $CD4^+$ T cells occurs at a rate $s$. The newly infected cells from mitosis to the resting infected cells compartment are $\varepsilon sy$, $\varepsilon \in (0,1)$, with $(1-\varepsilon)sy$ staying in the Tax-expressing infected $CD4^+$ T-cell compartment. The transfers among those three compartments are shown in Figure 1.

From the mechanism of the HTLV-1 infection and the schematic diagram we can have the following model consisting of three differential equations;

$$\begin{aligned} \frac{dx}{dt} &= \lambda - \beta xy - \mu_1 x, \\ \frac{du}{dt} &= \sigma\beta xy + \varepsilon sy - \tau u - \mu_2 u, \\ \frac{dy}{dt} &= \tau u + (1-\varepsilon)\, sy - \mu_3 y. \end{aligned} \tag{1}$$

In model (1), $\mu_1$, $\mu_2$, and $\mu_3$ are the removal rate of healthy $CD4^+$ T cells, resting infected $CD4^+$ T cells, and Tax-expressing infected $CD4^+$ T cells, respectively. From epidemiological background, it is natural to assume that the initial values of these variables and parameters are nonnegative.

We define the basic reproductive number of model (1) by the next generation matrix approach given in [27]. Let

$$F = \begin{bmatrix} 0 & \sigma\beta x + \varepsilon s \\ 0 & s - \varepsilon s \end{bmatrix}, \qquad V = \begin{bmatrix} \tau + \mu_2 & 0 \\ -\tau & \mu_3 \end{bmatrix}. \tag{2}$$

The calculation shows that the spectral radius (the basic reproductive number) of $FV^{-1}$ is

$$R_0 = \rho\left(FV^{-1}\right) = \frac{\sigma\beta\tau\lambda}{(\tau+\mu_2)\,\mu_1\mu_3} + \frac{\tau\varepsilon s}{(\tau+\mu_2)\,\mu_3} + \frac{(1-\varepsilon)\,s}{\mu_3}. \tag{3}$$

The basic reproductive number, $R_0$, gives the average number of the secondary infections caused by a single Tax-expressing infected $CD4^+$ T cell during its whole infectious period. The secondary infection caused by a single Tax-expressing infected $CD4^+$ T cell through horizontal transmission is $\sigma\beta \cdot (\lambda/\mu_1) \cdot (\tau/(\tau+\mu_2)) \cdot (1/\mu_3)$; the secondary infection caused by

a single Tax-expressing infected $CD4^+$ T cell through mitotic transmission is $\varepsilon s \cdot (\tau/(\tau+\mu_2)) \cdot (1/\mu_3) + (1-\varepsilon)s \cdot (1/\mu_3)$.

Throughout the paper, we use the assumption

$$s < \frac{(\tau+\mu_2)\mu_3}{\tau+\mu_2(1-\varepsilon)}. \tag{A1}$$

The inequality (A1) is equivalent to that $\tau\varepsilon s/(\tau+\mu_2)\mu_3 + (1-\varepsilon)s/\mu_3 < 1$, which requires that the average number of the secondary infections by a single Tax-expressing infected $CD4^+$ T cell through mitosis should not be larger than one. If the inequality in (A1) does not hold, then the number of the infected cells may increase to infinity. The biological interpretation of (A1) is to keep the solutions of the model bounded. From condition (A1), we have $s < \mu_3/(1-\varepsilon)$; that is, $\mu_3 > (1-\varepsilon)s$. We can get the following nonnegative and bounded conclusions on the solutions of model (1).

**Theorem 1.** *The solutions $(x(t), u(t), y(t))$ of model (1) with the nonnegative initial conditions are nonnegative and bounded for all $t > 0$ if (A1) holds.*

*Proof.* It is easy to have

$$\begin{aligned} \left.\frac{dx(t)}{dt}\right|_{x=0} &= \lambda > 0, \\ \left.\frac{du(t)}{dt}\right|_{u=0} &= \sigma\beta xy + \varepsilon sy \geq 0, \\ \left.\frac{dy(t)}{dt}\right|_{y=0} &= \tau u \geq 0. \end{aligned} \tag{4}$$

From Lemma 2 in [28], we know that any solutions of model (1) with nonnegative initial conditions will be nonnegative for all $t > 0$.

It follows from the first equation of model (1) that

$$\frac{dx}{dt} = \lambda - \beta xy - \mu_1 x \leq \lambda - \mu_1 x, \tag{5}$$

which leads to $\lim_{t\to+\infty} \sup x \leq \lambda/\mu_1$. Let $L = x + u + ((\tau+\mu_2)/\tau)y$; from model (1) we can obtain

$$\begin{aligned} \frac{dL}{dt} &= \frac{dx}{dt} + \frac{du}{dt} + \frac{\tau+\mu_2}{\tau}\frac{dy}{dt} \\ &= \lambda + (\sigma-1)\beta xy - \mu_1 x - Gy \leq \lambda - \mu_1 x - Gy, \end{aligned} \tag{6}$$

where $G = ((\tau+\mu_2)/\tau)(\mu_3 - (1-\varepsilon)s) - \varepsilon s > 0$ since (A1) holds. The inequality in (6) implies that $L = x+u+((\tau+\mu_2)/\tau)y$ will decrease along the solutions curve of model (1) if $\mu_1 x + Gy > \lambda$. Geometrically, all solution trajectories of model (1) will go through the plane $x + u + ((\tau+\mu_2)/\tau)y = L$ from outside to inside if $\mu_1 x + Gy > \lambda$.

Let $L_0$ be the maximal value of the function $x + ((\tau+\mu_2)/\tau)y$ on the bounded domain

$$G_0 = \{(x,y) \mid x \geq 0, y \geq 0, \mu_1 x + Gy \leq \lambda\}, \tag{7}$$

and let $M_0$ be the maximal value of the function $\sigma\beta xy + \varepsilon sy$ on the bounded domain

$$G_1 = \left\{(x,y) \mid x \geq 0, y \geq 0, x + \frac{\tau+\mu_2}{\tau}y \leq L_0\right\}. \tag{8}$$

When $x + ((\tau+\mu_2)/\tau)y \leq L_0$ holds, the second equation of model (1) yields

$$\frac{du}{dt} = \sigma\beta xy + \varepsilon sy - \tau u - \mu_2 u \leq M_0 - (\tau+\mu_2)u. \tag{9}$$

From the comparison principle and (9), it follows that there exists a positive $u_m = M_0/(\tau+\mu_2)$, such that $du/dt \leq 0$ when $u > u_m$ and $x + ((\tau+\mu_2)/\tau)y \leq L_0$.

