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Mathematical analysis of the global dynamics of a model for HTLV-I infection and ATL progression

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Abstract

Mathematical analysis is carried out that completely determines the global dynamics of a mathematical model for the transmission of human *T*-cell lymphotropic virus I (HTLV-I) infection and the development of adult *T*-cell leukemia (ATL). HTLV-I infection of healthy $CD4^+$ *T* cells takes place through cell-to-cell contact with infected *T* cells. The infected *T* cells can remain latent and harbor virus for several years before virus production occurs. Actively infected *T* cells can infect other *T* cells and can convert to ATL cells, whose growth is assumed to follow a classical logistic growth function. Our analysis establishes that the global dynamics of *T* cells are completely determined by a basic reproduction number R_0. If $R_0 \leqslant 1$, infected *T* cells always die out. If $R_0 > 1$, HTLV-I infection becomes chronic, and a unique endemic equilibrium is globally stable in the interior of the feasible region. We also show that the equilibrium level of ATL-cell proliferation is higher when the HTLV-I infection of *T* cells is chronic than when it is acute.

MSC: 92D30; 34D20
Keywords: Immunological models; Chronic HTLV-I infection; Adult *T*-cell leukemia; Basic reproduction number; Global stability

1. Introduction

Human *T*-cell lymphotropic virus I (HTLV-I) infection is linked to the development of adult *T*-cell leukemia/lymphoma (ATL), among many illness. Infection by HTLV-I is characterized by

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cell-to-cell infection [1–3] of CD4$^+$ T cells which HTLV-I preferentially infects [4,5]. Primary infection leads to a chronic infection that seems to last life-long. Typically, a small fraction of infected individuals progress to disease and about 2–5% of HTLV-I carriers develop symptoms of ATL [6].

HTLV-I is a single-stranded RNA retrovirus with reverse transcriptase activity that leads to a DNA copy of the viral genome. The viral DNA copy is then integrated into the DNA of the host genome. After integration, the viral DNA can latently persist within a T cell for a long time. The latent infected T cells contain the viral DNA but are not producing it, and they can not cause new infections of susceptible cells. Stimulation of the latent infected CD4$^+$ T cells by antigen can initiate activation of the infected cells. Actively infected T cells can produce virus and can cause new infections of susceptible T cells. Actively infected T cells may then convert to ATL cells through certain mechanisms which are not yet known.

In [7], Stilianakis and Seydel developed a mathematical model that describes the T-cell dynamics of the HTLV-I infection and the development of ATL. The model is formulated by the following system of non-linear differential equations:

$$\begin{aligned} T' &= \Lambda - \mu_T T - \kappa T_A T, \\ T'_L &= \kappa T_A T - (\mu_L + \alpha) T_L, \\ T'_A &= \alpha T_L - (\mu_A + \rho) T_A, \\ T'_M &= \rho T_A + \beta T_M \left(1 - \frac{T_M}{T_{M_{max}}}\right) - \mu_M T_M, \end{aligned} \tag{1.1}$$

where T, T_L, T_A denote the numbers of uninfected, latent infected, actively infected CD4$^+$ T cells, and T_M the number of leukemia cells, respectively. It is assumed that the body produces CD4$^+$ T cells at a constant rate Λ and newly produced T cells are assumed to be susceptible. HTLV-I infection in CD4$^+$ T cells takes place through cell-to-cell contact between actively infected cells and uninfected (susceptible) cells. The infection process is described by the mass-action term $\kappa T_A T$, where κ is the infection rate which accounts for the overall effects of HTLV-I reproduction such as contact rate and infectivity. Once infected, a CD4$^+$ T cell becomes latent for a period of time before it becomes actively infected. The parameter α is the transmission rate at which latent infected CD4$^+$ T cells become actively infected, and ρ is the transmission rate at which actively infected CD4$^+$ T cells convert to ATL cells; thus $1/\alpha$ and $1/\rho$ can be regarded as the mean latent and infectious periods, respectively. The death or removal rates for uninfected, latent infected, actively infected CD4$^+$ cells, and ATL cells are μ_T, μ_L, μ_A, and μ_M, respectively. ATL cells proliferate at rate β of a classical logistic growth function. $T_{M_{max}}$ is the maximal number that ATL cells can grow. All parameters in the model are assumed to be positive constants.

