COMPLETE DYNAMICAL ANALYSIS FOR A NONLINEAR HTLV-I INFECTION MODEL WITH DISTRIBUTED DELAY, CTL RESPONSE AND IMMUNE IMPAIRMENT

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ABSTRACT. It is well known that CTL (cytotoxic T lymphocyte) immune response could be broadly classified into lytic and nonlytic components, nonlinear functions can better reproduce saturated effects in the interaction processes between cell and viral populations, and distributed intracellular delay can realistically reflect the stochastic element in the delay effects. For these reasons, we develop an HTLV-I (Human T-cell leukemia virus type I) infection model with nonlinear lytic and nonlytic CTL immune responses, nonlinear incidence rate, distributed intracellular delay and immune impairment. Through conducting complete analysis, it is revealed that all these factors influence the concentration level of infected T-cells at the chronic-infection equilibrium, whereas intracellular distributed delay and nonlinear incidence rate may change the expression of the basic reproduction number $R_0$ in the context where the model proposed still preserves the threshold dynamics. Our analysis results obtained may improve several existing works by comparison. We also perform global sensitivity analysis for $R_0$ in order to explore the effective strategies of lowering the concentration level of infected T-cells.

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1. Introduction. Ecologically, the nonlinear interaction process that virus infections occur within vertebrate host, is essentially a process that virus population survive, evolve and struggle in the habitat-host tissue. Therefore, the proliferation of a virus within an infected host can be likened to a natural ecosystem with resources, predators (specific immunocytes), and prey (immunocytes prey on viruses or infected cells, and viruses prey on healthy cells) [18]. Within-host population dynamics of viral replication and immune responses can shed light on both qualitative and quantitative understanding of the immune response to virus in vivo (e.g., seeing [27]). A normal host immune response to a virus, comprised of antibodies, cytokines, natural killers cells and T cells, is broadly subdivided into lytic and non-lytic components. However, CTL (Cytotoxic T lymphocytes) immune response would be readily recognized as the main host immune factor in antiviral defense [28] in most virus infections such as HTLV-I, HIV, HBV, in which lytic CTL (L-CTL) response plays a critical part in killing infected cells via inducing apoptosis, while non-lytic CTL (NL-CTL) response inhibits viral replication through soluble mediators.

As the first retrovirus identified, HTLV-I is responsible for several diseases such as HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T-cell leukemia (ATL), and infects about 10-25 million people worldwide through blood transfusion, sexual contact, and breast feeding, mainly endemic in subtropical areas like Japan, South America, the Caribbean and Central Africa [8]. Within an infected host, HTLV-I predominantly targets CD4$^+$ T cells remarkably by cell-to-cell contact [3]. And it is a single-stranded RNA virus with reverse transcriptase (RT) activity giving rise to a DNA copy of viral genome that is then integrated into the DNA of host genome. Subsequently, the viral DNA succeeds in latently persisting within a T cell such that a chronic infection may last life-long [31]. Recent research has found that the high level of CTLs and their cytotoxicity may be the reason for the inflammatory responses in HAM/TSP patients [14]. Several mathematical models [2, 27, 37] have been developed to explore the complex interactions between persistent HTLV-1 and antiviral immune response. Wodarz et al. [37] proposed a nonlinear viral model with both L-CTL and NL-CTL responses to describe the virus-immune dynamics among susceptible host cells, a virus population, and immune responses and drawn a conclusion that resolution of the disease necessitates a collaboration between lytic and non-lytic effector mechanisms particularly if the virus replicates at a fast rate, and thus the pattern of the immune response is of significant interest. Recently, based on the works in [2, 37], Nakata et al. [26] performed the global stability analysis for an HTLV-I infection model with intracellular latent delay and CTL response, governed by the following delay differential equations (DDEs)

\[
\begin{align*}
    x'(t) &= \lambda - dx(t) - \frac{\beta x(t)y(t)}{1 + q_0 z(t)}, \\
    y'(t) &= \frac{\beta e^{-\rho \tau} x(t-\tau)y(t-\tau)}{1 + q_0 z(t-\tau)} - ay(t) - p_0 y(t)z(t), \\
    z'(t) &= cy(t) - bz(t),
\end{align*}
\]

where $x(t)$, $y(t)$ and $z(t)$ are the concentrations of healthy T-cells, infected T-cells and the effector CTLs at time $t$, respectively. Note that model (1) incorporates CTL responses. In particular, L-CTL results in an increase by $p_0 y(t)z(t)$ in the death rate of infected T-cells, where $p_0$ denotes the strength of L-CTL response, whereas NL-CTL leads to a decrease by $\beta x(t)y(t)/(1+q_0 z(t))$ in the viral replication
Table 1. Biological description of parameters in models (1) and (3)

| Para. (Unit) | Description | Value | Range | Ref. |
|--------------|-------------|-------|-------|------|
| $\lambda$ ($\mu l^{-1}d^{-1}$) | The recruitment rate of healthy T-cells | 105 | [10,200] | [20, 21, 22, 34, 37] |
| $d$ ($d^{-1}$) | The death rate of healthy T-cells | 0.11 | [0.01,0.2] | [20, 21, 22, 34, 37] |
| $\beta$ ($\mu l^{-1}d^{-1}$) | Viral infectivity rate | 0.026 | [0.001,0.05] | [20, 21, 22, 34, 37] |
| $\rho$ ($\mu l^{-1}d^{-1}$) | The death rate of infected not productive cells | 0.11 | [0.01,0.2] | [36] |
| $\tau$ ($d$) | The intracellular latent delay | 5 | [0.10] | [1] |
| $a$ ($d^{-1}$) | The sum of the released rate of viral particles and the death rate of infected T-cells | 1.005 | [0.01,0.2] | [20, 21, 22, 34, 37] |
| $q_0$ ($\mu l^{-1}d^{-1}$) | The efficacy of NL-CTL response | 0.5 | [0.1] | [34, 37] |
| $p_0$ ($\mu l^{-1}d^{-1}$) | The strength of L-CTL response | 0.1 | [0.1] | [20, 21, 22, 34, 37] |
| $c$ ($\mu l^{-1}d^{-1}$) | The proliferation rate of CTLs | 0.2 | [0.1] | [20, 21, 22, 34, 37] |
| $b$ ($d^{-1}$) | The decay rate of CTLs | 0.4 | [0.1] | [20, 21, 22, 34, 37] |
| $\sigma$ (-) | A fraction of cells newly infected by contacts that survive the antibody immune response | 0.5 | [0.1] | [9, 22] |
| $\alpha_1$ ($\mu l$) | The inhibitory rate from healthy T-cells | 0.003 | [0.1] | Estimated |
| $\alpha_2$ ($\mu l$) | The inhibitory rate from infected T-cells | 0.005 | [0.1] | Estimated |
| $\omega$ ($\mu l$) | The inhibitory rate from NL-CTL response | 10 | [0.10] | [32] |
| $m$ ($\mu l^{-1}d^{-1}$) | Immune impairment rate of virus | 0.01 | [0.1] | [1] |

