BACKWARD BIFURCATION OF AN HTLV-I MODEL WITH IMMUNE RESPONSE

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ABSTRACT. Human T-cell Lymphotropic virus type 1 (HTLV-I) causes HAM/TSP and other illnesses. HTLV-I mainly infects $CD4^+$ T cells and activates HTLV-I-specific immune response. In this paper, we formulate a mathematical model of HTLV-I to investigate the role of selective mitotic transmission, Tax expression, and CTL response in vivo. We define two parameters ($R_0$ and $R_1$) to study the model dynamics. The unique infection-free equilibrium $P_0$ is globally asymptotically stable if $R_0 < 1$. There exists the chronic-infection equilibrium $P_1$ if $R_1 < 1 < R_0$. There exists a unique chronic-infection equilibrium $P_2$ if $R_1 > 1$. There is a backward bifurcation of chronic-infection equilibria with CTL response if $R_1 < 1 < R_0$. The numerical simulations shown that the existence of backward bifurcation may lead to the existence of periodic solutions.

1. Introduction. HTLV-I is the first human pathogenic retrovirus isolated, which mainly infects $CD4^+$ T cells and persists lifelong in the infected individuals [1, 2, 3, 4]. Nowadays, there are approximately 10-20 million infected people in many countries [5, 6]. The viral load of HTLV-I of the infected people plays a critical role in the disease transmission. HTLV-I can result in two types of diseases: adult T-cell leukemia (ATL) and a spectrum of chronic inflammatory diseases which can affect the eye, as well as skeletal muscle and central nervous system. Among those inflammatory diseases, HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is well recognized, which is a chronic inflammation of the central nervous system [7]. The majority of the infected individuals have no symptom and never get rid of the virus, then they become the lifelong asymptomatic carriers. Among HTLV-I carriers, the risk of infected individuals develop into HAM/TSP ranges from 3% to 4% [8]. HTLV-I can be transmitted from mother to child, through sexual contact, by sharing needles and contaminating blood products [5, 9]. HTLV-I does not readily produce observable extracellular virion, thus viral burden in HTLV-I carriers is quantified as proviral load (the proportion of peripheral blood mononuclear cells that carry an integrated HTLV-I provirus), and the risk of HAM/TSP is correlated with the proviral load [1, 10]. So far, there is neither

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vaccine and satisfactory treatment nor means of assessing the risk of prognosis in infected individuals.

There are two routes of HTLV-I to persist within the host: (i) horizontal transmission, which spread virus from the infected cells to uninfected cells via pathways of cell-to-cell transmission, namely, cellular conduits, extracellular viral assemblies, infection via dendritic cells and the virological synapse [9]; (ii) vertical transmission, which spread virus from the mitotic proliferation of infected cells to reach the clonal expansion by passing the virus to the two daughter cells when a cell divides.

Identifying the mechanism that how does HTLV-I persist in vivo is important for public health though the precise mechanism that triggers HTLV-I persistence in vivo is still incompletely known currently. Studies have observed that HTLV-I varies little in genetic sequence [11, 12], which suggests that the vertical transmission through mitotic proliferation rather than horizontal transmission through cell-to-cell spread performs significantly [13, 14]. The experimental findings show that there is a large, chronically activated cytotoxic T lymphocyte (CTL) response in most infected individuals. HTLV-I causes a persistent infection with a high proviral load and remain ACs lifelong. How does HTLV-I persist despite a strong cell-mediated immune response? In agreement with the observations, Asquith and Bangham [1] have applied new experimental and mathematical techniques with biological concepts to propose a more likely candidate mechanism of viral persistence and pathogenesis in HTLV-I infection. They provide an alternative model of HTLV-I persistence and host immunity. The alternative model does involve Tax-driven proliferation and HTLV-I-specific CTL. First, HTLV-I infected cells expressing viral proteins, Tax, which induces the Tax-expressing cells selective proliferation with a more rapidly mitotic rate [15, 16, 17, 18]. They propose that the majority of infected cells are not expressing Tax. Second, the Tax-expressing infected cells can be exposed to the immune response and be rapidly killed by the efficient HTLV-I-specific CTL response. The expression of Tax can quicken up the rate of infected cell division and thus increase the amount of proviral load, meanwhile, it can expose Tax-expressing infected cells to effective immune surveillance, thus decreasing the proviral load. These is a dynamical struggle between viral persistence and individual’s immune response.

High proviral load and high proportion of infected cells that express viral protein play a crucial role for the development of HAM/TSP [10]. Clinical evidences have indicated that the amount of CD4+ T cells from HAM/TSP individuals express higher level of Tax than CD4+ T cells from ACs. At any given proviral load, the Tax expression is significantly higher in the HAM/TSP individuals than that in the ACs [19], thus a high rate of Tax expression is linked to a large increase in the prevalence and the risk of HAM/TSP [20].

Exploring the dynamics of HTLV-I infection has attracted much attention, with many mathematical models being proposed [7, 13, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28]. Wodarz et al. [21] described a basic three-dimensional mathematical model, took CTL response, infectious and mitotic transmission into account. They analyzed the model and numerically showed that the fraction σ of the infected cells survive the immune system attack can give rise to backward bifurcation. Li and Lim [22] explored the role of Tax expression in HTLV-I persistence in vivo. A three-dimensional compartmental model containing healthy, latently infected (Tax−) and actively infected (Tax+) CD4+ T cells was formulated. It was shown that the proportion of Tax expression τ can lead to backward bifurcation and bi-stability
occur. Li and Shu [26] developed a three-dimensional model for the CTL response of HTLV-I with time delay, and showed the coexistence of multiple stable periodic solutions can coexist in there model by the the time delay incurred during the production of CTLs. Lim and Maini [28] investigated a four-dimensional model to describe the dynamic interactions among viral expression, infected target cell activation, and the HTLV-I-specific CTL response. The global dynamics of the model was obtained. Based on the existing models and the new insights of HTLV-I persistence by Asquith and Bangham, we expanded the previous models by introducing the role of Tax-expressing T cells’ mitosis into a model with CTL response and horizontal infection.

