

# Analysis of a within-host age-structured model with mutations between two viral strains <sup>☆</sup>



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## ABSTRACT

In this paper, we study a within-host age-structured model with mutation and back mutation, which is in the form of partial differential equations with double-infections by two strains of viruses. For the case that the production rates of viruses are gamma distributions, the PDE model is transformed into an ODE one. To explore the effect of mutations, we analyze our model without mutations first. In this case, two strains of viruses are proved to die out when both of the individual reproductive numbers are less than one; otherwise, their evolution will comply with competitive exclusion principle meaning that the stronger one will survive finally. Then, the mutations are considered in the model. We verify that there may exist a coexistence equilibrium which is globally asymptotically stable under some specific conditions about mutation rates. Therefore, mutations can lead to coexistence of two strains.

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## 1. Introduction

Viruses using RNA (ribonucleic acid) as their genetic material are called RNA viruses. Because of their high infection rates, RNA viruses can cause extraordinary tough human diseases, such as HIV, hepatitis C, SARS and influenza [9]. Mathematical models have been used to study the diseases caused by RNA viruses, particularly HIV, for over 25 years [8,10,11]. Results from mathematical models on virus dynamics within-host virus have been fruitful. In particular, these results conclude, if there are two strains of viruses in a single host competing for the same type of T-cells as their host cells, the competition exclusion principle generically holds in the sense that either both strains go to extinction (when the basic reproduction ratios are less than one), or one strain (the one with larger basic reproduction ratio) will win the competition. Here, the word generically means except that the two basic reproduction ratios are identical which can barely hold since these two ratios depend on a large number of model parameters (see example in [4]).

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However, mutations may alter the previous competitive balance. In general, viral RNA polymerase lacks the proof-reading ability [12], so RNA viruses have higher mutation rates than DNA viruses. Under the natural selection, their short generation times and relatively high mutation rates can help RNA viruses quickly adapt to changes in their host environment. It is difficult for scientists to develop effective vaccines to prevent diseases caused by RNA viruses [17]. For this reason, people would like to know more about mutation. There are many good research results, but most of them only study the impact of forward mutation. Generally, the backward mutations rarely survive in natural state. Recently, some researches showed that the impact of backward mutants cannot be neglected for drug resistance surveillance [13,16,20]. Therefore, two directions of mutations, forward and backward, are considered in this paper.

Ordinary differential equations models are used in [4], for which a unique coexistence equilibrium is found and its global asymptotical stability is explored when mutations are treated as small perturbations. However, adopting ordinary differential equations is a bit too idealized and simple for studying the viral evolution in hosts. This is mainly because that treating the production rate of new virus particles (virions) by an infected cell as a constant (independent of the infection age) would have neglected some important processes in virus replication. Indeed, it is known that viral proteins and unspliced viral RNA accumulate within the cytoplasm of an infected cell, and thus, they actually ramps up [2,6,18]. Therefore, infection age should be incorporated into the model. Motivated by the age-structured model

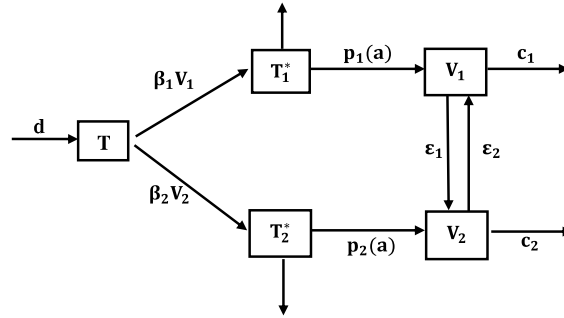
$$\begin{cases} \frac{dT}{dt} = s - dT(t) - kT(t)V(t), \\ \frac{\partial T^*}{\partial a} + \frac{\partial T^*}{\partial t} = -\delta(a)T^*(a, t), \\ \frac{dV}{dt} = \int_0^\infty p(a)T^*(a, t)da - cV(t), \\ T^*(0, t) = kV_1(t)T(t), \quad t \geq 0 \end{cases} \tag{1.1}$$

in [7], we extend the research by introducing a mutant strain of the virus into this age-structured model. More realistic representations about RNA virus infections will be allowed in our age-structured model. Meanwhile, the effect of forward and backward mutations between the wild strain and mutant strain on viral evolution is also considered in our work.

The rest of this paper is organized as follows. In the next section, we present the formulation of mathematical model. In Sections 3 and 4, we choose the Gamma distributions for the two kernels in the PDE model and utilize the linear chain trick to transform the partial differential equation model to an ordinary differential equations model, for which we work out the basic reproductive number. In Section 5, we study the equilibria and their respective stability in two situations, one is without mutations and the other is with mutations. Finally, we end this paper by a brief discussion about our results.

## 2. Model

Denote by  $T(t)$  the population of the susceptible host cells, by  $V_i(t)$  the population of viral strain  $i$  ( $i = 1, 2$ ), and let  $T_i^*(a, t)$  be the population of the target cells infected by viral strain  $i$  with infection age  $a$  at time  $t$ . Uninfected cells are produced at constant rate  $b$ , and die at rate  $d$ . After infection at constant rate  $\beta_i$  by strain  $i$ , they progress to the productively infected class. There are two death rates in this class: one is a constant background death rate  $m_i$ ; and the other is an infection dependent mortality rate  $\mu_i(a)$ . The infected cells can produce virus at an infection dependent rate  $p_i(a)$ . Free viruses are cleared at a constant rate  $c_i$ . Meanwhile, we suppose that the forward and backward mutations happen between the two



**Fig. 2.1.** The flow chart of the model (2.1).

viral strains at rate  $\epsilon_1$  and  $\epsilon_2$ , respectively. The corresponding transmission diagram is shown in Fig. 2.1. Translating the diagram in Fig. 2.1 into equations, our model takes the form:

$$\left\{ \begin{array}{l} \frac{dT}{dt} = b - dT(t) - \beta_1 T(t)V_1(t) - \beta_2 T(t)V_2(t), \\ \frac{\partial T_1^*}{\partial a} + \frac{\partial T_1^*}{\partial t} = -(\mu_1(a) + m_1)T_1^*(a, t), \\ \frac{\partial T_2^*}{\partial a} + \frac{\partial T_2^*}{\partial t} = -(\mu_2(a) + m_2)T_2^*(a, t), \\ \frac{dV_1}{dt} = (1 - \epsilon_1) \int_0^\infty p_1(a)T_1^*(a, t)da + \epsilon_2 \int_0^\infty p_2(a)T_2^*(a, t)da - c_1V_1(t), \\ \frac{dV_2}{dt} = (1 - \epsilon_2) \int_0^\infty p_2(a)T_2^*(a, t)da + \epsilon_1 \int_0^\infty p_1(a)T_1^*(a, t)da - c_2V_2(t), \\ T_1^*(0, t) = \beta_1 V_1(t)T(t), \\ T_2^*(0, t) = \beta_2 V_2(t)T(t), \quad t \geq 0. \end{array} \right. \quad (2.1)$$

System (2.1) will be reduced into DDE. By the method of characteristics, the following two partial differential equations with boundary conditions

$$\begin{aligned} \frac{\partial T_1^*}{\partial a} + \frac{\partial T_1^*}{\partial t} &= -(\mu_1(a) + m_1)T_1^*(a, t), & \frac{\partial T_2^*}{\partial a} + \frac{\partial T_2^*}{\partial t} &= -(\mu_2(a) + m_2)T_2^*(a, t), \\ T_1^*(0, t) &= \beta_1 V_1(t)T(t), & T_2^*(0, t) &= \beta_2 V_2(t)T(t), \quad t \geq 0, \end{aligned}$$

can be solved and their corresponding solutions are:

$$T_1^*(a, t) = \begin{cases} \beta_1 V_1(t - a)T(t - a)\sigma_1(a), & t \geq a, \\ 0, & t < a, \end{cases} \quad (2.2)$$

$$T_2^*(a, t) = \begin{cases} \beta_2 V_2(t - a)T(t - a)\sigma_2(a), & t \geq a, \\ 0, & t < a, \end{cases} \quad (2.3)$$

where  $\sigma_1(a) = e^{-\int_0^a (\mu_1(\xi) + m_1) d\xi}$  and  $\sigma_2(a) = e^{-\int_0^a (\mu_2(\xi) + m_2) d\xi}$ . Substituting (2.2) and (2.3) into the equations for  $V_1$  and  $V_2$  in (2.1), we obtain

$$\begin{cases} \frac{dT}{dt} = b - dT(t) - \beta_1 T(t)V_1(t) - \beta_2 T(t)V_2(t), \\ \frac{dV_1}{dt} = \beta_1(1 - \epsilon_1) \int_0^t p_1(a)T(t - a)V_1(t - a)\sigma_1(a)da + \beta_2\epsilon_2 \int_0^t p_2(a)T(t - a)V_2(t - a)\sigma_2(a)da - c_1V_1(t), \\ \frac{dV_2}{dt} = \beta_2(1 - \epsilon_2) \int_0^t p_2(a)T(t - a)V_2(t - a)\sigma_2(a)da + \beta_1\epsilon_1 \int_0^t p_1(a)T(t - a)V_1(t - a)\sigma_1(a)da - c_2V_2(t). \end{cases} \tag{2.4}$$