rate, where $q_0$ represents the efficacy of NL-CTL response. $\tau$ standing for the latency of HTLV-I within a T cell, during which the cell is infected but has not yet begun producing virus, is modeled as the intracellular delay. And $e^{-\rho \tau}$ measures the survival probability of infected cells, where $\rho$, the death rate of infected not productive cells. The sum of the rate for free viral particles released from infected T-cells and the death rate of infected T-cells due to viral cytopathicity (see, e.g., [13]) is denoted by $a$, obviously, $\rho < a$ holds. The detailed biological descriptions for the parameters in model (1) are presented in the upper part of Table 1.

Most recently, Wang et al. [36] developed an HTLV-I infection model with both intracellular delay $\tau$ and CTL response delay $\tau_1$. In the case of $\tau \geq 0$ and $\tau_1 = 0$, when the basic reproduction number $R_0 > 1$ the global attractivity for the chronic-infected equilibrium $E^*(x^*, y^*, z^*)$ of model (1) was achieved using two different Lyapunov functionals by [26] and [36], respectively. Moreover, Wang et al. [36] established the local stability and globally asymptotical stability of $E^*$ of the model.
(1) under the conditions that $R_0 > 1$ and
\[ \left( \frac{\lambda}{\tau} \right)^2 + b^2 - 2bpz^* > 0. \] (2)

In the case of $\tau = 0$ and $\tau_1 > 0$, the model in [36] experiences a destabilization of $E^*$ leading to Hopf bifurcation and periodic solutions. Thus, the CTL response delay $\tau_1$ essentially creates the Hopf bifurcation.

Different from the HTLV-I infection model described by ordinary differential equations (ODEs) in [31], the latency of HTLV-I was modeled by an intracellular delay $\tau$ instead of an explicit class of latently infected cells. Another more realistic way of modeling the latency is to utilize distributed intracellular delay (see, e.g., [5, 17, 29, 33]), which can reflect the stochastic element in delayed effects from the biological point of view, and both the ODE and DDE versions can be included by choosing different distributions from the mathematical point of view. In particular, $1/\rho$ measures the average life time of infected T-cells before becoming proliferative, and then the infinite distributed delay with kernel function $k(\tau) = e^{-\rho\tau}h(\tau)$ is the probability that a healthy T-cell contacted by infected cells at time $t-\tau$ survived $\tau$ time units and becomes infected cell at time $t$. The distribution function $h(\tau)$, accounting for the variance that infected cells become productively infected (see, e.g., [17, 33]), is assumed to satisfy $h(\tau) \geq 0$ for $\tau \geq 0$, and $\int_0^\infty h(\tau)d\tau = 1$ based on biological meaning. Consequently, $k(\tau) > 0$ holds for $\tau > 0$, and

\[ 0 < \kappa := \int_0^\infty k(\tau)d\tau \leq 1. \]

Meanwhile, some nonlinear functions can better reproduce saturated effects in the nonlinear virus-immune interaction processes than the simple bilinear cases [6, 7, 15, 19]. For example, De Boer [6] pointed that the bilinear rates cannot model several immune responses to together curb a chronic infection. There have been experiments reported [7] that the microparasitic infection rate is an increasing function (e.g., sigmoidal in shape) with the parasite dose. One of the purposes of the study is to explore the nonlinear saturated effects on the dynamics of the persistent HTLV-I infection. What’s more, the assumption in model (1) may not correspond to the biological reality that the presence of the antigen only stimulate immune response. In fact, the host immunity could be suppressed or even destroyed by some pathogens especially in the case of excessive load of pathogens, so the antigen can also impair immunity [35]. For these reasons, motivated by the works of [2, 35, 36, 37], our main purposes of this paper is concerned with the global dynamics of an HTLV-I infection model with intracellular distributed delay, nonlinear incidence rate, nonlinear L-CTL and NL-CTL responses and immune impairment, which reads

\[
\begin{align*}
x' &= \lambda - dx - g(x, y)q(z), \\
y' &= \sigma \int_0^{\infty} k(\tau)g(x_\tau, y_\tau)q(z_\tau)d\tau - ay - yp(z), \\
z' &= cy - bz - myz,
\end{align*}
\] (3)

with the nonnegative initial condition

\[ x(\vartheta) = u_1(\vartheta) \geq 0, \quad y(\vartheta) = u_2(\vartheta) \geq 0, \quad z(\vartheta) = u_3(\vartheta) \geq 0, \quad \text{for } \vartheta \in \mathbb{R}_{\leq 0} := (-\infty, 0], \] (4)

where for simplifying the presentation, denote $(u_1, u_2, u_3) = u := u(t), \quad u_\tau := u(t-\tau)$,

\[ g(x, y) := \frac{\beta xy}{(1 + \alpha_1 x)(1 + \alpha_2 y)}, \quad q(z) := \frac{1}{1 + q_0 z}, \quad p(z) := \frac{p_0 z}{1 + \omega z}. \] (5)
Here, the Crowley-Martin functional analysis $g(x, y)$ [4], which is a monotonic and concave function both with respect to $x$ and $y$ for $\alpha_1, \alpha_2 > 0$, can reduce to Holling type I or II functional responses for $\alpha_1, \alpha_2 \geq 0$. The parameter $\sigma \in [0, 1]$ is a fraction of cells newly infected through contacts that survive the antibody immune response [9, 22], $m$ is immune impairment rate of virus, and $\omega$ measures the inhibitory rate from NL-CTL in the saturated function $p(z)$ [38]. And the same parameters in (3) with (1) have the same meanings, and the biological meanings of the remaining parameters are also described in the lower part of Table 1.

