Multistrain virus dynamics with mutations: a global analysis

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To our mentor and good friend Hal Smith on the occasion of his 60th birthday

We consider within-host virus models with $n \geqslant 2$ strains and allow mutation between the strains. If there is no mutation, a Lyapunov function establishes global stability of the steady state corresponding to the fittest strain. For small perturbations, this steady state persists, perhaps with small concentrations of some or all other strains, depending on the connectivity of the graph describing all possible mutations. Moreover, using a perturbation result due to Smith & Waltman (1999), we show that this steady state also preserves global stability.

Keywords: within-host virus models; mutations; quasispecies; global stability; Lyapunov function.

1. Introduction

The study of the dynamics of within-host virus disease models has been a very fruitful area of research over the past few decades. Of particular importance has been the work on mathematical models of HIV infection by Perelson and coauthors (Perelson *et al.*, 1993; Perelson & Nelson, 1999) and Nowak & May (2000). It has spurred more recent research by among others Hal Smith with one of us (De Leenheer & Smith, 2003; Wang & Li, 2006; Rong *et al.*, 2007; Ball *et al.*, 2007).

For single-strain virus models, the understanding of the global behaviour has been largely based on the fact that they are competitive (De Leenheer & Smith, 2003) and the use of particular mathematical tools developed by Muldowney; see Li & Muldowney (1995) for an application of these techniques to the classical SEIR model in epidemiology. Of course, it is well known that for globally stable systems there is a Lyapunov function, but finding such a function is often difficult, as illustrated by the following quote from the classical work of Smith & Waltman (1994, p. 37) on chemostats:

'Considerable ingenuity, intuition, and perhaps luck are required to find a Liapunov function'.

One of the purposes of this paper is to find such Lyapunov functions for various within-host virus models following the ingenuity from Korobeinikov (2004) and Iggidr *et al.* (2006). Another purpose of the paper is to investigate what happens if we include mutation effects in the model by allowing different virus strains (also known as quasi-species; see Nowak & May, 2000) to mutate into each other. This is very relevant in the context of HIV where mutations have profound impact on treatment; see for instance Rong *et al.* where a two-strain model is considered. A similar model to the one we will present here was proposed in Ball *et al.* (2007), where the focus is on the transient dynamics using numerical methods and simulations. The purpose of this paper is to present a mathematical analysis of the global asymptotic behaviour of the within-host multistrain virus dynamics model.

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Mathematically, we will treat the model with mutations as a perturbation of the original model. It turns out that the structural properties of the mutation matrix that describes the possible mutations dictate how the single-strain steady states of the unperturbed model move in or out of the non-negative orthant for the perturbed model. For instance, assuming that all single-strain steady states exist for the unperturbed model, we show that if the mutation matrix is irreducible, then for small values of the mutation parameter, the perturbed model has only one positive and no other non-trivial disease steady states. This implies that at a disease equilibrium all strains will be present, although some are at very low levels. If the mutation matrix is reducible, then the situation is more complicated: some or all of the single-strain disease steady states persist in the non-negative orthant for the perturbed model, while others do not. Moreover, the structure of the mutation matrix coupled with the fitnesses of the various strains (as measured by the value of the healthy T-cell count at steady state) allows us to determine which strains persist and which ones do not.

An obvious problem is to determine if the globally stable single-strain steady state of the unperturbed model persists. We will show that this is always the case, regardless of the mutation matrix. Moreover, taking advantage of the perturbation result developed by Smith & Waltman (1999), we will show that this steady state remains globally stable for small values of the mutation parameter. In order to apply this perturbation result, we will first need to establish a particular persistence property, uniform in the perturbation parameter, and to achieve this, we invoke the theory developed by Hutson (1984) and Hutson & Schmitt (1992) (see also Hofbauer & Sigmund, 1998) which uses the notion of an average Lyapunov function. We will show that a rather simple—in fact, linear—average Lyapunov function exists.

The paper is organized as follows. In Section 2, we present a Lyapunov function to establish the global stability of the disease equilibrium of a single-strain virus model. We extend this Lyapunov function in Section 3 to prove a global stability result for a multistrain model which does not include mutations. In biological terms, we demonstrate that in the absence of mutations the fittest strain of the virus drives all other viral strains to extinction. In Section 4, we investigate what happens if mutations are taken into account for two different models. Finally, in Appendix A, we extend all our results to a slightly modified model which includes an often neglected loss term in the virus equation.

2. Single strain

In this paper, we consider the basic model of the form

$$
\begin{aligned}
\dot{T} &= f(T) - kVT, \\
\dot{T}^* &= kVT - \beta T^*, \\
\dot{V} &= N\beta T^* - \gamma V,
\end{aligned}
\tag{1}
$$

where T, T^* and V denote the concentrations of uninfected (healthy) and infected host cells and free virions, respectively. Equations (1) describe a general viral infection where the viral replication is limited by the availability of target cells T. In this model, we assume that all the infected cells T^* are virus-producing cells, that is, we do not include any intermediate stage(s) corresponding to latently infected cells. In addition, we do not explicitly consider the impact of the immune response. Implicitly, the immune response can be accounted for by the removal term $-\beta T^*$. The rate of viral production is assumed proportional to the removal of infected cells. In case of lytic viruses, N represents the average burst size of a single infected cell; whereas in case of budding viruses, N can be thought of as the average

number of virions produced over a lifetime of an infected cell. For different infections, the actual class of the target cells in (1) may vary from the $CD4+ T$ lymphocytes (in case of HIV), to the epithelial cells (in case of Influenza), to the red blood cells (in case of Malaria). The T, T^*, V notation is adopted from the classical HIV model (Perelson & Nelson, 1999).

All parameters are assumed to be positive. The parameters β and γ represent the removal rates of the infected cells and virus particles, respectively. Following Perelson & Nelson (1999) and Nowak & May (2000), we neglect the term in the V equation that represents the loss of a virus particle upon infection. But all subsequent results hold when this loss term is included, in which case the V equation reads as follows:

$$\dot{V} = N\beta T^* - \gamma V - kVT.$$

The corresponding results will be presented in Appendix A.

The growth rate of the uninfected cell population is given by the smooth function $f(T): \mathbb{R}_+ \to \mathbb{R}$, which is assumed to satisfy the following:

$$\exists T_0 > 0: f(T)(T - T_0) < 0, \quad T \neq T_0. \tag{2}$$

Since continuity of f implies that $f(T_0) = 0$, it is easy to see that

$$E_0 = (T_0, 0, 0)$$

is an equilibrium of (1). Effectively, T_0 is the carrying capacity for the healthy cell population.