We set up an ordinary differential equation model with four compartments: healthy CD4+ T cells x, silent infected CD4+ T cells u, Tax-expressing infected CD4+ T cells y, and HTLV-I-specific CD8+ T cells z.

In the next section, we present our model and give the required conditions. In section 3, we give two threshold parameters $R_0$ and $R_1$. The existence of equilibria and backward bifurcation are investigated. The stability of equilibria are studied in Section 4. Section 5 focus on simulations of the model and the existence of periodic solutions is observed. The biological implications are given in the last section.

2. Model formulation. In this section, we construct a mathematical model which takes the spontaneous HTLV-I antigen Tax expression, CTL immune response, cell-to-cell and mitotic transmission into account to explore the basic dynamics of virus-host interaction. The model is applicable to HAM/TSP among nonmalignant HTLV-I induced diseases. The factors associated with development of ATL and the risk of other inflammatory diseases are not known and may be different. The proliferation of silent infected cells is neglected since the Tax-expressing infected cells proliferate more rapidly than silent infected cells.

The numbers of healthy CD4+ T cells, silent infected CD4+ T cells and Tax-expressing infected CD4+ T cells at time $t$ are denoted by $x(t)$, $u(t)$ and $y(t)$, while the number of HTLV-I-specific CD8+ T cells at time $t$ is denoted by $z(t)$. Our objective is to explore the infection features by the simple model. We assume that the new healthy cells are produced at a logistic form of $\gamma x(1 - \frac{x}{K})$, where $\gamma$ is an intrinsic rate of natural increase, $K$ is the healthy CD4+ T cells’ carrying capacity. The healthy CD4+ T cells can be infected through cell-to-cell contact with infected CD4+ T cells. There are two types of contacts rate often used in modeling disease transmission. The bilinear contact rate is proportional to the total population size, while the standard contact rate is approximately constant. Here we use a saturation contact rate to describe the contact between healthy CD4+ T cells and Tax-expressing infected CD4+ T cells. When the total population size is small, it’s close to the bilinear contact rate, and it tends to the saturation value $\frac{\beta}{\omega}$ for large size. The saturating incidence rate is $\frac{\beta x y}{1 + \omega(x + u + y)}$, where $\omega \geq 0$ denotes the saturation level. When $\omega = 0$, the saturation rate reduces to the bilinear incidence. Since the majority proviral cells do not express Tax at any given time $t$, and HTLV-I varies little in sequence, which suggests the proviral load maintained by mitosis rather than horizontal transmission, $y(t) \ll u(t) \ll x(t)$. It’s biologically plausible to use the form $\frac{\beta x y}{1 + \omega x}$ to describe the incidence rate. The transmission coefficient
among CD4+ T cells is \( \beta \) [21]. We use a fraction \( \sigma \in (0, 1) \) for the silent infected cells since the newly infected cells experience the destruction by the adaptive immune response [13, 27]. There is a small proportion \( \tau \in (0, 3\%) \sim 3\% \) of silent infected cells expressing Tax every day [27]. The Tax-expressing CD4+ T cells are driven into proliferation by HTLV-I Tax gene at a rate \( \epsilon_{sy} \), with \( \epsilon_{sy} \) being the silent infected cells compartment (\( \epsilon \in (0, 1) \)), and \( (1 - \epsilon)sy \) staying in the Tax-expressing infected CD4+ T cells compartment. The Tax protein acting both as mitogen and antigen drives not only the division of infected CD4+ T cells, but also the proliferation of CD8+ T cells. The stimulated CD8+ T cells can recognize and kill the infected cells with Tax express [2]. The rate of per CD8+ cell killed Tax-expressing infected cells per day is \( p \). CTL population grows in response to a given concentration of antigen at a rate of \( \nu_{yz} \). The parameter \( \nu \) denotes the CTL responsiveness[20]. The transfers among those four compartments are shown in Fig.1.

\[
\begin{align*}
\frac{dx}{dt} &= \gamma x (1 - \frac{x}{K} - \frac{\beta xy}{1 + \omega x}), \\
\frac{du}{dt} &= \frac{\sigma \beta xy}{1 + \omega x} + \epsilon_{sy} - \tau u - \mu_2 u, \\
\frac{dy}{dt} &= \tau u + (1 - \epsilon)sy - p_{yz} - \mu_3 y, \\
\frac{dz}{dt} &= \nu_{yz} - \mu_4 z.
\end{align*}
\] (1)

In model (1), \( \mu_2, \mu_3, \) and \( \mu_4 \) represent the removal rates of silent infected CD4+ T cells, Tax-expressing infected CD4+ T cells, and CD8+ T cells, respectively. From the biology background, all parameters and the initial values of the variables are assumed to be non-negative, and \( s \) satisfies

\[ s < \frac{(\tau + \mu_2)\mu_3}{\tau + \mu_2(1 - \epsilon)}. \] (A1)

Condition (A1) implies \( s < \frac{\mu_3}{1 - \epsilon} \), and it is necessary to have the amount of infected CD4+ T cells bounded.

**Theorem 2.1.** The solutions \((x(t), u(t), y(t), z(t))\) of model (1) with the nonnegative initial conditions are nonnegative and bounded for all \( t > 0 \) if (A1) holds.
Proof. From the equations of the model (1), we can get
\[
\begin{align*}
\frac{dx(t)}{dt} \bigg|_{x=0} &= 0 \geq 0, \\
\frac{du(t)}{dt} \bigg|_{u=0} &= \frac{\sigma \beta xy}{1 + \omega x} + \varepsilon sy \geq 0, \\
\frac{dy(t)}{dt} \bigg|_{y=0} &= \tau u \geq 0, \quad \text{and} \\
\frac{dz(t)}{dt} \bigg|_{z=0} &= 0 \geq 0.
\end{align*}
\]
According to Lemma 2 in [30], we draw the conclusion that the solutions of the model (1) with nonnegative initial conditions will be nonnegative for all \( t > 0 \).

