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MATHEMATICAL ANALYSIS OF A HIV MODEL WITH FREQUENCY DEPENDENCE AND VIRAL DIVERSITY*

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Abstract. We consider the effect of viral diversity on the human immune system with the frequency dependent proliferation rate of CTLs and the elimination rate of infected cells by CTLs. The model has very complex mathematical structures such as limit cycle, quasi-periodic attractors, chaotic attractors, and so on. To understand the complexity we investigate the global behavior of the model and demonstrate the existence and stability conditions of the equilibria. Further we give some theoretical considerations obtained by our mathematical model to HIV infection.

1. **Introduction.** Patients infected with HIV have a long and variable incubation period between infection and the development of AIDS. HIV can infect $CD4^+$ T cells, which represent an important component of the human immune system. By infecting and depleting the $CD4^+$ T cell population, HIV attacks the immune system. During the incubation period of HIV infection (so-called asymptomatic phase), $CD4^+$ T cells decrease and eventually their number drops to essentially 0 (this implies the breakdown of immune system). AIDS is defined as a CD4 cell count of less than 200 μl in the peripheral blood. If AIDS develops, the patient is overwhelmed and killed by other opportunistic infections. Many studies have shown that viral diversity increases in the asymptomatic phase by the mutational escape of HIV. An error-prone nature of HIV reverse transcriptase contributes to the tremendous diversity of HIV [16]. Under the pressure of CTL responses which recognize and kill virus-infected cells, viruses that contain mutated critical amino acids in epitopes recognized by CTL are selected [17], [27]. In general, the new virus mutant escapes

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from the current immune response and grows unchecked initially, but it induces another immune response that brings it down after some time. Meanwhile another escape mutant has emerged, and so on. Thus the diversity increases over the disease progression.

In this study, we focus on the asymmetric interaction between immunological and viral diversity. Each virus strain can infect $CD4^+$ T cells, but individual strain-specific immune responses can only attack specific virus strains. Since the infection by the virus and the proliferation and elimination by the immune cell are due to the contacts between individuals, the asymmetric interactions are promoted in more heterogeneous virus populations. In [13] and [15], we proposed the following mathematical models in which CTL reactions (CTL proliferation and elimination of infected cells by CTLs) depend on the frequency of $CD4^+$ T cells characterized by viral diversity:

$$\begin{aligned} T' &= \lambda - dT - \sum_{l=1}^{n} \beta'_l T V_l, \\ I'_j &= \beta'_j T V_j - a I_j - q Z_j \frac{I_j}{T + \sum_{l=1}^{n} I_l}, \\ V'_j &= k a I_j - u V_j, \\ Z'_j &= c Z_j \frac{I_j}{T + \sum_{l=1}^{n} I_l} - \delta Z_j. \qquad (j = 1, 2, ..., n) \end{aligned} \tag{1}$$

This model consists of $3n+1$-variables: T denotes the population size of uninfected $CD4^+$ T cells, I_j denotes $CD4^+$ T cells infected with virus particle of type j, V_j denotes the free virus particle of type j, and Z_j denotes the CTLs of type j, respectively. The parameter λ is a rate at which new target cells are generated. Uninfected cells, infected cells, virus, and CTLs are assumed to die at respective rates d, a, u, and δ. Once cells are infected, we assume that they produce k times new virus particles during their life, which on average has a length $1/a$. Further, we can reduce the model (1) to a simpler form, using a quasi-steady-state approach and some scaling parameters, as follows (see [13]):

$$\begin{aligned} T' &= 1 - T - \sum_{l=1}^{n} \beta_l T I_l, \\ I'_j &= \beta_j T I_j - a I_j - q Z_j \frac{I_j}{T + \sum_{l=1}^{n} I_l}, \\ Z'_j &= c Z_j \frac{I_j}{T + \sum_{l=1}^{n} I_l} - \delta Z_j, \qquad (j = 1, 2, ..., n). \end{aligned} \tag{2}$$

In (2) we use scaling notations. Note that, as same as (1), the interactions between specific infected cells and specific CTLs depend on the frequency that specific CTLs encounter to the specific infected cells, but the interactions between uninfected cells and specific infected cells are not frequency dependent. Thus our mathematical model can characterize the asymmetric interactions emphasized by viral diversity. More detailed discussions of our model are given in [13] and [15].

2. **Mathematical analysis.**

The main purpose of this paper is to obtain the mathematical properties of model (2), such as the existence, uniqueness, and continuity for the solution and the existence and stability conditions for the equilibria.

Here we refer the basic results of the solution of (2). From the biological point of view, all solutions are necessary to lie in the region $\mathbb{R}^{2n+1}_+$. In this region, the local existence, uniqueness, and continuity of the solution are guaranteed by the standard theorem (see [7]). Namely, there exists a unique solution $(T(t), I_1(t), ..., I_n(t), Z_1(t), ..., Z_n(t))$ of (2) with $T_0 > 0, I_{10} > 0, ..., I_{n0} > 0, Z_{10} > 0, ..., Z_{n0} > 0$ on its maximal existence interval. Here $T_0, I_{10}, ..., I_{n0}, Z_{10}, ..., Z_{n0}$ denote initial values of (2) in Int $\mathbb{R}^{2n+1}_+$. If the solutions remain bounded, then the maximal interval is $[0, \infty)$. The following theorem implies that solutions starting in Int $\mathbb{R}^{2n+1}_+$ exist in $\mathbb{R}^{2n+1}_+$ for all $t \in [0, \infty)$. For convenience, we define $\sum_{j=1}^n I_j = I$, $\sum_{j=1}^n Z_j = Z$ and $N = T + I + Z$.

Theorem 2.1. *If $(T_0, I_{10}, ..., I_{n0}, Z_{10}, ..., Z_{n0}) \in$ Int $\mathbb{R}^{2n+1}_+$, then $(T(t), I_1(t), ..., I_n(t), Z_1(t), ..., Z_n(t))$ exists in $\mathbb{R}^{2n+1}_+$ for all $t \in [0, \infty)$. Moreover $(T(t), I_1(t), ..., I_n(t), Z_1(t), ..., Z_n(t))$ is ultimately bounded in $\mathbb{R}^{2n+1}_+$, i.e., model (2) is dissipative.*

The proof of this theorem is similar to the proof of Theorem 2.1 in [14].

2.1. **One-virus model.** We investigate the stability of equilibria for one-virus model (that is, the model without viral diversity), which is given by the following model of differential equations:

$$\begin{aligned} T' &= 1 - T - \beta_1 T I_1, \\ I_1' &= \beta_1 T I_1 - a I_1 - \frac{q Z_1 I_1}{T + I_1}, \\ Z_1' &= \frac{c Z_1 I_1}{T + I_1} - \delta Z_1. \end{aligned} \tag{3}$$

Here we introduce a basic reproduction number R_1, which is defined as the number of newly infected cells that arise from any one infected cell when all cells are uninfected. The rate at which one infected cell gives rise to new infected cells is given by $\beta_1 T$. If all cells are uninfected, then $T = 1$. Since the average lifespan of an infected cell is $1/a$, we obtain

$$R_1 = \frac{\beta_1}{a}.$$

Model (3) has three equilibria. The first one is $E_H = (1, 0, 0)$ which represents a state where infected cells are absent. The second equilibrium $E_U = (T^*, I_1^*, 0)$ represents a state where infected cells are present, while CTLs are absent. Here the components T^* and I_1^* are

$$T^* = \frac{a}{\beta_1}, \quad I_1^* = \frac{1}{a} - \frac{1}{\beta_1}.$$

If $R_1 > 1$, then E_U exists in $\mathbb{R}^3_+$. The third equilibrium E_C can be an interior equilibrium, which represents a state in which both infected cells and CTLs are present. Here the interior equilibrium $E_C = (\hat{T}, \hat{I}_1, \hat{Z}_1)$ is represented by the following form;

$$\hat{T} = \frac{-1 + \sqrt{1 + 4\hat{\beta}}}{2\hat{\beta}}, \quad \hat{I}_1 = \frac{\delta}{c - \delta}\hat{T}, \quad \hat{Z}_1 = \frac{c\hat{T}}{q(c - \delta)}(\beta_1 \hat{T} - a)$$

where $\hat{\beta} = \delta\beta_1/(c - \delta)$. If $R_1 > \dfrac{a\delta}{c - \delta} + 1$, then E_C exists in Int$\mathbb{R}^3_+$. Here we always assume that c is larger than δ i.e. $c > \delta$ in the following. Note that $Z_1' < 0$ if $c \leq \delta$. This model describes the situation where virus has not yet mutated. Iwasa

et al. [11] have proved that an interior equilibrium is globally stable, if the terms associated with immune reactions are given by cZ_1I_1 and qZ_1I_1 instead of $\frac{cZ_1I_1}{T+I_1}$ and $\frac{qZ_1I_1}{T+I_1}$ in model (3). However, we showed that the interior equilibrium of one-virus model (3) can be unstable [13]. Since we obtained some local results for model (3) in [13], we will prove the global properties of model (3) in this part.