A second, positive equilibrium may exist if the following quantities are positive:

$$\bar{T} = \frac{\gamma}{kN}, \quad \bar{T}^* = \frac{f(\bar{T})}{\beta}, \quad \bar{V} = \frac{f(\bar{T})}{k\bar{T}}. \tag{3}$$

Note that this is the case if and only if $f\left(\frac{\gamma}{kN}\right) > 0$ or equivalently by (2) that $\bar{T} = \frac{\gamma}{kN} < T_0$. In terms of the basic reproduction number

$$\mathcal{R}^0 := \frac{kN}{\gamma}T_0 = \frac{T_0}{\bar{T}_0},$$

existence of a positive equilibrium is therefore equivalent to $\mathcal{R}^0 > 1$. We assume henceforth that $\mathcal{R}^0 > 1$ and denote the disease steady state by $E = (\bar{T}, \bar{T}^*, \bar{V})$. Let us introduce the following sector condition:

$$\text{(C)} \quad (f(T) - f(\bar{T}))\left(1 - \frac{\bar{T}}{T}\right) \leqslant 0.$$

Note that this condition is satisfied when $f(T)$ is a decreasing function, independently of the value of $\bar{T}$. For instance, Nowak & May (2000) considers $f(T) = c_1 - c_2 T$, where c_i are positive constants. Another example (Perelson & Nelson, 1999) is $f(T) = s + rT\left(1 - \frac{T}{K}\right)$ provided that $f(0) = s \geqslant f(\bar{T})$.

THEOREM 1 Let (C) hold. Then, the equilibrium E is globally asymptotically stable for (1) with respect to the initial conditions satisfying $T^*(0) + V(0) > 0$.

Proof. Consider the following function on $\text{int}(\mathbb{R}_+^3)$:

$$W = \int_{\bar{T}}^T \left(1 - \frac{\bar{T}}{\tau}\right) d\tau + \int_{\bar{T}^*}^{T^*} \left(1 - \frac{\bar{T}^*}{\tau}\right) d\tau + \frac{\beta}{N\beta} \int_{\bar{V}}^V \left(1 - \frac{\bar{V}}{\tau}\right) d\tau.$$

Then,

$$\dot{W} = (f(T) - kVT)\left(1 - \frac{\bar{T}}{T}\right) + (kVT - \beta T^*)\left(1 - \frac{\bar{T}^*}{T^*}\right) + \frac{1}{N}(N\beta T^* - \gamma V)\left(1 - \frac{\bar{V}}{V}\right)$$

$$= f(T)\left(1 - \frac{\bar{T}}{T}\right) + kV\bar{T} - kVT\frac{\bar{T}^*}{T^*} + \beta\bar{T}^* - \beta T^*\frac{\bar{V}}{V} - \frac{\gamma}{N}V + \frac{\gamma}{N}\bar{V}.$$

Since from (3) we have that $\beta\bar{T}^* = k\bar{V}\bar{T} = \frac{\gamma}{N}\bar{V}$, it follows that

$$\dot{W} = f(T)\left(1 - \frac{\bar{T}}{T}\right) + \beta\bar{T}^*\frac{V}{\bar{V}} - \beta\bar{T}^*\frac{\bar{T}^*VT}{T^*\bar{V}\bar{T}} + \beta\bar{T}^* - \beta\bar{T}^*\frac{\bar{V}T^*}{V\bar{T}^*} - \beta T^*\frac{V}{\bar{V}} + \beta T^*$$

$$= (f(T) - f(\bar{T}))\left(1 - \frac{\bar{T}}{T}\right) + \beta T^*\left(1 - \frac{\bar{T}}{T}\right) + \beta\bar{T}^*\frac{V}{\bar{V}}$$

$$- \beta\bar{T}^*\frac{\bar{T}^*VT}{T^*\bar{V}\bar{T}} + \beta\bar{T}^* - \beta\bar{T}^*\frac{\bar{V}T^*}{V\bar{T}^*} - \beta T^*\frac{V}{\bar{V}} + \beta T^*$$

$$= (f(T) - f(\bar{T}))\left(1 - \frac{\bar{T}}{T}\right) - \beta\bar{T}^*\left[\frac{\bar{T}}{T} + \frac{\bar{T}^*VT}{T^*\bar{V}\bar{T}} + \frac{\bar{V}T^*}{V\bar{T}^*} - 3\right].$$

The first term is non-positive by (C). The second term is non-positive as well since the geometric mean of three non-negative numbers is not larger than the arithmetic mean of those numbers. Hence, $\dot{W} \leqslant 0$ in $\mathrm{int}(\mathbb{R}^3_+)$ and the local stability of E follows. Note that $\dot{W}$ equals zero iff both the first term and the second term are zero, and using (C), this happens at the points where

$$\frac{\bar{T}}{T} = 1 \quad \text{and} \quad \frac{\bar{T}^*V}{T^*\bar{V}} = 1.$$

Then LaSalle's (1968) invariance principle implies that all bounded solutions in $\mathrm{int}(\mathbb{R}^3_+)$ converge to the largest invariant set in

$$M = \left\{(T, T^*, V) \in \mathrm{int}(\mathbb{R}^3_+)\Big| \frac{\bar{T}}{T} = 1, \frac{\bar{T}^*V}{T^*\bar{V}} = 1\right\}.$$

Firstly, the boundedness of all solutions follows from Lemma 1 which is proved later in a more general setting. Secondly, it is clear that the largest invariant set in M is the singleton $\{E\}$. Finally, note that forward solutions starting on the boundary of $\mathbb{R}^3_+$ with either $T_1(0)$ or $V_1(0)$ positive enter $\mathrm{int}(\mathbb{R}^3_+)$ instantaneously. This concludes the proof.   □

3. Competitive exclusion in a multistrain model

Let us now consider a multistrain model:

$$\dot{T} = f(T) - \sum_{i=1}^{n} k_i V_i T, \tag{4}$$

$$\dot{T}_i^* = k_i V_i T - \beta_i T_i^*, \quad i = 1, \ldots, n, \tag{5}$$

$$\dot{V}_i = N_i \beta_i T_i^* - \gamma_i V_i, \quad i = 1, \ldots, n, \tag{6}$$

where all parameters are positive. A calculation similar to the single-strain model shows that there is a unique disease-free equilibrium $E_0 = (T_0, 0, 0)$. For each i, there is a corresponding single-strain equilibrium E_i with positive T, T_i^* and V_i components and zero components otherwise if and only if

$$1 < \mathcal{R}_i^0.$$

Here, $\mathcal{R}_i^0$ is the basic reproduction number for strain i which is defined as

$$\mathcal{R}_i^0 := \frac{T_0}{\bar{T}^i}.$$

The positive components of E_i are given by

$$\bar{T}^i = \frac{\gamma_i}{k_i N_i}, \quad \bar{T}_i^* = \frac{f(\bar{T}^i)}{\beta_i}, \quad \bar{V}_i = \frac{f(\bar{T}^i)}{k_i \bar{T}^i}. \tag{7}$$