From the first equation of model (1), we have
\[
\frac{dx}{dt} = \gamma x \left(1 - \frac{x}{K}\right) - \frac{\beta xy}{1 + \omega x} \leq \gamma x \left(1 - \frac{x}{K}\right). \tag{2}
\]
The comparison principle implies that \( \lim_{t \to +\infty} \sup \ x \leq K \).

Let \( L = x + u + \frac{\tau + \mu_2}{\tau} y + \frac{(\tau + \mu_2)p}{\tau \nu} z \) and \( G = \frac{\tau + \mu_2}{\tau} (\mu_3 - (1 - \varepsilon) s) - \varepsilon s \).
Condition (A1) implies \( G > 0 \). From equations of model (1), we obtain
\[
\frac{dL}{dt} = \frac{(\sigma - 1)\beta xy}{1 + \omega x} + \gamma x \left(1 - \frac{x}{K}\right) - Gy - \frac{(\tau + \mu_2)p}{\tau \nu} z \leq \gamma K - Gy - \frac{(\tau + \mu_2)p}{\tau \nu} z. \tag{3}
\]
Inequality (3) implies that \( L(t) = x(t) + u(t) + \frac{\tau + \mu_2}{\tau} y(t) + \frac{(\tau + \mu_2)p}{\tau \nu} z(t) \) decreases and all solution trajectories of model (1) will go through polyhedron \( x + u + \frac{\tau + \mu_2}{\tau} y + \frac{(\tau + \mu_2)p}{\tau \nu} z = L \) from outside to inside if \( Gy + \frac{(\tau + \mu_2)p}{\tau \nu} z > \gamma K \).

Let \( M_1 \) be the maximum of the function \( \frac{\tau + \mu_2}{\tau} y + \frac{(\tau + \mu_2)p}{\tau \nu} z \) on the bounded domain
\[
G_0 = \left\{ (y, z) \mid y \geq 0, \ z \geq 0, \ Gy + \frac{(\tau + \mu_2)p}{\tau \nu} z \leq \gamma K \right\},
\]
\( M_2 \) be the maximal value of \( \gamma K + \varepsilon sy \) on the bounded domain
\[
G_1 = \left\{ (y, z) \mid y \geq 0, \ z \geq 0, \ \frac{\tau + \mu_2}{\tau} y + \frac{(\tau + \mu_2)p}{\tau \nu} z \leq M_1 \right\}.
\]
When \( \frac{\tau + \mu_2}{\tau} y + \frac{(\tau + \mu_2)p}{\tau \nu} z \leq M_1 \) is satisfied, from the first two equations of model (1), we obtain
\[
\frac{dx}{dt} + \frac{du}{dt} = \frac{(\sigma - 1)\beta xy}{1 + \omega x} + \gamma x \left(1 - \frac{x}{K}\right) + \varepsilon sy - \tau u - \mu_2 u \\
\leq \gamma K + \varepsilon sy - (\tau + \mu_2)u \leq M_2 - (\tau + \mu_2)u. \tag{4}
\]
It follows that there exists a positive \( u_m = \frac{M_2}{\tau + \mu_2} \), such that \( \frac{dx}{dt} + \frac{du}{dt} \leq 0 \) if \( u > u_m \) and \( \frac{\tau + \mu_2}{\tau} y + \frac{(\tau + \mu_2)p}{\tau \nu} z \leq M_1 \).
From the inequalities in (3) and (4) we know that 
\[
\frac{dL}{dt} \leq 0, \quad \text{if} \quad \frac{\tau + \mu_2}{\tau} y + \frac{(\tau + \mu_2)p}{\tau} z \geq M_1,
\]
\[
\frac{dx}{dt} + \frac{du}{dt} \leq 0, \quad \text{if} \quad \frac{\tau + \mu_2}{\tau} y + \frac{(\tau + \mu_2)p}{\tau} z \leq M_1, \quad u \geq \frac{M_2}{\tau + \mu_2},
\]
\[
\frac{dx}{dt} \leq 0, \quad \text{if} \quad \frac{\tau + \mu_2}{\tau} y + \frac{(\tau + \mu_2)p}{\tau} z \leq M_1, \quad u \leq \frac{M_2}{\tau + \mu_2}, \quad x \geq K.
\]

The inequalities \( \frac{dL}{dt} \leq 0, \frac{dx}{dt} + \frac{du}{dt} \leq 0, \) and \( \frac{dx}{dt} \leq 0 \) imply that the domain 
\[
\Gamma = \{ (x, u, y, z) | 0 \leq x \leq K, 0 \leq u \leq u_m, y \geq 0, z \geq 0, x + u + \frac{\tau + \mu_2}{\tau} y + \frac{(\tau + \mu_2)p}{\tau} z \leq M_1 + K + u_m \}
\]
is a positively invariant for model (1), i.e., any solution of model (1) starting from \( \Gamma \) will stay in \( \Gamma \) for all \( t \geq 0 \). The similar argument implies that any solution of model (1) with nonnegative initial value is bounded, and will enter when the time is large enough.

In the rest part of the paper, we will investigate the dynamics of model (1) in the positively invariant set \( \Gamma \).