In [7], a threshold parameter

$$R_0 = \frac{\alpha \kappa \Lambda}{\mu_T (\mu_L + \alpha)(\mu_A + \rho)} \tag{1.2}$$

is derived. It represents the average number of secondary infections caused by a single primary actively infected T cell introduced into a pool of susceptible T cells during its entire infection period. R_0 is typically called a basic reproduction number or the contact number in the literature of epidemiological models [8,9]. Various parameters in the model were estimated in [7], and nu-

merical simulations using the estimated parameter values predict levels of infected CD4$^+$ T cells and leukemia cells in correspondence with those observed in infected individuals. Local stability analysis of equilibria is also given in [7].

In this paper, we present a rigorous mathematical analysis that completely determines the global dynamics of (1.1). When $R_0 \leqslant 1$, no chronic HTLV-I infection within the body is possible, and the ATL cells demonstrate a typical logistic behavior: if $\beta \leqslant \mu_M$, any ATL cells present will die out and the only uninfected steady-state (Λ/μ_T, 0, 0, 0) is globally stable in the feasible region; if $\beta > \mu_M$, a second uninfected steady-state $(\Lambda/\mu_T, 0, 0, T_{M_{max}}(\beta - \mu_M)/\beta)$ exists and is globally stable in the feasible region, and any existing ATL cells will proliferate to the carrying capacity $T_{M_{max}}(\beta - \mu_M)/\beta$. When $R_0 > 1$, a primary HTLV-I infection in T cells always leads to a chronic infection, and a unique endemic steady-state $P^* = (T^*, T_L^*, T_A^*, T_M^*)$, T^*, T_L^*, T_A^*, $T_M^* > 0$, exists and is globally stable in the interior of the feasible region. Due to the chronic HTLV-I infection in the T cells, the ATL cells will proliferate to an equilibrium level T_M^* that is higher than carrying capacity $T_{M_{max}}(\beta - \mu_M)/\beta$.

2. Model analysis and main results

Adding the first three equations in (1.1) gives

$$(T + T_L + T_A)' = \Lambda - \mu_T T - \mu_L T_L - (\mu_A + \rho)T_A \leqslant \Lambda - \gamma(T + T_L + T_A),$$

where $\gamma = \min\{\mu_T, \mu_L, \mu_A + \rho\}$. Hence $\limsup_{t\to\infty}(T + T_L + T_A) \leqslant \Lambda/\gamma$. The last equation of (1.1) then leads to the logistic inequality, $T_M' \leqslant \rho\Lambda/\gamma + \beta T_M(1 - T_M/T_{M_{max}}) - \mu_M T_M$, which in turn implies $\limsup_{t\to\infty} T_M \leqslant \tilde{T}_M$, where $\tilde{T}_M$ is the positive root of the quadratic equation $\rho\Lambda/\gamma + \beta T_M(1 - T_M/T_{M_{max}}) - \mu_M T_M = 0$. We thus study system (1.1) in the following feasible region:

$$\Gamma = \left\{(T, T_L, T_A, T_M) \in \mathbf{R}_+^4 : T + T_L + T_A \leqslant \Lambda/\gamma, T_M \leqslant \tilde{T}_M\right\},$$

and Γ is positively invariant with respect to (1.1). Let $\overset{\circ}{\Gamma}$ denote the interior of Γ.

The basic reproduction number R_0 of T cells, as derived in [7] and shown in (1.2), represents the number of secondary infections caused by one primary infectious T cell introduced into the susceptible T cells during the infectious period. If $R_0 \leqslant 1$, the system (1.1) has only one steady-state $P_0 = (\Lambda/\mu_T, 0, 0, 0)$ in Γ if $\beta \leqslant \mu_M$; and a second steady-state $P_1 = (\Lambda/\mu_T, 0, 0, T_{M_{max}}(\beta - \mu_M)/\beta)$ exists if $\beta > \mu_M$. Both P_0 and P_1 lie on the boundary of Γ. P_0 is the uninfected steady-state with no ATL progression and P_1 is the uninfected steady-state with ATL progression. No steady-states exist in the interior of Γ if $R_0 \leqslant 1$. If $R_0 > 1$, there are two steady-states in Γ: P_0 and a unique endemic steady-state $P^* = (T^*, T_L^*, T_A^*, T_M^*) \in \Gamma$ where

$$\begin{aligned} T^* &= \frac{\mu_T}{\Lambda} R_0, \quad T_L^* = \frac{\Lambda}{\mu_L + \alpha}\left(1 - \frac{1}{R_0}\right), \\ T_A^* &= \frac{\Lambda\alpha}{(\mu_L + \alpha)(\mu_A + \rho)}\left(1 - \frac{1}{R_0}\right), \end{aligned} \tag{2.1}$$

and T_M^* is the positive solution of the quadratic equation

$$\beta T_M^2 - T_{M_{max}}(\beta - \mu_M)T_M - \rho T_A^* T_{M_{max}} = 0. \tag{2.2}$$