In what follows, we assume that all E_is exist and that (without loss of generality, by permuting the indices i if necessary)

$$\bar{T}^1 < \bar{T}^2 \leqslant \cdots \leqslant \bar{T}^{n-1} \leqslant \bar{T}^n < T_0 \tag{8}$$

or, equivalently,

$$1 < \mathcal{R}_n^0 \leqslant \mathcal{R}_{n-1}^0 \leqslant \cdots \leqslant \mathcal{R}_2^0 < \mathcal{R}_1^0 \tag{9}$$

and will prove the following competitive exclusion principle. It asserts that the strain with the lowest target cell concentration at steady state (or equivalently, with highest basic reproduction number) will ultimately dominate, provided that such strain is present initially.

THEOREM 2 Assume that all E_i exist for (4–6), (C) holds with $\bar{T}^1$ instead of $\bar{T}$ and (8) holds. Then, E_1 is globally asymptotically stable for (4–6) with respect to the initial conditions satisfying $T_1^*(0) + V_1(0) > 0$.

Proof. Consider the following function on $U := \{(T, T_1^*, \ldots, T_n^*, V_1, \ldots, V_n) \in \mathbb{R}^{2n+1} | T, T_1^*, V_1 > 0\}$:

$$W = \int_{\bar{T}^1}^T \left(1 - \frac{\bar{T}^1}{\tau}\right) d\tau + \int_{\bar{T}_1^*}^{T_1^*} \left(1 - \frac{\bar{T}_1^*}{\tau}\right) d\tau + \frac{1}{N_1} \int_{\bar{V}_1}^{V_1} \left(1 - \frac{\bar{V}_1}{\tau}\right) d\tau + \sum_{i=2}^n \left(T_i^* + \frac{1}{N_i} V_i\right).$$

Then,

$$\dot{W} = \left(f(T) - \sum_{i=1}^n k_i V_i T\right)\left(1 - \frac{\bar{T}^1}{T}\right) + (k_1 V_1 T - \beta_1 T_1^*)\left(1 - \frac{\bar{T}_1^*}{T_1^*}\right)$$

$$+ \frac{1}{N_1}(N_1 \beta_1 T_1^* - \gamma_1 V_1)\left(1 - \frac{\bar{V}_1}{V_1}\right) + \sum_{i=2}^n \left(k_i V_i T - \frac{\gamma_i}{N_i} V_i\right)$$

$$= (f(T) - k_1 V_1 T)\left(1 - \frac{\bar{T}^1}{T}\right) + (k_1 V_1 T - \beta_1 T_1^*)\left(1 - \frac{\bar{T}_1^*}{T_1^*}\right)$$

$$+ \frac{1}{N_1}(N_1\beta_1 T_1^* - \gamma_1 V_1)\left(1 - \frac{\bar{V}_1}{V_1}\right) - \sum_{i=2}^{n}\left(-k_i V_i \bar{T}^1 + \frac{\gamma_i}{N_i} V_i\right).$$

Note that the first three terms can be simplified in a way similar as in the proof of Theorem 1, and using the expression for $\bar{T}^i$ in (7), we find that

$$\dot{W} = (f(T) - f(\bar{T}^1))\left(1 - \frac{\bar{T}^1}{T}\right) - \beta_1 \bar{T}_1^*\left[\frac{\bar{T}^1}{T} + \frac{\bar{T}_1^* V_1 T}{T_1^* \bar{V}_1 \bar{T}^1} + \frac{\bar{V}_1 T_1^*}{V_1 \bar{T}_1^*} - 3\right] - \sum_{i=2}^{n} k_i V_i (\bar{T}^i - \bar{T}^1).$$

The first two terms are non-positive as we have already shown in the proof of Theorem 1. The third part is also non-positive by (8). Thus $\dot{W} \leqslant 0$, establishing a local stability of E_1. An application of LaSalle's invariance principle shows that all bounded solutions in U (and as before, boundedness follows from Lemma 1 which is proved later) converge to the largest invariant set in

$$\left\{(T, T_1^*, \cdots, T_n^*, V_1, \cdots, V_n) \in U \,\middle|\, \frac{\bar{T}^1}{T} = 1, \frac{\bar{T}_1^* V_1}{T_1^* \bar{V}_1} = 1, V_i = 0, i > 2\right\},$$

which is easily shown to be the singleton $\{E_1\}$. Finally, we observe that all solutions on the boundary of U with $T_1^*(0) + V_1(0) > 0$ enter U instantaneously. This concludes the proof of Theorem 2. □

4. Perturbations by mutations

In this section, we expand the multistrain model (4–6) to account for possible mutations between the n strains. To be exact, we will study two different ways in which mutations occur. Our first extended model can be written compactly as follows:

$$\dot{T} = f(T) - k'VT, \quad T \in \mathbb{R}_+, \tag{10}$$

$$\dot{T}^* = P(\mu)KVT - BT^*, \quad T^* \in \mathbb{R}_+^n, \tag{11}$$

$$\dot{V} = \hat{N}BT^* - \Gamma V, \quad V \in \mathbb{R}_+^n, \tag{12}$$

while the second is written as

$$\dot{T} = f(T) - k'VT, \quad T \in \mathbb{R}_+, \tag{13}$$

$$\dot{T}^* = KVT - BT^*, \quad T^* \in \mathbb{R}_+^n, \tag{14}$$

$$\dot{V} = P(\mu)\hat{N}BT^* - \Gamma V, \quad V \in \mathbb{R}_+^n. \tag{15}$$

In both models, $K = \mathrm{diag}(k)$, $B = \mathrm{diag}(\beta)$, $\hat{N} = \mathrm{diag}(N)$ and $\Gamma = \mathrm{diag}(\gamma)$ and the matrix $P(\mu)$ with $\mu \in [0, 1]$ is defined as follows:

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

where Q is a matrix with $q_{ij} > 0$ if strain j can mutate to i (for $i \neq j$) so that different magnitudes of q_{ij} reflect the possible differences in the specific mutation rates. The diagonal entries of Q are such that each column of Q sums to zero. Note that P is a stochastic matrix (all its entries are in $[0, 1]$ and all its columns sum to one) provided that $\mu \leqslant -1/q_{ii}$ for all i (which is assumed henceforth) and that $P(0) = I$.