For convenience,  $\mu_i(a)$  is assumed to be a constant  $\mu_i$ , leading to  $\sigma_i(a) = e^{-(\mu_i+m_i)a}$  for  $i = 1, 2$ . System (2.4) can also be rewritten as

$$\begin{cases} \frac{dT}{dt} = b - dT(t) - \beta_1 T(t)V_1(t) - \beta_2 T(t)V_2(t), \\ \frac{dV_1}{dt} = \beta_1(1 - \epsilon_1) \int_0^t p_1(t - a)e^{-(\mu_1+m_1)(t-a)}T(a)V_1(a)da \\ \quad + \beta_2\epsilon_2 \int_0^t p_2(t - a)e^{-(\mu_2+m_2)(t-a)}T(a)V_2(a)da - c_1V_1(t), \\ \frac{dV_2}{dt} = \beta_2(1 - \epsilon_2) \int_0^t p_2(t - a)e^{-(\mu_2+m_2)(t-a)}T(a)V_2(a)da \\ \quad + \beta_1\epsilon_1 \int_0^t p_1(t - a)e^{-(\mu_1+m_1)(t-a)}T(a)V_1(a)da - c_2V_2(t). \end{cases} \tag{2.5}$$

### 3. Equivalent ODE system under Gamma distribution

For convenience to show our main idea, we assume that two strains have the same natural death rate and infection remove rate, i.e.,  $\mu_1 = \mu_2 = \mu$  and  $m_1 = m_2 = m$ . Moreover, according to the properties of production rate, we select the Gamma distribution as used in [21], which can approximate many other frequently used distributions, for  $p_1(a)$  and  $p_2(a)$ :

$$p_1(a) = p_2(a) = p_{\alpha,n}(a) = \frac{a^{n-1}}{(n - 1)! \alpha^n} e^{-\frac{a}{\alpha}}, \tag{3.1}$$

where  $n > 1$  is an integer and  $\alpha \in \mathbb{R}^+$ . Denote

$$\hat{\alpha} = \frac{\alpha}{1 + (\mu + m)\alpha},$$

leading to

$$[1 + (\mu + m)\alpha]^n = \left(\frac{\alpha}{\hat{\alpha}}\right)^n.$$

We can rewrite the last two equations in (2.5) as:

$$\frac{dV_1}{dt} = (1 - \epsilon_1) \left(\frac{\hat{\alpha}}{\alpha}\right)^n \int_0^t B_1(a)p_{\hat{\alpha},n}(t - a)da + \epsilon_2 \left(\frac{\hat{\alpha}}{\alpha}\right)^n \int_0^t B_2(a)p_{\hat{\alpha},n}(t - a)da - c_1V_1,$$

$$\frac{dV_2}{dt} = (1 - \epsilon_2) \left(\frac{\hat{\alpha}}{\alpha}\right)^n \int_0^t B_2(a) p_{\hat{\alpha},n}(t-a) da + \epsilon_1 \left(\frac{\hat{\alpha}}{\alpha}\right)^n \int_0^t B_1(a) p_{\hat{\alpha},n}(t-a) da - c_2 V_2,$$

where  $B_i(t) = \beta_i V_i(t) T(t)$ ,  $i = 1, 2$ .

Let

$$x_j(t) = \hat{\alpha} \left(\frac{\hat{\alpha}}{\alpha}\right)^n \int_0^t B_1(a) p_{\hat{\alpha},j}(t-a) da, \quad y_j(t) = \hat{\alpha} \left(\frac{\hat{\alpha}}{\alpha}\right)^n \int_0^t B_2(a) p_{\hat{\alpha},j}(t-a) da,$$

for  $j = 1, 2, \dots, n$ . Then, for  $j \in \{2, \dots, n\}$ ,

$$\begin{aligned} \frac{dx_j(t)}{dt} &= \hat{\alpha} \left(\frac{\hat{\alpha}}{\alpha}\right)^n \int_0^t \frac{(j-1)(t-a)^{j-2}}{(j-1)! \hat{\alpha}^j} e^{-\frac{(t-a)}{\hat{\alpha}}} B_1(a) da - \hat{\alpha} \left(\frac{\hat{\alpha}}{\alpha}\right)^n \int_0^t \frac{(t-a)^{j-1}}{(j-1)! \hat{\alpha}^{j+1}} e^{-\frac{(t-a)}{\hat{\alpha}}} B_1(a) da \\ &= \frac{1}{\hat{\alpha}} [x_{j-1}(t) - x_j(t)]. \end{aligned}$$

Similarly, for  $j = 2, \dots, n$ ,

$$\frac{dy_j(t)}{dt} = \frac{1}{\hat{\alpha}} [y_{j-1}(t) - y_j(t)].$$

When  $j = 1$ , there are

$$\begin{aligned} x_1(t) &= \hat{\alpha} \left(\frac{\hat{\alpha}}{\alpha}\right)^n \int_0^t B_1(a) \frac{1}{\hat{\alpha}} e^{-\frac{(t-a)}{\hat{\alpha}}} da, \\ y_1(t) &= \hat{\alpha} \left(\frac{\hat{\alpha}}{\alpha}\right)^n \int_0^t B_2(a) \frac{1}{\hat{\alpha}} e^{-\frac{(t-a)}{\hat{\alpha}}} da, \end{aligned}$$

and differentiating the above leads to

$$\begin{aligned} \frac{dx_1(t)}{dt} &= \beta_1 \left(\frac{\hat{\alpha}}{\alpha}\right)^n V_1(t) T(t) - \frac{1}{\hat{\alpha}} x_1(t), \\ \frac{dy_1(t)}{dt} &= \beta_2 \left(\frac{\hat{\alpha}}{\alpha}\right)^n V_2(t) T(t) - \frac{1}{\hat{\alpha}} y_1(t). \end{aligned}$$

Thus, with  $p_1(a)$  and  $p_2(a)$  specified by (3.1), the system (2.5) is equivalent to the following system of ordinary differential equations:

$$\left\{ \begin{aligned} \frac{dT}{dt} &= b - dT - \beta_1 TV_1 - \beta_2 TV_2, \\ \frac{dx_1}{dt} &= \beta_1 \left(\frac{\hat{\alpha}}{\alpha}\right)^n V_1 T - \frac{1}{\hat{\alpha}} x_1, \\ \frac{dx_2}{dt} &= \frac{1}{\hat{\alpha}}(x_1 - x_2), \\ &\vdots \\ \frac{dx_n}{dt} &= \frac{1}{\hat{\alpha}}(x_{n-1} - x_n), \\ \frac{dy_1}{dt} &= \beta_2 \left(\frac{\hat{\alpha}}{\alpha}\right)^n V_2 T - \frac{1}{\hat{\alpha}} y_1 \\ \frac{dy_2}{dt} &= \frac{1}{\hat{\alpha}}(y_1 - y_2), \\ &\vdots \\ \frac{dy_n}{dt} &= \frac{1}{\hat{\alpha}}(y_{n-1} - y_n), \\ \frac{dV_1}{dt} &= \frac{(1 - \epsilon_1)}{\hat{\alpha}} x_n + \frac{\epsilon_2}{\hat{\alpha}} y_n - c_1 V_1, \\ \frac{dV_2}{dt} &= \frac{(1 - \epsilon_2)}{\hat{\alpha}} y_n + \frac{\epsilon_1}{\hat{\alpha}} x_n - c_2 V_2. \end{aligned} \right. \tag{3.2}$$

Thus, in the rest of this paper, we only need to study the above ODE system.

For a nonnegative initial set, it is easy to prove that the corresponding solution of (3.2) remains nonnegative (e.g. by [14, pp. 81, Theorem 2.1]).

**Lemma 3.1.** *The system (3.2) is dissipative, i.e. there is a forward-invariant compact set  $\Gamma \subset \mathbb{R}_+^{2n+3}$  such that every solution eventually enters  $\Gamma$ .*

**Proof.** Adding equations about  $\frac{dT}{dt}$ ,  $\frac{dx_1}{dt}$  and  $\frac{dy_1}{dt}$  in (3.2) gives

$$\frac{d}{dt} \left[ T + \left(\frac{\alpha}{\hat{\alpha}}\right)^n x_1 + \left(\frac{\alpha}{\hat{\alpha}}\right)^n y_1 \right] = b - dT - \frac{\alpha^n}{\hat{\alpha}^{n+1}}(x_1 + y_1) \leq b - d^* \left[ T + \left(\frac{\alpha}{\hat{\alpha}}\right)^n x_1 + \left(\frac{\alpha}{\hat{\alpha}}\right)^n y_1 \right],$$

where  $d^* = \min\{d, \frac{1}{\hat{\alpha}}\}$ . Thus,  $\limsup_{t \rightarrow \infty} [T + (\frac{\alpha}{\hat{\alpha}})^n x_1 + (\frac{\alpha}{\hat{\alpha}})^n y_1] \leq \frac{b}{d^*}$ . Similarly, we can obtain that

$$\limsup_{t \rightarrow \infty} (V_1 + V_2) \leq \frac{b}{c\hat{\alpha}d^*} \left(\frac{\hat{\alpha}}{\alpha}\right)^n, \quad \limsup_{t \rightarrow \infty} T \leq \frac{b}{d^*},$$

and

$$\limsup_{t \rightarrow \infty} (x_j + y_j) \leq \frac{b}{d^*} \left(\frac{\hat{\alpha}}{\alpha}\right)^n, \quad j = 2, 3, \dots, n.$$

Consequently, the feasible region is given by:

$$\Gamma = \left\{ \begin{aligned} &(T, x_1, x_2, \dots, x_n, y_1, y_2, \dots, y_n, V_1, V_2) \in \mathbb{R}_+^{(2n+3)} \\ &T \leq \frac{b}{d^*}, \quad T + \left(\frac{\alpha}{\hat{\alpha}}\right)^n x_1 + [1 + (\mu + m\alpha)]^n y_1 \leq \frac{b}{d^*}, \\ &x_i + y_i \leq \frac{b}{d^*} \left(\frac{\hat{\alpha}}{\alpha}\right)^n, \quad V_1 + V_2 \leq \frac{b}{c\hat{\alpha}d^*} \left(\frac{\hat{\alpha}}{\alpha}\right)^n, \quad i = 2, \dots, n \end{aligned} \right\}. \tag{3.3}$$

It can be verified that  $\Gamma$  is positively invariant with respect to (3.2). Now, dissipativity follows because all upper bounds above are independent of the initial condition.  $\square$

In addition to the above set  $\Gamma$ , we will also refer to the set

$$\mathbf{H} := \{(T, x_1, y_1, x_2, y_2, \dots, x_n, y_n, V_1, v_2) \in \mathbb{R}^{(2n+3)} \mid T, x_i, y_i, V_1, V_2 > 0, i = 1, 2, \dots, n\},$$

in the remainder of the paper.