First of all, we consider the following one-virus model without immune response:

$$\begin{aligned} T' &= 1 - T - \beta_1 T I_1, \\ I_1' &= \beta_1 T I_1 - a I_1. \end{aligned} \tag{4}$$

The immune response is triggered in encountering to foreign antigens. Therefore this model describes the dynamics of the acute phase of HIV infection. Model (4) has two equilibria. One is a healthy equilibrium $E_h = (1, 0)$ which represents a state in which infected cells are absent. The other is infected equilibrium $E_u = (T^*, I_1^*)$. It represents a state in which infected cells are present. Note that there exists E_u in $\mathrm{Int}\mathbb{R}^2_+$ if and only if $R_1 > 1$. We obtain the following theorem for the global stability of two equilibria. The proof of this theorem is similar to the proof of Theorem 1.1.5 in [26].

Theorem 2.2. *If $R_1 \leq 1$, then E_h is globally asymptotically stable (in short, GAS). On the other hand, if $R_1 > 1$, then E_u is GAS.*

Proof. First we consider the local stability of the equilibrium E_h. The Jacobian matrix of the vector field corresponding to model (4) is

$$J = \begin{pmatrix} -1 - \beta_1 I_1 & -\beta_1 T \\ \beta_1 I_1 & \beta_1 T - a \end{pmatrix}.$$

J evaluated at E_h is

$$J_{E_h} = \begin{pmatrix} -1 & -\beta_1 \\ 0 & \beta_1 - a \end{pmatrix}.$$

Eigenvalues of J_{E_h} are "-1" and "$\beta_1 - a$". Remember that $R_1 = \beta_1/a$. If $R_1 < 1$, then E_h is locally asymptotically stable (in short, LAS). To show that E_h is GAS, we define the following function:

$$V = \frac{(T-1)^2}{2} + I_1.$$

If $R_1 \leq 1$, then

$$\begin{aligned} \dot{V} &= (T-1)(1 - T - \beta_1 T I_1) + \beta_1 T I_1 - a I_1 \\ &= (T-1)\{-(T-1) - \beta_1 I_1 (T-1) - \beta_1 I_1\} + \beta_1 T I_1 - a I_1 \\ &= -(1 + \beta_1 I_1)(T-1)^2 + (\beta_1 - a) I_1 \\ &= -(1 + \beta_1 I_1)(T-1)^2 - a(1 - R_1) I_1 \\ &\leq -(1 + \beta_1 I_1)(T-1)^2 \leq 0. \end{aligned}$$

Here "$\dot{}$" denotes the time differentiation along an orbit. Note that $\dot{V} = 0$ if and only if $T = 1$ and $I_1 = 0$ when $R_1 < 1$. Moreover $\dot{V} = 0$ if and only if $T = 1$ when $R_1 = 1$. However, in each case, the largest invariant subset of $\dot{V}(t) = 0$ is the singleton $\{E_h\}$. Thus, by LaSalle Invariance Principle, E_h is GAS on $\mathbb{R}^2_+$ when $R_1 \leq 1$.

Next we consider the local stability of equilibrium E_u. If $R_1 > 1$, then E_u exists in $\mathbb{R}^2_+$. Otherwise E_u does not exist in $\mathbb{R}^2_+$. J evaluated at E_u is

$$J_{E_u} = \begin{pmatrix} -1 - \beta_1 I_1^* & -\beta_1 T^* \\ \beta_1 I_1^* & \beta_1 T^* - a \end{pmatrix}.$$

Note that $\beta_1 T^* - a = 0$. The characteristic equation of J_{E_u} is

$$p^2 + (1 + \beta_1 I_1^*)p + \beta_1^2 T^* I_1^* = 0.$$

Here p denotes the indeterminate of the polynomial. Since $T^* > 0$, $I_1^* > 0$ and $\beta_1 > 0$, all roots of this characteristic equation have negative real part if $R_1 > 1$. This implies that E_u is LAS whenever it exists in $\mathbb{R}^2_+$. Now the stable manifold of E_h is one-dimensional and, since E_h attracts along the T-axis, the stable manifold of E_h lies on T-axis. Then the Butler-McGehee theorem (see [26]) allows one to conclude that no trajectory with positive initial condition can have E_h as an omega limit point. Since the initial value is positive, the omega limit set can not correspond to E_h. If it contains E_h, then it must also contain an entire orbit different from E_h belonging to the stable manifold of E_h. There are only two possible orbits: these are unbounded. But the omega limit set can not contain an unbounded orbit. Therefore, E_h is not a limit point. Now choose a positive (Dulac) function $\rho = 1/(TI_1)$ in Int $\mathbb{R}^2_+$ and denote the right hand side of (4) as $f(T, I_1)$. Then we have

$$\mathrm{div}\rho f = -\frac{1}{T^2 I_1} < 0.$$

Dulac criterion implies that there is no periodic solution in Int $\mathbb{R}^2_+$. Thus, applying Poincare-Bendixon theorem to model (4), we can conclude that E_u is GAS on Int $\mathbb{R}^2_+$ if $R_1 > 1$. □

This theorem implies that if $R_1 > 1$, then HIV spreads in individual, i.e., HIV infects an individual. On the other hand, if $R_1 \leq 1$, then HIV is cleared, i.e., HIV misses infecting an individual.

Further, we give some global and geometric analysis to immunological phenomena for model (3). First, we prove that there exists a lower limit of T.

Lemma 2.3. *Uninfected cells persist uniformly, i.e.,* $\liminf_{t\to\infty} T \geq k_T > 0$*, where* k_T *is a positive constant.*

Proof. It follows from Theorem 2.1 that there exists a positive constant K such that $I_1 \leq K$ for sufficiently large time. Thus we have the following inequality for the first equation of (3):

$$T' \geq 1 - T - \beta_1 TK = 1 - (1 + \beta_1 K)T$$

for sufficiently large time. Therefore $\liminf_{t\to\infty} T \geq 1/(1 + \beta_1 K) = k_T$. □

Remark 1. In similar manner, we can show that uninfected cells persist uniformly for model (2).

Next, we prove the situation where infected cells are absent in a steady state. In [13], we showed that E_H is LAS if $R_1 < 1$. This argument does not state a global behavior but only a local behavior. The following results deal with the global stability of E_H. To obtain the global stability theorem, we need the following Lemma 2.4. We will exploit an analogous techniques given in [28].

Lemma 2.4. *If* $R_1 < 1$*, then infected cells are cleared, i.e.,* $\lim_{t\to\infty} I_1(t) = 0$.

Proof. It follows from the first equation of (3) that

$$T' = 1 - T - \beta_1 T I_1 \leq 1 - T.$$

Thus, integrating the both sides of this inequality over $[0, t]$ gives

$$T(t) \leq 1 + |T_0 - 1|e^{-t}.$$

Given $\varepsilon > 0$, we can choose sufficiently large t_1 such that $|T_0 - 1|e^{-t} \leq \varepsilon$ for $t \geq t_1$. Then $T(t) \leq 1 + \varepsilon$ for all $t \geq t_1$.