The biological interpretation of the difference between models (10–12) and (13–15) is motivated by distinct mutation mechanisms. The first model (10–12) is appropriate to describe the mutations of retroviruses such as HIV. In case of retroviruses, mutations can occur during the reverse transcription of the viral RNA into viral DNA. The process of reverse transcription is highly error prone due to the lack of an appropriate correction mechanism. Thus, a virion of type i that entered a previously healthy T cell may be converted to viral DNA of type j, yielding an infected T cell of type j. The resulting DNA is then integrated into the DNA of the T cell creating the so-called provirus that will ultimately be used as a template to produce type-j virions until the infected T cell bursts. The second model (13–15) is appropriate to describe the mutation mechanism of DNA viruses such as the herpes virus. Such viruses bring their own DNA which is transcribed after infection. The transcription process uses both cellular machinery and viral proteins and is subject to mistakes that give rise to mutations; see for instance López-Bueno *et al.* (2003). Thus, a virion of type i that entered a previously healthy T cell yields an infected T cell of the same type i that may go on to produce virions of different types.

Despite the structural differences between these models, it will later become clear that their qualitative behaviour is identical; see our main result in Theorem 5.

We also note that both models ignore the possibility of co-infections. A co-infection occurs when a given T cell becomes simultaneously infected with virions of several distinct types. As a result, several proviruses may coexist within a single T cell.

We start our analysis with the following result.

LEMMA 1 Both systems (10–12) and (13–15) are dissipative, i.e. there exists a forward-invariant compact set $K \subset \mathbb{R}_+^{2n+1}$ such that every solution eventually enters K.

Proof. From (10) and (13) follows that $\dot{T} \leqslant f(T)$, hence

$$\limsup_{t \to \infty} T(t) \leqslant T_0, \tag{16}$$

provided that solutions to both systems are defined for all $t \geqslant 0$. To see that this is indeed the case, we argue by contradiction and let $(T(t), T^*(t), V(t))$ be a solution with bounded maximal interval of existence $\mathcal{I}_+ := [0, t_{\max})$. Then, necessarily $T(t) \leqslant \max(T(0), T_0) := T_{\max}$ for all $t \in \mathcal{I}_+$. This implies that on $\mathcal{I}_+$, the following differential inequality holds for the solution of system (10–12):

$$\dot{T}^* \leqslant P(\mu)KVT_{\max} - BT^*, \tag{17}$$

$$\dot{V} \leqslant \hat{N}BT^* - \Gamma V \tag{18}$$

or for system (13–15):

$$\dot{T}^* \leqslant KVT_{\max} - BT^*, \tag{19}$$

$$\dot{V} \leqslant P(\mu)\hat{N}BT^* - \Gamma V, \tag{20}$$

respectively. Note that the right-hand sides in the above inequalities are cooperative and linear vector fields. By a comparison principle for such inequalities, we obtain that $T(t) \leqslant \tilde{T}(t)$ and $V(t) \leqslant \tilde{V}(t)$

(interpreted componentwise) for all t in the intersection of the domains where the solutions are defined. Here, $(\tilde{T}(t), \tilde{V}(t))$ is the solution to the linear system whose vector field appears on the right-hand side of the above inequalities, hence these solutions are defined for all $t \geqslant 0$. But then $T(t)$ and $V(t)$ can be extended continuously to the closed interval $[0, T_{\max}]$, contradicting maximality of $\mathcal{I}_+$.

Inequality (16) implies that for an arbitrary small $\epsilon > 0$, there holds that $T(t) \leqslant T_0 + \epsilon$ for all sufficiently large t. Now consider the behaviour of the quantity $T + 1'T^*$ (here, $1'$ denotes a row vector whose entries are all equal to 1) along the solutions of both systems (10–12) and (13–15):

$$\frac{\mathrm{d}}{\mathrm{d}t}(T + 1'T^*) = f(T) - 1'BT^* \leqslant f(T) - b1'T^*,$$

where $b := \min_i(\beta_i)$. By continuity of f on the compact interval $[0, T_0 + \epsilon]$, there exists (a sufficiently large) $a > 0$ such that

$$f(T) + bT \leqslant a, \quad \text{for all } T \in [0, T_0 + \epsilon].$$

Therefore, for all sufficiently large t, there holds that

$$\frac{\mathrm{d}}{\mathrm{d}t}(T + 1'T^*) \leqslant a - bT - b1'T^* \leqslant a - b(T + 1'T^*),$$

and hence

$$\limsup_{t \to \infty} T(t) + 1'T^*(t) \leqslant \frac{a}{b}.$$

Finally, from (12) and (15), it follows that

$$\limsup_{t \to \infty} V(t) \leqslant \frac{a}{b}, \frac{\max_i(NB)_i}{\min_i f_i}.$$

Dissipativity now follows by observing that all the above bounds are independent of the initial condition. □

LEMMA 2 For $\mu = 0$, let all the single-strain equilibria $E_1, E_2, \ldots, E_n$ exist for either (10–12) or (13–15), and assume that

$$\bar{T}^1 < \bar{T}^2 < \cdots < \bar{T}^n < \bar{T}^{n+1} := T_0 \tag{21}$$

and

$$f'(\bar{T}^j) \leqslant 0, \quad \text{for all } j = 1, \ldots, n+1. \tag{22}$$

Then, the Jacobian matrices of (10–12) or (13–15), evaluated at any of the E_is, $i = 1, \ldots, n+1$ (where $E_{n+1} := E_0$), have the following properties: $J(E_i)$ has $i - 1$ eigenvalues (counting the multiplicities) in the open right half-plane and $2(n+1) - i$ eigenvalues in the open left half-plane. In particular, $J(E_1)$ is Hurwitz.

Proof. Note that when $\mu = 0$, the Jacobian matrix associated to both model (10–12) and (13–15) is the same and given by the following:

$$J = \begin{pmatrix} f'(T) - k'V & 0 & -k'T \\ KV & -B & KT \\ 0 & \hat{N}B & -\Gamma \end{pmatrix}.$$

To evaluate the Jacobian at any of the E_is, it is more convenient to permute the components of the state vector as follows:

1. for $i = 1, \ldots, n$, we use $(T, T^*, V) \rightarrow (T, T_i^*, V_i, T_1^*, V_1, \ldots, T_{i-1}^*, V_{i-1}, T_{i+1}^*, V_{i+1}, \ldots, T_n^*, V_n)$.