For any given initial values $x(0) = x_0 \geq 0$, $u(0) = u_0 \geq 0$, and $y(0) = y_0 \geq 0$, there exists a plane $P$, given by the equation

$$P : x + u + \frac{\tau+\mu_2}{\tau}y = L_0 + u_m + x_0 + u_0 + \frac{\tau+\mu_2}{\tau}y_0, \tag{10}$$

such that the point $(x_0, u_0, y_0)$ locates inside the domain with the boundaries $x = 0$, $u = 0$, $y = 0$, $u = u_m + x_0 + u_0 + ((\tau+\mu_2)/\tau)y_0$, and $P$. It is not difficult to verify that those two planes $u = u_m + x_0 + u_0 + ((\tau+\mu_2)/\tau)y_0$ and $P$ have the intersection line $x + ((\tau+\mu_2)/\tau)y = L_0$. The equations in (6) and (9) imply that

$$\begin{aligned} &\frac{du}{dt} \leq 0, \quad \text{if } u = u_m + x_0 + u_0 + \frac{\tau+\mu_2}{\tau}y_0 \geq u_m, \\ &\qquad x + \frac{\tau+\mu_2}{\tau}y \leq L_0, \\ &\frac{dL}{dt} \leq 0 \quad \text{if } x + \frac{\tau+\mu_2}{\tau}y \geq L_0. \end{aligned} \tag{11}$$

Those inequalities imply that the domain with the boundaries $x = 0$, $u = 0$, $y = 0$, $u = u_m + x_0 + u_0 + ((\tau+\mu_2)/\tau)y_0$, and $P$ is positively invariant for solutions of model (1). That is, any solution of model (1) with nonnegative initial value is bounded. □

With a similar argument as used in the proof of Theorem 1, we know that the domain

$$\begin{aligned} \Gamma = \Big\{&(x,u,y) \mid 0 \leq x \leq \frac{\lambda}{\mu_1}, 0 \leq u \leq u_m, \\ &y \geq 0, x + u + \frac{\tau+\mu_2}{\tau}y \leq L_0 + u_m\Big\} \end{aligned} \tag{12}$$

is positively invariant with respect to model (1). In fact, the solutions of model (1) located on the boundary planes of $\Gamma$, $x = \lambda/\mu_1$, or $u = u_m$, or $x + u + ((\tau+\mu_2)/\tau)y = L_0 + u_m$, will enter $\Gamma^0$, where $\Gamma^0$ is the interior of $\Gamma$. From (5), (6), and (9) we can prove that all the solutions of model (1) with positive initial values will enter $\Gamma$ when the time is large enough. We will investigate the dynamic behavior of model (1) on $\Gamma$ in the rest of the paper.

The straightforward calculation shows that model (1) has two equilibria: the infection-free equilibrium $P_0 = (x_0, 0, 0)$, located on the boundary of $\Gamma$, where $x_0 = \lambda/\mu_1$, and the chronic infection equilibrium $P_1 = (x_1, u_1, y_1)$, where

$$\begin{aligned} x_1 &= \frac{\lambda}{\beta y_1 + \mu_1}, \qquad u_1 = \frac{(\mu_3 - (1-\varepsilon)s)y_1}{\tau}, \\ y_1 &= \frac{\mu_1}{\beta}(R_0 - 1)\frac{(\tau+\mu_2)\mu_3}{(\tau+\mu_2)\mu_3 - \tau s - \mu_2(1-\varepsilon)s}. \end{aligned} \tag{13}$$

$x_1$, $u_1$, and $y_1$ are positive if and only if $R_0 > 1$ and (A1) holds. We have the following conclusion on the existence of the equilibrium of model (1).

**Theorem 2.** *If $R_0 \le 1$, then $P_0 = (\lambda/\mu_1, 0, 0)$ is the only equilibrium of model (1). If $R_0 > 1$ and (A1) holds, then $P_1 = (x_1, u_1, y_1)$ is the unique chronic infection equilibrium.*

## 3. Stability Analysis of Equilibria

*3.1. Stability of Infection-Free Equilibrium.* Intuitively, if $R_0 < 1$, then a Tax-expressing infected $CD4^+$ T cell will produce less than one secondary infection on average in its lifetime. This fact may lead to the extinction of the infection. We will try to prove the global stability of the infection-free equilibrium when $R_0 < 1$.

**Theorem 3.** *If $R_0 < 1$, then the infection-free equilibrium $P_0$ of model (1) is stable, and it is unstable if $R_0 > 1$.*

*Proof.* We use the linearized system of model (1) to discuss the stability of $P_0$. The characteristic equation of the matrix of the linearized system of model (1) at the infection-free equilibrium $P_0$ is

$$\left(\rho + \mu_1\right)\left(\rho^2 + b_0\rho + c_0\right) = 0, \tag{14}$$

where $b_0 = \mu_3(1 - R_0 + (\sigma\beta\tau x_0 + \tau\varepsilon s)/(\tau + \mu_2)\mu_3) + \tau + \mu_2$, $c_0 = (1 - R_0)(\tau + \mu_2)\mu_3$. From the Routh-Hurwitz criterion, it is easy to know that all the roots of (14) have negative real parts if $R_0 < 1$, and (14) has at least one root with positive real part if $R_0 > 1$. This completes the proof. □

**Theorem 4.** *If $R_0 < 1$, then the infection-free equilibrium $P_0$ of model (1) is globally asymptotically stable in $\Gamma$.*

*Proof.* We consider a Lyapunov function $L = \tau u + (\tau + \mu_2)y$. Calculating the derivative of $L$ along the solutions of model (1) gives

$$\begin{aligned}\left.\frac{dL}{dt}\right|_{(1)} &= \tau\frac{du}{dt} + \left(\tau + \mu_2\right)\frac{dy}{dt}\\ &= y\left(\tau\sigma\beta x + \tau\varepsilon s + \left(\tau + \mu_2\right)(1 - \varepsilon)s - \left(\tau + \mu_2\right)\mu_3\right)\\ &\le y\left(\tau\sigma\beta\frac{\lambda}{\mu_1} + \tau\varepsilon s + \left(\tau + \mu_2\right)(1 - \varepsilon)s - \left(\tau + \mu_2\right)\mu_3\right)\\ &= y\mu_3\left(\tau + \mu_2\right)\left(R_0 - 1\right).\end{aligned} \tag{15}$$

Therefore, $R_0 < 1$ implies that $(dL/dt)|_{(1)} \le 0$ for all $t > 0$, and $(dL/dt)|_{(1)} = 0$ only if $y = 0$. From the inequality in (15) we can have that $\lim_{t\to\infty} y(t) = 0$, $\lim_{t\to\infty} u(t) = 0$. By using the limiting theory for ordinary differential equations we can have $\lim_{t\to\infty} x(t) = \lambda/\mu_1$. That is, the infection-free equilibrium $P_0$ attracts all solutions of model (1) with initial values in $\Gamma$. The global stability conclusion of Theorem 4 is proved. □

*3.2. Stability of the Chronic Infection Equilibrium*

**Theorem 5.** *Assume that (A1) holds; if $R_0 > 1$, then the unique chronic infection equilibrium $P_1$ of model (1) is stable.*

*Proof.* The characteristic equation of the matrix of the linearized system of model (1) at the chronic infection equilibrium $P_1$ is

$$\rho^3 + b_1\rho^2 + c_1\rho + d_1 = 0, \tag{16}$$

where

$$\begin{aligned} b_1 &= \mu_3 - (1 - \varepsilon)s + \tau + \mu_2 + \beta y_1 + \mu_1,\\ c_1 &= \left(\tau + \mu_2\right)\left(\mu_3 - (1 - \varepsilon)s\right)\\ &\quad + \left(\beta y_1 + \mu_1\right)\left(\mu_3 - (1 - \varepsilon)s\right)\\ &\quad + \left(\beta y_1 + \mu_1\right)\left(\tau + \mu_2\right) - \left(\sigma\beta\tau x_1 + \varepsilon\tau s\right),\\ d_1 &= \left(\beta y_1 + \mu_1\right)\left(\tau + \mu_2\right)\left(\mu_3 - (1 - \varepsilon)s\right)\\ &\quad - \varepsilon\tau s\beta y_1 - \sigma\beta\tau\mu_1 x_1 - \mu_1\varepsilon\tau s. \end{aligned} \tag{17}$$

Since $\beta y_1 + \mu_1 = \lambda/x_1$, $\sigma\beta\tau x_1 + \varepsilon\tau s = (\tau + \mu_2)(\mu_3 - (1 - \varepsilon)s)$, we have $c_1 = (\lambda^2/x_1)b_0 > 0$, $d_1 = \mu_1\mu_3(\tau + \mu_2)(R_0 - 1)$. The straightforward calculation yields $b_1c_1 - d_1 > 0$. According to the Routh-Hurwitz criterion, we can see that all the roots of (16) have negative real parts if $R_0 > 1$. This completes the proof of Theorem 5. □

The following two lemmas, which can be found in [29], are used for the study of the uniform persistence of model (1). We show that the disease persists when $R_0 > 1$; that is, the infected proportion of the $CD4^+$ T cells persists above a certain positive level for sufficiently large $t$.