#### 4. Basic reproductive number

The infection-free equilibrium of the system (3.2) is

$$E_0 = \left(\frac{b}{d}, 0, 0, \dots, 0\right). \tag{4.1}$$

The basic reproductive number of the model is closely related to the stability of the  $E_0$ .

Typically, next generation matrix is utilized to calculate reproductive number for ODE models (see example in [19]). To reveal some special relation of the two viral strains for the model (3.2), we choose an alternative approach developed in [3] to calculate this important number.

Following [3], we now rewrite (3.2) as

$$\begin{cases} \frac{dT}{dt} = b - dT - \beta_1TV_1 - \beta_2TV_2, \\ \frac{dx}{dt} = Ax + \beta_1TV_1B, \\ \frac{dy}{dt} = Ay + \beta_2TV_2B, \\ \frac{dV}{dt} = D_1x + D_2y - CV, \end{cases} \tag{4.2}$$

where  $x = (x_1, x_2, \dots, x_n)^T$ ,  $y = (y_1, y_2, \dots, y_n)^T$ ,  $V = (V_1, V_2)^T$ ,  $C = (c_1, 0; 0, c_2)$ ,  $B = (\frac{\hat{\alpha}}{\alpha})^n e_1(n)$ ,

$$D_1 = \begin{pmatrix} 0 & 0 & \dots & \frac{(1-\epsilon_1)}{\alpha} \\ 0 & 0 & \dots & \frac{\epsilon_1}{\alpha} \end{pmatrix}, \quad D_2 = \begin{pmatrix} 0 & 0 & \dots & \frac{\epsilon_2}{\alpha} \\ 0 & 0 & \dots & \frac{(1-\epsilon_2)}{\alpha} \end{pmatrix},$$

$$A = \begin{pmatrix} -\frac{1}{\alpha} & 0 & 0 & \dots & \dots & 0 \\ \frac{1}{\alpha} & -\frac{1}{\alpha} & 0 & \dots & \dots & 0 \\ 0 & \frac{1}{\alpha} & -\frac{1}{\alpha} & \dots & \dots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & \dots & -\frac{1}{\alpha} \end{pmatrix},$$

and  $e_1(n) = (1, 0, \dots, 0)^T$ .

During the mean duration of its lifetime, a virion of the strain 1 can actually generate a Dirac input  $b\beta_1/c_1d$  in the second controlled system  $x' = Ax + \beta_1TV_1B$  (see demonstration in [3]). This input then generates secondary viruses given by formula:

$$\frac{b\beta_1}{c_1d} \int_0^{+\infty} D_1 e^{tA} B dt = \frac{b\beta_1}{c_1d} D_1 (-A^{-1}) B.$$

Since

$$-A^{-1} = \begin{pmatrix} \hat{\alpha} & 0 & 0 & \cdots & \cdots & 0 \\ \hat{\alpha} & \hat{\alpha} & 0 & \cdots & \cdots & 0 \\ \hat{\alpha} & \hat{\alpha} & \hat{\alpha} & \cdots & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \hat{\alpha} & \hat{\alpha} & \hat{\alpha} & \cdots & \cdots & \hat{\alpha} \end{pmatrix},$$

we obtain

$$D_1(-A^{-1})B = \begin{pmatrix} (1 - \epsilon_1)\left(\frac{\hat{\alpha}}{\alpha}\right)^n \\ \epsilon_1\left(\frac{\hat{\alpha}}{\alpha}\right)^n \end{pmatrix}.$$

Therefore, based on the input  $b\beta_1/c_1d$ , two fractions of offsprings for strains 1 and 2 respectively are given by

$$\mathbf{R}_{11} = (1 - \epsilon_1)\left(\frac{\hat{\alpha}}{\alpha}\right)^n \frac{b\beta_1}{c_1d}, \quad \mathbf{R}_{12} = \epsilon_1\left(\frac{\hat{\alpha}}{\alpha}\right)^n \frac{b\beta_1}{c_1d}, \tag{4.3}$$

both of which result from viral strain 1.

Similarly, the numbers of offspring of strains 1 and 2 produced by a single virion of strain 2 are given respectively by

$$\mathbf{R}_{21} = \epsilon_2\left(\frac{\hat{\alpha}}{\alpha}\right)^n \frac{\beta_2b}{c_2d}, \quad \mathbf{R}_{22} = (1 - \epsilon_2)\left(\frac{\hat{\alpha}}{\alpha}\right)^n \frac{\beta_2b}{c_2d}. \tag{4.4}$$

Now, assume that a single viral particle is brought into a host, and let  $p$  ( $q$ ) be the probability that the initial invasion is caused by a virion of strain 1 (strain 2). So,  $p + q = 1$ , and all new viruses resulted from this virion are distributed among the two strains by the following formula:

$$\begin{pmatrix} \mathbf{R}_{11} & \mathbf{R}_{12} \\ \mathbf{R}_{21} & \mathbf{R}_{22} \end{pmatrix} \begin{pmatrix} p \\ q \end{pmatrix} = \begin{pmatrix} p\mathbf{R}_{11} + q\mathbf{R}_{12} \\ p\mathbf{R}_{21} + q\mathbf{R}_{22} \end{pmatrix}.$$

Therefore, the total number of new viruses resulted from an initial virion is the  $L_1$  norm of the above vector, i.e.,

$$\begin{aligned} \left| \begin{pmatrix} p\mathbf{R}_{11} + q\mathbf{R}_{12} \\ p\mathbf{R}_{21} + q\mathbf{R}_{22} \end{pmatrix} \right|_1 &= (p\mathbf{R}_{11} + q\mathbf{R}_{12}) + (p\mathbf{R}_{21} + q\mathbf{R}_{22}) \\ &= p(\mathbf{R}_{11} + \mathbf{R}_{21}) + q(\mathbf{R}_{12} + \mathbf{R}_{22}) = p\mathbf{R}_1 + q\mathbf{R}_2, \end{aligned}$$

where

$$\mathbf{R}_1 = \mathbf{R}_{11} + \mathbf{R}_{12} = \frac{\beta_1b}{c_1d} \left(\frac{\hat{\alpha}}{\alpha}\right)^n, \quad \mathbf{R}_2 = \mathbf{R}_{21} + \mathbf{R}_{22} = \frac{\beta_2b}{c_2d} \left(\frac{\hat{\alpha}}{\alpha}\right)^n, \tag{4.5}$$

account for the individual reproductive numbers of strain 1 and strain 2 virus respectively. Thus, the basic reproductive number corresponding to the model (3.2) is obtained by taking the maximum over all possible initial distributions:

$$\mathbf{R}_0 = \max_{p+q=1} \left| \begin{pmatrix} \mathbf{R}_{11} & \mathbf{R}_{12} \\ \mathbf{R}_{21} & \mathbf{R}_{22} \end{pmatrix} \begin{pmatrix} p \\ q \end{pmatrix} \right|_1 = \left| \begin{pmatrix} \mathbf{R}_{11} & \mathbf{R}_{12} \\ \mathbf{R}_{21} & \mathbf{R}_{22} \end{pmatrix} \right|_1 = \max\{\mathbf{R}_{11} + \mathbf{R}_{12}, \mathbf{R}_{21} + \mathbf{R}_{22}\} = \max\{\mathbf{R}_1, \mathbf{R}_2\}.$$



### 5. Equilibria and their stability

In this section, we will prove the existence of other equilibria for system (3.2) and analyze their stability. The following theorem discusses the stability of the infection-free equilibrium  $E_0$ .