2. for $i = n + 1$, we use $(T, T^*, V) \rightarrow (T, T_1^*, V_1, T_2^*, V_2, \ldots, T_n^*, V_n)$.

Then, the Jacobian matrices have the following structure:

1. For $i = 1, \ldots, n$,

$$
J(E_i) = \begin{pmatrix}
A_1^i & * & \cdots & * & * & \cdots & * \\
0 & B_1^i & \cdots & 0 & 0 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots & \vdots & \cdots & 0 \\
0 & 0 & \cdots & B_{i-1}^i & 0 & \cdots & 0 \\
0 & 0 & \cdots & 0 & B_{i+1}^i & \cdots & 0 \\
\vdots & \vdots & \cdots & \vdots & \vdots & \ddots & 0 \\
0 & 0 & \cdots & 0 & 0 & \cdots & B_n^i
\end{pmatrix},
$$

where

$$
A_1^i = \begin{pmatrix}
f'(\bar{T}^i) - k_i \bar{V}_i & 0 & -k_i \bar{T}^i \\
k_i \bar{V}_i & -\beta_i & k_i \bar{T}^i \\
0 & N_i \beta_i & -\gamma_i
\end{pmatrix}
\quad \text{and} \quad
B_l^i = \begin{pmatrix}
-\beta_l & k_l \bar{T}^i \\
N_l \beta_l & -\gamma_l
\end{pmatrix}, \quad l \neq i,
$$

and therefore, the eigenvalues of $J(E_i)$ coincide with those of A_1^i and $B_l^i, l \neq i$. Since $f'(\bar{T}^i) \leqslant 0$, Lemma 3.4 in De Leenheer & Smith (2003) implies that the eigenvalues of A_1^i belong to the open left half-plane. The matrices B_l^i are quasi-positive, irreducible matrices, hence by the Perron–Frobenius theorem, they have a simple real eigenvalue λ_l^i with corresponding (componentwise) positive eigenvector. In addition, we have that

$$
\mathrm{tr}(B_l^i) < 0 \quad \text{and} \quad \det(B_l^i) = \beta_l \gamma_l \left(1 - \frac{\bar{T}^i}{\bar{T}^l} \right),
$$

and thus by (21) that

$$
\lambda_l^i \begin{cases}
< 0, & \text{for all } l > i, \\
> 0, & \text{for all } l < i.
\end{cases}
$$

There are $i - 1$ unstable B-blocks on the diagonal of $J(E_i)$, each of which contributes one positive eigenvalue to $J(E_i)$.

2. For $i = n + 1$,

$$J(E_{n+1}) = \begin{pmatrix} A_1^{n+1} & * & \cdots & * \\ 0 & B_1^{n+1} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & B_n^{n+1} \end{pmatrix},$$

where

$$A_1^{n+1} = \left(f'(\bar{T}^{n+1}) \right) \text{ and } B_l^{n+1} = \begin{pmatrix} -\beta_l & k_l \bar{T}^{n+1} \\ N_l \beta_l & -\gamma_l \end{pmatrix}, \quad l = 1, ..., n.$$

Note that by a similar argument as in the previous case, all n B-blocks on the diagonal of $J(E_{n+1})$ are unstable with one positive and one negative eigenvalue.

□

When $\mu \neq 0$, the question arises as to what happens to the equilibria $E_1, \ldots, E_{n+1}$. The previous lemma allows us to apply the implicit function theorem which for small positive μ establishes the existence of (unique) equilibria $E_j(\mu)$ near each E_j. Indeed, denoting the vector field of either (10–12) or (13–15) by $F(X, \mu)$, we have that for all $j = 1, \ldots, n + 1$, $F(E_j, 0) = 0$, and under the conditions of the previous lemma, we also have that $\partial F/\partial X(E_j, 0)$ is invertible. It is also clear that $E_{n+1}(\mu) = E_{n+1}(0)$ for all $\mu \geqslant 0$, i.e. the disease-free equilibrium is not affected by mutations.

The main issue is of course whether or not the remaining equilibria $E_j(\mu)$, $j = 1, ..., n$, are non-negative. We study this problem next and derive the results in terms of the properties of the mutation matrix Q.

For the steady-state analysis, we will need the following lemma which is a relevant modification of Theorem A.12(ii) in Smith & Waltman (1994).

LEMMA 3 Let M be an irreducible square matrix with non-negative off-diagonal entries and let $s(M)$ be the stability modulus of M. Suppose that there exist $x, r \geqslant 0$ such that $Mx + r = 0$. Then, the following hold:

1. if $s(M) > 0$, then $x = r = 0$;

2. if $s(M) = 0$, then $r = 0$ and x is a multiple of the positive eigenvector of M.

Proof. Due to the Perron–Frobenius theorem, $s(M)$ is the principal eigenvalue of M. It is also the principal eigenvalue of M'. Since M' is also irreducible and non-negative off-diagonal, there exists a $v > 0$ such that $M'v = s(M)v$. Equivalently, $v'M = s(M)v'$. Hence,

$$0 = v'(Mx + r) = s(M)v'x + v'r.$$

If $s(M) > 0$, then both non-negative products $v'x$ and $v'r$ must be zero which implies that $x = r = 0$. If $s(M) = 0$, then $v'r = 0$ which implies that $r = 0$. Hence, $Mx = 0 = s(M)x$ so that x is a multiple of the positive eigenvector of M. □

For convenience, we introduce the following notation. We define $A(\mu) := \Gamma^{-1} \hat{N} P(\mu) K$ and assume (by renumbering the strains if necessary) that the strains are numbered in such a way that the matrix $A(\mu)$ has the lower block-triangular structure

$$A(\mu) = \begin{pmatrix} A_1(\mu) & 0 & \cdots & 0 \\ \mu B_{2,1} & A_2(\mu) & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ \mu B_{k,1} & \mu B_{k,2} & \cdots & \mu A_k(\mu) \end{pmatrix}, \tag{23}$$

where each diagonal block

$$A_i(\mu) = \text{diag}\left(\frac{1}{\bar{T}_{i1}}, \ldots, \frac{1}{\bar{T}_{is_i}}\right) + \mu B_i$$

is such that B_i, $i = 1, ..., k$, are irreducible with non-negative off-diagonal entries. The off-diagonal blocks $B_{i,j}$, $i > j$, are non-negative. We note that the diagonal entries of $A(0)$ are a permutation of

$$0 < \frac{1}{\bar{T}_n} < \frac{1}{\bar{T}_{n-1}} < \cdots < \frac{1}{\bar{T}_1}.$$

We say that the strain group j is reachable from strain group i if there exists a sequence of indices $i = l_1 < l_2 < ... < l_m = j$ such that all matrices B_{l_{s+1}, l_s} are non-zero. Our first result is as follows.