The general distribution function considered here allows us to include several special forms of intracellular delays existing in the literatures (e.g., [1, 5, 22, 25, 26, 36]). More specifically, when the distribution $h(r) = \delta(r - \tau)$ is a delta function on $\tau \geq 0$, where $\delta(\cdot)$ stands for the Dirac delta function, model (3) becomes a DDE system with a discrete delay for $\tau > 0$, and for $\tau = 0$ it reduces to the DDE model (1) studied in [26, 36] if $\alpha_1 = \alpha_2 = \omega = m = 0$ and $\sigma = 1$. Further, we assume that $\tau = 0$, model (3) reduces to an ODE version, and its special cases has been widely studied in literature (see [34] and references therein). Recently, by the Lyapunov function methods, Vargas-De-Leon [32] reached the global threshold stability of an ODE viral model with $g(x, y) = \beta xy$ and $m = 0$, a constant production rate of CTLs export and general nonlinear L-CTL and NL-CTL responses. It should be pointed out that the construction of the Lyapunov functional utilized in this contribution is motivated by [32] and considerably different from the forms in [26] and [36]. In our work, through complete analysis for the local stability of $E^*$ and uniform persistence of the model one achieves its globally asymptotical stability for $\mathcal{R}_0 > 1$, improving the results on the local and global stability of $E^*$ (see Theorems 3.3 and 3.5 in [36]) in spite of the strong nonlinearity of model (3).

The basic structure of this paper is as follows. The next section presents some preliminary results, including the well-posedness of model (3), the useful properties of nonlinear functions $g(x, y)$, $p(z)$ and $q(z)$, and the existence of equilibria. Sections 3 and 4 respectively establish the local stability, uniform persistence and global stability, which reveal that model (3) preserves the threshold stability. Finally, we further perform global sensitivity analysis for the basic reproduction number $\mathcal{R}_0$ and discuss the conclusions obtained in this paper in Section 5.

2. Preliminaries. To begin with, we shall address the well-posedness of model (3) consisting of integro-differential equations with infinite distributed delay. From viewpoint of both biology and math we consider model (3) with initial condition (4) in the appropriate phase space accounting for fading memory as in [11, 12]. To this end, assign $I: \mathbb{R}_{\leq 0} \rightarrow [1, +\infty)$ to be a continuous nondecreasing function satisfying: (I1) $l(0) = 1$; (I2) $l(s + \mu)/l(s) \rightarrow 1$ uniformly for $\mathbb{R}_{<0}$ as $\mu \rightarrow 0^+$; (I3) $l(s) \rightarrow +\infty$ as $s \rightarrow -\infty$. Especially, the exponential fading memory, $l(s) = e^{-\Delta s}$ with $\Delta \in (0, \rho/2)$, satisfies (I1)-(I3) and is thus chosen to define the following Banach space of continuous functions:

$$
C_\Delta = \{ u \in C(\mathbb{R}_{\leq 0}, \mathbb{R}) | u(s)e^{\Delta s} \text{ is bounded and uniformly continuous for } s \in \mathbb{R}_{\leq 0} \},
$$

equipped with the usual supremum norm $\|u\| = \sup_{s \leq 0} \{|u(s)e^{\Delta s}\} < +\infty$.

Note that the variables $x$, $y$, $z$ represent the relevant concentrations, so one only takes into consideration of nonnegative initial functions. The nonnegative cone of $C_\Delta$ is denoted by $C_\Delta^+ = C_\Delta(\mathbb{R}_{\leq 0}, \mathbb{R}^+)$, where $\mathbb{R}^+ := [0, +\infty)$. Let us define $u_\tau \in C_\Delta$ as $u_\tau(s) = u(t + s)$, $s \in \mathbb{R}_{\leq 0}$. Then applying the fundamental theory of functional
differential equations with infinitely distributed delays [11, 12] to model (3) with
for any nonnegative initial condition
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\( \frac{dx}{dt} = g(x, y) \), \( \frac{dy}{dt} = q(x, y) \)

we can check out the existence, uniqueness and continuity of the solution \((x_t, y_t, z_t) \in X^+ := C_x^+ \times C_y^+ \times C_\sigma^+\).

Moreover, through a similar proof of Theorem 2.1 in [36] with some minor modifications, the nonnegativity and ultimately boundedness of the solutions in \( X \) can be obtained, and we omitted it here. Accordingly, the following feasible region is positively invariant with respect to model (3)

\[ \Gamma = \left\{ (\vartheta) \in C_\sigma^3 : l_1(\vartheta) \leq \frac{\lambda}{d}, \quad l_2(\vartheta) \leq \frac{\sigma_\kappa \lambda}{\min\{\sigma d, a\}}, \quad l_3(\vartheta) \leq \frac{\sigma_\kappa \lambda}{\min\{\sigma d, a\}} \right\}, \]

so model (3) is well posed. Additionally, the interior of \( \Gamma \) is denoted by \( \hat{\Gamma} \).

Before carrying on further analysis, we refine several useful properties on the continuously differentiable functions \( g(x, y) \), \( p(z) \) and \( q(z) \) in (5) as follows:

\((G_1)\) For \( x, y > 0 \), \( g(x, y) \), \( g_x(x, y) \), \( g_y(x, y) \), \( g_y(x, 0) \), \( g_y(x, 0) > 0 \), and \( g(0, y) = g(x, 0) = g_x(x, 0) = 0 \);

\((G_2)\) For \( x, y \geq 0 \), \( g_y(x, y) y \leq g(x, y) \leq g_y(x, 0) y \);

\((P_1)\) For \( z > 0 \), \( p(z) \), \( p'(z) > 0 \) and \( p(0) = 0 \);

\((P_2)\) For \( z \geq 0 \), \( p'(z) z \leq p(z) \leq p'(0) z \);

\((Q_1)\) For \( z > 0 \), \( q(z) \), \( q'(z) < 0 \) and \( q(0) = 1 \);

\((Q_2)\) For \( z \geq 0 \), \( q'(z) z \geq q(z) \geq q'(0) z \),

where the subscripts represent the partial derivatives for the indicated variables.