**Theorem 5.1.** *If  $\mathbf{R}_0 < 1$ , the infection-free equilibrium  $E_0$  is globally asymptotically stable on  $\mathbb{R}_+^{2n+3}$ .*

**Proof.** Let us consider the stability of infection-free equilibrium  $E_0$  in  $\Gamma$  under the condition  $\mathbf{R}_0 < 1$ . We construct a Lyapunov function as follows:

$$\mathcal{V} = T_0 \left( \frac{T}{T_0} - \ln \frac{T}{T_0} - 1 \right) + \left( \frac{\alpha}{\hat{\alpha}} \right)^n \left\{ \sum_{i=1}^n (x_i + y_i) + V_1 + V_2 \right\}.$$

Calculating the derivative of  $\mathcal{V}$  along trajectories of (3.2), we obtain:

$$\begin{aligned} \frac{d\mathcal{V}}{dt} &= \frac{dT}{dt} \left( 1 - \frac{T_0}{T} \right) + \left( \frac{\alpha}{\hat{\alpha}} \right)^n \left[ \beta_1 \left( \frac{\hat{\alpha}}{\alpha} \right)^n V_1 T - c_1 V_1 + \beta_2 \left( \frac{\hat{\alpha}}{\alpha} \right)^n V_2 T - c_2 V_2 \right] \\ &= b - dT - b \frac{T_0}{T} + dT_0 + \beta_1 V_1 T_0 + \beta_2 V_2 T_0 - c_1 \left( \frac{\alpha}{\hat{\alpha}} \right)^n V_1 - c_2 \left( \frac{\alpha}{\hat{\alpha}} \right)^n V_2 \\ &= b \left( 2 - \frac{T}{T_0} - \frac{T_0}{T} \right) + \left[ \beta_1 \left( \frac{\hat{\alpha}}{\alpha} \right)^n \frac{b}{dc_1} - 1 \right] \left( \frac{\alpha}{\hat{\alpha}} \right)^n c_1 V_1 + \left[ \beta_2 \left( \frac{\hat{\alpha}}{\alpha} \right)^n \frac{b}{dc_2} - 1 \right] \left( \frac{\alpha}{\hat{\alpha}} \right)^n c_2 V_2 \\ &= b \left( 2 - \frac{T}{T_0} - \frac{T_0}{T} \right) + (\mathbf{R}_1 - 1) \left( \frac{\alpha}{\hat{\alpha}} \right)^n c_1 V_1 + (\mathbf{R}_2 - 1) \left( \frac{\alpha}{\hat{\alpha}} \right)^n c_2 V_2. \end{aligned}$$

Notice that  $2 - T/T_0 - T_0/T \leq 0$  and the equality holds if and only if  $T = T_0$ . Thus, if  $R_0 < 1$ , then  $\frac{d\mathcal{V}}{dt} \geq 0$  and  $\frac{d\mathcal{V}}{dt} = 0$  if and only if  $T = T_0$ ,  $V_1 = 0$  and  $V_2 = 0$ . Thus,  $\frac{d\mathcal{V}}{dt} \leq 0$  if  $\mathbf{R}_0 < 1$ ; and  $\frac{d\mathcal{V}}{dt} = 0$  is if and only if  $(T, x, y, V)$  is at  $E_0$ . Consequently, we can conclude that the virus free equilibrium  $E_0$  is globally asymptotically stable in  $\mathbf{H}$ .  $\square$

When  $\mathbf{R}_0 > 1$ , then either  $\mathbf{R}_1 > 1$  or  $\mathbf{R}_2 > 1$ . If  $\mathbf{R}_1 > 1$ , there is a single-strain equilibrium  $E_1 = (\hat{T}^1, \hat{x}_1^1, \dots, \hat{x}_n^1, 0, \dots, \hat{V}_1^1, 0)$  given by

$$\hat{T}^1 = \frac{c_1}{\beta_1} \left( \frac{\alpha}{\hat{\alpha}} \right)^n, \quad \hat{x}_l^1 = \hat{\alpha} f(\hat{T}^1) \left( \frac{\hat{\alpha}}{\alpha} \right)^n, \quad l = 1, \dots, n, \quad \hat{V}_1^1 = \frac{f(\hat{T}^1)}{c_1} \left( \frac{\hat{\alpha}}{\alpha} \right)^n, \quad (5.1)$$

where  $f(\hat{T}^1) = b - d\hat{T}^1$ . In parallel, if  $\mathbf{R}_2 > 1$ , there is another single-strain equilibrium  $E_2 = (\hat{T}^1, 0, \dots, 0, \hat{y}_1^2, \dots, \hat{y}_n^2, 0, \hat{V}_2^2)$  given by

$$\hat{T}^2 = \frac{c_2}{\beta_2} \left( \frac{\alpha}{\hat{\alpha}} \right)^n, \quad \hat{y}_l^2 = \hat{\alpha} f(\hat{T}^2) \left( \frac{\hat{\alpha}}{\alpha} \right)^n, \quad l = 1, \dots, n, \quad \hat{V}_2^2 = \frac{f(\hat{T}^2)}{c_2} \left( \frac{\hat{\alpha}}{\alpha} \right)^n, \quad (5.2)$$

where  $f(\hat{T}^2) = b - d\hat{T}^2$ . In the sequel, we will discuss the stability of  $E_1$  and  $E_2$ , and the existence of a positive (coexistence) equilibrium. To study the effect of mutations, we distinguish the case when the mutations are absent and the case when the mutations are present.

#### 5.1. In the absence of mutations

First, let us consider the case  $\epsilon_1 = \epsilon_2 = 0$ . Since  $\mathbf{R}_1$  and  $\mathbf{R}_2$  depend on many model parameters, the critical case  $\mathbf{R}_1 = \mathbf{R}_2$  is sensitive in the sense that a small change of any model parameter would destroy this identity. Thus, for practical purpose, we exclude this case in our discussion.

Note that  $\mathbf{R}_i = b/(d\hat{T}^i)$  for  $i = 1, 2$ . Thus

$$\mathbf{R}_1 > \mathbf{R}_2 \quad \text{iff} \quad \hat{T}^1 < \hat{T}^2. \tag{5.3}$$

The following theorem establishes the global stability of  $E_1$  or  $E_2$ , depending on which strain has larger basic reproduction number.

**Theorem 5.2.** *Assume that  $\mathbf{R}_0 > 1$ .*

- (i) *If  $\mathbf{R}_1 > \mathbf{R}_2$  and  $\mathbf{R}_1 > 1$ , then  $E_1$  is globally asymptotically stable with respect to positive initial conditions.*
- (ii) *If  $\mathbf{R}_2 > \mathbf{R}_1$  and  $\mathbf{R}_2 > 1$ , then  $E_2$  is globally asymptotically stable with respect to positive initial conditions.*

**Proof.** We only need to prove (i), since (ii) is parallel to (i). We construct the following Lyapunov function on  $\mathbf{H}$ :

$$\mathcal{L} = \hat{T}^1 \left( \frac{T}{\hat{T}^1} - \ln \frac{T}{\hat{T}^1} - 1 \right) + \left( \frac{\alpha}{\hat{\alpha}} \right)^n \left[ \sum_{i=1}^n \hat{x}_i^1 \left( \frac{x_i}{\hat{x}_i^1} - \ln \frac{x_i}{\hat{x}_i^1} - 1 \right) + \hat{V}_1^1 \left( \frac{V_1}{\hat{V}_1^1} - \ln \frac{V_1}{\hat{V}_1^1} - 1 \right) + \sum_{i=1}^n y_i + V_2 \right].$$

The derivative of  $\mathcal{L}$  along the trajectories of (3.2) is calculated as below:

$$\begin{aligned} \frac{d\mathcal{L}}{dt} &= \frac{dT}{dt} \left( 1 - \frac{\hat{T}^1}{T} \right) + \left( \frac{\alpha}{\hat{\alpha}} \right)^n \left[ \dot{x}_1 \left( 1 - \frac{\hat{x}_1^1}{x_1} \right) + \sum_{i=2}^n \dot{x}_i \left( 1 - \frac{\hat{x}_i^1}{x_i} \right) + \dot{V}_1 \left( 1 - \frac{\hat{V}_1^1}{V_1} \right) + \sum_{i=1}^n \dot{y}_i + \dot{V}_2 \right] \\ &= f(T) \left( 1 - \frac{\hat{T}^1}{T} \right) - (\beta_1 T V_1 + \beta_2 T V_2) \left( 1 - \frac{\hat{T}^1}{T} \right) + \left( \frac{\alpha}{\hat{\alpha}} \right)^n \left[ \beta_1 V_1 T \left( \frac{\hat{\alpha}}{\alpha} \right)^n \right. \\ &\quad \left. - \frac{1}{\hat{\alpha}} x_1 - \beta_1 V_1 T \left( \frac{\hat{\alpha}}{\alpha} \right)^n \frac{\hat{x}_1^1}{x_1} + \frac{1}{\hat{\alpha}} \hat{x}_1^1 + \frac{1}{\hat{\alpha}} (x_1 - x_2) - \frac{1}{\hat{\alpha}} \frac{\hat{x}_2^1}{x_2} x_1 + \frac{1}{\hat{\alpha}} \hat{x}_2^1 + \frac{1}{\hat{\alpha}} (x_2 - x_3) \right. \\ &\quad \left. - \frac{1}{\hat{\alpha}} \frac{\hat{x}_3^1}{x_3} x_2 + \frac{1}{\hat{\alpha}} \hat{x}_3^1 + \dots + \frac{1}{\hat{\alpha}} (x_{n-1} - x_n) - \frac{1}{\hat{\alpha}} \frac{\hat{x}_n^1}{x_n} x_{n-1} + \frac{1}{\hat{\alpha}} \hat{x}_n^1 - \frac{1}{\hat{\alpha}} \frac{\hat{V}_1^1}{v_1} x_n + c \hat{V}_1^1 \right. \\ &\quad \left. + \frac{1}{\hat{\alpha}} x_n - c_1 V_1 + \beta_2 V_2 T \left( \frac{\hat{\alpha}}{\alpha} \right)^n - \frac{1}{\hat{\alpha}} y_1 + \frac{1}{\hat{\alpha}} (y_1 - y_2) + \dots + \frac{1}{\hat{\alpha}} (y_{n-1} - y_n) + \frac{1}{\hat{\alpha}} y_n - c_2 V_2 \right] \\ &= f(T) \left( 1 - \frac{\hat{T}^1}{T} \right) + \beta_1 V_1 \hat{T}^1 + \beta_2 V_2 \hat{T}^1 + \left( \frac{\alpha}{\hat{\alpha}} \right)^n \left[ \frac{n}{\hat{\alpha}} \hat{x}_n^1 - \beta_1 V_1 T \left( \frac{\hat{\alpha}}{\alpha} \right)^n \frac{\hat{x}_1^1}{x_1} \right. \\ &\quad \left. - \frac{1}{\hat{\alpha}} \frac{\hat{x}_2^1}{x_2} x_1 - \frac{1}{\hat{\alpha}} \frac{\hat{x}_3^1}{x_3} x_2 - \dots - \frac{1}{\hat{\alpha}} \frac{\hat{x}_n^1}{x_n} x_{n-1} - \frac{\hat{V}_1^1}{V_1} x_n + c_1 \hat{V}_1^1 - c_1 V_1 - c_2 V_2 \right] \\ &= f(T) \left( 1 - \frac{\hat{T}^1}{T} \right) + \beta_2 V_2 \hat{T}^1 - c_2 \left( \frac{\alpha}{\hat{\alpha}} \right)^n V_2 + \frac{\hat{x}_n^1}{\hat{\alpha}} \left( \frac{\alpha}{\hat{\alpha}} \right)^n \left[ (n+1) \right. \\ &\quad \left. - \frac{V_1 T \hat{x}_1^1}{\hat{V}_1^1 \hat{T}^1 x_1} - \frac{x_1}{x_2} - \frac{x_2}{x_3} - \frac{x_3}{x_4} - \dots - \frac{x_{n-1}}{x_n} - \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} \right] \\ &= f(T) \left( 1 - \frac{\hat{T}^1}{T} \right) + \beta_2 V_2 \hat{T}^1 - \beta_2 V_2 \hat{T}^2 - f(\hat{T}^1) \left( 1 - \frac{\hat{T}^1}{T} \right) + \frac{\hat{x}_1^1}{\hat{\alpha}} \left( \frac{\alpha}{\hat{\alpha}} \right)^n \left[ (n+2) \right. \\ &\quad \left. - \frac{\hat{T}^1}{T} - \frac{V_1 T \hat{x}_1^1}{\hat{V}_1^1 \hat{T}^1 x_1} - \frac{x_1}{x_2} - \frac{x_2}{x_3} - \frac{x_3}{x_4} - \dots - \frac{x_{n-1}}{x_n} - \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} \right] \end{aligned}$$