The second equation of (3) satisfies

$$I_1' = (\beta_1 T - a - \frac{qZ_1}{T + I_1})I_1 \leq (\beta_1 T - a)I_1.$$

Thus we obtain the following inequality:

$$I_1(t_1 + t) \leq I_1(t_1) \exp\left\{\int_{t_1}^{t_1+t} (\beta_1 T - a)ds\right\}.$$

Remember that $T(t) \leq 1 + \varepsilon$ for all $t \geq t_1$. Hence

$$I_1(t_1 + t) \leq I_1(t_1) \exp\left\{\int_{t_1}^{t_1+t} (\beta_1(1 + \varepsilon) - a)ds\right\}.$$

It follows from the definition of R_1 that

$$I_1(t_1 + t) \leq I_1(t_1) \exp\left\{\int_{t_1}^{t_1+t} (a(R_1 - 1) + \beta_1\varepsilon)ds\right\}.$$

Choosing $\varepsilon > 0$ small enough so that $g \equiv a(1-R_1)-\beta_1\varepsilon > 0$ in the above inequality yields

$$I_1(t + t_1) \leq I_1(t_1)e^{-gt}.$$

Hence $I_1(t + t_1) \to 0$ as $t \to \infty$. i.e. $\lim_{t\to\infty} I_1(t) = 0$. □

Remark 2. In a similar manner, we can show that $\lim_{t\to\infty} I_i(t) = 0$ for all $i = 1, 2, 3, ..., n$ if $R_i < 1$ in the model (2). Here $R_i = \beta_i/a$ $(i = 1, 2, 3, ..., n)$.

Now we shall give the following theorem which proves that E_H is GAS when $R_1 < 1$. Let x_0 denote an initial value of model (3) (i.e. $x_0 = (T_0, I_{10}, Z_{10})$) and $\omega(x_0)$ denote an ω-limit set of orbit through x_0.

Theorem 2.5. *If $R_1 < 1$, then E_H is GAS on $\mathbb{R}^3_+$.*

Proof. It follows from Lemma 2.4 that $\lim_{t\to\infty} I_1(t) = 0$. Thus it is clear that $\lim_{t\to\infty} Z_1(t) = 0$ because of the form of the third equation of (3). This implies that $\omega(x_0)$ exists in the T axis for all $x_0 \in \mathbb{R}^3_+$. Moreover the orbit through the point on the T axis converges to "1" on the T axis. Thus we can conclude that E_H is GAS on $\mathbb{R}^3_+$ by *Theorem A.1* in [14]. □

Remark 3. In a similar manner, we can show that the equilibrium $(1, 0, 0, ..., 0)$ for the model (2) is GAS on $\mathbb{R}^{2n+1}_+$ if $R_i < 1$ for all $i = 1, 2, 3, ..., n$.

Next, we consider the situation where infected cells are present. We are now ready to apply a theorem on average Lyapunov function which is developed in [5] and [10]. There are the other papers associated with average Lyapunov function and property of repeller set (see [8] and [9]). Define

$$X_I = \{(T, I_1, Z_1) \in \mathbb{R}^3_+ : T \geq k_T, k \leq N \leq K\},$$
$$S_I = \{(T, I_1, Z_1) : T \geq k_T, I_1 = 0, Z_1 \geq 0, k \leq N \leq K\}.$$

Here $k_T = 1/(1+\beta_1 K)$ is given in the proof of Lemma 2.1, k and K are also given in the proof of Theorem 2.1. Then X_I is compact and S_I is a compact subset of X_I with empty interior. We can write

$$X_I \setminus S_I = \{(T, I_1, Z_1) : T \geq k_T, I_1 > 0, Z_1 \geq 0, k \leq N \leq K\}.$$

Thus S_I and $X_I \setminus S_I$ are forward invariant sets because of the form of the second equation of (3). Define $P_I = I_1$. Then $P_I : X_I \setminus S_I \to \mathbb{R}^+$ is a C^1-class function and $P_I(x) = 0$ if and only if $x \in S_I$. For $y \in X_I \setminus S_I$, the function

$$\psi_I(y) = \frac{\dot{P}_I(y)}{P_I(y)} = \beta_1 T - a - \frac{qZ_1}{T + I_1}$$

is continuous, where "$\cdot$" denotes the time differentiation along an orbit. Moreover, it is also bounded below, and hence we can define its extension to X_I, still denoted by ψ_I, by setting

$$\psi_I(x) = \liminf_{y \to x, y \in X_I \setminus S_I} \psi_I(y) \quad (x \in S_I).$$

Obviously ψ_I is lower semicontinuous on X_I. If

$$\sup_{t \geq 0} \int_0^t \psi_I(\pi(x, s))ds > 0$$

for all $x \in \omega(S_I)$, we can apply a theorem on average Lyapunov function. Here $\pi(x, s)$ denotes a semiflow generated by the solution of model (3) and $\omega(S_I)$ is defined as $\omega(S_I) = \bigcup_{x \in S_I} \omega(x)$.

Lemma 2.6. *If $R_1 > 1$, then infected cells persist uniformly, i.e., $\liminf_{t \to \infty} I_1(t) > k_I > 0$, where k_I is a positive constant.*

Proof. By Theorem 2.2, it is clear that $\omega(S_I) = \{E_H\}$. It suffices to show the above condition only for $x = E_H$. In fact, substituting $x = E_H$ into $\psi_I(x)$ gives

$$\psi_I(x) = \beta_1 - a = a(\frac{\beta_1}{a} - 1) = a(R_1 - 1).$$

Since $R_1 > 1$, $\psi_I(x) = a(R_1 - 1) > 0$. This implies that

$$\sup_{t \geq 0} \int_0^t \psi_I(\pi(x, s))ds > 0$$

for all $x \in \omega(S_I)$. Therefore there is a compact forward invariant set Y_I with *dist* $(Y_I, S_I) > 0$ such that every semiorbit in $X_I \setminus S_I$ is ultimately in Y_I, i.e., there exists a positive constant k_I such that $\liminf_{t \to \infty} I_1(t) > k_I$ [10]. □

We can choose a constant k_I such that $0 < k_I < 1/a - 1/\beta_1$. Lemma 2.6 states that immune system can not eradicate HIV forever if $R_1 > 1$.

Moreover we consider the situation where immune cells are present. Set

$$X_Z = \{(T, I_1, Z_1) : T \geq k_T, I_1 \geq k_I, Z_1 \geq 0, k \leq N \leq K\},$$
$$S_Z = \{(T, I_1, Z_1) : T \geq k_T, I_1 \geq k_I, Z_1 = 0, k \leq N \leq K\}.$$

Moreover, define $P_Z = Z_1$. For $z \in X_Z \setminus S_Z$, the function

$$\psi_Z(z) = \frac{\dot{P}_Z(z)}{P_Z(z)} = \frac{cI_1}{T + I_1} - \delta$$

is continuous. In addition, it is bounded below, and hence we can define its extension to X_Z, which is still denoted by ψ_Z, by setting

$$\psi_Z(x) = \liminf_{z \to x, z \in X_Z \setminus S_Z} \psi_Z(z) \quad (x \in S_Z).$$

Obviously ψ_Z is lower semicontinuous on X_Z. In the similar manner, if

$$\sup_{t \geq 0} \int_0^t \psi_Z(\pi(x,s))ds > 0$$

for all $x \in \omega(S_Z)$, then we can also apply a theorem on average Lyapunov function.

Lemma 2.7. *If* $R_1 > \dfrac{a\delta}{c-\delta} + 1$, *then immune cells persist uniformly, which is equivalent to* $\liminf_{t\to\infty} Z_1(t) > k_Z > 0$, *where* k_Z *is a positive constant.*

Proof. It is clear that $\omega(S_Z) = \{E_U\}$ by Theorem 2.1 because $R_1 > 1$. It suffices to show the above condition only for $x = E_U$. In fact, substituting $x = E_U$ into $\psi_Z(x)$ gives

$$\psi_Z(x) = \frac{c(\dfrac{1}{a} - \dfrac{1}{\beta_1})}{\dfrac{a}{\beta_1} + \dfrac{1}{a} - \dfrac{1}{\beta_1}} - \delta = \frac{\dfrac{c}{a}(R_1 - 1)}{1 + \dfrac{1}{a}(R_1 - 1)} - \delta.$$

Since $R_1 > \dfrac{a\delta}{c-\delta} + 1$, $\psi_Z(x) = \{c/a(R_1-1)\}/\{1 + 1/a(R_1-1)\} - \delta > 0$. This implies that

$$\sup_{t \geq 0} \int_0^t \psi_Z(\pi(x,s))ds > 0$$

for all $x \in \omega(S_Z)$. Therefore there is a compact forward invariant set Y_Z with *dist* $(Y_Z, S_Z) > 0$ such that every semiorbit in $X_Z \setminus S_Z$ is ultimately in Y_Z, i.e., there exists a positive constant k_Z such that $\liminf_{t\to\infty} Z_1(t) > k_Z$ [10]. □

It is important for us to check the existence of uninfected cells, infected cells and immune cells in $\mathrm{Int}\mathbb{R}^3_+$. Here we define "Permanence" as follows:

Definition 2.8. System (3) is permanent if and only if

$$k_T \leq \liminf_{t\to+\infty} T(t) \leq \limsup_{t\to+\infty} T(t) \leq K_T,$$
$$k_I \leq \liminf_{t\to+\infty} I(t) \leq \limsup_{t\to+\infty} I(t) \leq K_I,$$
$$k_Z \leq \liminf_{t\to+\infty} Z(t) \leq \limsup_{t\to+\infty} Z(t) \leq K_Z,$$

for any solutions of model (3) with any $x_0 \in \mathrm{Int}\ \mathbb{R}^3_+$. Here k_i and K_i $(i = T, I, Z)$ are positive constants which are independent of x_0.