3. Equilibria and backward bifurcation. The straightforward calculation shows that model (1) may have three types of equilibria: infection-free equilibrium \( P_0 = (x_0, u_0, 0, 0) \), chronic-infection equilibrium without CTL response \( P_1 = (x_1, u_1, y_1, 0) \), and chronic-infection equilibrium with CTL response \( P_2 = (x_2, u_2, y_2, z_2) \), where \( x_0, x_1, u_1, y_1, x_2, u_2, y_2, z_2 \) are nonnegative. At equilibrium \( P_0 \), the amount of infected cells and CD8+ cells are 0 which show that there is no infection in the individuals. At equilibrium \( P_1 \), persistent infection can be found in the asymptotical carriers but with no CTL response. At equilibrium \( P_2 \), there is chronically CTL response in the infected people, and the persist infection is linked to a high risk of HAM/TSP.

Next, we define the basic reproduction number for HTLV-I infection and CTL response of model (1) successively. By the next generation matrix approach given in [31], we have
\[
F = \begin{bmatrix} 0 & \sigma \beta x \\ 0 & \frac{1 + \omega x}{s - \varepsilon s} \end{bmatrix}, \quad V = \begin{bmatrix} \tau + \mu_2 & 0 \\ -\tau & \mu_3 \end{bmatrix},
\]
and
\[
R_0 = \rho(FV^{-1}) = \frac{\sigma \beta \tau K}{(\tau + \mu_2)(1 + \omega K)\mu_3} + \frac{\tau \varepsilon s}{(\tau + \mu_2)\mu_3} + \frac{(1 - \varepsilon) s}{\mu_3}.
\]
The biological interpretation of \( R_0 \) is the same as it in [23]. Both mitotic and horizontal transmission contribute to the reproduction number.

From the equilibrium equations of model (1)
\[
\gamma x(1 - \frac{x}{K}) - \frac{\beta x y}{1 + \omega x} = 0, \quad \frac{\sigma \beta x y}{1 + \omega x} + \varepsilon s y - \tau u - \mu_2 u = 0, \quad \tau u + (1 - \varepsilon) s y - p y z - \mu_3 y = 0,
\]
\[
\nu y z - \mu_4 z = 0,
\]

(5)
We know that the infection-free equilibrium $P_0 = (x_0, 0, 0, 0)$ always exists, where $x_0 = K$. The chronic-infection equilibrium without CTL response $P_1 = (x_1, u_1, y_1, 0)$ exists if and only if $R_0 > 1$ and (A1) holds, with

$$x_1 = \frac{(\tau + \mu_2)\mu_3 K - \tau s K - \mu_2(1 - \varepsilon)s K}{(R_0 - 1)(\tau + \mu_2)(1 + \omega K)\mu_3 + (\tau + \mu_2)\mu_3 - \tau s - \mu_2(1 - \varepsilon)s},$$

$$u_1 = \frac{\tau}{\rho} (R_0 - 1)(\tau + \mu_2)(1 + \omega K)(1 + \omega x_1)\gamma \mu_3,$$

$$y_1 = \frac{(R_0 - 1)(\tau + \mu_2)(1 + \omega K)\mu_3 \beta + (\tau + \mu_2)\mu_3 \beta - \tau s \beta - \mu_2(1 - \varepsilon)s \beta}{(R_0 - 1)(\tau + \mu_2)(1 + \omega K)(1 + \omega x_1)\gamma \mu_3}.$$

To discuss the existence of $P_2$, we introduce a threshold value for CTL response

$$R_1 = \frac{(1 + \omega x_1)^2(1 + \omega K)(\tau + \mu_2)\mu_3 \gamma \nu R_0}{\sigma \beta^2 \tau K \mu_4 + (1 + \omega x_1)^2(1 + \omega K)(\tau + \mu_2)\mu_3 \gamma \nu 
u}.$$

From the expressions we know $R_1 < R_0$, and $R_1 > 1$ is equivalent to $\frac{dz(t)}{dt} |_{z = y_1} > 0$.

From equations (5), we obtain $P_2 = (x_2, u_2, y_2, z_2)$, where $x_2 > 0$, $u_2 > 0$, $y_2 > 0$, $z_2 > 0$ satisfy

$$u_2 = \frac{\mu_3 \mu_4 - (1 - \varepsilon)s \mu_4 + p \mu_4 z_2}{\tau \nu},$$

$$y_2 = \frac{\mu_4}{\nu},$$

$$z_2 = \frac{\sigma \beta \tau (x_2 - x_1)}{(\tau + \mu_2)(1 + \omega x_2)(1 + \omega x_1)p}.$$

From the expression of equilibrium $P_2$, we see that the concentration of Tax-expressing infected $CD4^+$ T cells depends only on the immunological parameters $\nu$ and $\mu_4$. The analysis shows that $x_2 > x_1$, which means that the persistent CTL response will reduce $y$ and lead to the increase of the concentration of healthy $CD4^+$ T cells.

$x_2$ is the positive solution of the equation $f_1(x) = f_2(x)$, where $f_1(x) = \frac{\mu_4}{\nu}$,

$$f_2(x) = \frac{-\omega \gamma x^2}{\beta K} + \frac{(\omega K - 1)\gamma x}{\beta K} + \frac{\gamma}{\beta}.$$ Graphically, $x_2$ is the coordinate of the intersection points of the function of $f_1(x)$ and $f_2(x)$ in the first quadrant. There is one chronic-infection equilibrium with CTL response may if $R_1 > 1$. There may be zero, one, or two intersections (see Fig.2) if $R_1 < 1 < R_0$.

When $R_1 < 1 < R_0$, we define $H(x) = f_1(x) - f_2(x)$ and $m = \min\{H(x) : x_1 \leq x \leq K\}$. The conclusion on the existence of the equilibrium of model (1) is given in the following theorem.

**Theorem 3.1.** (1) There always exists the infection-free equilibrium $P_0$.

(2) There is the chronic-infection equilibrium without CTL response $P_1$ if and only if $R_0 > 1$.

(3) If $R_1 < 1 < R_0$ and $m > 0$, then there is no chronic-infection equilibrium with CTL response.