Since $T_A^* > 0$, T_M^* is greater than $T_{M_{max}}(\beta - \mu_M)/\beta$, the carrying capacity for the logistic growth of ATL cells in the absence of chronic HTLV-I infection.

We first analyze the following subsystem of (1.1) that describes the T-cell dynamics,

$$\begin{aligned} T' &= \Lambda - (\mu_T + \kappa T_A)T, \\ T_L' &= \kappa T_A T - (\mu_L + \alpha)T_L, \\ T_A' &= \alpha T_L - (\mu_A + \rho)T_A, \end{aligned} \tag{2.3}$$

in its feasible region

$$\Delta = \left\{(T, T_L, T_A) \in \mathbf{R}_+^3 : T + T_L + T_A \leqslant \Lambda/\gamma\right\},$$

which is the projection of Γ onto the (T, T_L, T_A) subspace. Let $\overset{\circ}{\Delta}$ denote the interior of Δ. The dynamics of ATL cells can then be determined from the equation

$$T_M' = \rho T_A + \beta T_M\left(1 - \frac{T_M}{T_{M_{max}}}\right) - \mu_M T_M. \tag{2.4}$$

If $R_0 \leqslant 1$, system (2.3) has only the infection-free steady-state $Q_0 = (\Lambda/\mu_T, 0, 0)$. If $R_0 > 1$, system (2.3) has two steady-states: Q_0 and a unique endemic steady-state $Q^* = (T^*, T_L^*, T_A^*) \in \overset{\circ}{\Delta}$ where T^*, T_L^* and T_A^* are given in (2.1). The following theorem describes the global dynamics of (2.3). Its proof will be given in Section 3.

Theorem 2.1. (1) *If $R_0 \leqslant 1$, then the infection-free steady-state $Q_0 = (\Lambda/\mu_T, 0, 0)$ is globally asymptotically stable in Δ.* (2) *If $R_0 > 1$, then Q_0 is unstable and Q^* is globally asymptotically stable in $\overset{\circ}{\Delta}$.*

Theorem 2.1 completely determines the bifurcation and the global dynamics of T cells, which demonstrate the classical threshold phenomenon of standard epidemic models. It establishes R_0 as a sharp threshold parameter. If $R_0 \leqslant 1$, then the infection-free steady-state is globally stable in the feasible region, and infected T-cell population always dies out. If $R_0 > 1$, then the infection-free steady-state loses its stability, and a unique endemic steady-state Q^* comes to exist and is globally stable in the interior of the feasible region, and HTLV-I infection becomes chronic and persists at the endemic steady-state Q^*.

Information on T-cell dynamics is used to determine the fate of the leukemia cells and the global dynamics of (1.1). This is carried out in two different cases: $R_0 \leqslant 1$ or $R_0 > 1$.

When $R_0 \leqslant 1$, infected T-cell population dies out, by Theorem 2.1 (1). In particular, $T_A \to 0$ exponentially as $t \to \infty$. This implies that the dynamics of T_M satisfies the following logistic equation

$$T_M' = \beta T_M\left(1 - \frac{T_M}{T_{M_{max}}}\right) - \mu_M T_M.$$

Simple analysis of this equation yields the following conclusion. If $\beta \leqslant \mu_M$, then $T_M \to 0$ as $t \to \infty$ for all non-negative initial conditions. If $\beta > \mu_M$, then $T_M \to T_{M_{max}}(\beta - \mu_M)/\beta$, the carrying capacity of T_M, as $t \to \infty$, for all positive initial conditions. This and Theorem 2.1 (1) completes the determination of the global dynamics of system (1.1) when $R_0 \leqslant 1$, which we summarize in the following theorem.