Let $f : X \to X$ be a continuous map and $X_0 \subset X$ an open set. Define $\partial X_0 = X/X_0$ and $M_\partial := \{x \in \partial X_0 \mid f^n(x) \in \partial X_0,\ n \ge 0\}$.

**Lemma 6** (see [29]). *If $f : X \to X$ is compact and point dissipative, then there is a connected global attractor $A$ that attracts each bounded set in $X$.*

**Lemma 7** (see [29]). *Let $f : X \to X$ be a continuous map and $X_0 \subset X$ an open set. Assume that*

(C1) *$f(X_0) \to X_0$ and $f$ has a global attractor $A$;*

(C2) *the maximal compact invariant set $A_\partial = A \cap M_\partial$ of $f$ in $\partial X_0$, possibly empty, admits a Morse decomposition $\{M_1, \ldots, M_K\}$ with the following properties:*

(a) *$M_i$ is isolated in $X$;*

(b) *$W^s(M_i) \cap X_0 = \phi$ for each $1 \le i \le k$.*

*Then there exists $\rho > 0$ such that, for any compact internally chain transitive set $L$ with $L \not\subset M_i$ for all $1 \le i \le k$, we have $\inf_{x\in L} d(x, \partial X_0) > \rho$.*

We deal with the uniform persistence of model (1) now. Let $X = \{(x, u, y) \mid x \ge 0, u \ge 0, y \ge 0\}$, $X_0 = \{(x, u, y) \mid$

$x \geq 0, u > 0, y > 0\}$; define $\partial X_0 = X/X_0$, and $M_\partial = \{(x(0), u(0), y(0)) \in \partial X_0 \mid \Phi_t(x(0), u(0), y(0)) \in \partial X_0, t \geq 0\}$, where $\Phi_t : X \to X$ is the semiflow defined by model (1).

**Proposition 8.** *One has* $M_\partial = \{(x, 0, 0) \mid x \geq 0\}$.

*Proof.* We first show that $M_\partial \subset \{(x, 0, 0) \mid x \geq 0\}$; that is, if $(x(0), u(0), y(0)) \in M_\partial$, then $u(0) = y(0) = 0$. Due to the definition of $M_\partial$, we can get $\Phi_t(x(0), u(0), y(0)) \in \partial X_0$ for all $t \geq 0$, especially, $\Phi_0(x(0), u(0), y(0)) = (x(0), u(0), y(0)) \in \partial X_0$. If $M_\partial \subset \{(x, 0, 0) \mid x \geq 0\}$ does not hold, then at least one of $u(0)$, $y(0)$ is greater than zero. Without loss of generality, we assume that $u(0) > 0$. When $u(0) > 0$ we can prove that $u(t)$ and $y(t)$ are all greater than zero for $t \in [0, 1]$. In fact, from the second equation of model (1) we have

$$\frac{du}{dt} = \sigma\beta xy + \varepsilon sy - \tau u - \mu_2 u \geq -(\tau + \mu_2) u, \quad t \in [0, 1]. \tag{18}$$

It follows that

$$u(t) \geq u(0) \exp[-(\tau + \mu_2)] \triangleq M_1 > 0. \tag{19}$$

From the third equation of model (1) we have

$$\frac{dy}{dt} = \tau u + (1 - \varepsilon) sy - \mu_3 y \geq \tau M_1 + (1 - \varepsilon) sy - \mu_3 y; \tag{20}$$

then, for $t \in [0, 1]$, we can have

$$\begin{aligned} y(t) &\geq \frac{\tau M_1}{\mu_3 - (1 - \varepsilon) s} [1 - \exp[-(\mu_3 - (1 - \varepsilon) s) t]] \\ &\quad + y(0) \exp[-(\mu_3 - (1 - \varepsilon) s) t] \\ &\geq \frac{\tau M_1}{\mu_3 - (1 - \varepsilon) s} [1 - \exp[-(\mu_3 - (1 - \varepsilon) s)]] > 0. \end{aligned} \tag{21}$$

The inequalities $u(t) \geq M_1 > 0$ and $y(t) \geq (\tau M_1/(\mu_3 - (1 - \varepsilon)s))[1 - \exp[-(\mu_3 - (1 - \varepsilon)s)]] > 0$ for $t \in [0, 1]$ imply that $(x(t), u(t), y(t)) \in X_0$ for $t \in [0, 1]$. From the definition of $M_\partial$ and $(x(t), u(t), y(t)) \in X_0$ for $t \in [0, 1]$ we know that $\Phi_0(x(0), u(0), y(0)) \notin \partial X_0$ if $u(0) > 0$. This contradiction implies that $(x(0), u(0), y(0)) \in M_\partial$ only if $u(0) = y(0) = 0$; that is, $M_\partial \subset \{(x, 0, 0) \mid x \geq 0\}$.

On the other hand, for any initial values $(x(0), 0, 0) \in \{(x, 0, 0) \mid x \geq 0\}$, we have $du/dt = 0$, $dy/dt = 0$, and $u(t) = y(t) = 0$ for $t \geq 0$, $\{(x, 0, 0) \mid x \geq 0\} \subset M_\partial$. The proposition is proved. □

From Proposition 8, we can get the conclusion that $M_\partial$ is the maximal invariant set in $\partial X_0$. Next we show that the solutions with the initial values in $X_0$ cannot go to the boundary.

**Proposition 9.** *Assume that* (A1) *holds. If* $R_0 > 1$, *then there exists a* $\delta > 0$ *such that the solution of model* (1) *with initial value* $(x(t_0), u(t_0), y(t_0)) \in X_0$ *satisfies* $\lim_{t \to +\infty} \sup \max\{u(t), y(t)\} > \delta$.