Thus, if model (3) is permanent, then uninfected cells, infected cells and immune cells exist persistently in individual. By Lemma 2.3, Lemma 2.6 and Lemma 2.7, we have the following result on permanence.

Theorem 2.9. *If* $R_1 > \dfrac{a\delta}{c-\delta} + 1$, *then model (3) is permanent.*

Theorem 2.9 states that the immune system can not eradicate HIV forever under the condition $R_1 > a\delta/(c-\delta) + 1$, even if immune system attacks HIV. In practice, most of patients who are infected with HIV develop AIDS after the long fight between immune system and HIV.

2.2. **Multi-virus model.** Model (2) has very complex mathematical structures such as limit cycle, quasi-periodic attractors, chaotic attractors, and so on [13]. In order to understand the complexity, we have to demonstrate the existence and stability conditions of the equilibria although the global behavior may be very difficult. We will explain elegant relations between these conditions in this paper.

System (2) has various equilibria and the maximum number of nonnegative equilibria of (2) is given by the following expression:

$$({}_nC_n + {}_nC_{n-1} + ... + {}_nC_1) + ({}_nC_n \cdot {}_nC_1 + {}_nC_{n-1} \cdot {}_{n-1}C_1 + ... + {}_nC_1 \cdot {}_1C_1) + 1.$$

Further these equilibria can be divided into three types (i), (ii), (iii):

(i) *Controlled equilibrium* : E_c-type, which means that all specific immune strains are activated by its corresponding HIV strains. For example, E_c-type equilibrium can include the following equilibrium:

$$(\tilde{T}; \tilde{I}_1, ..., \tilde{I}_k, 0, ..., 0; \tilde{Z}_1, ..., \tilde{Z}_k, 0, ..., 0)$$

where

$$\tilde{T} = \frac{2}{1 + \sqrt{1 + \frac{4\delta \sum_{l=1}^{k} \beta_l}{c - k\delta}}},$$

$$\tilde{I}_1 = ... = \tilde{I}_k = \frac{-1 + \sqrt{1 + \frac{4\delta \sum_{l=1}^{k} \beta_l}{c - k\delta}}}{2 \sum_{l=1}^{k} \beta_l},$$

$$\tilde{Z}_j = \frac{(\beta_j \tilde{T} - a)(\tilde{T} + \sum_{l=1}^{k} \tilde{I}_l)}{q}$$

for $j = 1, ..., k$. The other equilibria can be written in the similar manner. From the definition of E_c-type, the number of E_c-type equilibrium is ${}_nC_n + {}_nC_{n-1} + ... + {}_nC_1$.

(ii) *Uncontrolled equilibrium* : E_u-type, which means that one of all specific immune strains is inactivated but the other immune strains are activated by its corresponding HIV strains. For example, E_u-type equilibrium can include the following equilibrium:

$$(\hat{T}; \hat{I}_1, ..., \hat{I}_k, 0, ..., 0; 0, \hat{Z}_2, ..., \hat{Z}_k, 0, ..., 0)$$

where

$$\hat{T} = \frac{a}{\beta_1},$$

$$\hat{I}_2 = ... = \hat{I}_k = \frac{1 - \hat{T} + \beta_1 \hat{T}^2}{\{\sum_{l=2}^{k} \beta_l + \beta_1 (\frac{c}{\delta} - (k-1))\}\hat{T}},$$

$$\hat{I}_1 = (\frac{c}{\delta} - (k-1))\hat{I}_j - \hat{T},$$

$$\hat{Z}_j = \frac{c(\beta_j \hat{T} - a)}{q\delta} \hat{I}_j$$

for $j = 2, ..., k$. The other equilibria can be written in the similar manner. From the definition of E_u-type, the number of E_u-type equilibrium is ${}_nC_n \cdot {}_nC_1 + {}_nC_{n-1} \cdot {}_{n-1}C_1 + ... + {}_nC_1 \cdot {}_1C_1$.

(iii) *Healthy equilibrium* : E_h-type, which means that all HIV strains do not exist. In this type, $(1; 0, ..., 0; 0, ..., 0)$ is a unique equilibrium.

For arbitrary strain number, we can obtain the exact expression of equilibria. This implies that we will obtain the general existence condition of equilibria but the general analysis is very complex and tedious. Therefore, in order to avoid a mathematical difficulty, we let $n = 3$ and discuss with this model because the model with $n = 3$ has enough information to understand the mathematical structure. The equilibria can be written out as follows for $n = 3$:

$$
\begin{aligned}
&E_H = (T_H; 0, 0, 0; 0, 0, 0),\ E_1 = (T_1; I_{1:1}, 0, 0; 0, 0, 0),\ E_2 = (T_2; 0, I_{2:2}, 0; 0, 0, 0),\\
&E_3 = (T_3; 0, 0, I_{3:3}; 0, 0, 0),\ E_1^1 = (T_1^1; I_{1:1}^1, 0, 0; Z_{1:1}^1, 0, 0),\\
&E_2^2 = (T_2^2; 0, I_{2:2}^2, 0; 0, Z_{2:2}^2, 0),\\
&E_3^3 = (T_3^3; 0, 0, I_{3:3}^3; 0, 0, Z_{3:3}^3), \quad E_{12}^1 = (T_{12}^1; I_{1:12}^1, I_{2:12}^1, 0; Z_{1:12}^1, 0, 0),\\
&E_{13}^1 = (T_{13}^1; I_{1:13}^1, 0, I_{3:13}^1; Z_{1:13}^1, 0, 0), \quad E_{23}^2 = (T_{23}^2; 0, I_{2:23}^2, I_{3:23}^2; 0, Z_{2:23}^2, 0),\\
&E_{12}^2 = (T_{12}^2; I_{1:12}^2, I_{2:12}^2, 0; 0, Z_{2:12}^2, 0), \quad E_{13}^3 = (T_{13}^3; I_{1:13}^3, 0, I_{3:13}^3; 0, 0, Z_{3:13}^3),\\
&E_{23}^3 = (T_{23}^3; 0, I_{2:23}^3, I_{3:23}^3; 0, 0, Z_{3:23}^3), \quad E_{12}^{12} = (T_{12}^{12}; I_{1:12}^{12}, I_{2:12}^{12}, 0; Z_{1:12}^{12}, Z_{2:12}^{12}, 0),\\
&E_{13}^{13} = (T_{13}^{13}; I_{1:13}^{13}, 0, I_{3:13}^{13}; Z_{1:13}^{13}, 0, Z_{3:13}^{13}), \quad E_{23}^{23} = (T_{23}^{23}; 0, I_{2:23}^{23}, I_{3:23}^{23}; 0, Z_{2:23}^{23}, Z_{3:23}^{23}),
\end{aligned}
$$

$$
\begin{aligned}
E_{123}^{12} &= (T_{123}^{12}; I_{1:123}^{12}, I_{2:123}^{12}, I_{3:123}^{12}; Z_{1:123}^{12}, Z_{2:123}^{12}, 0),\\
E_{123}^{13} &= (T_{123}^{13}; I_{1:123}^{13}, I_{2:123}^{13}, I_{3:123}^{13}; Z_{1:123}^{13}, 0, Z_{3:123}^{13}),\\
E_{123}^{23} &= (T_{123}^{23}; I_{1:123}^{23}, I_{2:123}^{23}, I_{3:123}^{23}; 0, Z_{2:123}^{23}, Z_{3:123}^{23}),\\
E_+ &= (T_+; I_{1:+}, I_{2:+}, I_{3:+}; Z_{1:+}, Z_{2:+}, Z_{3:+})
\end{aligned}
$$

and these equilibria can be divided into three types:

$$
\begin{aligned}
E_c &= \{E_1^1, E_2^2, E_3^3, E_{12}^{12}, E_{13}^{13}, E_{23}^{23}, E_+\},\\
E_u &= \{E_1, E_2, E_3, E_{12}^1, E_{13}^1, E_{23}^2, E_{12}^2, E_{13}^3, E_{23}^3, E_{123}^{12}, E_{123}^{13}, E_{123}^{23}\},\\
E_h &= \{E_H\}.
\end{aligned}
$$

In this part, we will focus a local behavior of the model (2). For theoretical results about some threshold phenomenon of immnue inducement refer to [15].