PROPOSITION 1 Let the assumptions of Lemma 2 hold, then the following hold:

1. For all sufficiently small $\mu > 0$, matrix $A(\mu)$ admits n distinct positive eigenvalues given by

$$\frac{1}{\hat{T}_n(\mu)} < \frac{1}{\hat{T}_{n-1}(\mu)} < \cdots < \frac{1}{\hat{T}_1(\mu)}$$

such that $\hat{T}_i(0) = \bar{T}_i$ for $i = 1, ..., n$.

2. Matrix $A(\mu)$, $\mu > 0$, admits a positive eigenvector $(v_1, v_2, \ldots, v_k)$ if and only if $\frac{1}{\hat{T}_1(\mu)}$ is a principal eigenvalue of $A_1(\mu)$, and all strain groups $j \geqslant 2$ are reachable from strain group 1.

3. Matrix $A(\mu)$, $\mu > 0$, admits a non-negative eigenvector $(v_1, v_2, \ldots, v_k)$ for each eigenvalue $\frac{1}{\hat{T}_r(\mu)}$ such that $\frac{1}{\hat{T}_r(\mu)}$ is a principal eigenvalue of some diagonal block $A_i(\mu)$, and $s(A_j(\mu)) < \frac{1}{\hat{T}_r(\mu)}$ for all $j = i + 1, \ldots, k$ such that strain group j is reachable from strain group i. The component v_j is positive (zero) if group j is reachable (not reachable) from strain group i.

4. All other eigenvectors of $A(\mu)$, $\mu > 0$, are not sign definite.

Proof. The first assertion follows readily because $A(0)$ has n real distinct eigenvalues and $A(\mu)$ is continuous (actually, linear) in μ. The continuity of eigenvalues with respect to μ implies that $\hat{T}_i(0) = \bar{T}_i$ for $i = 1, \ldots, n$.

To prove the second assertion, we begin with sufficiency of the condition. Let $\mu > 0$ be small and suppose that $\frac{1}{\hat{T}_1(\mu)}$ is a principal eigenvalue of $A_1(\mu)$ and all strain groups $j \geqslant 2$ are reachable from strain group 1. Since $A_1(\mu)$ is irreducible with non-negative off-diagonal entries, Perron–Frobenius

theorem implies that the eigenvector v_1 associated with $\frac{1}{\hat{T}_1(\mu)}$ is positive. Since $\frac{1}{\hat{T}_1(\mu)}$ is also the principal eigenvalue of $A(\mu)$, it follows that

$$s\left(A_j(\mu) - \frac{1}{\hat{T}_1(\mu)}I\right) < 0, \quad j \geqslant 2,$$

hence $\left(A_j(\mu) - \frac{1}{\hat{T}_1(\mu)}I\right)^{-1} < 0$ (see, e.g. Theorem A.12(i) in Smith & Waltman, 1994). The remaining components $v_2, \ldots, v_k$ of the eigenvector satisfy the triangular system

$$0 = \mu B_{2,1} v_1 + \left(A_2(\mu) - \frac{1}{\hat{T}_1(\mu)}I\right)v_2,$$

$$0 = \mu B_{3,1} v_1 + \mu B_{3,2} v_2 + \left(A_3(\mu) - \frac{1}{\hat{T}_1(\mu)}I\right)v_3,$$

$$\vdots$$

$$0 = \mu B_{k,1} v_1 + \cdots + \mu B_{k,k-1} v_{k-1} + \left(A_k(\mu) - \frac{1}{\hat{T}_1(\mu)}I\right)v_k.$$

Solving this system recursively, we obtain

$$v_j = -\left(A_j(\mu) - \frac{1}{\hat{T}_1(\mu)}I\right)^{-1}(\mu B_{j,1} v_1 + \cdots + \mu B_{j,j-1} v_{j-1}), \quad j = 2, \ldots, k.$$

Since the strain group 2 is reachable from strain group 1, the vector $\mu B_{2,1} v_1 \geqslant 0$ is non-zero. Positivity of the matrix $-\left(A_2(\mu) - \frac{1}{\hat{T}_1(\mu)}I\right)^{-1}$ then implies that $v_2 > 0$. By induction on j, it follows that $v_j > 0$ for all $j = 2, \ldots, k$, and hence $v = (v_1, v_2, \ldots, v_k)$ is a positive eigenvector.

To prove the converse (the necessary condition), let $v = (v_1, v_2, \ldots, v_k)$ be a positive eigenvector of $A(\mu)$ and let $\frac{1}{\hat{T}_q(\mu)}$ be the corresponding eigenvalue. Since $\left(A_1(\mu) - \frac{1}{\hat{T}_q(\mu)}I\right)v_1 = 0$ and $v_1 > 0$, $\frac{1}{\hat{T}_q(\mu)}$ must be the principal eigenvalue of $A_1(\mu)$ (Perron–Frobenius theorem). It remains to prove that $s(A_j(\mu)) < \frac{1}{\hat{T}_q(\mu)}$ for all $j \geqslant 2$. Consider $j = 2$, and for the sake of contradiction, suppose that $s\left(A_j(\mu) - \frac{1}{\hat{T}_q(\mu)}I\right) \geqslant 0$. Since the eigenvalues are real and distinct for small $\mu > 0$, this actually implies that $s\left(A_j(\mu) - \frac{1}{\hat{T}_q(\mu)}I\right) > 0$. Then, we have that

$$\left(A_j(\mu) - \frac{1}{\hat{T}_q(\mu)}I\right)v_2 + \mu B_{2,1} v_1 = 0$$

holds with non-negative vectors v_2 and $\mu B_{2,1} v_1$ which are both non-zero. By Lemma 3, we have $v_2 = 0$, a contradiction. Hence, $s\left(A_2(\mu) - \frac{1}{\hat{T}_q(\mu)}I\right) < 0$. Proceeding by induction on j, we find that $s\left(A_j(\mu) - \frac{1}{\hat{T}_q(\mu)}I\right) < 0$ for all $j \geqslant 2$. Therefore, $\frac{1}{\hat{T}_q(\mu)}$ must be the principal eigenvalue of $A(\mu)$, that is, $\frac{1}{\hat{T}_q(\mu)} = \frac{1}{\hat{T}_1(\mu)}$. This proves the second assertion.