*Proof.* If the conclusion in Proposition 9 does not hold, then, for any $\delta > 0$, there exists a $T$ such that $u(t) \leq \delta$ and $y(t) \leq \delta$ for all $t > T$. Consider the following equation:

$$\frac{d\hat{x}}{dt} = \lambda - \beta\delta\hat{x} - \mu_1\hat{x}. \tag{22}$$

The solution of (22) with the any initial value $x(t_0) > 0$ is

$$\begin{aligned} \hat{x}(t) &= \frac{\lambda}{\beta\delta + \mu_1} [1 - \exp[(\beta\delta + \mu_1)(t_0 - t)]] \\ &\quad + x(t_0) \exp[(\beta\delta + \mu_1)(t_0 - t)], \end{aligned} \tag{23}$$

and $\lim_{t \to +\infty} \hat{x}(t) = \lambda/(\beta\delta + \mu_1)$. For $\varepsilon_1 > 0$, there exists a $T_1 > T$, such that $\hat{x}(t) > \lambda/(\beta\delta + \mu_1) - \varepsilon_1$ holds when $t \geq T_1$. $\hat{x}_1(\delta) = \lambda/(\beta\delta + \mu_1)$ is an equilibrium of (22). The fact that $\lim_{\delta \to 0} \hat{x}_1(\delta) = \lambda/\mu_1 = x_0$ implies that $\hat{x}_1(\delta) \geq x_0 - \varepsilon_1$ when $\delta$ is small enough. By the comparison principle, we can have $x(t) \geq \hat{x}(t)$ and $x(t) \geq x_0 - 2\varepsilon_1$, for $t > T_1$.

Consider the following linear system:

$$\begin{aligned} \frac{d\hat{u}}{dt} &= \sigma\beta(x_0 - 2\varepsilon_1)\hat{y} + \varepsilon s\hat{y} - \tau\hat{u} - \mu_2\hat{u}, \\ \frac{d\hat{y}}{dt} &= \tau\hat{u} + (1 - \varepsilon) s\hat{y} - \mu_3\hat{y}. \end{aligned} \tag{24}$$

The characteristic equation is

$$\rho^2 + b_2\rho + c_2 = 0, \tag{25}$$

where $b_2 = \tau + \mu_2 + \mu_3 - (1 - \varepsilon)s > 0$, $c_2 = (1 - R_0)(\tau + \mu_2)\mu_3 + 2\tau\sigma\beta\varepsilon_1$. From the expression of $c_2$ we see that $c_2 < 0$ if $R_0 > 1$ and $\varepsilon_1$ is small enough. Let $\rho_1$ and $\rho_2$ be the two roots of $\rho^2 + b_2\rho + c_2 = 0$ and $\rho_1 > 0 > \rho_2$. The solution of model (24) with the initial value $(\hat{u}(0), \hat{y}(0)) > 0$ satisfies

$$(\hat{u}(t), \hat{y}(t))^T = d_1\xi_1 \exp(\rho_1 t) + d_2\xi_2 \exp(\rho_2 t), \tag{26}$$

where $\xi_1$ and $\xi_2$ are the eigenvectors corresponding to $\rho_1$ and $\rho_2$, respectively. $d_1$ and $d_2$ are two constants depending on $(\hat{u}(0), \hat{y}(0))$. The solution expression of model (24) indicates that $\max\{\hat{u}(t), \hat{y}(t)\} \to \infty$ as $t \to \infty$. For the same initial values, the comparison principle implies that $u(t) > \hat{u}(t)$ and $y(t) > \hat{y}(t)$, where $u(t)$ and $y(t)$ are the solutions of model (1). Subsequently, we have $u(t) \to \infty$ or $y(t) \to \infty$ as $t \to \infty$. The contradiction shows that Proposition 9 holds true. □

By using Propositions 8 and 9, we can get the uniform persistence of model (1).

**Theorem 10.** *Assume that* (A1) *holds. If* $R_0 > 1$, *then model* (1) *is uniformly persistent with respect to* $(X_0, \partial X_0)$; *that is, there exists a positive number* $\eta$ *such that* $\min\{\lim_{t \to \infty} \inf x(t), \lim_{t \to \infty} \inf u(t), \lim_{t \to \infty} \inf y(t)\} \geq \eta$.

*Proof.* $X$ and $X_0$ are positively invariant for model (1). $\Phi_t$ is point dissipative and compact. By Lemma 6 we know that there is a connected global attractor $A$ for $\Phi_t$ that attracts each bounded set in $X$.

From the discussion of Proposition 8, we know that $M_\partial$ is the maximal compact invariant set in $\partial X_0$. Since we choose the Morse decomposition of $M_\partial$ as $\{P_0\}$ and $\cup_{x\in M_\partial}\omega(x) = \{P_0\}$, the set $\{P_0\}$ is isolated. Proposition 9 shows that the solutions of model (1) with initial values in $X_0$ cannot go to the boundary, which implies that $W^s(P_0)\cap X_0 = \phi$. It follows from Lemma 7 that model (1) is uniformly persistent with respect to $(X_0, \partial X_0)$. □

The following lemmas in [30–32] are used to study the global stability of the chronic infection equilibrium $P_1$. We will show that all the solutions of model (1) in $\Gamma^0$ converge to $P_1$ if $R_0 > 1$.

Let $x \to f(x) \in R^n$ be a $C^1$ function for $x$ in an open set $D \subset R^n$. Consider the system of differential equations

$$\frac{dx}{dt} = f(x). \tag{27}$$

Let $x(t, x_0)$ be the solution of model (27) satisfying $x(0, x_0) = x_0$.

A set $K$ is said to be absorbing in $D$ for model (27) if $x(t, K_1) \subset K$ for each compact $K_1 \subset D$ and sufficiently large $t$. We make the following two basic assumptions.

($H_1$) There exists a compact absorbing set $K \subset D$.

($H_2$) System (27) has a unique equilibrium $\overline{x}$ in $D$.

System (27) is said to have the Poincaré-Bendixson Property if any nonempty compact omega limit set that contains no equilibrium is a closed orbit [31]. It is known that a three-dimensional competitive system has the Poincaré-Bendixson property in a convex region.

**Lemma 11** (see [30]). *Let $D \in R^n$ be convex. The autonomous system $dx/dt = f(x)$, $x \in D$, is cooperative in $D$ if there exists a diagonal matrix $P = \mathrm{diag}(\alpha_1, \ldots, \alpha_n)$ ($\alpha_i = -1$ or $1$, $i = 1, 2, \ldots, n$), such that $P(\partial f_i/\partial x_j)(x)P \geq 0$, for $i \neq j$, $x \in D$; that is, all off-diagonal entries of $P(\partial f/\partial x)(x)P$ are nonnegative. It is competitive in $D$ if there exists a diagonal matrix $P = \mathrm{diag}(\alpha_1, \ldots, \alpha_n)$ ($\alpha_i = -1$ or $1$, $i = 1, 2, \ldots, n$), such that $P(\partial f_i/\partial x_j)(x)P \leq 0$, for $i \neq j$, $x \in D$; that is, all off-diagonal entries of $P(\partial f/\partial x)(x)P$ are nonpositive.*

**Lemma 12** (see [32]). *Assume that $n = 3$ and $D$ is convex; suppose that model (27) is competitive in $D$; then it satisfies the Poincaré-Bendixson property [32].*

**Lemma 13** (see [31]). *Assume that the following conditions hold.*

(1) *Assumptions ($H_1$) and ($H_2$) hold;*

(2) *model (27) satisfies the Poincaré-Bendixson property;*

(3) *for each periodic solution $x = p(t)$ with $p(0) \in D$, model (27) is asymptotically stable;*

(4) $(-1)^n \det((\partial f/\partial x)(\overline{x})) > 0$.

*Then the unique equilibrium $\overline{x}$ is globally asymptotically stable in $D$.*

Next, we show that model (1) is a competitive system which implies that model (1) has the Poincaré-Bendixson property.