2.2.1. *Existence condition.* We introduce a basic reproductive number $R_j = \beta_j/a$ $(j = 1, ..., n)$. For our convenience, let $\beta_1 < \beta_2 < ... < \beta_n$ without loss of generality. Then the basic reproductive numbers satisfy the following relation:

$$R_1 < R_2 < ... < R_n.$$

It is clear that E_H always exists in $\mathbb{R}_+^7$.

Since

$$I_{1:1} = \frac{1}{a} - \frac{1}{\beta_1}, \quad I_{2:2} = \frac{1}{a} - \frac{1}{\beta_2}, \quad I_{3:3} = \frac{1}{a} - \frac{1}{\beta_3},$$

E_1, E_2, E_3 exists in $\mathbb{R}_+^7$ if $R_1 > 1$, $R_2 > 1$, $R_3 > 1$, respectively.

It is clear that $T_1^1 > 0$, $T_2^2 > 0$, $T_3^3 > 0$, $I_{1:1}^1 > 0$, $I_{2:2}^2 > 0$, $I_{3:3}^3 > 0$ because E_1^1, E_2^2, E_3^3 belong to E_c-type equilibrium. Therefore, we have only to check conditions

which ensure $Z^1_{1:1} > 0$, $Z^2_{2:2} > 0$, $Z^3_{3:3} > 0$. Since

$$Z^1_{1:1} = \frac{(\beta_1 T^1_1 - a)(T^1_1 + I^1_{1:1})}{q},\ Z^2_{2:2} = \frac{(\beta_2 T^2_2 - a)(T^2_2 + I^2_{2:2})}{q},$$
$$Z^3_{3:3} = \frac{(\beta_3 T^3_3 - a)(T^3_3 + I^3_{3:3})}{q},$$
$$T^1_1 = \frac{2}{1+\sqrt{1+\frac{4\delta\beta_1}{c-\delta}}},\ T^2_2 = \frac{2}{1+\sqrt{1+\frac{4\delta\beta_2}{c-\delta}}},\ T^3_3 = \frac{2}{1+\sqrt{1+\frac{4\delta\beta_3}{c-\delta}}},$$

E^1_1, E^2_2, E^3_3 exists in $\mathbb{R}^7_+$ if $R_1 > 1+a\delta/(c-\delta)$, $R_2 > 1+a\delta/(c-\delta)$, $R_3 > 1+a\delta/(c-\delta)$, respectively.

It is clear that $T^1_{12} > 0$, $T^1_{13} > 0$, $T^2_{23} > 0$, $T^2_{12} > 0$, $T^3_{13} > 0$, $T^3_{23} > 0$ because E^1_{12}, E^1_{13}, E^2_{23}, E^2_{12}, E^3_{13}, E^3_{23} belong to E_u-type equilibrium. Since

$$I^1_{1:12} = \frac{1-T^1_{12}+\beta_2(T^1_{12})^2}{T^1_{12}\{\beta_1+\beta_2(\frac{c}{\delta}-1)\}}, I^1_{1:13} = \frac{1-T^1_{13}+\beta_3(T^1_{13})^2}{T^1_{13}\{\beta_1+\beta_3(\frac{c}{\delta}-1)\}}, I^2_{2:23} = \frac{1-T^2_{23}+\beta_3(T^2_{23})^2}{T^2_{23}\{\beta_2+\beta_3(\frac{c}{\delta}-1)\}},$$
$$I^2_{2:12} = \frac{1-T^2_{12}+\beta_1(T^2_{12})^2}{T^2_{12}\{\beta_2+\beta_1(\frac{c}{\delta}-1)\}}, I^3_{3:13} = \frac{1-T^3_{13}+\beta_1(T^3_{13})^2}{T^3_{13}\{\beta_3+\beta_1(\frac{c}{\delta}-1)\}}, I^3_{3:23} = \frac{1-T^3_{23}+\beta_2(T^3_{23})^2}{T^3_{23}\{\beta_3+\beta_2(\frac{c}{\delta}-1)\}},$$

$I^1_{1:12} > 0$, $I^1_{1:13} > 0$, $I^2_{2:23} > 0$, $I^2_{2:12} > 0$, $I^3_{3:13} > 0$, $I^3_{3:23} > 0$ since $\limsup_{t\to\infty} T(t) \le 1$ for (2). Moreover the other components of these equilibria are as follows:

$$I^1_{2:12} = (\frac{c}{\delta}-1)I^1_{1:12} - T^1_{12}, \qquad I^1_{3:13} = (\frac{c}{\delta}-1)I^1_{1:13} - T^1_{13}, \qquad I^2_{3:23} = (\frac{c}{\delta}-1)I^2_{2:23} - T^2_{23},$$
$$I^2_{1:12} = (\frac{c}{\delta}-1)I^2_{2:12} - T^2_{12}, \qquad I^3_{1:13} = (\frac{c}{\delta}-1)I^3_{3:13} - T^3_{13}, \quad I^3_{2:23} = (\frac{c}{\delta}-1)I^3_{3:23} - T^3_{23},$$
$$Z^1_{1:12} = \frac{c(\beta_1 T^1_{12}-a)I^1_{1:12}}{q\delta}, \qquad Z^1_{1:13} = \frac{c(\beta_1 T^1_{13}-a)I^1_{1:13}}{q\delta}, \qquad Z^2_{2:23} = \frac{c(\beta_2 T^2_{23}-a)I^2_{2:23}}{q\delta},$$
$$Z^2_{2:12} = \frac{c(\beta_2 T^2_{12}-a)I^2_{2:12}}{q\delta}, \qquad Z^3_{3:13} = \frac{c(\beta_3 T^3_{13}-a)I^3_{3:13}}{q\delta}, \qquad Z^3_{3:23} = \frac{c(\beta_3 T^3_{23}-a)I^3_{3:23}}{q\delta}.$$

Therefore, we can obtain the following conditions:

$$I^1_{2:12} > 0,\ Z^1_{1:12} > 0 \iff R_1 > R_2 > \frac{1+\sqrt{1+\frac{4\beta_1\delta}{c-\delta}}}{2} \iff E^1_{12} \in \mathbb{R}^7_+,$$
$$I^1_{3:13} > 0,\ Z^1_{1:13} > 0 \iff R_1 > R_3 > \frac{1+\sqrt{1+\frac{4\beta_1\delta}{c-\delta}}}{2} \iff E^1_{13} \in \mathbb{R}^7_+,$$
$$I^2_{3:23} > 0,\ Z^2_{2:23} > 0 \iff R_2 > R_3 > \frac{1+\sqrt{1+\frac{4\beta_2\delta}{c-\delta}}}{2} \iff E^2_{23} \in \mathbb{R}^7_+,$$
$$I^2_{1:12} > 0,\ Z^2_{2:12} > 0 \iff R_2 > R_1 > \frac{1+\sqrt{1+\frac{4\beta_2\delta}{c-\delta}}}{2} \iff E^2_{12} \in \mathbb{R}^7_+,$$
$$I^3_{1:13} > 0,\ Z^3_{3:13} > 0 \iff R_3 > R_1 > \frac{1+\sqrt{1+\frac{4\beta_3\delta}{c-\delta}}}{2} \iff E^3_{13} \in \mathbb{R}^7_+,$$
$$I^3_{2:23} > 0,\ Z^3_{3:23} > 0 \iff R_3 > R_2 > \frac{1+\sqrt{1+\frac{4\beta_3\delta}{c-\delta}}}{2} \iff E^3_{23} \in \mathbb{R}^7_+.$$