Theorem 2.2. *Assume that* $R_0 \leqslant 1$. *Then*

1. *If* $\beta \leqslant \mu_M$, *then* $P_0 = (\Lambda/\mu_T, 0, 0, 0)$ *is the only steady-state of* (1.1) *and is globally stable in* Γ.
2. *If* $\beta > \mu_M$, *then* (1.1) *has two steady-states* P_0 *and* P_1 *in* Γ. P_0 *is unstable and* P_1 *is globally stable in* $\Gamma \setminus \{(T, 0, 0, 0) : 0 \leqslant T \leqslant \Lambda/\mu_T\}$.

When $R_0 > 1$, the HTLV-I infection is endemic, by Theorem 2.1 (2). In particular, $T_A \to T_A^*$ exponentially as $t \to \infty$. Thus, the dynamics of ATL cells T_M satisfies the forced logistic equation

$$T_M' = \rho T_A^* + \beta T_M\left(1 - \frac{T_M}{T_{M_{max}}}\right) - \mu_M T_M.$$

Simple phase-line analysis of this equation shows that T_M converges to the unique positive steady-state T_M^* as $t \to \infty$ for all non-negative initial conditions. Combining this with Theorem 2.1 (2), we complete the determination of the global dynamics of (1.1) when $R_0 > 1$.

Theorem 2.3. *Assume that* $R_0 > 1$. *Then the unique endemically infected steady-state* P^* *is globally stable in* $\overset{\circ}{\Gamma}$.

Theorems 2.2 and 2.3 completely determine the global dynamics of (1.1). If $R_0 \leqslant 1$, all infected T cells die out. The fate of the ATL cells that are present is determined by a simple logistic equation; they die out if death rate μ_M dominates the proliferation rate β; or proliferate to their carrying capacity at $T_{M_{max}}(\beta - \mu_M)/\beta$ if $\mu_M \leqslant \beta$. If $R_0 > 1$, any HTLV-I infection of the T cells will become chronic, both infected T cells and ATL cells persist if present. In this case, due to the chronic T-cell infection, the equilibrium level of the ATL cell proliferation, T_M^*, is higher than the carrying capacity $T_{M_{max}}(\beta - \mu_M)/\beta$.

3. Proof of Theorem 2.1

In this section, we provide a proof of Theorem 2.1. Define a Lyapunov function L of (2.3) as follows:

$$L = \alpha T_L + (\alpha + \mu_L) T_A.$$

Then the derivative of L along a solution of (2.3) is

$$\begin{aligned} L' &= \alpha[\kappa T_A T - (\mu_L + \alpha) T_L] + (\alpha + \mu_L)[\alpha T_L - (\mu_A + \rho) T_A] \\ &= \alpha\kappa T_A T - (\mu_L + \alpha)(\mu_A + \rho) T_A \\ &= (\mu_L + \alpha)(\mu_A + \rho) T_A\left(R_0 \frac{\mu_T}{\Lambda} T - 1\right) \leqslant 0. \end{aligned}$$

This follows as $R_0 \leqslant 1$ and $T \leqslant \Lambda/\mu_T$ in Δ. Furthermore, $L' = 0$ if and only if $T_A = 0$ or $R_0 = 1$ and $T = \Lambda/\mu_T$. Therefore the largest compact invariant set in $\{(T, T_L, T_A) : L' = 0\}$ is the singleton $\{Q_0\}$, where Q_0 is the uninfected steady-state. LaSalle's invariant principle [10] then implies that $\{Q_0\}$ is globally stable in Δ. In particular, $T_A \to 0$ exponentially as $t \to \infty$. This proves Theorem 2.1 (1). □

Remark. The same Lyapunov function L can also be used to show that Q_0 is unstable when $R_0 > 1$. In fact, if $R_0 > 1$ then $L' > 0$ for T sufficiently close to Λ/μ_T except when $T_A = 0$. Solutions starting sufficiently close to Q_0 leave a neighborhood of Q_0 except those on the invariant T-axis. The instability of Q_0 will imply the uniform persistence of (2.3), as we show in the following.

System (2.3) is said to be uniformly persistent [11,12] if there exists a constant $c > 0$, independent of initial data in $\mathring{\Delta}$, such that, any solution $(T(t), T_L(t), T_A(t))$ of (2.3) satisfies

$$\liminf_{t\to\infty} T(t) > c, \quad \liminf_{t\to\infty} T_L(t) > c, \quad \text{and} \quad \liminf_{t\to\infty} T_A(t) > c$$

provided $(T(0), T_L(0), T_A(0)) \in \mathring{\Delta}$. The uniform persistence characterizes chronic HTLV-I infection of T cells. Using a uniform persistence result from [13], and the same argument as in the proof of Proposition 3.3 from [14], we can show that, when $R_0 > 1$, the instability of Q_0 implies the uniform persistence of (2.3). The proof is omitted.