In the sequel, we analyze the existence of equilibria for model (3). Obviously, model (3) always admits an infection-free equilibrium \( E^0 = (x^0, 0, 0) \), where \( x^0 = \lambda/d \). We define a key quantity

\[ \mathcal{R}_0 = \frac{\sigma_\kappa \lambda x^0}{a}, \quad (6) \]

so-called the basic reproduction number of model (3). Moreover, its positive equilibrium is determined by the equations

\[ \begin{cases} 0 = \lambda - dx - g(x, y) q(z), \\ 0 = \sigma_\kappa g(x, y) q(z) - ay - yp(z), \\ 0 = cy - bz - myz. \end{cases} \]

Combining its first and second equations results in

\[ x = \frac{P(y)}{\sigma_\kappa d}, \quad (8) \]

where

\[ P(y) := -yp(z) - ay + \sigma_\kappa \lambda. \]

From the third equation we directly arrive at

\[ z = \frac{cy}{my + b}. \]

Accordingly, it is true that \( dz/dy > 0 \). It is easy to ascertain that \( x > 0 \) iff \( 0 < y < \hat{y} \), where \( \hat{y} \) is the unique positive solution of the equation \( P(y) = 0 \), since \( P'(y) < 0 \), \( P(0^+) = \sigma_\kappa \lambda > 0 \) and \( P(+\infty) = -\infty \) follow from \((P_1)\). Accordingly, \( dx/dy < 0 \) holds for \( y \in (0, \hat{y}) \).
Now, by the second equation of (6) we only need to discuss on the existence of the positive solution for the equation

\[ \Psi(y) := \frac{\sigma_0 g(x, y) q(y)}{y} - a - p(z) = 0, \text{ for } z \in (0, \hat{y}). \]  

(11)

Together with \((G_1), (G_2), (P_1), (Q_1)\), one thus derives that

\[ \Psi'(y) = \alpha \kappa \left[ \frac{q(y)}{y} \frac{dx}{dy} + q(y) \frac{\partial}{\partial y} \left( \frac{g(x, y)}{y} \right) + \frac{g(x, y)}{y} \frac{d\hat{z}}{dy} \right] - p'(z) \frac{dz}{dy} < 0. \]  

(12)

Namely, the function \(\Psi(y)\) monotonically decreases in \((0, \hat{y})\). Applying L'Hospital's rule further yields that \(\Psi(0^+) = \sigma_0 g_0(x^0, 0)(1 - 1/\mathcal{R}_0) > 0\) if \(\mathcal{R}_0 > 1\). Note that \(\Psi(\hat{y}) = -a - p(c\hat{y} / (m\hat{y} + b)) < 0\). This suggests that \(\Psi = 0\) admits a unique positive solution \(y^* \in (0, \hat{y})\) when \(\mathcal{R}_0 > 1\), whereas it has no real solution if \(\mathcal{R}_0 \leq 1\).

Furthermore, one reaches that model (3) has a unique chronic-infection equilibrium \(E^* = (x^*, y^*, z^*)\), from (8) and (10).

**Theorem 2.1.** Model (3) always admits an infection-free equilibrium \(E_0 = (x^0, 0, 0)\), and the unique chronic-infection equilibrium \(E^* = (x^*, y^*, z^*)\) appears when \(\mathcal{R}_0 > 1\).

3. Local stability. Now we are in the position in addressing the local stability of the equilibrium \(E^* = (x^*, y^*, z^*)\) (i.e., \(E^0\) or \(E^*\)). For ease of notation, denotes \(f(x, y, z) := g(x, y) q(y)\). Similar to [36], linearizing model (3) at \(E^*\) reduces to the characteristic equation governed by

\[
\begin{vmatrix}
-(d + f^*_y) - \xi & -f^*_z \kappa(\xi) & -f^*_z \\
\sigma f^*_y \kappa(\xi) - (a + p(z^*)) - \xi & 0 & \sigma f^*_y \kappa(\xi) - y^* p'(z^*) \\
0 & c - m z^* & - (b + m y^*) - \xi
\end{vmatrix} = 0,
\]  

(13)

where the asterisk denotes the functions evaluated at \(E^*\), and

\[ \kappa(\xi) := \int_0^\infty e^{-(\eta + \tau) + \kappa(\tau)} d\tau. \]

**Theorem 3.1.** For model (3), \(E^0\) is locally stable if \(\mathcal{R}_0 < 1\). And if \(\mathcal{R}_0 > 1\), it becomes unstable but \(E^*\) is locally stable.

**Proof.** From (13), the characteristic equation at \(E^0\) is calculated as

\[
(\xi + b)(\xi + d) \kappa(\xi) = 0,
\]  

(14)

where \(K(\xi) := \xi + a - \sigma \kappa(\xi) g_0(x^0, 0) = 0\) in view of \(p(z^0) = 0\) and \(q(z^0) = 1\).

Obviously, \(\xi_1 = -b < 0\), \(\xi_2 = -d < 0\), and the remaining eigenvalues satisfy \(\kappa(\xi) = 0\). Assume by contradiction that its any solution \(\xi\) of \(\kappa(\xi) = 0\) satisfies \(Re \xi \geq 0\), and then

\[ a < |\xi + a| = \sigma g_0(x^0, 0)|K(\xi)| \leq \sigma g_0(x^0, 0) < a, \text{ if } \mathcal{R}_0 < 1. \]  

(15)

Thus a contradiction occurs in (14). This implies that all eigenvalue of the equation \(K(\xi) = 0\) possess negative real part, so \(E^0\) is locally stable if \(\mathcal{R}_0 < 1\).