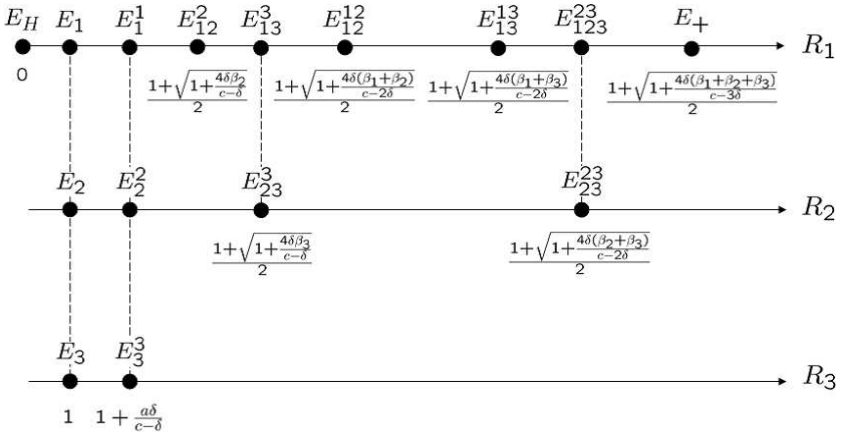

FIGURE 1. The existence condition of equilibria for $n = 3$ with $R_1 < R_2 < R_3$: A bullet mark denotes the bifurcation point. This means that if basic reproductive number exceeds the bullet mark then its corresponding equilibrium exists in $\mathbb{R}^7_+$. In the figure, we assumed that $\beta_3/(c-\delta) < (\beta_1+\beta_2)/(c-2\delta)$. Otherwise, the position of E^3_{13} and E^{12}_{12} is exchanged.

In the similar manner, we have the existence conditions for E^{12}_{12}, E^{13}_{13}, E^{23}_{23}, E^{12}_{123}, E^{13}_{123}, E^{23}_{123}, E_+:

$$\frac{1+\sqrt{1+\dfrac{4(\beta_1+\beta_2)\delta}{c-2\delta}}}{2} < R_1,\ R_2 \iff E^{12}_{12} \in \mathbb{R}^7_+,$$

$$\frac{1+\sqrt{1+\dfrac{4(\beta_1+\beta_3)\delta}{c-2\delta}}}{2} < R_1,\ R_3 \iff E^{13}_{13} \in \mathbb{R}^7_+,$$

$$\frac{1+\sqrt{1+\dfrac{4(\beta_2+\beta_3)\delta}{c-2\delta}}}{2} < R_2,\ R_3 \iff E^{23}_{23} \in \mathbb{R}^7_+,$$

$$\frac{1+\sqrt{1+\dfrac{4(\beta_1+\beta_2)\delta}{c-2\delta}}}{2} < R_3 < R_1,\ R_2 \iff E^{12}_{123} \in \mathbb{R}^7_+,$$

$$\frac{1+\sqrt{1+\dfrac{4(\beta_1+\beta_3)\delta}{c-2\delta}}}{2} < R_2 < R_1,\ R_3 \iff E^{13}_{123} \in \mathbb{R}^7_+,$$

$$\frac{1+\sqrt{1+\dfrac{4(\beta_2+\beta_3)\delta}{c-2\delta}}}{2} < R_1 < R_2,\ R_3 \iff E^{23}_{123} \in \mathbb{R}^7_+,$$

$$\frac{1+\sqrt{1+\dfrac{4(\beta_1+\beta_2+\beta_3)\delta}{c-3\delta}}}{2} < R_1,\ R_2,\ R_3 \iff E_+ \in \mathbb{R}^7_+,$$

Here we assume that $c - 3\delta > 0$.

However, E^1_{12}, E^1_{13}, E^2_{23}, E^{12}_{123}, E^{13}_{123} can not exist in $\mathbb{R}^7_+$ because of $R_1 < R_2 < R_3$. Then the number of equilibria which can exist in $\mathbb{R}^7_+$ is

$$({}_3C_3 + {}_3C_2 + {}_3C_1) + (\frac{{}_3C_3 \cdot {}_3C_1}{1} + \frac{{}_3C_2 \cdot {}_2C_1}{2} + \frac{{}_3C_1 \cdot {}_1C_1}{3}) + 1 = 15.$$

In general, the number of equilibria which can exist in nonnegative cone is given by the following expression:

$$({}_nC_n + {}_nC_{n-1} + ... + {}_nC_1) + (\frac{{}_nC_n \cdot {}_nC_1}{1} + \frac{{}_nC_{n-1} \cdot {}_{n-1}C_1}{2} + ... + \frac{{}_nC_1 \cdot {}_1C_1}{n}) + 1.$$

In this way, we can obtain a relation among the existence condition for the equilibria (see Fig. 1) and also have the relation for $n \geq 3$ in the same manner.

2.2.2. *Instability condition of boundary equilibria.* For $n = 1$, some stability condition of equilibria was obtained in [13]. Furthermore, we observed strange attractors and periodic attractors for $n = 2$ in [13]. That is, the behavior of (2) tends to be complex as viral diversity increases.

In this part, we investigate the instability condition of boundary equilibria for $n = 3$ except E^1_{12}, E^1_{13}, E^2_{23}, E^{12}_{123}, E^{13}_{123}.

Let us evaluate J at equilibrium E_H. Here J denotes the Jacobian matrix of (2) for $n = 3$. The eigenvalues of J_{E_H} are -1, $\beta_j - a$ $(j = 1, 2, 3)$, $-\delta$, $-\delta$ and $-\delta$. Remember that $R_j = \beta_j/a$ $(j = 1, 2, 3)$ and $R_1 < R_2 < R_3$. If $R_3 < 1$, then E_H is LAS. But if $R_3 > 1$, then E_H is unstable.

For E_1, one of the eigenvalues of J_{E_1} is $\beta_2 T_1 - a$. However $\beta_2 T_1 - a$ is always positive because of $R_1 < R_2$. This implies that E_1 is always unstable. In the similar manner, E_2 is also always unstable.

For E_3, the eigenvalues of J_{E_3} are p_1, p_2, $\beta_1 T_3 - a$, $\beta_2 T_3 - a$, $-\delta$, $-\delta$ and $cI_{3:3}/(T_3 + I_{3:3}) - \delta$. Here p_1 and p_2 are the roots of the following equation:

$$p^2 + (1 + \beta_3 I_{3:3})p + \beta_3^2 T_3 I_{3:3} = 0.$$

From the Routh-Hurwitz criterion, the real part of p_1 and p_2 are negative. Further $\beta_1 T_3 - a$ and $\beta_2 T_3 - a$ are negative because of $R_1 < R_2 < R_3$. Therefore, if $cI_{3:3}/(T_3 + I_{3:3}) - \delta < 0$, then E_3 is LAS. By substituting T_3 and $I_{3:3}$ into the inequality, we obtain that

$$cI_{3:3}/(T_3 + I_{3:3}) - \delta < 0 \iff R_3 < 1 + \frac{a\delta}{c - \delta}.$$

Thus, if $R_3 < 1 + a\delta/(c - \delta)$, then E_3 is LAS. But if $R_3 > 1 + a\delta/(c - \delta)$, then E_3 is unstable.

For E^1_1, one of the eigenvalues of $J_{E^1_1}$ is $\beta_3 T^1_1 - a$. If $\beta_3 T^1_1 - a < 0$, then E^1_1 can be stable although it is a necessary condition. By substituting T^1_1 into the above inequality, we obtain that

$$\beta_3 T^1_1 - a < 0 \iff R_3 < \frac{1 + \sqrt{1 + \dfrac{4\delta\beta_1}{c - \delta}}}{2}.$$

Remember that the existence condition of E^1_1 is

$$1 + \frac{a\delta}{(c - \delta)} < R_1.$$

Note that the above condition is equivalent to

$$\frac{1+\sqrt{1+\dfrac{4\delta\beta_1}{c-\delta}}}{2} < R_1.$$

This implies that E_1^1 is always unstable because of $R_1 < R_3$. In the similar manner, E_2^2 is also unstable.