Proposition 3.1. *System* (2.3) *is uniformly persistent in* $\mathring{\Delta}$ *if and only if* $R_0 > 1$.

To establish Theorem 2.1(2), we apply a general method of Li and Muldowney [15] for proving global stability.

Let $\Omega \subset \mathbf{R}^n$ be an open subset and $f : \Omega \to \mathbf{R}^n$ be a C^1 function. Consider the differential equation

$$x' = f(x). \tag{3.1}$$

A steady-state $\bar{x}$ of (3.1) is said to be *globally stable* in Ω if it is locally stable and all trajectories in Ω converge to $\bar{x}$. Let $x(t, x_0)$ denote the solution of (3.1) satisfying $x(0, x_0) = x_0$ and $Df(x)$ the Jacobian matrix of f at x. Assume that (3.1) satisfies the following two conditions:

(H_1) System (3.1) has a unique steady-state $\bar{x}$ in Ω.
(H_2) System (3.1) has a compact absorbing set $K \subset \Omega$.

Let $x \mapsto P(x)$ be an $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function that is C^1 on Ω. Assume that $P^{-1}(x)$ exists and is continuous for $x \in K$. For a Lozinskiĭ measure μ (see Appendix A), a quantity $\bar{q}_2$ is defined as

$$\bar{q}_2 = \limsup_{t\to\infty} \sup_{x_0\in K} \frac{1}{t} \int_0^t \mu(B(x(s, x_0)))\,\mathrm{d}s, \tag{3.2}$$

where

$$B = P_f P^{-1} + P(Df)^{[2]} P^{-1} \tag{3.3}$$

and the matrix P_f is obtained by replacing each entry p_{ij} in P by its directional derivative in the direction f, $\nabla p_{ij}^* f$. The matrix $Df(x)^{[2]}$ is the *second additive compound matrix* of the Jacobian matrix $Df(x)$ (see Appendix B). It is an $\binom{n}{2} \times \binom{n}{2}$ matrix. The following criterion of global stability is due to Li and Muldowney (see [15, Theorem 3.5]).

Theorem 3.1. (Li and Muldowney) *Assume that Ω is simply connected and that the assumptions* (H_1) *and* (H_2) *hold. Then $\bar{x}$ is globally stable in Ω if there exists a function $P(x)$ and a Lozinskiĭ measure μ such that $\bar{q}_2$ defined in* (3.2) *satisfies $\bar{q}_2 < 0$.*

In the rest of the section, we use Theorem 3.1 to prove Theorem 2.1(2).

Proof of Theorem 2.1(2). To see that system (2.3) satisfies the assumptions (H_1) and (H_2), we first note that uniform persistence of (2.3), together with the boundedness of solutions, implies the existence of a compact absorbing set in $\mathring{\Delta}$ (see [11]). This verifies the assumption (H_2). Since Q^* is the only equilibrium in $\mathring{\Delta}$, the assumption (H_1) also holds for system (2.3). In the following, we construct a 3×3 matrix-valued function P, and choose a suitable vector norm $|\cdot|$ in $\mathbf{R}^3 \cong \mathbf{R}^{\binom{3}{2}}$ such that the corresponding Lozinskiĭ measure μ and $\bar{q}_2$ in (3.2) satisfies $\bar{q}_2 < 0$.

Let $x = (T, T_L, T_A)$ and $f(x)$ denote the vector field of (2.3). The Jacobian matrix $J = Df(x)$ along each solution of (2.3) is

$$J = \begin{bmatrix} -\kappa T_A - \mu_T & 0 & -\kappa T \\ \kappa T_A & -(\mu_L + \alpha) & \kappa T \\ 0 & \alpha & -(\mu_A + \rho) \end{bmatrix},$$

and its second additive compound matrix $J^{[2]}$ is, see Appendix B,

$$J^{[2]} = \begin{bmatrix} -\kappa T_A - \mu_T - \mu_L - \alpha & \kappa T & \kappa T \\ \alpha & -\kappa T_A - \mu_T - \mu_A - \rho & 0 \\ 0 & \kappa T_A & -\mu_L - \alpha - \mu_A - \rho \end{bmatrix}.$$