**Theorem 14.** *Model (1) is competitive in $\Gamma$.*

*Proof.* The Jacobian matrix of model (1) is

$$J(x, u, y) = \begin{bmatrix} -\beta y - \mu_1 & 0 & -\beta x \\ \sigma\beta y & -\tau - \mu_2 & \sigma\beta x + \varepsilon s \\ 0 & \tau & (1-\varepsilon)s - \mu_3 \end{bmatrix}. \tag{28}$$

Choose $P = \mathrm{diag}(1, -1, 1)$; we can obtain

$$PJP = \begin{bmatrix} -\beta y - \mu_1 & 0 & -\beta x \\ -\sigma\beta y & -\tau - \mu_2 & -\sigma\beta x - \varepsilon s \\ 0 & -\tau & (1-\varepsilon)s - \mu_3 \end{bmatrix}. \tag{29}$$

All off-diagonal entries of $PJP$ are nonpositive. It follows from Lemma 11 that model (1) is competitive in the convex region $\Gamma$. □

Now, we are ready to prove the global stability of the unique chronic infection equilibrium $P_1$ of model (1).

**Theorem 15.** *Assume that (A1) holds. If $R_0 > 1$, then the unique chronic infection equilibrium $P_1$ of model (1) is globally asymptotically stable in $\Gamma^0$.*

*Proof.* From Theorem 10 and Lemma 6, we know that $\Phi_t$ is compact and point dissipative, and there is a global attractor $A$ for $\Phi_t$. Subsequently, model (1) satisfies ($H_1$). From Theorem 2, model (1) satisfies ($H_2$). By Theorem 14 and Lemma 12, model (1) has the Poincaré-Bendixson property. Thus conditions (1) and (5) of Lemma 13 hold.

The second compound system of the linearized system along a periodic solution $(x(t), u(t), y(t))$ of model (1) is

$$\begin{aligned} \frac{dX}{dt} &= -(\beta y + \mu_1 + \tau + \mu_2)X + (\sigma\beta x + \varepsilon s)Y + \beta x Z, \\ \frac{dY}{dt} &= \tau X - (\beta y + \mu_1 - (1-\varepsilon)s + \mu_3)Y, \\ \frac{dZ}{dt} &= \sigma\beta y Y - (\tau + \mu_2 - (1-\varepsilon)s + \mu_3)Z. \end{aligned} \tag{30}$$

In order to verify that model (30) is asymptotically stable, we define a Lyapunov function

$$V(X, Y, Z; x, u, y) = \sup\left\{|X|, \frac{u}{y}\left(|Y| + \frac{\beta\lambda}{\sigma\beta\lambda + \varepsilon s\mu_1}|Z|\right)\right\}. \tag{31}$$

From the uniform persistence, we know that the orbit $\mathcal{O}$ of the periodic solution $(x(t), u(t), y(t))$ has a positive distance from the boundary of $\Gamma$. There exists a constant $c > 0$ such that

$$V(X, Y, Z; x, u, y) \geq c\sup\{|X|, |Y|, |Z|\}. \tag{32}$$

For all $(X,Y,Z) \in R^3$ and $(x,u,y) \in \mathcal{O}$, we have the following estimates on the right derivatives along the solutions $(X(t),Y(t),Z(t))$ of model (30):

$$\begin{aligned}
D_+(|X|) &= \frac{X}{|X|}\left(-(\beta y+\mu_1+\tau+\mu_2)X + (\sigma\beta x+\varepsilon s)Y+\beta xZ\right)\\
&\le -(\beta y+\mu_1+\tau+\mu_2)|X| + (\sigma\beta x+\varepsilon s)|Y|+\beta x|Z|\\
&= -(\beta y+\mu_1+\tau+\mu_2)|X| + (\sigma\beta x+\varepsilon s)\frac{y}{u}\cdot\frac{u}{y}\left(|Y|+\frac{\beta x}{\sigma\beta x+\varepsilon s}|Z|\right)\\
&= -(\beta y+\mu_1+\tau+\mu_2)|X| + (\sigma\beta x+\varepsilon s)\frac{y}{u}\cdot\frac{u}{y}\left(|Y|+\frac{\beta\lambda}{\sigma\beta\lambda+\varepsilon s\mu_1}|Z|\right);\\
D_+(|Y|) &= \frac{Y}{|Y|}\left(\tau X-(\beta y+\mu_1-(1-\varepsilon)s+\mu_3)Y\right)\\
&\le \tau|X|-(\beta y+\mu_1-(1-\varepsilon)s+\mu_3)|Y|;\\
D_+(|Z|) &= \frac{Z}{|Z|}\left(\sigma\beta yY-(\tau+\mu_2-(1-\varepsilon)s+\mu_3)Z\right)\\
&\le \sigma\beta y|Y|-(\tau+\mu_2-(1-\varepsilon)s+\mu_3)|Z|.
\end{aligned} \tag{33}$$

From (33) we have

$$\begin{aligned}
&D_+\left(\frac{u}{y}\left(|Y|+\frac{\beta\lambda}{\sigma\beta\lambda+\varepsilon s\mu_1}|Z|\right)\right)\\
&= \frac{u'y-uy'}{y^2}\left(|Y|+\frac{\beta\lambda}{\sigma\beta\lambda+\varepsilon s\mu_1}|Z|\right)\\
&\quad+\frac{u}{y}\left(D_+|Y|+\frac{\beta\lambda}{\sigma\beta\lambda+\varepsilon s\mu_1}D_+|Z|\right)\\
&\le \left(\frac{u'}{u}-\frac{y'}{y}\right)\cdot\frac{u}{y}\left(|Y|+\frac{\beta\lambda}{\sigma\beta\lambda+\varepsilon s\mu_1}|Z|\right)\\
&\quad+\frac{u}{y}\left(\tau|X|-(\beta y+\mu_1-(1-\varepsilon)s+\mu_3)|Y|\right)\\
&\quad+\frac{u}{y}\cdot\frac{\beta\lambda}{\sigma\beta\lambda+\varepsilon s\mu_1}\\
&\quad\times\left(\sigma\beta y|Y|-(\tau+\mu_2-(1-\varepsilon)s+\mu_3)|Z|\right)\\
&= \left(\frac{u'}{u}-\frac{y'}{y}\right)\cdot\frac{u}{y}\left(|Y|+\frac{\beta\lambda}{\sigma\beta\lambda+\varepsilon s\mu_1}|Z|\right)\\
&\quad+\frac{u}{y}\cdot\frac{\beta\lambda}{\sigma\beta\lambda+\varepsilon s\mu_1}|Z|\left(-\tau-\mu_2+(1-\varepsilon)s-\mu_3\right)\\
&\quad+\frac{u}{y}\tau|X|+\frac{u}{y}|Y|\Bigg(-\mu_1+(1-\varepsilon)s-\mu_3-\beta y\\
&\qquad+\frac{\sigma\beta\lambda}{\sigma\beta\lambda+\varepsilon s\mu_1}\beta y\Bigg)\\
&\le \left(\frac{u'}{u}-\frac{y'}{y}\right)\cdot\frac{u}{y}\left(|Y|+\frac{\beta\lambda}{\sigma\beta\lambda+\varepsilon s\mu_1}|Z|\right)+\frac{u}{y}\tau|X|\\
&\quad+\frac{u}{y}|Y|\left(-\mu_1+(1-\varepsilon)s-\mu_3\right)\\
&\quad+\frac{u}{y}\cdot\frac{\beta\lambda}{\sigma\beta\lambda+\varepsilon s\mu_1}|Z|\left(-\tau-\mu_2+(1-\varepsilon)s-\mu_3\right)\\
&\le \frac{u}{y}\tau|X|+\Bigg(\frac{u'}{u}-\frac{y'}{y}+(1-\varepsilon)s\\
&\qquad-\mu_3-\min\{\mu_1,\tau+\mu_2\}\Bigg)\\
&\quad\times\frac{u}{y}\left(|Y|+\frac{\beta\lambda}{\sigma\beta\lambda+\varepsilon s\mu_1}|Z|\right).
\end{aligned} \tag{34}$$