For E_3^3, the eigenvalues of $J_{E_3^3}$ are p_1, p_2, p_3, $\beta_1 T_3^3 - a$, $\beta_2 T_3^3 - a$, $-\delta$ and $-\delta$. Here p_1, p_1 and p_3 are the roots of the following equation:

$$|p\cdot Q - J_{E_3^3}| = \begin{vmatrix} p+1+\beta_3 I_{3:3}^3 & \beta_3 T_3^3 & 0 \\ -\beta_3 I_{3:3}^3 - \dfrac{\delta}{c}(\beta_3 T_3^3 - a) & p - \dfrac{\delta}{c}(\beta_3 T_3^3 - a) & \dfrac{q\delta}{c} \\ \dfrac{\delta}{q}(\beta_3 T_3^3 - a) & -\dfrac{c-\delta}{q}(\beta_3 T_3^3 - a) & p \end{vmatrix} = 0,$$

where Q is a 3×3 identity matrix. Assume that p_1, p_2, p_3 have negative real parts. Refer to [13] for a condition satisfying the above assumption. Therefore, if $\beta_2 T_3^3 - a < 0$, then E_3^3 is LAS. By substituting T_3^3 into the inequality, we obtain that

$$\beta_2 T_3^3 - a < 0 \iff R_2 < \frac{1+\sqrt{1+\dfrac{4\delta\beta_3}{c-\delta}}}{2}.$$

Thus, if $R_2 < (1+\sqrt{1+4\delta\beta_3/(c-\delta)})/2$ and p_1, p_2, p_3 have negative real parts, then E_3^3 is LAS. But if $R_2 > (1+\sqrt{1+4\delta\beta_3/(c-\delta)})/2$, then E_3^3 is unstable.

For E_{12}^2, one of the eigenvalues of $J_{E_{12}^2}$ is $\beta_3 T_{12}^2 - a$. However $\beta_3 T_{12}^2 - a$ is always positive because of $R_1 < R_3$. This implies that E_{12}^2 is always unstable. In a similar manner, E_{13}^3 is also always unstable.

For E_{23}^3, two of the eigenvalues of $J_{E_{23}^3}$ are $\beta_1 T_{23}^3 - a$ and $cI_{2:23}^3/(T_{23}^3 + I_{2:23}^3 + I_{3:23}^3) - \delta$. Since $R_1 < R_2$, $\beta_1 T_{23}^3 - a$ is always negative. Therefore, if $cI_{2:23}^3/(T_{23}^3 + I_{2:23}^3 + I_{3:23}^3) - \delta > 0$, then E_{23}^3 is unstable although it is a sufficient condition. Remark that this equilibrium can be stable with reasonable condition. By substituting T_{23}^3, $I_{2:23}^3$, and $I_{3:23}^3$ into the above inequality, we obtain that

$$\begin{aligned} \frac{cI_{2:23}^3}{T_{23}^3 + I_{2:23}^3 + I_{3:23}^3} - \delta > 0 &\iff I_{2:23}^3 > I_{3:23}^3 \\ &\iff R_2 > \frac{1+\sqrt{1+\dfrac{4\delta(\beta_2+\beta_3)}{c-2\delta}}}{2}. \end{aligned}$$

Note that $T_{23}^3 + I_{2:23}^3 + I_{3:23}^3 = cI_{3:23}^3/\delta$. Thus, if $R_2 > (1+\sqrt{1+4\delta(\beta_2+\beta_3)/(c-2\delta)})/2$, then E_{23}^3 is unstable.

For E_{12}^{12}, one of the eigenvalues of $J_{E_{12}^{12}}$ is $\beta_3 T_{12}^{12} - a$. Therefore, if $\beta_3 T_{12}^{12} - a < 0$, then E_{12}^{12} can be stable. By substituting T_{12}^{12} into the above inequality, we obtain that

$$\beta_3 T_{12}^{12} - a < 0 \iff R_3 < \frac{1+\sqrt{1+\dfrac{4\delta(\beta_1+\beta_2)}{c-2\delta}}}{2}.$$

However it is impossible because of the existence condition of E_{12}^{12}. That is, E_{12}^{12} is always unstable. In the similar manner, E_{13}^{13} is also always unstable.

For E_{23}^{23}, one of the eigenvalues of $J_{E_{23}^{23}}$ is $\beta_1 T_{23}^{23} - a$. Therefore, if $\beta_1 T_{23}^{23} - a > 0$, then E_{23}^{23} is unstable. Remark that this equilibrium can be stable with reasonable condition. By substituting T_{23}^{23} into the above inequality, we obtain that

$$\beta_1 T_{23}^{23} - a > 0 \iff R_1 > \frac{1 + \sqrt{1 + \dfrac{4\delta(\beta_2 + \beta_3)}{c - 2\delta}}}{2}.$$

Thus, if $R_1 > (1 + \sqrt{1 + 4\delta(\beta_2 + \beta_3)/(c - 2\delta)})/2$, then E_{23}^{23} is unstable.

For E_{123}^{23}, one of the eigenvalues of $J_{E_{123}^{23}}$ is $cI_{1:123}^{23}/(T_{123}^{23} + I_{1:123}^{23} + I_{2:123}^{23} + I_{3:123}^{23}) - \delta$. Therefore, if $cI_{1:123}^{23}/(T_{123}^{23} + I_{1:123}^{23} + I_{2:123}^{23} + I_{3:123}^{23}) - \delta > 0$, then E_{123}^{23} is unstable. Remark that this equilibrium can be stable with reasonable condition. By substituting T_{123}^{23}, $I_{1:123}^{23}$, $I_{2:123}^{23}$ and $I_{3:123}^{23}$ into the above inequality, we obtain that

$$\frac{cI_{1:123}^{23}}{T_{123}^{23} + I_{1:123}^{23} + I_{2:123}^{23} + I_{3:123}^{23}} - \delta > 0 \iff I_{1:123}^{23} > I_{2:123}^{23} = I_{3:123}^{23}$$

$$\iff R_1 > \frac{1 + \sqrt{1 + \dfrac{4\delta(\beta_1 + \beta_2 + \beta_3)}{c - 3\delta}}}{2}.$$

Thus, if $R_1 > (1 + \sqrt{1 + 4\delta(\beta_1 + \beta_2 + \beta_3)/(c - 3\delta)})/2$, then E_{123}^{23} is unstable.

In this way, we obtain instability conditions of the boundary equilibria (see Fig. 2) and also can obtain the condition for $n \geq 3$ in the same manner. For $n = 3$, the

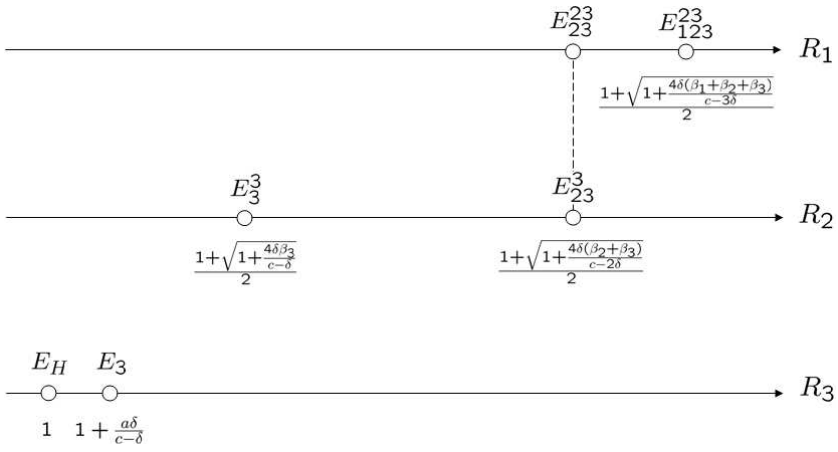

FIGURE 2. The instability condition of boundary equilibria for $n = 3$ with $R_1 < R_2 < R_3$: A circle mark denotes the threshold point. This means that if the basic reproductive number exceeds the circle mark then its corresponding equilibrium becomes surely unstable although it is a sufficient condition. E_1, E_2, E_1^1, E_2^2, E_{12}^2, E_{13}^3, E_{12}^{12}, and E_{13}^{13} are always unstable.

equilibria which can be stable are E_H, E_3, E_3^3, E_{23}^3, E_{23}^{23}, E_{123}^{23}, and E_+. The other equilibria are always unstable whenever they exist in $\mathbb{R}_+^7$. Comparing Figure 1 with 2, we can note as follows. If an equilibrium which can be stable bifurcates in $\mathbb{R}_+^7$, then all existing equilibria become unstable. We can conclude that two equilibria can not be stable simultaneously. That is, all boundary equilibria are unstable

whenever the interior equilibrium exists for arbitrary n. Therefore, our conjecture is that (2) is permanent whenever the interior equilibrium exists. To prove this is our future work.