(4) If $R_1 < 1 < R_0$ and $m = 0$, then there is one chronic-infection equilibrium with CTL response, $P_2(x_2, u_2, y_2, z_2)$, where $x_2, u_2, y_2, z_2 > 0$.

(5) If $R_1 < 1 < R_0$ and $m < 0$, then there are two chronic-infection equilibria with CTL response, $P_2(x_2, u_2, y_2, z_2)$ and $P_2^*(x_2^*, u_2^*, y_2^*, z_2^*)$ with $x_2 > x_2^* > 0$. 

Figure 2. Intersections of $f_1(x)$ and $f_2(x)$.

Figure 3. Backward bifurcation of equilibrium with respect to $\nu$. 
(6) If $R_1 > 1$, then there is always one chronic-infection equilibrium with CTL response $P_2(x_2, y_2, z_2)$.

Theorem 3.1 establishes the existence of a backward bifurcation. The backward bifurcation diagram is shown in Fig.3 with following of parameter values $\sigma = 0.1, \beta = 0.005, \mu_2 = 0.03, \mu_3 = 0.05, \mu_4 = 0.2, K = 1000, p = 0.2, s = 0.09, \varepsilon = 0.9, \tau = 0.03, \omega = 0.03, \gamma = 0.05$. The biological implications of backward bifurcation is discussed in section 6.

4. Stability analysis of equilibria.

4.1. Stability of the infection-free equilibrium. From the biological interpretation of the basic reproductive number $R_0$, we know that a Tax-expressing infected $CD4^+$ T cell will infect less than one healthy $CD4^+$ T cell on average if $R_0 < 1$, leading to the extinction of HTLV-I. We can prove the global asymptotically stable of infection-free equilibrium $P_0$.

**Theorem 4.1.** If $R_0 < 1$, then the infection free equilibrium $P_0$ of model (1) is global asymptotically stable, and it is unstable if $R_0 > 1$.

**Proof.** The characteristic equation of the linearized system of model (1) at $P_0$ is

$$
(\lambda + \gamma)(\lambda + \mu_4)(\lambda^2 + a_1\lambda + a_2) = 0,
$$

where, $a_1 = \mu_3 \left(1 - R_0 + \frac{\sigma \beta \tau K + \tau \varepsilon s}{(\tau + \mu_2)\mu_3}\right) + \tau + \mu_2, a_2 = (1 - R_0)(\tau + \mu_2)\mu_3$. From the Routh-Hurwitz criterion and the expression of $a_1, a_2$, we obtain that the all roots of the characteristic equation have negative parts if $R_0 < 1$, and at lest one root has positive real part if $R_0 > 1$.

Let $L_1 = \tau u + (\tau + \mu_2)y$, then the derivative of $L_1(u, y)$ along the solutions of model (1) is

$$
\frac{dL_1}{dt} \bigg|_{(1)} = \frac{\tau}{\mu_1} \frac{du}{dt} + (\tau + \mu_2)\frac{dy}{dt}
$$

$$= y \left( \frac{\tau \sigma \beta x}{1 + \omega x} + \tau \varepsilon s + (\tau + \mu_2)(1 - \varepsilon)s - (\tau + \mu_2)\mu_3 - \rho z \right)
$$

$$\leq y \left( \frac{\tau \sigma \beta K}{1 + \omega K} + \tau \varepsilon s + (\tau + \mu_2)(1 - \varepsilon)s - (\tau + \mu_2)\mu_3 \right)$$

$$= (R_0 - 1)(\tau + \mu_2)\mu_3 y.
$$

The expression in (8) and $R_0 \leq 1$ imply that $\frac{dL_1}{dt} \bigg|_{(1)} \leq 0$ for all $t > 0$, and $\frac{dL_1}{dt} \bigg|_{(1)} = 0$ holds only at $P_0$. By Lasalle’s invariance principle [32], we get the conclusion that $L_1(t) = \tau u(t) + (\tau + \mu_2)y(t)$ is a decreasing function if $R_0 < 1$ and $\lim_{t \to \infty} L_1(t) = 0$. Substituting $u = 0$ and $y = 0$ into model (1) the limiting theory of the ordinary differential equations can yield that $\lim_{t \to \infty} z(t) = 0$ and $\lim_{t \to \infty} x(t) = x_0$. This completed the proof.

4.2. Stability of the chronic infection equilibria when $\omega = 0$. This subsection concentrate on the dynamics of model (1) with $\omega = 0$. 

$$\frac{dx}{dt} = \gamma x \left(1 - \frac{x}{K}\right) - \beta xy.$$
\[
\begin{align*}
\frac{du}{dt} &= \sigma \beta xy + \varepsilon sy - \tau u - \mu_2 u, \\
\frac{dy}{dt} &= \tau u + (1 - \varepsilon) sy - pyz - \mu_3 y, \\
\frac{dz}{dt} &= \nu yz - \mu_4 z.
\end{align*}
\]

When \( \omega = 0 \), there is no chronic-infection equilibrium with CTL response, and the backward bifurcation will not occur when \( 0 < R_1 < 1 < R_0 \), \( P_1 \) is the only chronic-infection equilibrium.

**Theorem 4.2.** If \( 0 < R_1 < 1 < R_0 \), then the unique chronic infection equilibrium \( P_1 \) without CTL response of model (9) is global asymptotically stable when \( \omega = 0 \).