The inequalities in (33) and (34) lead to

$$D_+V(t)\le\max\{g_1(t),g_2(t)\}V(t), \tag{35}$$

where

$$\begin{aligned}
g_1(t) &= -(\beta y+\mu_1+\tau+\mu_2)+(\sigma\beta x+\varepsilon s)\frac{y}{u},\\
g_2(t) &= \frac{u}{y}\tau+\frac{u'}{u}-\frac{y'}{y}+(1-\varepsilon)s-\mu_3-\min\{\mu_1,\tau+\mu_2\}.
\end{aligned} \tag{36}$$

After rewriting the last two equations of model (1), we find that

$$(\sigma\beta x+\varepsilon s)\cdot\frac{y}{u}=\frac{u'}{u}+\tau+\mu_2,\qquad \frac{y'}{y}=\frac{u}{y}\tau+(1-\varepsilon)s-\mu_3. \tag{37}$$

From (36) and (37), we obtain

$$\begin{aligned}
&\max\{g_1(t),g_2(t)\}\le\frac{u'}{u}-\min\{\mu_1,\tau+\mu_2\},\\
&\int_0^\omega\max\{g_1(t),g_2(t)\}dt\\
&\quad\le\int_0^\omega\left(\frac{u'}{u}-\min\{\mu_1,\tau+\mu_2\}\right)dt\\
&\quad=\ln u(t)|_0^\omega-\omega\min\{\mu_1,\tau+\mu_2\}\\
&\quad=-\omega\min\{\mu_1,\tau+\mu_2\}.
\end{aligned} \tag{38}$$

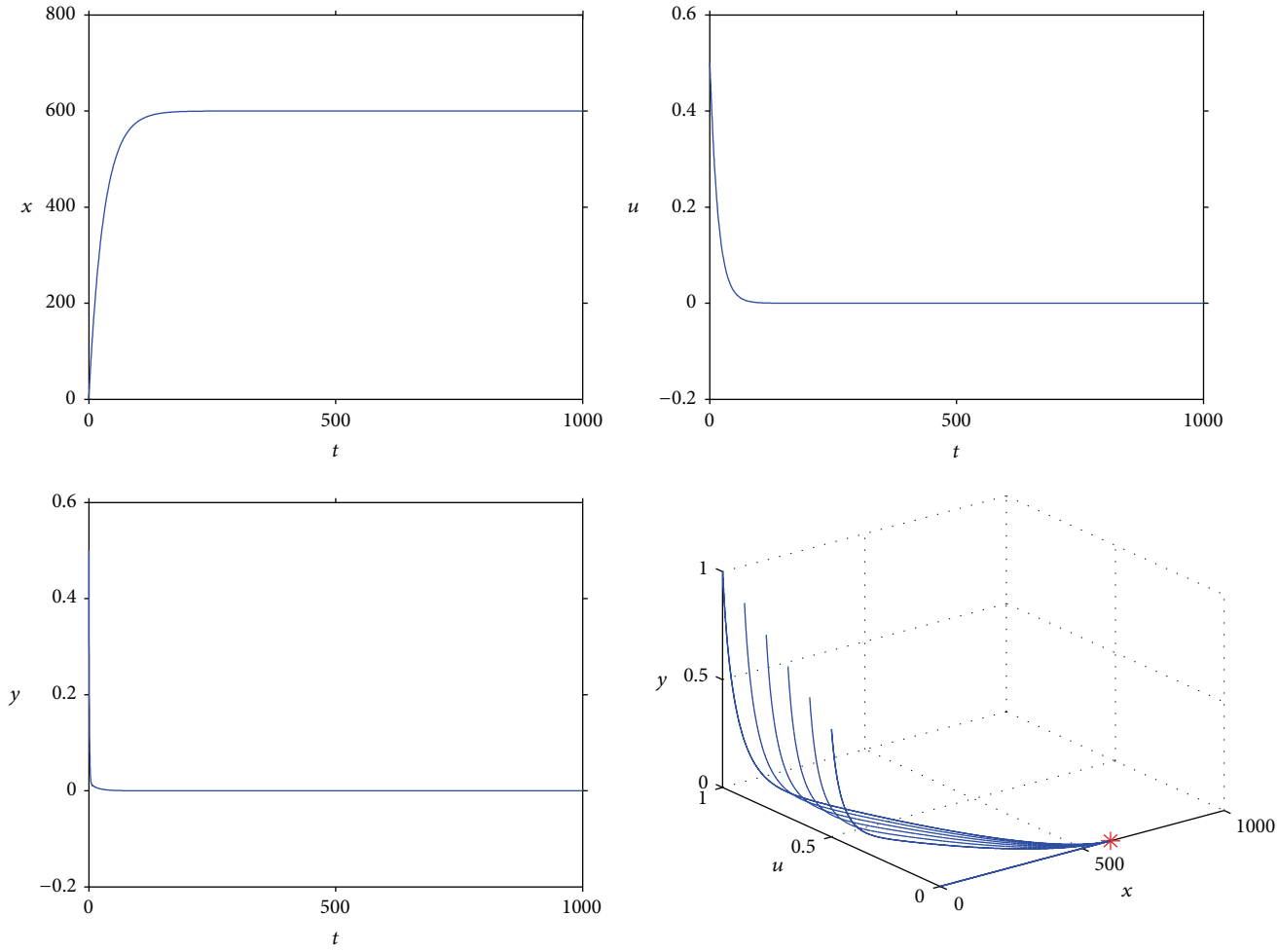


FIGURE 2: Global stability of the infection-free equilibrium $P_0$ when $R_0 < 1$.

The inequalities in (35) and (38) imply that $V(t) \to 0$ as $t \to \infty$, which leads to $(X(t), Y(t), Z(t)) \to 0$ as $t \to \infty$ because of (32). As a result, the second compound system (30) is asymptotically stable. This verifies condition (6) of Lemma 13.

Let $J(P_1)$ be the Jacobian matrix of model (1) at $P_1$. Then we have

$$\begin{aligned}
&(-1)^3 \det\left(\frac{\partial f}{\partial x}(P_1)\right) \\
&= -\begin{bmatrix} -\beta y_1 - \mu_1 & 0 & -\beta x_1 \\ \sigma\beta y_1 & -\tau - \mu_2 & \sigma\beta x_1 + \varepsilon s \\ 0 & -\tau & (1-\varepsilon)s - \mu_3 \end{bmatrix} \\
&= (\beta y_1 + \mu_1)\left((\mu_3 - (1-\varepsilon)s)(\tau + \mu_2) + \varepsilon s\tau\right) \\
&\quad + \sigma\beta\tau\mu_1 x_1 > 0.
\end{aligned} \tag{39}$$

Condition (9) of Lemma 13 holds. The chronic infection equilibrium $P_1$ of model (1) is globally asymptotically stable in $\Gamma^0$ since all conditions of Lemma 13 are satisfied. □

## 4. Numerical Simulation

Numerical simulations are done to demonstrate the results in Section 3. The sensitive analysis is given to show the effects of the model parameters on the solutions.