3. **Simulation.** We investigate how equilibrium distribution of uninfected CD4$^+$ T cells changes with respect to the change in the parameter c or δ for $n = 3$. Numerical simulations are implemented with the following parameters

$$\beta_1 = 7.0, \beta_2 = 10.0, \beta_3 = 12.0, a = 2.0, \delta = 2.0, c = 40 \text{ and } q = 40. \tag{5}$$

So far as numerical simulations were performed with (5), we confirmed that one of equilibria is stable. Therefore we will plot the number of uninfected cells at the stable equilibrium. Firstly we investigate how the maximum proliferation of CTLs affects the structure of populations in equilibrium by using c as our control parameter (see Fig. 3). As analytical results suggest, uninfected cells in equilibrium

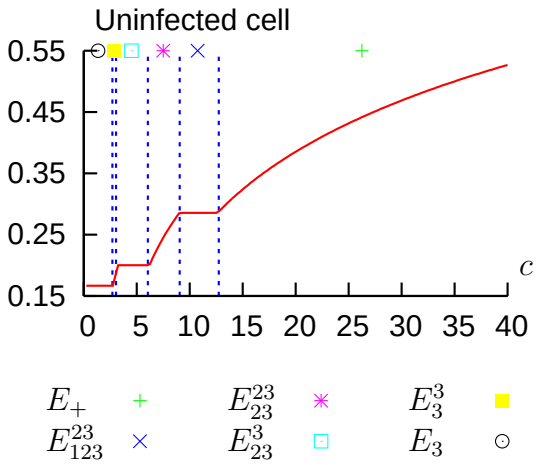

FIGURE 3. Equilibrium distribution of uninfected CD4 T cells with respect to c. Parameter c measures the maximum proliferation of CTLs. Active proliferative CTL allows the invasion of viral strains with lower infectivity.

increase with c increasing if stable equilibrium is E_c-type. On the other hand, uninfected cell count does not change with c increasing if stable equilibrium is E_u-type. If the proliferation of CTLs increases, interestingly, the immune system allows the invasion of HIV strain type 2 and 1, which should possess lower infectivity than HIV strain type 3. Although uninfected CD4$^+$ T cell count increases as c increases, the diversity of viral strains also increases. Next we investigate how the death rate of CTLs affects to determine the structure of populations. Here δ is used our control parameter. As analytical results suggest, uninfected cells in equilibrium decrease with δ increasing f stable equilibrium is E_c-type. On the other hand, uninfected cell count does not change with δ increasing if stable equilibrium is E_u-type. Equilibrium distribution in Figure 4 can be interpreted similarly to that in Figure 3 in the opposite way: diversity of viral strains decreases because uninfected CD4$^+$ T cell count decreases.

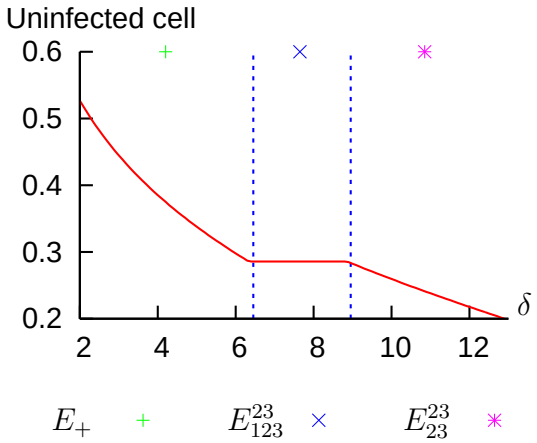

FIGURE 4. Equilibrium distribution of uninfected CD4 T cells with respect to δ. Parameter δ measures the death rate of CTLs. High death rate of CTLs reduces immunosuppression of infected cells. This leads to more competition and competitive exclusion.

4. **Discussion.** Today, there are still many problems surrounding HIV infection that have not yet been completely elucidated, in particular the problems on viral diversity, on so long asymptomatic phase and on collapse of immune system. Mathematical models have contributed to solve many problems on virus infections. In fact, the models are exploited to provide estimation for rate constants of HIV dynamics (see [3], [4], [6], [18], [19]), clear views of complex interactions between virus and immune system (see [11], [12], [22], [23], [24], [25]) and even HIV therapeutic strategies (see [1], [2]). Many studies about HIV infection are collected by M. Nowak in an interesting book [20]. In this study, we focus on the viral diversity and the frequency dependence among the interactions for the virus and immune cells.

In a natural setting, the original infection occurs with a heterogeneous HIV population. But the immune system in the newly infected patient has not yet been activated. There is exponential expansion of the invading virus, selecting for the fastest-growing strain without consideration for immunological escape. This initial phase will lead to a virus population with very low genetic and antigenic diversity. Subsequently the immune system becomes activated and the patient passes to the asymptomatic phase [21]. From our mathematical analysis our immune system can not eradicate HIV forever if $R_1 > a\delta/(c-\delta)+1$. In fact, immune cells can not eradicate the virus in the initial phase because of very high HIV proliferation. Afterward the immune system selects for antigenic variation in those epitopes that are recognized by relevant immune responses. Therefore it is important to consider the viral diversity for the disease progression, in particular in the asymptomatic phase. For the multi-virus model the general analysis of the equilibria gives some interesting considerations about the $CD4^+$ T cell size and the possibility of the maintenance of the viral diversity concerned with immune response against HIV. For example, we consider the situation that the proliferation of CTL, c, is high and the death rate of CTL, δ, is low. This situations is reasonable for the immune system. In fact $1/\delta$ denotes the average life-time of an immune cell and c can

be interpreted as the maximum efficiency of immune inducement. This implies that the increasing of c and the decreasing of δ can induce the efficient immune response. Interestingly, the efficient immune response allows the increasing of the viral diversity because E_+ is stable. This is because that the amount of uninfected $CD4^+$ T cells as a growth limiting single resource for HIV strains remains to high level (see Fig. 3 and 4). Thus the efficient immune response leads to the increasing of viral diversity in the course of HIV infection because of the sufficient amount of uninfected $CD4^+$ T cells. If c is low and δ is high, which are not reasonable situation for the immune system, then the immunosuppression of CTL response is reduced and hence the total amount of infected cells will increase relatively. The increasing of infected cells emphasizes the effect of exploitative competition among different HIV strains for uninfected $CD4^+$ T cells. The exploitative competition will lead to competitive exclusion because of the shortage of uninfected $CD4^+$ T cells (see Fig. 3 and 4). The HIV strain with the highest infectivity outcompete the other HIV strains. Thus the competitive exclusion possibly reduces the diversity of viral strains. Therefore our results imply that the maintenance of the viral diversity depends on the amount of the available uninfected $CD4^+$ T cells (we remark that the basic reproductive numbers do not change in Fig. 3 and 4). However, in our model, we do not consider the effect of immune impairment by HIV or the helper effect by CD4 T cells. Moreover we should consider the cross reactivity of CTL because HIV strains do not have completely different epitopes and many types of CTL will recognize the majority of infected cells even though they are infected with different strains. Although these effects may change our implication of the possibility, we leave the inclusion of these additional effects as future work.

In [13], we explained that the interior equilibrium of our model can become unstable without viral diversity and we observed stable periodic orbits. Further our mathematical models suggested that viral diversity produces strange attractors. In [15], we explained that a new diversity threshold theory which states that the specific CTLs to the viral strain become inactivated (that is, some HIV strain can escape from its specific immune response) when the diversity of HIV strains exceeds some threshold number. In order to understand these interesting phenomena we proved some global behavior of the model and demonstrated the existence and stability conditions of the equilibria in this paper. These observations, such as complex behavior or threshold phenomenon, are due to the frequency dependence term because Iwasa et al. [11] have proved that an interior equilibrium is globally stable if the terms associated with immune reactions are given by cZ_jI_j and qZ_jI_j instead of $\frac{cZ_jI_j}{T+\sum_{l=1}^{n} I_l}$ and $\frac{qZ_jI_j}{T+\sum_{l=1}^{n} I_l}$ in model (2). As the viral diversity increases, it would be expected that the frequency dependence relatively is emphasized in our model. This is because that the effect of viral diversity is reflected in the rate of CTL proliferation and the elimination of infected cells. Further increasing of the diversity leads to a loss of the recognition ability of the immune cells and the efficiency between infections of the virus and eliminations of the immune cells is shifted in favor of the virus in the high viral diversity. Therefore the asymmetric interactions characterized by the frequency and the diversity may be an essential factor of the complex immune response or breakdown of the immune system in the disease.

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