In the case that \(\mathcal{R}_0 > 1\). The equation \(K(\xi) = 0\) at least admits a positive solution \(\xi^*\) in view of \(K(0) = a(1 - \mathcal{R}_0) < 0\) and \(\lim_{\xi \to -\infty} K(\xi) = +\infty\). Hence, \(E^0\) becomes unstable. On the other hand, it follows from (13) that the characteristic equation at \(E^*\) reads as

\[
(\xi + d + f^*_z)[(\xi + b + m y^*)(\xi + a + p(z^*)) + y^* p'(z^*)(c - m z^*)] - \sigma f^*_y \kappa(\xi)(\xi + d) = \sigma f^*_y \kappa(\xi)(\xi + d)(\xi + b + m y^*).
\]  

(16)
One claims that all eigenvalues of (16) satisfy \( \text{Re}\xi < 0 \). Otherwise, there exists one eigenvalue \( \xi \) with \( \text{Re}\xi \geq 0 \). However, these facts that \( c - mz^* = bz^*/y^* \), \( f_2^* \geq 0 \), \( 0 \leq f_2^* = g(z^*g_y(x^*, y^*) \leq g(x^*, y^*)g(z^*)/y^* \), \( f_2^* < 0 \) and the second equation of (6), are such that

\[
a + p(z^*) < \left| \left( 1 + f_2^* \right) \left( \xi + a + p(z^*) + \frac{bz^*p'(z^*)}{\xi + b + my^*} \right) - \frac{A(z^*)}{y^*} \right|
\]

leading to a contradiction in (17), and it turns out that our claim is true. \( \square \)

4. Global stability.

**Theorem 4.1.** If \( \mathcal{R}_0 \leq 1 \), \( E^0 \) is global asymptotically stable in \( \Gamma \).

**Proof.** Construct a Lyapunov functional as follows:

\[
V_1 = x - x^0 - \int_0^\tau \frac{g(x^0, y)}{g(\theta, y)} d\theta + \frac{1}{\sigma} \int_0^\tau \frac{g(x^0, y)}{y^0} \left( z - \int_0^\tau q(\theta) d\theta \right) + \frac{1}{\sigma} \int_0^\tau p(\theta) d\theta + \frac{1}{\sigma} \int_0^\tau k(\tau) q(z(\theta)) d\theta d\tau.
\]

It is easy to ascertain that \( V_1 > 0 \) for each positive solution of model (3) except for \( E^0 \). Making use of \( \lambda = dx^0 \) and \( g(x, y) \leq g_y(x, 0)y \), we compute the time derivatives of \( V_1 \) along any positive solution of model (3) as follows:

\[
V_1' = dx^0 \left( 1 - \frac{x^0}{x} \right) \left( 1 + \frac{g(x^0, y)}{g(x, y)} \right) - g(x, y)q(z) + g(x, y)q(z) \lim_{y \to 0} \frac{g(x^0, y)}{g(x, y)} + \frac{1}{\sigma} \int_0^\tau k(\tau) g(x, y) q(z(\theta)) d\tau - \frac{a}{\sigma} y - \frac{1}{\sigma} yp(z)
\]

\[
+ g_y(x^0, 0)y - g_y(x^0, 0)yz(1 - q(z)) + \frac{1}{\sigma} yp(z) - \frac{1}{\sigma} k(\tau) (b + my) q(z(\theta)) d\tau
\]

\[
= dx^0 \left( 1 - \frac{x^0}{x} \right) \left( 1 - \frac{g_y(x^0, 0)}{g_y(x, 0)} \right) - \frac{z(b + my)}{\sigma} \frac{[\sigma k g_y(x, 0) (1 - q(z)) + p(z)]}{\sigma k}
\]

In the last equality of the above equation, the first term is less than or equal to zero because the function \( g_y(x, 0) \) is an increasing function with respect to \( x > 0 \) thanks to \( g_{yx}(x, 0) > 0 \), so also is the second term due to (P1) and (Q1). Therefore, we immediately see that

\[
V_1' \leq g_y(x^0, 0)y - \frac{a}{\sigma} y = \frac{a g_y}{\sigma} (\mathcal{R}_0 - 1) \leq 0,
\]

with “=” only if \( x = x^0, y = 0, z = 0 \). By the application of LaSalle’s invariance principle [16], any solution of model (3) is attracted to the largest invariant subset of \( \{ V_1 = 0 \} \) in \( \Gamma \), denoted by \( \mathcal{L}_1 \), thus, \( \mathcal{L}_1 = \{ E^0 \} \) since \( \mathcal{L}_1 \) is invariant for (3). Remembering the local stability of \( E^0 \) obtained in Theorem 3.1, one concludes that \( E^0 \) is global asymptotically stable in \( \Gamma \) if \( \mathcal{R}_0 \leq 1 \), proving the desired. \( \square \)

Establishing the global stability of \( E^* \) entails uniform persistence of model (3).
Theorem 4.2. Model (3) is uniformly persistent if $\mathcal{R}_0 > 1$, e.g., there exists a constant $\varepsilon > 0$, independent of initial values, such that
\[
\liminf_{t \to +\infty} \| x(t, \psi), y(t, \psi), z(t, \psi) \| > \varepsilon.
\]

Proof. Since the proof is similar to that of Theorem 4.2 in [17], we only sketch the modifications that $E^0$ is a weak repeller for $X$. Suppose, for contradiction, that there exists a solution $(x, y, z)$ of model (3) tending to $(x^0, 0, 0)$. For any sufficiently small $\varepsilon > 0$, there thus is a $t_0 = t_0(\varepsilon) > 0$ such that
\[
x^0 - \varepsilon < x < x^0 + \varepsilon, \quad y < \varepsilon, \quad z < \varepsilon, \quad \text{for} \ t > t_0. \tag{18}
\]

Since $\mathcal{R}_0 > 1$, there always exists a constant $t_1 > t_0$ such that
\[
\sigma q(\varepsilon)[g_y(x^0 - \varepsilon, 0) - \varepsilon] \int_{0}^{\infty} k(\tau) d\tau - a - p(\varepsilon) > \varepsilon, \quad \text{for} \ t > t_1. \tag{19}
\]

Truncating the integral in (19), we can be ensured by another a constant $t_2 > t_1$ such that
\[
\sigma q(\varepsilon)[g_y(x^0 - \varepsilon, 0) - \varepsilon] \int_{0}^{t_2} k(\tau) d\tau - a - p(\varepsilon) > \varepsilon, \quad \text{for} \ t > t_2. \tag{20}
\]

Considering $0 \leq \tau \leq t_2$, by L’Hospital’s rule, we obtain $\lim_{t \to +\infty} g(x_\tau, y_\tau)/y = g_y(x^0, 0)$. Hence, for the constant $\varepsilon$ given above, there exists a constant $t_3 > t_2$ such that
\[
g(x_\tau, y_\tau) \geq g_y(x^0 - \varepsilon, 0) - \varepsilon, \quad \text{for} \ t > t_3. \tag{21}
\]

It follows from the second equation of model (3) that, for $t > t_3$, one can show
\[
y' \geq y \left( \sigma \int_{0}^{t_2} k(\tau) g(x_\tau, y_\tau) q(z_\tau) d\tau - a - p z \right)
\geq y \left( \sigma q(\varepsilon) \int_{0}^{t_2} k(\tau) g_y(x^0 - \varepsilon, 0) - \varepsilon d\tau - a - p(\varepsilon) \right).
\]

As $t \to +\infty$ we infer that $y \to +\infty$, with a contradiction. The desired holds. \hfill \Box

Theorem 4.3. If $\mathcal{R}_1 > 1$, $E^*$ is globally asymptotically stable in $\tilde{X}$.