$$\begin{aligned}
 &= (f(T) - f(\hat{T}^1)) \left(1 - \frac{\hat{T}^1}{T}\right) + \beta_2 V_2 (\hat{T}^1 - \hat{T}^2) + \frac{\hat{x}_1^1}{\hat{\alpha}} \left(\frac{\alpha}{\hat{\alpha}}\right)^n \left[ (n+2) - \frac{\hat{T}^1}{T} \right. \\
 &\quad \left. - \frac{V_1 T \hat{x}_1^1}{\hat{V}_1^1 \hat{T}^1 x_1} - \frac{x_1}{x_2} - \frac{x_2}{x_3} - \frac{x_3}{x_4} - \dots - \frac{x_{n-1}}{x_n} - \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} \right].
 \end{aligned}$$

It is obvious that

$$[f(T) - f(\hat{T}^1)] \left(1 - \frac{\hat{T}^1}{T}\right) = d(\hat{T}^1 - T) \left(1 - \frac{\hat{T}^1}{T}\right) \leq 0.$$

The second term of the right side in the expression of  $\frac{d\mathcal{L}}{dt}$  is also nonpositive. Moreover, the relation of arithmetic and geometric means implies that

$$\frac{\hat{T}^1}{T} + \frac{V_1 T \hat{x}_1^1}{\hat{V}_1^1 \hat{T}^1 x_1} + \frac{x_1}{x_2} + \frac{x_2}{x_3} + \frac{x_3}{x_4} + \dots + \frac{x_{n-1}}{x_n} + \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} \geq (n+2).$$

Thus, we have proved  $\frac{d\mathcal{L}}{dt} \leq 0$ ; and  $\frac{d\mathcal{L}}{dt} = 0$  if and only if the state is at the equilibrium  $E_1$ , implying that  $E_1$  is globally asymptotically stable in  $\mathbf{H}$ .  $\square$

This theorem shows that when the basic reproduction number is larger than 1, then competition exclusion would be the generic result in the absence of mutations, implying that coexistence is generally impossible. Taking (i) in Theorem 5.2 as an example, if  $\mathbf{R}_1 > \mathbf{R}_2$  and  $\mathbf{R}_1 > 1$ , then regardless of whether  $\mathbf{R}_2 < 1$  or  $\mathbf{R}_2 > 1$ ,  $E_1$  is globally asymptotically stable, which means that strain 1 will win the competition. Therefore there is no coexistence equilibrium.

### 5.2. With the effect of mutations

In this section, we investigate the effect of the mutations by assuming that  $\epsilon_1 > 0$  and  $\epsilon_2 > 0$ . Let  $\epsilon = (\epsilon_1, \epsilon_2)$ , so  $\epsilon \neq 0$  in this case. The first result along this line is that the coexistence equilibrium becomes possible due to the presence of mutations.

**Theorem 5.3.** Assume  $\epsilon_1 > 0$  and  $\epsilon_2 > 0$ , and suppose  $c_1 \neq c_2$ . If one of the following conditions holds, then system (3.2) will have a unique positive equilibrium  $\bar{E}$ :

- (i)  $\mathbf{R}_1 > 1$  and  $\mathbf{R}_2 > 1$ ;
- (ii)  $\mathbf{R}_2 < 1$  but  $\mathbf{R}_1 > 1 + \frac{c_2 k}{c_1} (1 - \mathbf{R}_2)$ ;
- (iii)  $\mathbf{R}_1 < 1$  but  $\mathbf{R}_2 > 1 + \frac{c_1 k}{c_2} (1 - \mathbf{R}_1)$ ,

where  $k$  is a positive constant to be determined by a quadratic equation in the proof of the theorem.

**Proof.** If a positive equilibrium exists, its components are given by

$$\begin{aligned}
 \bar{x}_n = \bar{x}_{n-1} = \dots = \bar{x}_1 &= \hat{\alpha} \beta_1 \bar{T} \bar{V}_1 \left(\frac{\hat{\alpha}}{\alpha}\right)^n, & \bar{y}_n = \bar{y}_{n-1} = \dots = \bar{y}_1 &= \hat{\alpha} \beta_2 \bar{T} \bar{V}_2 \left(\frac{\hat{\alpha}}{\alpha}\right)^n, \\
 \bar{T} &= \frac{b}{d + \beta_1 \bar{V}_1 + \beta_2 \bar{V}_2},
 \end{aligned}$$

with  $\bar{V}_1$  and  $\bar{V}_2$  being determined by

$$\begin{cases} \frac{\beta_1(1 - \epsilon_1)b}{(d + \beta_1\bar{V}_1 + \beta_2\bar{V}_2)} \left(\frac{\hat{\alpha}}{\alpha}\right)^n \bar{V}_1 + \frac{\beta_2\epsilon_2b}{(d + \beta_1\bar{V}_1 + \beta_2\bar{V}_1)} \left(\frac{\hat{\alpha}}{\alpha}\right)^n \bar{V}_2 = c_1\bar{V}_1, \\ \frac{\beta_2(1 - \epsilon_2)b}{(d + \beta_1\bar{V}_1 + \beta_2\bar{V}_2)} \left(\frac{\hat{\alpha}}{\alpha}\right)^n \bar{V}_2 + \frac{\beta_1\epsilon_1b}{(d + \beta_1\bar{V}_1 + \beta_2\bar{V}_2)} \left(\frac{\hat{\alpha}}{\alpha}\right)^n \bar{V}_1 = c_2\bar{V}_2. \end{cases} \tag{5.4}$$

By simplification, Eqs. (5.4) can be rewritten as

$$\begin{cases} (\mathbf{R}_{11} - 1)c_1c_2\bar{V}_1\bar{V}_2 + \mathbf{R}_{21}c_2^2\bar{V}_2^2 - c_1c_2\bar{V}_1\bar{V}_2 \left(\frac{\beta_1}{d}\bar{V}_1 + \frac{\beta_2}{d}\bar{V}_2\right) = 0, \\ \mathbf{R}_{12}c_1^2\bar{V}_1^2 + (\mathbf{R}_{22} - 1)c_1c_2\bar{V}_1\bar{V}_2 - c_1c_2\bar{V}_1\bar{V}_2 \left(\frac{\beta_1}{d}\bar{V}_1 + \frac{\beta_2}{d}\bar{V}_2\right) = 0. \end{cases} \tag{5.5}$$

Because  $\bar{V}_1 \neq 0$ , subtracting the second equation in (5.5) from the first one leads to

$$\mathbf{R}_{21}c_2^2\left(\frac{\bar{V}_2}{\bar{V}_1}\right)^2 + (\mathbf{R}_{11} - \mathbf{R}_{22})c_1c_2\left(\frac{\bar{V}_2}{\bar{V}_1}\right) - \mathbf{R}_{12}c_1^2 = 0. \tag{5.6}$$

Setting  $z = \bar{V}_2/\bar{V}_1$ , Eq. (5.6) becomes a quadratic equation

$$a_2z^2 + a_1z + a_0 = 0, \tag{5.7}$$

where

$$a_0 = -\mathbf{R}_{12}c_1^2, \quad a_1 = (\mathbf{R}_{11} - \mathbf{R}_{22})c_1c_2, \quad a_2 = \mathbf{R}_{21}c_2^2.$$

Note that if  $\epsilon_1 = 0 = \epsilon_2$ , then  $\mathbf{R}_{12} = 0 = \mathbf{R}_{21}$ , i.e.  $a_0 = 0 = a_2$ , and thus, (5.7) cannot have a positive root, unless  $\mathbf{R}_{11} = \mathbf{R}_{22}$  (which will be assumed to not hold), i.e. (3.2) cannot have a positive equilibrium. But now, we have assumed  $\epsilon_1 > 0$  and  $\epsilon_2 > 0$ , implying  $\mathbf{R}_{21} > 0$  and  $\mathbf{R}_{12} > 0$ . Hence  $a_0 < 0$  and  $a_2 > 0$ , implying that the quadratic equation (5.7) has one positive root, denoting it by  $k$ , corresponding to a nonzero solution  $(\hat{V}_1, \hat{V}_2)$  of (5.5) with  $\bar{V}_1, \bar{V}_2$  having the same sign.