**Proof.** We define a Lyapunov function

\[
L_2 = L_2(x, u, y, z) = x - x_1 \ln x + \frac{u - u_1 \ln u}{\sigma} + \frac{(\tau + \mu_2)(y - y_1 \ln y)}{\sigma \tau} + \frac{(\tau + \mu_2)p yz}{\sigma \nu}.
\]

Differentiating \( L_2(t) \) along the solutions of model (9), we have

\[
\frac{dL_2}{dt} = x' - \frac{x_1 u'}{x} + \frac{u' - u_1}{u} \ln \frac{u}{u_1} + \frac{(\tau + \mu_2) + \beta x y}{\sigma \tau} y' + \frac{(\tau + \mu_2)p yz}{\sigma \nu} z' - \frac{\beta x y (\tau + \mu_2)(\mu_3 - (1 - \varepsilon)s)}{\sigma \tau} y_1 - \frac{\gamma x_1 y_1}{K}.
\]

Using the equalities \( \beta x_1 y_1 - \frac{\gamma x_1^2}{K} = 0 \) and \( x_1 = \frac{(\tau + \mu_2)(\mu_3 - \tau s - \mu_2(1 - \varepsilon)s)}{\sigma \beta \tau} \) in the expression of \( \frac{dL_2}{dt} \), we have

\[
\frac{dL_2}{dt} = \beta x_1 y_1 - \gamma x_1^2 + \gamma x - \frac{\gamma x_1^2}{K} - \beta x_1 y_1 - \frac{\gamma x_1^2}{K} + \frac{\gamma x_1^2}{K} \frac{x_1}{x} \]

\[
- \beta x y - \frac{(\tau + \mu_2)u - \varepsilon s y u_1}{\sigma} - \frac{(\tau + \mu_2)\tau u - (\tau + \mu_2)(\mu_3 - (1 - \varepsilon)s)y}{\sigma \tau} \]

\[
- \frac{(\tau + \mu_2)p yz}{\sigma \tau} y_1 - \frac{(\tau + \mu_2)p yz}{\sigma \tau} \frac{y_1}{y} - \frac{\beta x y (\tau + \mu_2)(\mu_3 - (1 - \varepsilon)s)}{\sigma \tau} y_1 - \frac{\beta x y_1}{\sigma}.
\]

From model (9), it follows that \( (\tau + \mu_2)u_1 = \frac{(\tau + \mu_2)(\mu_3 - (1 - \varepsilon)s)}{\tau} y_1 = (\sigma \beta x_1 + \varepsilon s)y_1 \), and we have

\[
\frac{dL_2}{dt} = -\gamma x_1 (2 - \frac{x}{x_1} - \frac{x_1}{x}) - \frac{\gamma}{K} (x_1 - x)^2 (1 + \frac{x_1}{x}) + \beta x_1 y_1 - \frac{\beta x_1^2 y_1}{x} \]

\[
- \beta x y \frac{u_1}{u} + 2 \beta x_1 y_1 - \frac{\varepsilon s y_1}{u_1 y} + \frac{2 \varepsilon s y_1}{\sigma u} - \frac{\varepsilon s y_1}{\sigma u_1 y} + \frac{2 \varepsilon s y_1}{\sigma u} - \frac{\varepsilon s y_1}{\sigma y_1}.
\]
Theorem 4.3. If
\[ \tau u, \quad x, \quad L, \quad x \]
where
\[ \delta L, \quad x \]
we obtain
\[ \beta x_1 y_1 (3 - \frac{x}{x} - \frac{x u_1 y_1}{x_1 u_1 y_1}) + \frac{(\tau + \mu_2) y z}{\sigma \tau} \left( \frac{\tau + \mu_2}{\sigma \beta^2 K} + \frac{\mu_3}{\nu} \right) (R_1 - 1) \]
\[ \leq 0 \]
The equality \( \frac{dL_2}{dt} \biggr|_{(9)} = 0 \) holds only if \( x = x_1, u = u_1, y = y_1, z = 0 \). The LaSalle’s invariance principle implies that the chronic-infection equilibrium \( P_1 \) of model (9) is globally asymptotically stable.

\[ \text{Theorem 4.3.} \quad \text{If } 1 < R_1 < R_0 \text{ then unique chronic infection equilibrium } P_2 \text{ with } \text{CTL response of model (9) is globally asymptotically stable when } \omega = 0. \]

**Proof.** Consider a Lyapunov function
\[ L_3 = L_3(x, u, y, z) = x - x_2 ln x + \frac{u - u_2 ln u}{\sigma} + \frac{(\tau + \mu_2) (y - y_2 ln y)}{\sigma} \]
where \( x_2, u_2, y_2, z_2 \) are coordinates of equilibrium \( P_2 \) of model (9). Differentiating \( L_3(t) \) along the trajectories of model (9) leads to
\[ \frac{dL_3}{dt} = x' (1 - \frac{x_2}{x}) + \frac{u'}{(1 - \frac{u_2}{u})} + \frac{(\tau + \mu_2) y'}{(1 - \frac{y_2}{y})} + \frac{(\tau + \mu_2) y z'}{(1 - \frac{y_2}{y})} \]
\[ = (\gamma x - \gamma x^2) - \frac{(\tau + \mu_2) y z}{\sigma^2} y + (\tau + \mu_2) y z \gamma x \]
\[ + \frac{\gamma x_2 x}{K} + \frac{(\tau + \mu_2) y z}{\sigma^2} y + (\tau + \mu_2) y z \gamma x \]
\[ = (\beta x_2 y_2 - \gamma x_2 + \frac{\gamma x_2^2}{K}) = 0, \quad \sigma \beta x_2 = (\tau + \mu_2) \mu_3 - \tau s - \mu_2 (1 - \epsilon) s + (\tau + \mu_2) py z, \]
we obtain
\[ \frac{dL_3}{dt} = (\beta x_2 y_2 - \gamma x_2 + \frac{\gamma x_2^2}{K}) + \frac{(\tau + \mu_2) py z}{\sigma^2} y + \frac{(\tau + \mu_2) py z}{\sigma^2} y \]
\[ - (\beta x y - \frac{(\tau + \mu_2) u - \epsilon y u_2}{\sigma^2} u_2 - (\tau + \mu_2) y z \gamma x + \frac{\gamma x_2 x}{K} + \frac{(\tau + \mu_2) py z}{\sigma^2} y) \]
\[ - (\beta x_2 y_2 - \gamma x_2 + \frac{\gamma x_2^2}{K}) \frac{x_2}{x} \]
The equalities \( \tau u_2 = py z y_2 + \mu_3 y_2 - (1 - \epsilon) sy_2 \) and \( (\tau + \mu_2) u_2 = \sigma \beta x_2 y_2 + \epsilon y_2 \) yield
\[ \frac{dL_3}{dt} = \beta x_2 y_2 - \gamma x_2 + \frac{\gamma x_2^2}{K} + \gamma x - \frac{\gamma x_2^2}{K} - \beta x_2 y_2 - \gamma x_2 + \frac{\gamma x_2^2}{K} \frac{x_2}{x} - \gamma x \]
\[ - \frac{\epsilon y u_2}{\sigma u_2 y} + 2 \beta x_2 y_2 + \frac{2 \epsilon y u_2}{\sigma} + \frac{(\tau + \mu_2) py z}{\sigma^2} y + \frac{(\tau + \mu_2) py z}{\sigma^2} y \]
by Asquith and Bangham[1], Wodarz and Bangham[21], Lim and Maini[28], 
we consider those parameter values which have been estimated in studies of HTLV-I
The characteristic equation of the linearized system of model (1) at