Proof. Let us define the Volterra-type function: $\phi(u) = u - 1 - \ln u, u > 0$. It is straightforward to check that $\phi(u) \geq \phi(1) = 0$. To facilitate the narrative, denote
\[
G := g(x, y)q(z), \quad G^* := g(x^*, y^*)q(z^*), \quad G_r := g(x_\tau, y_\tau)q(z_\tau).
\]

Construct a Lyapunov functional: $V_2 = \sum_{i=1}^{5} V_i$, where
\[
V_1 = x - x^* - \int_{x^*}^{x} g(x^*, y^*) d\theta, \quad V_2 = \frac{1}{\sigma K} y^* \phi \left( \frac{y}{y^*} \right),
V_3 = \frac{g(x^*, y^*)}{b z^*} \left( z - z^* - \int_{z^*}^{z} q(\theta) d\theta \right), \quad V_4 = \frac{y^*}{\sigma K b z^*} \int_{z^*}^{z} p(\theta) \left( 1 - p(z^*) \right) d\theta, \quad V_5 = \frac{G^*}{K} \int_{0}^{\infty} k(\tau) \int_{t-\tau}^{t} \phi \left( \frac{G(s)}{G^*} \right) ds d\tau.
\]

It turns out to be $V_2 > 0$ for any positive solution of model (3) except for $E^*$.

Taking advantages of the following equalities
\[
\lambda = dx^* + G^*, \quad a = \frac{\sigma K G^*}{y^*} - p(z^*),
\]
we compute $V'_1$, $V'_2$ along the positive solutions of model (3), respectively, which are rearranged into

$$V'_1 = \left(1 - \frac{g(x^*, y^*)}{g(x, y^*)} \right) \left[ dx^* \left(1 - \frac{x^*}{x} \right) + \frac{G}{G^*} \left(1 - \frac{G}{G^*} \right) \right]$$

$$= dx^* \left(1 - \frac{x^*}{x} \right) \left(1 - \frac{g(x^*, y^*)}{g(x, y^*)} \right) + \frac{G}{G^*} \left(1 - \frac{G}{g(x, y^*)} + \frac{G}{g(x, y^*)q(z^*)} \right),$$

and

$$V'_2 = \frac{1}{\sigma \kappa} \left(1 - \frac{y^*}{y} \right) \left[ \int_0^\infty k(\tau)G_\tau d\tau - \sigma \kappa G^* \frac{y}{y^*} + yp(z^*) - yp(z) \right]$$

$$= \frac{G^*}{\sigma \kappa} \left[ \int_0^\infty k(\tau)G_\tau d\tau - \frac{1}{\kappa} \int_0^\infty k(\tau)G_\tau \frac{y}{G^*} \right]$$

$$+ \frac{y^* p(z)}{\sigma \kappa} \left(\frac{1}{p(z)} \left(1 - \frac{y}{y^*} \right) \right).$$

With the help of

$$b = \frac{(c - mz^*)y^*}{z^*}, \quad (c - mz^*) y^* = bz^*,$$

the time derivatives of $V_3$ and $V_4$ respectively read

$$V'_3 = \frac{G^*}{bz^*} \left(1 - \frac{q(z)}{q(z^*)} \right) \left[ (c - mz^*) y^* \left(\frac{y}{y^*} - \frac{z}{z^*} \right) + myz^* \left(1 - \frac{z}{z^*} \right) \right]$$

$$= \frac{G^*}{\sigma \kappa} \left[ \int_0^\infty k(\tau)G_\tau d\tau - \sigma \kappa G^* \frac{z^*}{y^*} + Gp(z) \right] \left(1 - \frac{z}{z^*} \right),$$

$$V'_4 = \frac{y^* p(z)}{\sigma \kappa b z^*} \left[ \frac{1}{p(z^*)} \left(1 - \frac{y}{y^*} - z \right) + myz^* \left(1 - \frac{z}{z^*} \right) \right]$$

$$= \frac{y^* p(z)}{\sigma \kappa b z^*} \left[ \frac{1}{p(z^*)} \left(1 - \frac{y}{y^*} - z \right) + \frac{myy* p(z)}{\sigma \kappa b} \left(1 - \frac{p(z^*)}{p(z)} \right) \right].$$

And $V'_5$ along any positive solution of model (3) can be directly derived

$$V'_5 = \frac{G^*}{\kappa} \int_0^\infty k(\tau) \left[ \phi \left(\frac{G}{G^*} \right) - \phi \left(\frac{G_\tau}{G^*} \right) \right] d\tau$$

$$= \frac{G^*}{\kappa} \int_0^\infty k(\tau) \left( \frac{G}{G^*} \right) - \ln \frac{G}{G^*} \right] d\tau.$$

Rearranging the results above and dropping the same terms yields

$$V'_2 = \sum_{i=1}^5 V'_i(t) = dx^* \left(1 - \frac{x^*}{x} \right) \left(1 - \frac{g(x^*, y^*)}{g(x, y^*)} \right) + \frac{y^* p(z)}{\sigma \kappa b} \left(1 - \frac{p(z^*)}{p(z)} \right) \left(1 - \frac{z}{z^*} \right)$$

$$+ \frac{myG^*}{b} \left(1 - \frac{q(z)}{q(z^*)} \right) \left(1 - \frac{z}{z^*} \right) + \frac{G^*}{\kappa} \left[ \int_0^\infty k(\tau) \left( \frac{G_\tau y^*}{G^* y} \frac{g(x, y^*)q(z^*)}{z^* q(z^*)} \right) \right] d\tau.$$

One asserts that the first three terms are less than or equal to zero just because of the monotonicity of the functions $g(x, y)$ with respect to $x$, $p(z)$ and $q(z)$. We
that the stability of $E^0$ number $R_0$ may change the expression of its basic reproduction $(G_{\text{CTL}}$ and NL-CTL immune responses satisfying the properties $E_d$ dynamics, namely, the basic reproduction number fully determines the stability of $E^0$, whereas distributed intracellular delay and immune impairment have influences on the concentration level of infected T-cells at $(\tau)$. Remark 2. It is natural to develop a viral model with distributed intracellular delay, nonlinear incidence rate, nonlinear L-CTL and NL-CTL immune responses satisfying the properties $(G_1)-(Q_2)$. Similar to the proofs in Theorems 2.1-4.3, the local and global stability of $E^0$ and $E^*$, and persistence of the general nonlinear model can be established.