Substituting  $\bar{V}_2 = k\bar{V}_1$  into (5.5) gives

$$\begin{cases} \mathbf{R}_{11}c_1\bar{V}_1 + \mathbf{R}_{21}c_2k\bar{V}_1 - c_1\bar{V}_1 \left(1 + \frac{\beta_1}{d}\bar{V}_1 + \frac{\beta_2}{d}k\bar{V}_1\right) = 0, \\ \mathbf{R}_{12}c_1\bar{V}_1 + \mathbf{R}_{22}c_2k\bar{V}_1 - c_2k\bar{V}_1 \left(1 + \frac{\beta_1}{d}\bar{V}_1 + \frac{\beta_2}{d}k\bar{V}_1\right) = 0, \end{cases}$$

from which, we obtain the following expression for  $\bar{V}_1$ :

$$\bar{V}_1 = \frac{[(\mathbf{R}_1 - 1)c_1 + (\mathbf{R}_2 - 1)c_2k]d}{(c_1 + kc_2)(\beta_1 + k\beta_2)}. \tag{5.8}$$

Therefore,  $\bar{V}_1 > 0$  provided that at least one of the three conditions stated in the theorem holds. The proof is completed.  $\square$

We have proved the existence of the positive equilibrium  $\bar{E}$  as  $\epsilon$  changes. Furthermore, we begin the analysis with the two boundary equilibria  $E_1$  and  $E_2$  to investigate the origin of the equilibrium  $\bar{E}$ . Denoting the vector field of system (3.2) by  $g(X, \epsilon)$ , we find that  $g(E_i, 0) = 0$ , where  $i = 1, 2$ . Then, if  $\frac{\partial g}{\partial X}(E_i, 0)$  is invertible, we can establish a unique equilibrium  $E_i(\epsilon)$  near  $E_i$  by implicit function theorem for small  $\epsilon$ . We verify this condition below.

**Proposition 5.1.** *Assume the equilibrium  $E_i$  exists (i.e.,  $\mathbf{R}_i > 1$ ). Then,  $\frac{\partial g}{\partial X}(E_i, 0)$  is invertible for  $i = 1, 2$ , respectively.*

**Proof.** Firstly, we consider the situation for  $E_1$ . The Jacobian matrix of linearized system (3.2) at  $E_1$  is given by

$$J = \begin{pmatrix} J_1(n) & J_2(n) \\ 0 & J_4(n) \end{pmatrix},$$

where

$$J_1(n) = \begin{pmatrix} -\beta_1(\frac{\hat{\alpha}}{\alpha})^n \hat{V}_1^1 & 0 & 0 & \cdots & 0 & -\beta_1 \hat{T}^1 \\ \beta_1(\frac{\hat{\alpha}}{\alpha})^n \hat{V}_1^1 & -\frac{1}{\alpha} & 0 & \cdots & 0 & \beta_1(\frac{\hat{\alpha}}{\alpha})^n \hat{T}^1 \\ 0 & \frac{1}{\alpha} & -\frac{1}{\alpha} & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & -\frac{1}{\alpha} & 0 \\ 0 & 0 & 0 & \cdots & \frac{1}{\alpha} & -c_1 \end{pmatrix}_{(n+1) \times (n+1)},$$

$$J_2(n) = \begin{pmatrix} 0 & 0 & \cdots & 0 & -\beta_2 \hat{T}^1 \\ 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & \cdots & 0 & 0 \end{pmatrix}_{(n+1) \times n},$$

and

$$J_4(n) = \begin{pmatrix} -\frac{1}{\alpha} & 0 & \cdots & 0 & \beta_1(\frac{\hat{\alpha}}{\alpha})^n \hat{T}^1 \\ \frac{1}{\alpha} & -\frac{1}{\alpha} & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & -\frac{1}{\alpha} & 0 \\ 0 & 0 & \cdots & \frac{1}{\alpha} & -c_2 \end{pmatrix}_{n \times n}.$$

Then,  $\det(J) = \det(J_1(n)) \det(J_4(n))$ . It means that, if both  $\det(J_1(n))$  and  $\det(J_4(n))$  do not equal zero, the determinant of  $J$  at  $E_1$  is nonzero. Next, we will prove that neither  $\det(J_1(n))$  nor  $\det(J_4(n))$  is zero.

Indeed, direct calculation of the determinants give

$$\det(J_1(n)) = \left(-\frac{1}{\alpha}\right)^{(n-2)} \det \begin{pmatrix} -d - \beta_1 \hat{V}_1^1 & 0 & -\beta_1 \hat{T}^1 \\ \beta_1 \hat{V}_1^1 (\frac{\hat{\alpha}}{\alpha})^n & -\frac{1}{\alpha} & \beta_1 \hat{T}^1 (\frac{\hat{\alpha}}{\alpha})^n \\ 0 & \frac{1}{\alpha} & -c_1 \end{pmatrix} = (-1)^{(n-1)} \frac{\beta_1 \hat{V}_1^1 c_1}{\hat{\alpha}^{(n-1)}} \neq 0$$

and

$$\det(J_4(n)) = \left(-\frac{1}{\alpha}\right)^{(n-2)} \det \begin{pmatrix} -\frac{1}{\alpha} & \beta_1 \hat{T}^1 (\frac{\hat{\alpha}}{\alpha})^n \\ \frac{1}{\alpha} & -c_2 \end{pmatrix} = (-1)^{(n-2)} \frac{c_2 - c_1}{\hat{\alpha}^{(n-1)}} \neq 0$$

under the assumption  $c_1 \neq c_2$ . Therefore, the determinant of Jacobian matrix  $J$  is nonzero at  $E_1$ .

In the same way, we can demonstrate that  $\det(J) \neq 0$  at  $E_2$ . Hence,  $\frac{\partial g}{\partial X}(E_i, 0)$  are invertible for all  $i = 1, 2$ .  $\square$

When  $\mathbf{R}_2 < 1$ , only  $E_1$  exists in yhr absence of mutations. Obviously, the positive equilibrium  $\bar{E}$  bifurcates from the equilibrium  $E_1$  when mutation happens. However, the situation about the origin of  $\bar{E}$  becomes more complicated when  $\mathbf{R}_2 > 1$ . Next, we will analyze the case when (5.3) holds (i.e.,  $\mathbf{R}_1 > \mathbf{R}_2$ ) to find out whether  $\bar{E}$  is equal to  $E_1(\epsilon)$  or  $E_2(\epsilon)$ .

Define a mutation matrix

$$P(\epsilon) = I + Q(\epsilon),$$

where

$$Q(\epsilon) = \begin{pmatrix} -\epsilon_1 & \epsilon_1 \\ \epsilon_2 & -\epsilon_2 \end{pmatrix}.$$

Note that in the equilibrium equations,  $\bar{x}_n = \bar{x}_{n-1} = \dots = \bar{x}_1$  and  $\bar{y}_n = \bar{y}_{n-1} = \dots = \bar{y}_1$ , and the rest of the equations except for the first one can be simplified to

$$K\bar{V}\bar{T} - S\bar{T}^* = 0, \tag{5.9}$$

$$P(\epsilon)N\bar{T}^* - M\bar{V} = 0, \tag{5.10}$$

where

$$K = \begin{bmatrix} \beta_1(\frac{\hat{\alpha}}{\alpha})^n & 0 \\ 0 & \beta_2(\frac{\hat{\alpha}}{\alpha})^n \end{bmatrix}, \quad S = \begin{bmatrix} \frac{1}{\hat{\alpha}} & 0 \\ 0 & \frac{1}{\hat{\alpha}} \end{bmatrix}, \quad M = \begin{bmatrix} c_1 & 0 \\ 0 & c_2 \end{bmatrix}.$$

Substitute  $S\bar{T}^* = K\bar{V}\bar{T}$  into (5.10), we obtain

$$\left[ U(\epsilon) - \frac{1}{\bar{T}} \right] \bar{V} = 0,$$

where

$$U(\epsilon) = \begin{bmatrix} \frac{\beta_1(1-\epsilon_1)}{c_1}(\frac{\hat{\alpha}}{\alpha})^n & \frac{\beta_2\epsilon_2}{c_2}(\frac{\hat{\alpha}}{\alpha})^n \\ \frac{\beta_1\epsilon_1}{c_1}(\frac{\hat{\alpha}}{\alpha})^n & \frac{\beta_2(1-\epsilon_2)}{c_2}(\frac{\hat{\alpha}}{\alpha})^n \end{bmatrix}.$$