\[ \lambda - \nu y_1 + \mu_4 (\lambda^3 + (\tau + \mu_2 + \mu_3 - (1 - \epsilon)s - a)\lambda^2 - \\
(\tau a + \mu_2 a + \mu_3 a - (1 - \epsilon)s a) \lambda + \frac{\sigma \beta^2 \tau a y_1}{(1 + \omega x_1)^3} ) = 0 \]  
(10)

where, \( a = \gamma - \frac{2 \gamma x_1}{k} - \frac{\beta y_1}{(1 + \omega x_1)^2} \). From the expression, we can calculate that 
\( \lambda = \nu y_1 - \mu_4 \), which is equivalent to \( R_1 > 1 \), so there are at least one positive 
eigenvalue when \( R_1 > 1 \). This completed the proof. \( \square \)

As presented in Theorem 3.1 and Fig.3, when parameters vary, model (1) may change from having no chronic equilibrium with CTL response to have two equilibria. Since the complexity of model (1) with thirteen parameters, Here, we use a vector \( P \) which includes twelve parameters, \( P = (\gamma, k, \beta, \omega, \sigma, \epsilon, s, \tau, \mu_2, p, \mu_3, \mu_4) \), and we consider those parameter values which have been estimated in studies of HTLV-I by Asquith and Bangham[1], Wodarz and Bangham[21], Lim and Maini[28], \( P = (0.05, 500, 0.0009, 0.05, 0.09, 0.9, 0.09, 0.03, 0.03, 0.1, 0.05, 0.2) \). Next, we provide the results as \( \nu \) varying under estimated parameters \( P \). Define \( \nu_0 = \frac{4 \mu_4 \beta K \omega}{\gamma (\omega K + 1)^2} \), \( \nu_1 = \mu_4 / y_1 \). From the previous analysis, we obtain \( \nu = \nu_0 \) is equivalent to \( m = 0 \), \( \nu = \nu_1 \) is equivalent to \( R_1 = 1 \). \( \square \)

Theorem 4.5. With given \( P \):
When \( \nu_0 < \nu < \nu_1 \), \( P_1 \) is locally asymptotically stable, and \( P_2^* \) is unstable.
When \( \nu > \nu_0 \), \( P_2 \) is locally asymptotically stable.

Proof. First, let’s submit \( P \) into (10), we can get four eigenvalues of the linearized system of model at \( P_1 \), \( \nu y_1 - \mu_4 \), 0.1011, -0.0002+0.0038 i, -0.0002-0.0038 i. This establishes the locally stability at \( P_1 \). The characteristic equation of the linearized system of model (1) at chronic infection equilibrium with immune response is 

\[ \lambda^3 + (\tau + \mu_2 + \mu_3 - (1 - \epsilon)s - a)\lambda^3 + (\tau a + \mu_2 a + \mu_3 a - (1 - \epsilon)s a + p y z) \lambda^2 + (a p y z + \tau p y z + \mu_2 p y z + \frac{\sigma \beta^2 \tau a y_1}{(1 + \omega x_1)^3}) \lambda - a (\tau + \mu_2) p y z = 0 \]  
(11)
where, \( a = \gamma - \frac{2\gamma x}{k} - \frac{\beta y}{(1 + \omega x)^2} \). From the expression and \( P \), we know \( x_2 = 200 + \sqrt{90000 - \frac{180}{\nu}} \), \( x_2^* = 200 - \sqrt{90000 - \frac{180}{\nu}} \), \( \nu_0 = 0.0002 \), and \( \nu_1 = 0.00033 \).

When we submit \( x_2^* \) and \( P \) into \( a \), we get:

\[
a = 0.01 + 0.0002200 \sqrt{90000 - \frac{180}{\nu}} - \frac{1.8}{180000\nu - 180 - 600\sqrt{90000\nu^2 - 180\nu}} > 0.01 - \frac{18000\nu - 180 - 600\sqrt{90000\nu^2 - 180\nu}}{1.8} > 0.01 - \frac{180000 \times 0.0002 - 180 - 600\sqrt{90000 \times 0.00033^2 - 180 \times 0.00033}}{1.8} > 0
\]

Next, by submitting \( P_2 \) and \( P \) into (11), as \( \nu \) varying, the eigenvalues of characteristic equation at \( P_2 \) is changing, the results is shown in Fig.4. This established

\[\text{Figure 4.} \text{ Eigenvalues of } P_2 \text{ when } \nu > \nu_0 \text{ with estimated parameters}\]

the theorem.

5. **Numerical simulation.** In this section, we use numerical simulations to demonstrate the dynamics of model (1). All the simulations are done using ODE45 by Matlab.