5. Discussion. In order to reproduce the scenario of the complex interaction between within-host cell and viral populations, we develop an HTLV-I infection model with distributed intracellular delay, nonlinear incidence rate, nonlinear L-CTL and NL-CTL responses, and immune impairment. Through conducting complete analysis, it is revealed that all these factors influence the concentration level of infected T-cells at the chronic-infection equilibrium $E^*$, whereas distributed intracellular delay and nonlinear incidence rate may change the expression of its basic reproduction number $R_0$ in the context where model (3) still preserves the threshold dynamics that the stability of $E^0$ and $E^*$ is fully determined by $R_0$. Thanks to $(G_2)$ and Proposition A.1 in [30], a simple induction then shows

$$\phi\left(\frac{G}{g(x, y')}q(z')\right) - \phi\left(\frac{yyq(z)}{y'q(z')}\right) = \phi\left(\frac{g(x, y)}{g(x, y')}q(z')\right) - \phi\left(\frac{yyq(z)}{g(x, y')}\right)$$

is less than or equal to zero, so also is the third term in $\Sigma$. And the latter is an immediate consequence of Lemma A.1 in [32].

Given the above, we draw a conclusion that $V_2 \leq 0$ with “$=$” if $x = x^* = x_r$, $y = y^* = y_r$, and $z = z^* = z_r$ for almost all $\tau \in [0, \infty)$. Hence, all solutions of model (3) are attracted to the largest invariant subset of $\mathcal{L}_2 := \{ (x, y, z) \in \Gamma \}$ via LaSalle’s invariance principle for delay differential systems (e.g., see Theorem 5.3.1 in [10]). Also, $\mathcal{L}_2 = \{ E^* \}$ is invariant with respect to (3). The global attractivity and the local stability of $E^*$ established in Theorem 3.1 result that $E^*$ is globally asymptotically stable in $\Gamma$ if $R_0 > 1$. The desired is attained. □

Remark 1. From the equation (9), together with Theorems 2.1, 4.3, it can be found that nonlinear L-CTL and NL-CTL responses, nonlinear incidence rate, distributed intracellular delay and immune impairment have influences on the concentration level of infected T-cells at $E^*$, although model (3) still preserves the threshold dynamics, namely, the basic reproduction number fully determines the stability of $E^0$ and $E^*$.
5.1. **The model with special distribution.** The general distribution function in model (3) allows us to include two special forms of intracellular delays existing in the literature, including the Dirac delta function and Gamma distribution, seeing [1, 5, 22, 25, 26, 36]. We first consider the generic delay kernel of the Dirac’s form \( h(r) = \delta(r - \tau) \) for \( \tau \geq 0 \). Let us set \( \tau = 0 \), then model (3) reduces to an ODE model, and its special cases has been widely studied in literature (see [34] and references therein). Note that Vargas-De-Leon [32] reached the global threshold stability of an ODE viral model with \( g(x, y) = \beta xy \), \( m = 0 \), constant production rate of CTLs export and general nonlinear L-CTL and NL-CTL responses via Lyapunov functions. In fact, in this paper the construction of the Lyapunov functional \( V \) in Theorem 4.3 is motivated by the work of Vargas-De-Leon [32]. It should be pointed out that, the form of \( V \) is that is effective for model (3) with strong nonlinear properties is considerably different from the Lyapunov functionals in [26, 36].

Let us set \( \tau > 0 \), then the latent period of HTLV-I within a T cell is a fixed constant \( \tau \), and model (3) reduces to the following DDE model

\[
\begin{align*}
x' &= \lambda - dx - g(x, y)q(z), \\
y' &= \sigma e^{-\rho \tau} g(x_r, y_r)q(z_r) - ay - yp(z), \\
z' &= cy - bz - myz.
\end{align*}
\]

(22)

It should be mentioned that, for model (22) with \( \alpha_1 = \alpha_2 = \omega = m = 0 \) and \( \sigma = 1 \), Wang et al. [36] established the local and global stability of \( E^* \) under the conditions (2) and \( R_0 > 1 \) by Lyapunov functional. In our work, based on complete analysis for the local stability of \( E^* \) in Theorem 3.1 one achieves its globally asymptotical stability for \( R_0 > 1 \) in Theorem 4.3, abandoning (2) and thus improving the results on the local and global stability of \( E^* \) (see Theorems 3.3 and 3.5 in [36]).

Next, in order to demonstrate the biological necessity of introducing the distributed delay, the delay kernel governed by Gamma distribution [23] is considered

\[ h(\tau) = \frac{\tau^{n-1}}{(n-1)!} e^{-\tau}, \]

(23)

where the scale parameter \( 1/u > 0 \), the shape parameter \( n = 1, 2, \ldots \). Especially, \( h(\tau) \) in the cases of \( n = 1, 2 \) are respectively known as the weak and strong kernels, which are utilized to show that different delay distribution functions \( k(\tau) \) may bring out different short-term dynamics of model (3). Biologically, the weak kernel suggests that the maximum influence of incidence rate comes from the current infection while past infection has exponentially decreasing contributions, and the strong kernel indicates that the maximum influence of incidence rate at any time \( t \) is owing to the infection at the previous time \( t - \tilde{\tau} \), where \( \tilde{\tau} = \int_0^\infty \tilde{h}(\tau)d\tau = 2/u \) is the average delay. By the similar conversion and derivation in Appendix A of [25], model (3) with Gamma distribution is equivalent to the ODE system

\[
\begin{align*}
x' &= \lambda - dx - g(x, y)q(z), \\
y' &= -\frac{\sigma u^n}{(\rho + u)^n} w_n - ay - yp(z), \\
w'_1 &= (\rho + u)[g(x, y)q(z) - w_1], \\
w'_i &= (\rho + u)(w_{i-1} - w_i), \quad i = 2, \ldots, n, \\
z' &= cy - bz - myz,
\end{align*}
\]