In numerical simulations, the time scale is a day. The rate of healthy $CD4^+$ helper T cells produced in the bone marrow, $\lambda$, is 15–25 cells/mm$^3$/day. The coefficient of infectious transmissibility, $\beta$, is 0.0005–0.003 mm$^3$/cell/day. The proportion of infected cells expressing Tax, $\tau$, is (0.003–0.03)/day. The removal rates of healthy $CD4^+$ T cells, resting infected $CD4^+$ T cells, and Tax-expressing infected $CD4^+$ T cells, $\mu_1$, $\mu_2$, and $\mu_3$, are taken to be the value 0.01–0.05/day. The death rate of the Tax-expressing infected $CD4^+$ T cells is considerably shorter than the natural lifespan of $CD4^+$ T cells [33].

In Figure 2, we use the following set of parameters: $\lambda = 20$, $\beta = 0.001$, $\mu_1 = \mu_2 = 1/30$, $s = 0.05$, $\sigma = 0.01$, $\varepsilon = 0.9$, $\tau = 0.03$, $\mu_3 = 0.05$, and $R_0 = 0.5832 < 1$. All solutions converge to the infection-free equilibrium $P_0$.

In Figure 3, we use the following set of parameters: $\lambda = 20$, $\beta = 0.001$, $\mu_1 = 1/30$, $\mu_2 = 0.02$, $s = 0.1$, $\sigma = 0.1$, $\varepsilon = 0.8$,

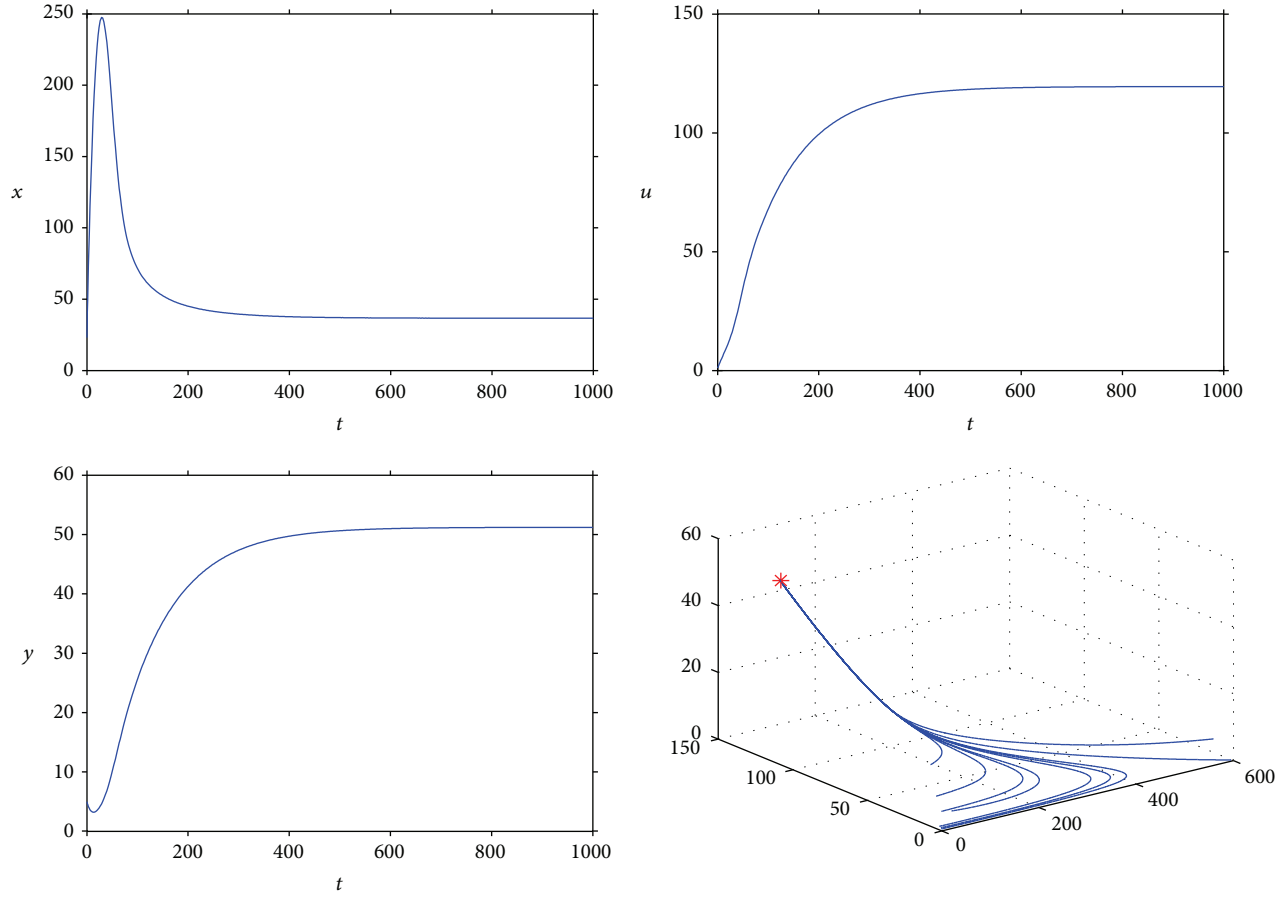


Figure 3: Global stability of the infection-free equilibrium $P_1$ when $R_0 > 1$.

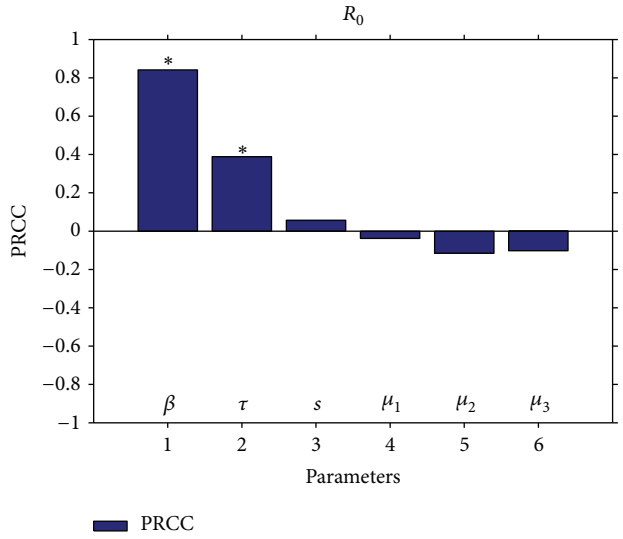


Figure 4: Sensitivity analysis of $R_0$ with the parameters came from LHS sampling.

$\tau = 0.03$, $\mu_3 = 0.09$, and $R_0 = 1.1556 > 1$. All solutions converge to the chronic infection equilibrium $P_1$.