In Fig.5, parameter values are \( \sigma = 0.1, \beta = 0.005, \mu_2 = 0.05, \mu_3 = 0.05, \mu_4 = 0.2, K = 1000, p = 0.2, s = 0.09, \varepsilon = 0.9, \tau = 0.03, \omega = 0.05, \gamma = 0.05, \nu = 0.03 \). All the solutions converges to the infection-free equilibrium \( P_0 \), when \( R_0 < 1 \). Fig.6 and Fig.7 show the solutions for \( \nu = 0.0023 \) and \( \nu = 0.32 \), respectively. The parameters are \( \sigma = 0.1, \beta = 0.005, \mu_2 = 0.03, \mu_3 = 0.05, \mu_4 = 0.2, K = 1000, p = 0.2, s = 0.09, \varepsilon = 0.9, \tau = 0.03, \omega = 0.03, \gamma = 0.05 \). For Fig.6, \( \nu = 0.0023, R_1 = 0.9746, \) and \( R_0 = 1.0650 \), the simulation results exhibit the periodic solutions. Noted that the
vertical coordinates is in the logarithm scale. The observation is consistent with the finding by Wodarz, Nowak, and Bangham [21]. For Fig.7, $\nu = 0.32$, $R_1 = 1.1411$, and $R_0 = 1.1513$, the figure shows that all the solution converges to the chronic-infection equilibrium $P_2$.

Experimental observations suggests the HTLV-I can persist in human beings through horizontal and vertical transmission routes. Both the proviral load and the proportion of infected cells that express Tax are the risk factors for the development of HAM/TSP. At the chronic-infection equilibrium with CTL response, we let $v^* = u_2 + y_2$ be the viral load, $PL = \frac{u_2 + y_2}{x_2 + u_2 + y_2}$ be the proviral load, and $PPL = \frac{y_2}{u_2 + y_2}$ be the proportion of infected cells that express Tax. Fig.8 (a) and (b) illustrate that both the $\beta$ and $s$ contribute significantly to the viral load. The rate, $\tau$, of the spontaneous expression of the HTLV-I express Tax also has dramatically effect on PL and PPL. From Fig.8 (c) we observe that the proviral load declines with the $\tau$ increase. The feature is consistent with the recent experimental observations by Melamed et al.[33], who found that there was a significant negative correlation between the abundance of the infected cells (quantified by PL) and the proportion of the respective clone that spontaneously expresses the provirus (quantified by $\tau$) in HAM/TSP patients. In Fig.8 (d), the PPL increases with the increasing $\tau$. The virus-host reaction between Tax expression and CTL response play an important role on the individuals proviral load. In Fig.8, we use the following set of parameters: $\sigma = 0.1$, $\mu_2 = 0.03$, $\mu_3 = 0.05$, $\mu_4 = 0.2$, $K = 1000$, $p = 0.2$, $\varepsilon = 0.9$, $\omega = 0.03$, $\gamma = 0.05$, $\nu = 0.5$.

Fig.9 shows that the CTL response plays a critical role on the individuals’ proviral load and antigen expression. When an infected individuals is in chronic infection
Figure 6. Periodic solutions when $R_1 < 1 < R_0$ with $\nu \in (\nu_0, \nu_1)$

Figure 7. A typical solution converges to $P_2$ when $R_1 > 1$ with $\nu > \nu_1$
state, a weaker rate of CTL lysis results in a higher proportion antigen expression in infected cells which influence the risk of HAM/TSP. The parameter values in Fig. 9 are \( \sigma = 0.1, \beta = 0.04, \mu_2 = 0.03, \mu_3 = 0.05, \mu_4 = 0.2, K = 1000, p = 0.2, s = 0.09, \varepsilon = 0.9, \tau = 0.03, \omega = 0.05, \gamma = 0.05. \)

**Figure 8.** Effect of \( \beta, s, \tau \) on the equilibrium viral load.

**Figure 9.** Effect of \( \nu \) on the equilibrium viral load.
6. **Concluding remarks.** We use a four-dimensional mathematical model including mitotic proliferation, Tax expression, and the CTL response to investigate the persistence of HTLV-I in vivo. We take rigorous analysis and get the sufficient conditions for the existence and stability of the model. Numerical simulations are also done to demonstrate the dynamics of the model. Although the model is simple, the simulation results are consistent with the recent experimental observations [1, 33].

From the simulation results of Fig.7, an interesting behavior occurs, two periodic solutions have been shown to co-exist for the same parameters with different initial viral dosages. The two solutions differ in both the period and amplitude. Our observations show that the final outcome of dynamic struggle between viral persistence and host immunity during the chronic phase depends on the initial viral dosages in the individuals with same levels of CTL responsiveness. Some experimental findings by Wodarz, Nowak, and Bangham [1] can be explained by the observations, they have observed such fluctuations during treatment of a HAM/TSP patient with drugs.

As shown in Fig.8(a) and Fig.8(b), both the horizontal and vertical transmission routes contribute significantly to the viral load. As the rate of the HTLV-I express Tax is increased, the proviral load declines. The observations are consistent with the recent experimental observations by Melamed et al. [33], who found that there was a negative correlation between the abundance of the infected cells (quantified by PL) and the proportion of the respective clone that spontaneously expresses the provirus (quantified by $\tau$) in HAM/TSP patients. As previous literatures mentioned [20], infected cells from HAM/TSP patients have a higher proportion expressing Tax than those from asymptotically carriers. Fig.8(d) shown that the increase of $\tau$ results in higher proportion of Tax-expressing cells in infected $CD^4^+T$ cells.

CTL inhibit the pathway of viral persistence, and thus have a large impact on proviral load. Asquith and Bangham [1] observed that increase in proviral load conferred by Tax expression was higher in individuals with a weaker CTL response than in individuals with a stronger CTL response. Fig.9 keep consistent with the observation.

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