Finally, the problem about a positive solution becomes the existence of positive eigenvalue associated with positive eigenvector of matrix  $U(\epsilon)$ . Calculating

$$\begin{vmatrix} \frac{\beta_1(1-\epsilon_1)}{c_1}(\frac{\hat{\alpha}}{\alpha})^n - \lambda & -\frac{\beta_2\epsilon_2}{c_2}(\frac{\hat{\alpha}}{\alpha})^n \\ -\frac{\beta_1\epsilon_1}{c_1}(\frac{\hat{\alpha}}{\alpha})^n & \frac{\beta_2(1-\epsilon_2)}{c_2}(\frac{\hat{\alpha}}{\alpha})^n - \lambda \end{vmatrix} = 0, \tag{5.11}$$

we obtain the two eigenvalues of  $U(\epsilon)$  as

$$\lambda_1(\epsilon) = \frac{[\frac{\beta_1}{c_1}(1-\epsilon_1) + \frac{\beta_2}{c_2}(1-\epsilon_2)] + \sqrt{[\frac{\beta_1}{c_1}(1-\epsilon_1) + \frac{\beta_2}{c_2}(1-\epsilon_2)]^2 + 4\frac{\beta_1\beta_2}{c_1c_2}(1-\epsilon_1-\epsilon_2)}}{2(\frac{\alpha}{\hat{\alpha}})^n}, \tag{5.12}$$

and

$$\lambda_2(\epsilon) = \frac{[\frac{\beta_1}{c_1}(1-\epsilon_1) + \frac{\beta_2}{c_2}(1-\epsilon_2)] - \sqrt{[\frac{\beta_1}{c_1}(1-\epsilon_1) + \frac{\beta_2}{c_2}(1-\epsilon_2)]^2 + 4\frac{\beta_1\beta_2}{c_1c_2}(1-\epsilon_1-\epsilon_2)}}{2(\frac{\alpha}{\hat{\alpha}})^n}. \tag{5.13}$$

Because of  $\lambda_1(\epsilon) > 0 > \lambda_2(\epsilon)$ , the principle eigenvalue is  $\lambda_1(\epsilon)$  which generates a positive eigenvector by Perron–Frobenius theorem. In addition, it is easy to find that  $\lambda_1(0) = \hat{T}^1$  and  $\lambda_2(0) = \hat{T}^2$ . Thus,  $E_2(\epsilon)$  is nonpositive, i.e., the unique positive equilibrium  $\bar{E}$  equals  $E_1(\epsilon)$  when  $\mathbf{R}_1 > \mathbf{R}_2 > 1$ .

In the following, we apply Lyapunov function method to analyze the stability of the equilibrium  $\bar{E}$ .

**Theorem 5.4.** *Assume that  $\mathbf{R}_1 > \mathbf{R}_2 > 1$ . Then,  $\bar{E}$  is globally asymptotically stable in  $\mathbf{H}'$  for all sufficiently small  $\epsilon_1$  and  $\epsilon_2$ .*

**Proof.** We will use the same Lyapunov function

$$\mathcal{L} = \hat{T}^1 \left( \frac{T}{\hat{T}^1} - \ln \frac{T}{\hat{T}^1} - 1 \right) + \left( \frac{\alpha}{\hat{\alpha}} \right)^n \left[ \sum_{i=1}^n \hat{x}_i^1 \left( \frac{x_i}{\hat{x}_i^1} - \ln \frac{x_i}{\hat{x}_i^1} - 1 \right) + \hat{V}_1^1 \left( \frac{V_1}{\hat{V}_1^1} - \ln \frac{V_1}{\hat{V}_1^1} - 1 \right) + \sum_{i=1}^n y_i + V_2 \right]$$

as before. Calculating  $\frac{d\mathcal{L}}{dt}$  along the trajectories of system (3.2), we have

$$\begin{aligned} \frac{d\mathcal{L}}{dt} &= [f(T) - f(\hat{T}^1)] \left( 1 - \frac{\hat{T}^1}{T} \right) + \beta_2 V_2 (\hat{T}^1 - \hat{T}^2) + \frac{\hat{x}_1^1}{\hat{\alpha}} \left( \frac{\alpha}{\hat{\alpha}} \right)^n \left[ (n+2) - \frac{\hat{T}^1}{T} \right. \\ &\quad \left. - \frac{V_1 T \hat{x}_1^1}{\hat{V}_1^1 \hat{T}^1 x_1} - \frac{x_1}{x_2} - \frac{x_2}{x_3} - \frac{x_3}{x_4} - \dots - \frac{x_{n-1}}{x_n} - \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} \right] - \left( \frac{\alpha}{\hat{\alpha}} \right)^n \frac{\hat{V}_1^1}{V_1} \left( \frac{-\epsilon_1}{\hat{\alpha}} x_n + \frac{\epsilon_2}{\hat{\alpha}} y_n \right) \\ &= [f(T) - f(\hat{T}^1)] \left( 1 - \frac{\hat{T}^1}{T} \right) - \frac{\hat{x}_1^1}{\hat{\alpha}} \left( \frac{\alpha}{\hat{\alpha}} \right)^n \left[ \frac{\hat{T}^1}{T} + \frac{V_1 T \hat{x}_1^1}{\hat{V}_1^1 \hat{T}^1 x_1} + \frac{x_1}{x_2} + \frac{x_2}{x_3} + \frac{x_3}{x_4} \right. \\ &\quad \left. + \dots + \frac{x_{n-1}}{x_n} + (1 - \epsilon_1) \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} - (n+2)(1 - \epsilon_1)^{\frac{1}{n+2}} \right] - \beta_2 V_2 (\hat{T}^2 - \hat{T}^1) \\ &\quad + \frac{1}{\hat{\alpha}} (n+2) \left[ 1 - (1 - \epsilon_1)^{\frac{1}{n+2}} \right] \left( \frac{\alpha}{\hat{\alpha}} \right)^n \hat{x}_n^1 - \frac{1}{\hat{\alpha}} \left( \frac{\alpha}{\hat{\alpha}} \right)^n \epsilon_2 y_n \\ &\leq [f(T) - f(\hat{T}^1)] \left( 1 - \frac{\hat{T}^1}{T} \right) - \frac{\hat{x}_1^1}{\hat{\alpha}} \left( \frac{\alpha}{\hat{\alpha}} \right)^n \left[ \frac{\hat{T}^1}{T} + \frac{V_1 T \hat{x}_1^1}{\hat{V}_1^1 \hat{T}^1 x_1} + \frac{x_1}{x_2} + \frac{x_2}{x_3} + \frac{x_3}{x_4} \right. \\ &\quad \left. + \dots + \frac{x_{n-1}}{x_n} + (1 - \epsilon_1) \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} - (n+2)(1 - \epsilon_1)^{\frac{1}{n+2}} \right] - \beta_2 V_2 (\hat{T}^2 - \hat{T}^1) \\ &\quad + \frac{1}{\hat{\alpha}} (n+2) \left[ 1 - (1 - \epsilon_1)^{\frac{1}{n+2}} \right] \left( \frac{\alpha}{\hat{\alpha}} \right)^n \hat{x}_n^1. \end{aligned}$$

When (5.3) holds, we can find  $\epsilon_a, \eta > 0$  such that  $V_1(t) + V_2(t) > \eta$  for all  $\epsilon \in (0, \epsilon_a]$  and all sufficiently large  $t$  by Lemma 5 in [4]. Let  $\gamma = \beta_2(\hat{T}^2 - \hat{T}^1)$ , then

$$\beta_2(\hat{T}^2 - \hat{T}^1) V_2 = \gamma V_2 \geq \gamma(\eta - V_1).$$

So, the following inequality holds in  $\Gamma$  for  $\epsilon_1 \in (0, \epsilon_a]$ :

$$\begin{aligned} \frac{d\mathcal{L}}{dt} &\leq [f(T) - f(\hat{T}^1)] \left( 1 - \frac{\hat{T}^1}{T} \right) - \frac{\hat{x}_1^1}{\hat{\alpha}} \left( \frac{\alpha}{\hat{\alpha}} \right)^n \left[ \frac{\hat{T}^1}{T} + \frac{V_1 T \hat{x}_1^1}{\hat{V}_1^1 \hat{T}^1 x_1} + \frac{x_1}{x_2} + \frac{x_2}{x_3} \right. \\ &\quad \left. + \frac{x_3}{x_4} + \dots + \frac{x_{n-1}}{x_n} + (1 - \epsilon_1) \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} - (n+2)(1 - \epsilon_1)^{\frac{1}{n+2}} \right] - \gamma \eta + \gamma V_1 \\ &\quad + \frac{1}{\hat{\alpha}} (n+2) \left[ 1 - (1 - \epsilon_1)^{\frac{1}{n+2}} \right] \left( \frac{\alpha}{\hat{\alpha}} \right)^n \hat{x}_n^1 \end{aligned}$$

By the relation of arithmetic and geometric means, we then obtain

$$-\frac{\bar{x}_1}{\hat{\alpha}} \left(\frac{\alpha}{\hat{\alpha}}\right)^n \left[ \frac{\hat{T}^1}{T} + \frac{V_1 T \hat{x}_1^1}{\hat{V}_1 \hat{T}^1 x_1} + \frac{x_1}{x_2} + \frac{x_2}{x_3} + \frac{x_3}{x_4} + \dots + \frac{x_{n-1}}{x_n} + (1 - \epsilon_1) \frac{\hat{V}_1^1 x_n}{V_1 \hat{x}_n^1} - (n + 2)(1 - \epsilon_1)^{\frac{1}{n+2}} \right] \leq 0,$$

i.e.,

$$\frac{d\mathcal{L}}{dt} \leq [f(T) - f(\hat{T}^1)] \left(1 - \frac{\hat{T}^1}{T}\right) - \gamma\eta + \gamma V_1 + \frac{1}{\hat{\alpha}}(n + 2) [1 - (1 - \epsilon_1)^{\frac{1}{n+2}}] \left(\frac{\alpha}{\hat{\alpha}}\right)^n \hat{x}_n^1$$

for all  $\epsilon \in (0, \epsilon_a]$ .