Table 1: PRCC results and $P$ value.

| Parameters | $\beta$ | $\tau$ | $s$ | $\mu_1$ | $\mu_2$ | $\mu_3$ |
|---|---|---|---|---|---|---|
| PRCC | 0.8597 | 0.3421 | 0.0214 | −0.0575 | −0.0813 | −0.0610 |
| $P$ value | 0.0000 | 0.0000 | 0.4994 | 0.0696 | 0.0103 | 0.0545 |

A sensitivity analysis quantifies how changes in the values of the input parameters alter the value of the outcome variable [34]. The sensitivity analysis is performed to explore the behavior of model (1) by calculating the partial rank correlation coefficients (PRCC) for each input parameter, which are sampled by the Latin hypercube sample (LHS) and $R_0$ (Table 1). Figure 4 shows that a significantly strong positive correlation exists between parameters $\beta$ and $R_0$ (PRCC = 0.8597; $P$ value = 0 < 0.01). The second sensitive parameter to $R_0$ is $\tau$ (PRCC = 0.3421; $P$ value = 0 < 0.01). The result indicates that the cell-to-cell contact transmission and Tax expression contribute a lot to the viral infection.

The sensitivity analysis result shows that $\beta$ and $\tau$ are two significant parameters for the infection. We illustrate the impact of $\beta$ and $\tau$ on the magnitude of the chronic infection equilibrium $P_1$ by numerical simulations. The curves in Figures 5(a) and 5(b) show the dependence of $u_1$ and $y_1$ on the parameters $\beta$ and $\tau$, respectively. The surfaces in Figures

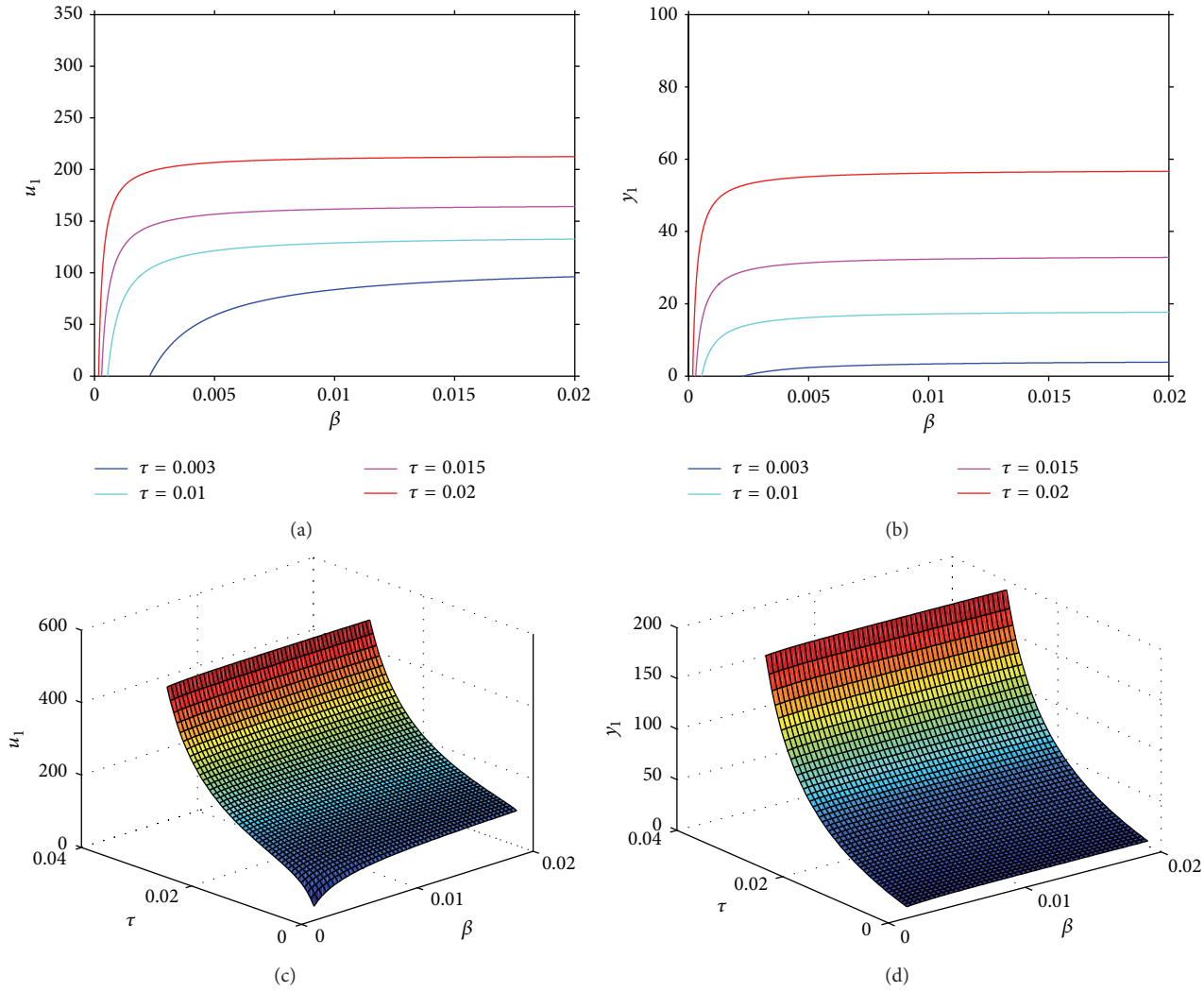


FIGURE 5: The impact of $\beta$ and $\tau$ on the magnitude of the chronic infection equilibrium $P_1$.

5(c) and 5(d) give the values of $u_1$ or $y_1$ as the functions of $\beta$ and $\tau$, respectively. Those curves and surfaces in Figure 5 indicate that $u_1$ and $y_1$ will increase with $\beta$ and $\tau$. For any given $\tau$, $u_1$ or $y_1$ increases very fast for small $\beta$ and quite slow for large $\beta$.

## 5. Concluding Remarks

We have formulated and studied a mathematical model of HTLV-1 in vivo including the spontaneous HTLV-1 antigen Tax expression, cell-to-cell contact, and mitotic infectious route to the viral dynamics. The persistence of the model is discussed. Sufficient conditions are established for the global asymptotic stability of the infection-free equilibrium and chronic infection equilibrium. The sensitivity analysis by PRCC with the LHS sample is presented to show the impact of the parameters on the model dynamics.

As we know, infected cells from HAM/TSP patients have a significantly higher probability of expressing Tax protein than infected cells from ACs. When an infected individual has settled at a chronic infection state, the proportion of Tax-expressing cells in infected cells is $\overline{y}/(\overline{u} + \overline{y})$, where $\overline{u} = ((\mu_3 - (1 - \varepsilon)s)/\tau)\overline{y}$. Hence $(\partial/\partial\tau)(\overline{y}/(\overline{u} + \overline{y})) = (\mu_3 - (1 - \varepsilon)s)/(\mu_3 - (1 - \varepsilon)s + \tau)^2 > 0$. That is, a faster rate of spontaneous expression of the Tax results in a higher proportion of $y$ in infected $CD4^+$ T cells which influence the risk of HAM/TSP.

It follows from our sensitivity analysis that $\beta$ and $\tau$ are significantly sensitive to the reproduction number $R_0$. In particular, increasing the rate of Tax expression results in a reduction of the proportion of proviral cell at the equilibrium state. This conclusion implies that Tax expression should be controlled in the therapeutic intervention in order to reduce the risk of HAM/TSP.

Our conclusions are based on a simple model; with the recent progress in HTLV-1 pathogenesis and new findings in immune reactions against HTLV-1 infection and Tax expression, more factors should be investigated in improved models.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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