Set $P(x) = P(T, T_L, T_A)$ as

$$P = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \frac{T_L}{T_A} & 0 \\ 0 & 0 & \frac{T_L}{T_A} \end{bmatrix}.$$

Then

$$P_f P^{-1} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & \frac{T_L'}{T_L} - \frac{T_A'}{T_A} & 0 \\ 0 & 0 & \frac{T_L'}{T_L} - \frac{T_A'}{T_A} \end{bmatrix}$$

and the matrix $B = P_f P^{-1} + P J^{[2]} P^{-1}$ in (3.3) can be written in block form

$$B = \begin{bmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{bmatrix},$$

where

$$B_{11} = -\kappa T_A - \mu_T - \mu_L - \alpha,$$

$$B_{12} = \begin{bmatrix} \frac{\kappa T T_A}{T_L} & \frac{\kappa T T_A}{T_L} \end{bmatrix}, \quad B_{21} = \begin{bmatrix} \frac{\alpha T_L}{T_A} \\ 0 \end{bmatrix}$$

and

$$B_{22} = \begin{bmatrix} \frac{T'_L}{T_L} - \frac{T'_A}{T_A} - \kappa T_A - \mu_T - \mu_A - \rho & 0 \\ \kappa T_A & \frac{T'_L}{T_L} - \frac{T'_A}{T_A} - \mu_L - \mu_A - \alpha - \rho \end{bmatrix}.$$

Let (u, v, w) be a vector in $\mathbf{R}^3$. We choose a vector norm in $\mathbf{R}^3$ as

$$|(u, v, w)| = \max\{|u|,\ |v| + |w|\}.$$

Let μ be the Lozinskiĭ measure with respect to this norm. Then as described in [16], we have the estimate

$$\mu(B) \leqslant \max\{g_1, g_2\}, \tag{3.4}$$

with

$$g_1 = \mu_1(B_{11}) + |B_{12}|,$$
$$g_2 = |B_{21}| + \mu_1(B_{22}).$$

Here $|B_{12}|$, $|B_{21}|$ are matrix norms with respect to the l_1 vector norm, and μ_1 denotes the Lozinskiĭ measure with respect to the l_1 norm, see Appendix A. More specifically, $\mu_1(B_{11}) = -\kappa T_A - \mu_T - \mu_L - \alpha$, $|B_{12}| = \kappa T T_A/T_L$, $|B_{21}| = \alpha T_L/T_A$. To calculate $\mu_1(B_{22})$, add the absolute value of the off-diagonal elements to the diagonal one in each column of B_{22}, and then take the maximum of two sums, see [17, p. 41]. We thus obtain

$$\mu_1(B_{22}) = \frac{T'_L}{T_L} - \frac{T'_A}{T_A} - \mu_A - \rho + \max\{-\mu_T, -\mu_L - \alpha\} = \frac{T'_L}{T_L} - \frac{T'_A}{T_A} - \mu_A - \rho - \min\{\mu_T, \mu_L + \alpha\}.$$

Therefore,

$$g_1 = -\kappa T_A - \mu_T - \mu_L - \alpha + \frac{\kappa T T_A}{T_L}, \tag{3.5}$$

$$g_2 = \frac{T'_L}{T_L} - \frac{T'_A}{T_A} - \mu_A - \rho - \min\{\mu_T, \mu_L + \alpha\} + \frac{\alpha T_L}{T_A}. \tag{3.6}$$

Rewriting equations 2 and 3 in (2.3), we obtain, respectively,

$$\frac{\kappa T T_A}{T_L} = \frac{T'_L}{T_L} + \mu_L + \alpha, \tag{3.7}$$

$$\frac{\alpha T_L}{T_A} = \frac{T'_A}{T_A} + \mu_A + \rho. \tag{3.8}$$

Substituting (3.7) into (3.5) and (3.8) into (3.6), respectively, we have

$$g_1 = \frac{T'_L}{T_L} - \mu_T - \kappa T_A \leqslant \frac{T'_L}{T_L} - \mu_T$$

and

$$g_2 = \frac{T'_L}{T_L} - \min\{\mu_T, \mu_L + \alpha\} = \frac{T'_L}{T_L} - \delta,$$