(24)

where the auxiliary functions related to the delay kernels are denoted by

\[ w_i := \int_0^\infty \frac{\tau^{i-1}}{(i-1)!} e^{-(\rho + u)\tau} g(x(t - \tau), y(t - \tau))q(z(t - \tau))d\tau. \]

(25)
Thus, system (24) can be used to compare the dynamical behaviors of model (3) with these two kernels through numerical simulations. Let us choose $u_1 = 1.6396$, $u_2 = 3.3333$, and the remaining parameter values keep consistent with Table 1. It is can be deduced from integration by parts and incomplete induction that

$$\kappa = \int_0^\infty k(\tau) d\tau = \frac{u^n}{(\rho + u)^n}. \quad (26)$$

Hence, one obtains that $\kappa = u_1/(\rho + u_1) = u_2^2/(\rho + u_2)^2 = 0.9371$, such that model (3) with the weak kernel have the equal basic reproduction number $R_0 = 2.9949 > 1$ and the equal concentration of infected T-cells $y(t)$ as the strong kernel case from (6) and (9). So for these two cases, the long-term dynamics of $y(t)$ have no difference (see Figure 1 (a)) since $E^*$ is globally asymptotically stable according to Theorem 4.3. However, it can be seen from Figure 1 (b) that the short-term dynamics of $y(t)$ have a significant difference under the same initial condition, but it will not happen to any ODE model. Therefore, the general distributed intracellular delay, including a variety of biologically plausible delay distributions such as Gamma distribution and the Dirac delta function, should be incorporated into model (3) to realistically reflect the stochastic element in the delay effects in the process of HTLV-I infection.

5.2. Global sensitivity analysis for $R_0$. From the perspective of biological significances, the basic reproduction number $R_0$ of model (3) measures the expected number of new viruses produced from a single virus particle during its lifespan in a fully susceptible cell environment. As is well known, $R_0$ may play the vital role in determining the process, severity and outcome of the infection. Especially, the basic reproduction number of model (22) is expressed as

$$R_0 = \frac{\sigma \beta \lambda e^{-\sigma \tau}}{a(d + \alpha_1 \lambda)}. \quad (27)$$

In the following, we shall perform global uncertainty and sensitivity analysis based on Latin Hypercube Sampling (LHS) and partial rank correlation coefficients (PRCCs) [24] to examine the dependence of the basic reproduction number (27) on these uncertain input parameters $\lambda, d, \beta, \alpha_1, \sigma, \rho, \tau, a$. The ranges of these
parameters are estimated according to some related references [1, 20, 21, 22, 34, 36, 37], see Table 1. Given the lack of available data, all input parameters are assigned to follow uniform distributions in Table 2. And their PRCC values are calculated through 3500 simulations per run, revealing the influence degree on model outcomes. We may assign the absolute values of PRCC belonging to $[0, 0.2), [0.2, 0.4), [0.4, 0.8)$ and $(0.8, 1]$ as weak correlation, moderate correlation, important correlation and strong correlation, respectively.

Table 2. PRCC values for $R_0$

| Para. | Distribution1 | PRCC1 | p-value1 | Distribution2 | PRCC2 | p-value2 | Rank |
|-------|---------------|-------|----------|---------------|-------|----------|------|
| $\lambda$ | U(10,200) | $-0.0193$ | 0.2554 | N(105,30) | 0.0230 | 0.1732 | 7 |
| $d$ | U(0.01,0.2) | $-0.0180$ | 0.2880 | N(0.11,0.03) | 0.0149 | 0.3799 | 8 |
| $\beta$ | U(0.001,0.05) | 0.6968 | 0 | N(0.026,0.005) | 0.5697 | 0 | 4 |
| $\alpha_1$ | U(10) | $-0.7167$ | 0 | N(5.1667) | $-0.7789$ | 0 | 3 |
| $\sigma$ | U(0.1) | 0.7411 | 0 | N(0.5,0.167) | 0.7885 | 0 | 1 |
| $\rho$ | U(0.01,0.2) | $-0.3574$ | 0 | N(0.11,0.03) | $-0.4692$ | 0 | 6 |
| $\tau$ | U(10) | $-0.3753$ | 0 | N(5.1667) | $-0.5536$ | 0 | 5 |
| $a$ | U(0.01,0.2) | $-0.7211$ | 0 | N(1.005,0.332) | $-0.7811$ | 0 | 2 |

From Figure 2 (a), PRCC values for $R_0$ are listed in Table 2, and we rank them in order by the absolute values. It is shown that input parameters $\sigma$, $a$, $\alpha_1$, $\beta$ (in descending order) are important correlations with new infections, and $\tau$, $\rho$ are moderate correlations with new infections. Meanwhile, similar conclusions can be reached in the case where these input parameters follow normal distributions given in Table 2, seeing Figure 2 (b). What this means in practice is that, it is vital to implement strategies to enhance the antibody immune response (to reduce $\sigma$ such that fewer healthy T-cells are infected, see Figure 3 (a)) and CTL immune response (to increase the death rate of infected T-cells such that $a$ turns bigger, see Figure 3 (b)), increase the inhibitory rate from healthy T-cells $\alpha_1$ (Figure 3 (c)), and reduce viral infectivity rate $\beta$ (Figure 3 (d)). In addition, we also see that the nonlinear incidence and the delay (related to the parameters $\tau$, $\rho$) have great influences on new infections, thus the factors should not be ignored.

![Figure 2](https://example.com/image2.png)
Figure 3. Simulations for the concentrations of infected T-cells of model (22) when (a) $\sigma$ varies by 0.75 and 0.5, (b) $a$ varies by 1.5 and 2 times, (c) $\alpha_1$ varies by 1.5 and 2 times and (d) $\beta$ varies by 0.75 and 0.5 of their baseline values in Table 1, respectively.

In the end, the same approach that worked for the distributed delay model (3) also works for the corresponding discrete delay version. Avila-Vales et al. [1] studied a viral model with immune impairment, general nonlinear incidence and discrete delay, however the local stability and persistence of this model were not analyzed, and we may be able to carry on complete research on its dynamical behaviors.

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