Next, choose  $\epsilon_b > 0$  such that

$$1 - \epsilon_1 \in \left(\frac{1}{2}, 1\right], \quad \frac{1}{\hat{\alpha}}(n + 2) [1 - (1 - \epsilon_1)^{\frac{1}{n+2}}] \left(\frac{\alpha}{\hat{\alpha}}\right)^n \hat{x}_n^1 - \gamma\eta \leq -\frac{\gamma\eta}{4}$$

for all  $\epsilon_1 \in (0, \epsilon_b]$ . Let  $\bar{\epsilon} = \min(\epsilon_a, \epsilon_b)$ . Thus, for any  $\epsilon \in [0, \bar{\epsilon}]$ , we obtain that

$$\frac{d\mathcal{L}}{dt} \leq [f(T) - f(\hat{T}^1)] \left(1 - \frac{\hat{T}^1}{T}\right) - \frac{\gamma\eta}{4} + \gamma V_1.$$

Choose  $N > 0$  sufficiently large such that

$$-\frac{\gamma\eta}{4} + \gamma V_1 < N$$

for all solutions of (3.2) in  $\Gamma$  and all  $\epsilon \in (0, \bar{\epsilon}]$ . Meanwhile, let  $\delta_1 > 0$  be such that

$$[f(T) - f(\hat{T}^1)] \left(1 - \frac{\hat{T}^1}{T}\right) < -(N + 1),$$

for all  $T < \delta_1$  and all  $\epsilon \in (0, \bar{\epsilon}]$ .

At last, choose a  $\delta_2 > 0$  such that

$$-\frac{\gamma\eta}{4} + \gamma V_1 < -\frac{\gamma\eta}{8}$$

for all  $V_1 < \delta_2$  and all  $\epsilon_1 \in (0, \bar{\epsilon}]$ . Now, denote

$$\hat{\Gamma}_\delta = \{(T, x_1, y_1, x_2, y_2, \dots, x_n, y_n, V_1, V_2) \in \mathbf{H} \cap \Gamma : T \geq \delta_1, V_1 \geq \delta_2\}.$$

If  $(T, x_1, y_1, x_2, y_2, \dots, x_n, y_n, V_1, V_2) \in (\mathbf{H} \cap \Gamma) \setminus \hat{\Gamma}_\delta$  and all  $\epsilon \in (0, \bar{\epsilon}]$ , at least one of following results holds:

- (i)  $T < \delta_1$ , then  $\frac{d\mathcal{L}}{dt} \leq -(N + 1) + N = -1$ ;
- (ii)  $V_1 < \delta_2$ , then  $\frac{d\mathcal{L}}{dt} \leq -\frac{\gamma\eta}{8}$ .

Therefore, for all  $(T, x_1, y_1, x_2, y_2, \dots, x_n, y_n, V_1, V_2) \in (\mathbf{H} \cap \Gamma) \setminus \hat{\Gamma}_\delta$  and all  $\epsilon \in (0, \bar{\epsilon}]$ , there holds

$$\frac{d\mathcal{L}}{dt} \leq 0.$$

Note that the positive equilibrium  $\bar{E}$  depends on  $\epsilon = (\epsilon_1, \epsilon_2)$ , and so does the Lyapunov function  $\mathcal{L}$ . It is easy to see that the nonnegative function  $\mathcal{L}(T, x_1, y_1, \dots, x_n, y_n, V_1, V_2, \epsilon)$  is continuous and bounded on set  $\hat{\Gamma}_\delta \times (0, \bar{\epsilon}]$  and it can reach a finite positive maximum:



$$\rho := \max_{\hat{\Gamma}_\delta \times (0, \bar{\epsilon}]} \mathcal{L}(T, x_1, y_1, \dots, x_n, y_n, V_1, V_2, \epsilon) > 0.$$

Define a new set

$$\Gamma_\delta = \{(T, x_1, y_1, x_2, y_2, \dots, x_n, y_n, V_1, V_2) \in \mathbf{H} \cap \Gamma : \mathcal{L}(T, x_1, y_1, \dots, x_n, y_n, V_1, V_2, \epsilon) \leq \rho, \forall \epsilon \in (0, \bar{\epsilon}]\}.$$

So, there holds  $\hat{\Gamma}_\delta \subset \Gamma_\delta \subset \mathbf{H} \cap \Gamma$  and  $\Gamma_\delta$  is closed which can be implied by the continuity of  $\mathcal{L}$ . Obviously  $\Gamma_\delta$  is compact.

In the following, we need to show that all solutions of (3.2) in  $\mathbf{H}$  enter and remain in  $\Gamma_\delta$  for all large time. Because  $\Gamma$  is an absorbing set for all  $\epsilon \geq 0$ , without loss of generality, we need to prove this for all solutions in  $\Gamma$  (instead of in  $\mathbf{H}$ ).

Let  $\Phi(t) = (T, x_1, y_1, x_2, y_2, \dots, x_n, y_n, V_1, V_2) \in \Gamma$  be a solution of (3.2) for some fixed  $\epsilon \in [0, \bar{\epsilon}]$ . It is easy to verify that the inequality  $\frac{d\mathcal{L}}{dt} \leq 0$  holds in set  $\Gamma \setminus \hat{\Gamma}_\delta$ . Because of  $\mathcal{L} \geq 0$ , there exists a  $t_0 \geq 0$  such that  $\Phi(t_0) \in \hat{\Gamma}_\delta \subset \Gamma_\delta$ . Next, we will prove that  $\Phi(t) \in \Gamma_\delta$  for all  $t \geq t_0$ . For the sake of contradiction, let us assume that there is a  $t_1 > t_0$  such that  $\Phi(t_1) \notin \Gamma_\delta$ . Then there should be a  $t_2 \in [t_0, t_1]$  such that  $\Phi(t_2) \in \Gamma_\delta$  and  $\Phi(t) \notin \Gamma_\delta$  for all  $t \in (t_2, t_1]$ . On the one hand, we have

$$\mathcal{L}(\Phi(t_2), \epsilon) \leq \rho < \mathcal{L}(\Phi(t_1), \epsilon)$$

by definition of  $\Gamma_\delta$ . On the other hand, however, for all  $t \in (t_2, t_1]$ , we have  $\Phi(t) \notin \Gamma_\delta$  and consequently  $\Phi(t) \notin \hat{\Gamma}_\delta$  so that  $\frac{d}{dt} \mathcal{L}(\Phi(t), \epsilon) = \frac{d\mathcal{L}}{dt} < 0$ . This contradiction shows that  $\Phi(t) \in \Gamma_\delta$  for all  $t \geq t_0$ .

Let us define

$$\mathbf{H}' = \left\{ (T, x_1, y_1, x_2, y_2, \dots, x_n, y_n, V_1, v_2) \in \mathbb{R}^{(2n+3)} \mid T + \sum_i x_i + V_1 > 0, i = 1, 2, \dots, n \right\} \supset \mathbf{H}.$$

Since  $E_1(0) \in \text{Int}\mathbf{H}'$  is globally asymptotically stable in  $\mathbf{H}'$  for  $\epsilon = 0$  when  $\mathbf{R}_1 > \mathbf{R}_2 > 1$ . The condition (H1) of Corollary 2.3 in [15] holds. As a result,  $\bar{E}$  (or  $E_1(\epsilon)$ ) is globally asymptotically stable in  $\mathbf{H}'$  for all  $\epsilon \in (0, \bar{\epsilon}]$  if  $\mathbf{R}_1 > \mathbf{R}_2 > 1$ .  $\square$

### 6. Discussion and conclusion

In this paper, we study the effect of mutations on the evolution of two viral strains through proposing a within-host age-structured model. Comparing with the ordinary differential system in [4], our age-structured model better presented the biology of RNA viruses infection. Meanwhile, the corresponding analysis of the model becomes harder. Fortunately, under some assumptions, we are able to restore the information about viral infection age to new variables by which the age-structured model is transformed into an ODE model with discrete stages. We treat the resulting stage model as a controlled system to gain its corresponding basic reproductive number for the model. In this way, the process that begins with viral attachment and ends with the release of new viruses is better understood. When mutation is absent, unlike in [7] where only numerical simulations were presented, here an analytical proof about global stabilities of two boundary equilibria without the effects of mutations is given in this paper. Moreover, we demonstrate that the evolution of two viral strains would comply with competitive exclusion principle, meaning that the stronger one would survive finally when both boundary equilibria exist. Furthermore, when both forward and backward mutations are present, the existence and stability of a unique positive equilibrium are discussed. We also offer a mathematical explanation on how these two strains coexist with the help of small mutation rates. Moreover, we show that the coexisting equilibrium would be globally asymptotically stable when the mutation rates are a small.

We point out some general models of multi-strain virus with infected cell age structure have also been proposed and discussed in P. Magal et al. [5] and Browne [1]. But our model allows both forward and backward mutations, which makes the analysis a challenging job, and in mean time, demonstrates some thing that cannot be observed in [1,5].

In real world, mutation rates cannot always be fixed in viral evolution. When a mutation rate changes as times goes by, how would it affect the viral evolution? Moreover, when mutation rates exceed the critical values in our paper, will the stability of the related equilibria change or not? Although we found that the stability remains unchanged in our numeric simulations, we cannot assert that it is globally asymptotically stable with any values of mutations. Rigorous mathematical proof/disproof is needed, but it seems to be very challenging. For viral evolution, the environmental selection is another significant factor. Even for a small change in environment, it might alter the direction of viral evolution. Hence, it worthwhile to take into consideration natural selection in a model. We leave these for possible future research projects.

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