where $\delta = \min\{\mu_T, \mu_L + \alpha\} > 0$. Thus, (3.4) implies

$$\mu(B) \leqslant \frac{T_L'}{T_L} - \bar{\delta},$$

where $\bar{\delta} = \min\{\mu_T, \delta\} > 0$. Along each solution $x(t, x_0)$ to (2.3) such that $x_0 \in K$, the absorbing set, we thus have

$$\frac{1}{t}\int_0^t \mu(B)\,ds \leqslant \frac{1}{t}\log\frac{T_L(t)}{T_L(0)} - \bar{\delta},$$

which implies $\bar{q}_2 < 0$, thus completing the proof. □

4. Discussion

In this paper, we present a complete mathematical analysis for the global dynamics of a model for the infection of $CD4^+$ T cells by HTLV-I virus and progression of ATL. The model was formulated in [7], in which the global dynamics were not rigorously established. In the model, the $CD4^+$ T-cell population is partitioned into three subclasses: uninfected (susceptible) T, latent infected (infected but not yet infectious) T_L, and actively infected (infectious) T_A. The infection is through direct contact with actively infected T cells. After infection, a T cell stays latent for a period of time, then becomes actively infected. The actively infected T cells may eventually convert to ATL cells.

Whether a chronic infection of the T cells by HTLV-I is possible depends completely on the value of the basic reproduction number R_0 for the T-cell dynamics. We prove that no chronic HTLV-I infection is possible if $R_0 \leqslant 1$, and infected T cells always die out. An HTLV-I infection becomes chronic if $R_0 > 1$, and a unique endemic equilibrium is globally stable in this case.

Correspondingly, the two different outcomes of the T-cell dynamics influence the saturated level of the ATL progression. If $R_0 \leqslant 1$, chronic HTLV-I infection of the T cells is not possible, the growth of the ATL cells follows a simple logistic growth, and the saturation level of the ATL cells is at most its carrying capacity $T_{M_{max}}(\beta - \mu_M)/\beta$. If $R_0 > 1$, primary HTLV-I infections always become chronic at a unique endemic equilibrium P^*. The equilibrium level of the chronic infection $T_L^* + T_M^*$ is independent of the initial level. Due to the contribution of the chronic T-cell infection, the persistence level of the ATL cells in this case, which is given by the positive root of the equation

$$\beta T_M^2 - T_{M_{max}}(\beta - \mu_M)T_M - \rho T_A^* T_{M_{max}} = 0,$$

is higher than the carrying capacity $T_{M_{max}}(\beta - \mu_M)/\beta$ when the infection is acute.

Appendix A. Lozinskiĭ measures

Let $|\cdot|$ denote a vector norm in $\mathbf{R}^n$ and the corresponding matrix norm it induces. The Lozinskiĭ measure μ on matrices with respect to $|\cdot|$ is defined by (see [17, p. 41]),

$$\mu(A) = \lim_{h\to 0^+} \frac{|I + hA| - 1}{h}$$

for an $n \times n$ matrix A. For properties and calculations of Lozinskiĭ measures we refer the reader to [17, p. 41].

Appendix B. The second additive compound matrix

Let A be a linear operator on $\mathbf{R}^n$ and also denote its matrix representation with respect to the standard basis of $\mathbf{R}^n$. Let $\wedge^2\mathbf{R}^n$ denote the exterior product of $\mathbf{R}^n$. A induces canonically a linear operator $A^{[2]}$ on $\wedge^2\mathbf{R}^n$: for $u_1, u_2 \in \mathbf{R}^n$, define

$$A^{[2]}(u_1 \wedge u_2) := A(u_1) \wedge u_2 + u_1 \wedge A(u_2)$$

and extend the definition over $\wedge^2\mathbf{R}^n$ by linearity. The matrix representation of $A^{[2]}$ with respect to the canonical basis in $\wedge^2\mathbf{R}^n$ is called the *second additive compound matrix* of A. This is an $\binom{n}{2} \times \binom{n}{2}$ matrix and satisfies the property $(A + B)^{[2]} = A^{[2]} + B^{[2]}$. In the special case when $n = 2$, we have $A^{[2]}_{2\times 2} = \mathrm{tr}A$. In general, each entry of $A^{[2]}$ is a linear expression of those of A. For instance, when $n = 3$, the second additive compound matrix of $A = (a_{ij})$ is

$$A^{[2]} = \begin{bmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{bmatrix}.$$

For detailed discussions of compound matrices and their properties we refer the reader to [18]. A comprehensive survey on compound matrices and their relations to differential equations is given in [19].

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