To prove the third assertion, we again start with the sufficient condition. Suppose that $\frac{1}{\hat{T}_r(\mu)}$ is a principal eigenvalue of some diagonal block $A_i(\mu)$ and $s(A_j(\mu)) < \frac{1}{\hat{T}_r(\mu)}$ for all $j = i + 1, ..., k$

such that strain group j is reachable from strain group i. It follows immediately that all the matrices $A_l(\mu) - \frac{1}{\hat{T}_r(\mu)}I, l < i$, are non-singular, and thus $v_l = 0, l < i$. The component v_i is the eigenvector of $A_i(\mu) - \frac{1}{\hat{T}_r(\mu)}I$ and it is positive by Perron–Frobenius theorem. Let $j = i + 1$, then one of the following holds. If $i + 1$ is not reachable from i, that is, $B_{i+1,i} = 0$ so that

$$\left(A_{i+1}(\mu) - \frac{1}{\hat{T}_r(\mu)}I \right) v_{i+1} = 0$$

implies that $v_{i+1} = 0$ because $A_{i+1}(\mu) - \frac{1}{\hat{T}_r(\mu)}I$ is non-singular. If $i + 1$ is reachable from i and $s\left(A_{i+1}(\mu) - \frac{1}{\hat{T}_r(\mu)}I \right) < 0$, then

$$v_{i+1} = -\left(A_{i+1}(\mu) - \frac{1}{\hat{T}_r(\mu)}I \right)^{-1} \mu B_{i+1,i} v_i > 0.$$

By induction on j, it follows that $v_j = 0$ for all $j > i$ that are not reachable from i and $v_j > 0$ for all $j > i$ that are reachable from i. Hence, $v = (0, \ldots, 0, v_i, v_{i+1}, \ldots, v_k)$ is a non-negative eigenvector.

Now, we prove the necessary condition of the third assertion. Let $v = (v_1, v_2, \ldots, v_k)$ be a non-negative eigenvector of $A(\mu)$ associated with eigenvalue $\frac{1}{\hat{T}_r(\mu)}$. Let $v_i \geqslant 0$ be the first non-zero component of v, that is, $v = (0, \ldots, 0, v_i, \ldots, v_k)$. Then, v_i satisfies $\left(A_i(\mu) - \frac{1}{\hat{T}_r(\mu)}I \right) v_i = 0$, hence $\frac{1}{\hat{T}_r(\mu)}$ must be an eigenvalue of $A_i(\mu) - \frac{1}{\hat{T}_r(\mu)}I$. Moreover, by Perron–Frobenius theorem, it must be the principal eigenvalue and $v_i > 0$. Now, consider $j = i + 1$ and the equation

$$\left(A_{i+1}(\mu) - \frac{1}{\hat{T}_r(\mu)}I \right) v_{i+1} + \mu B_{i+1,i} v_i = 0.$$

The vectors v_{i+1} and $\mu B_{i+1,i} v_i$ are non-negative. If $s\left(A_{i+1}(\mu) - \frac{1}{\hat{T}_r(\mu)}I \right) > 0$, then by Lemma 3, $\mu B_{i+1,i} v_i = 0$. Since $\mu > 0$ and $v_i > 0$, this implies that $B_{i+1,i} = 0$. Equivalently, $j = i + 1$ is not reachable from i. An induction argument concludes the proof of the third assertion.

The final assertion of this theorem is a simple one. Let $\frac{1}{\hat{T}_r(\mu)}$ be an eigenvalue of $A_i(\mu)$ but not the principal eigenvalue and let $v = (v_1, v_2, \ldots, v_n)$ be the corresponding eigenvector. Since all eigenvalues of $A(\mu)$ are distinct, the matrices $A_l(\mu) - \frac{1}{\hat{T}_r(\mu)}I, l < i$, are non-singular so that $v_l = 0, l < i$. Then, v_i must be an eigenvector of $A_i(\mu)$ and it cannot be sign definite due to Perron–Frobenius theorem. It follows that v is not sign definite. $\qquad\square$

Our second result concerns the existence and the number of non-negative equilibria for the systems (10–12) and (13–15) with small $\mu > 0$.

PROPOSITION 2 Let the assumptions of Lemma 2 hold and suppose that the strains are renumbered so that $A(\mu)$ has the form (23). Let $E_j(\mu) = (\hat{T}_j(\mu), \hat{T}_j^*(\mu), \hat{V}_j(\mu))$ denote the non-trivial equilibria of both (10–12) and (13–15) for small $\mu > 0$. Then,

1. $E_j(\mu)$ is positive if and only if $\frac{1}{\hat{T}_j(\mu)}$ is an eigenvalue of $A(\mu)$ with a positive eigenvector V_j;

2. $E_j(\mu)$ is non-negative if and only if $\frac{1}{\hat{T}_j(\mu)}$ is an eigenvalue of $A(\mu)$ with a non-negative eigenvector V_j;

3. $E_j(\mu) \notin \mathbb{R}_+^{2n+1}$ if and only if $\frac{1}{\hat{T}_j(\mu)}$ is an eigenvalue of $A(\mu)$ with eigenvector V_j which is not sign definite.

Proof. We will prove the proposition only for system (10–12) (the proof for (13–15) is similar). Observe that the equilibrium relation following from (12) can be expressed as $\hat{T}_j^*(\mu) = (\hat{N}B)^{-1}\Gamma\hat{V}_j(\mu)$. Hence, the signs of the corresponding components of $\hat{T}_j^*(\mu)$ and $\hat{V}_j(\mu)$ are the same. Substituting the above expression into (11) and (12), we find that $\hat{V}_j(\mu)$ must satisfy -

$$\left[\Gamma^{-1}\hat{N}P(\mu)K - \frac{1}{\hat{T}_j(\mu)}I\right]\hat{V}_j(\mu) = \left[A(\mu) - \frac{1}{\hat{T}_j(\mu)}I\right]\hat{V}_j(\mu) = 0.$$

Thus, for each non-trivial equilibrium $E_j(\mu)$, the quantity $\frac{1}{\hat{T}_j(\mu)}$ must be an eigenvalue of $A(\mu)$ and $\hat{V}_j(\mu)$ must be a multiple of the corresponding eigenvector V_j. If V_j is not sign definite, it follows that $E_j(\mu) \notin \mathbb{R}_+^{2n+1}$. For all $V_j \geqslant 0$, the components of $E_j(\mu)$ are uniquely determined via

$$\hat{V}_j(\mu) = \frac{f(\hat{T}_j(\mu))}{\hat{T}_j(\mu)k'V_j}V_j, \quad \hat{T}_j^*(\mu) = (\hat{N}B)^{-1}\Gamma\hat{V}_j(\mu).$$

Hence, $E_j(\mu)$ is positive (non-negative) if and only if V_j is positive (non-negative). □

An immediate corollary to Propositions 1 and 2 is that if the mutation matrix Q is irreducible, then $A(\mu)$ is irreducible and systems (10–12) and (13–15) with small $\mu > 0$ admit a unique positive equilibrium $E_1(\mu)$ and no other non-trivial non-negative equilibria. If the mutation matrix Q is reducible, then a positive equilibrium exists if and only if the fittest strain (with lowest value $\bar{T}_1$) belongs to strain group 1 and all other strain groups are reachable from group 1, meaning that the fittest strain can eventually mutate into any other strain. In addition, non-trivial non-negative equilibria (that are not positive) are feasible for $\mu > 0$ only if Q is reducible. Specifically, if the strains can be numbered according to (23), then at most k non-trivial non-negative equilibria exist. An extreme case is when the fittest strain belongs to group k, in which case no positive and only one non-negative equilibrium exist. We illustrate a few mutation scenarios in Fig. 1, and indicate the number and type of the various disease equilibria for models (10–12) and (13–15) when the mutation parameter $\mu > 0$ is sufficiently small.

4.1   *On uniform strong repellers*

To prove our main result (Theorem 5), we first need to establish a particular uniform persistence property that models (10–12) and (13–15) exhibit for small positive values of the mutation parameter μ. To establish this property, we need to introduce several preliminary concepts and results. Inspired by Thieme (1993), we make the following definition.

DEFINITION 1 Consider a system

$$\dot{x} = F(x) \tag{24}$$

on a compact forward-invariant set $K \subset \mathbb{R}^m$ with a continuous flow $\phi(t, x)$. Let $K_0 \subset K$ be a closed forward-invariant subset of K. Let $d(x, A)$ denote the distance from a point x to the set A. We say that K_0 is a uniform strong repeller in K if there exists a $\delta > 0$ such that for all solutions $\phi(t, x) \in K \backslash K_0$, $\liminf_{t\to\infty} d(\phi(t, x), K_0) \geqslant \delta$.
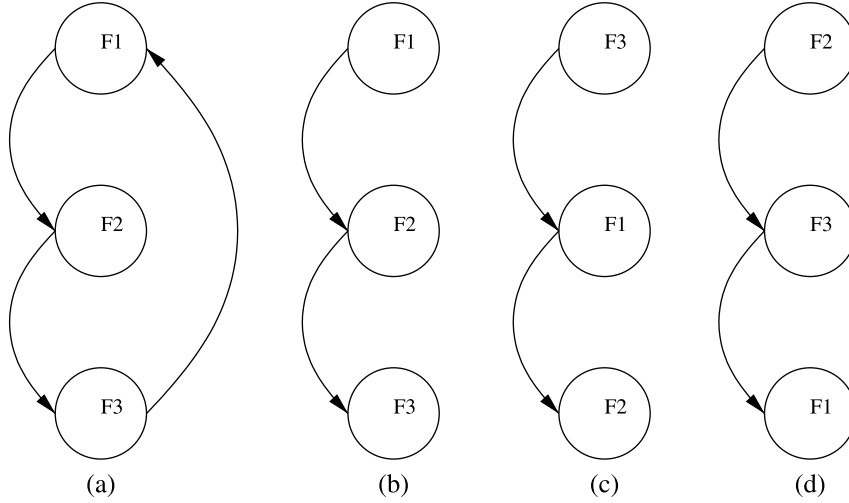
FIG. 1. Representative mutation graphs with three strains. F1 denotes the fittest strain, F2 the second fittest and F3 the least-fit strain (fitter strains have lower T-value at equilibrium; see (21)). (a) is an irreducible case and (b), (c) and (d) are reducible cases. Non-trivial equilibria for (10–12) and (13–15) for small $\mu > 0$: (a) one positive equilibrium ($E_1(\mu)$), (b) one positive ($E_1(\mu)$) and two distinct non-negative non-trivial equilibria ($E_2(\mu)$, $E_3(\mu)$), (c) no positive and two non-negative non-trivial equilibria ($E_1(\mu)$, $E_2(\mu)$) and (d) no positive and one non-negative non-trivial equilibrium ($E_1(\mu)$).

THEOREM 3 Let $\Pi\colon K \to \mathbb{R}^+$ be a continuously differentiable function such that $\Pi(x) = 0$ if and only if $x \in K_0$. Suppose there exists a lower semi-continuous function $\psi\colon K \to \mathbb{R}$ such that

$$\frac{\dot{\Pi}}{\Pi} = \psi, \quad \forall x \in K \backslash K_0. \tag{25}$$

In addition, suppose that the following condition holds:

$$(\text{H}) \quad \forall x \in K_0, \quad \exists T > 0 \colon \langle \psi(\phi(T, x)) \rangle > 0,$$

where $\langle \psi(\phi(T, x)) \rangle$ denotes the average value of $\psi(\phi(t, x))$ on the interval $[0, T]$. Then, K_0 is a uniform strong repellor in K.

Proof.

Step 1. Note that by lower semi-continuity of ψ and continuity of ϕ, for every $p \in K_0$, there exists an open set U_p containing p and a lower semi-continuous map $T_p\colon U_p \to (0, +\infty)$ such that for every $q \in U_p$, (H) holds with $x = q$ and $T = T_p(q)$. For every $p \in K_0$, we choose a non-empty open set V_p with $\bar{V}_p \subset U_p$. Then, by the lower semi-continuity of each map T_p and compactness of $\bar{V}_p$, we have that

$$\inf_{q \in \bar{V}_p} T_p(q) > 0$$

is achieved at some point in $\bar{V}_p$. Since $\cup_{p \in K_0} V_p$ is an open cover of K_0, there exists a finite open subcover $\cup_{i=1,\ldots,n} V_{p_i}$. Let $\tau_i = \inf_{q \in \bar{V}_{p_i}} T_{p_i}(q) > 0$ and let

$$\tau := \min_{i=1,\ldots,n} \tau_i > 0.$$

Note that for every $p \in K_0$, there is a $T \geqslant \tau$ such that (H) holds with $x = p$. Hence, τ is a uniform (in K_0) lower bound for Ts for which (H) holds.

Step 2. Let $h > 0$ be given. Define

$$U_h = \{x \in K | \exists T > \tau \colon \langle \psi(\phi(T, x)) \rangle > h\}. \tag{26}$$

We claim that U_h is open. Indeed, let $z \in U_h$. Then, there is some $T > \tau$ such that

$$\epsilon := \langle \psi(\phi(T, z)) \rangle - h > 0.$$

Then, from the continuity of ϕ and the lower semi-continuity of ψ (and therefore uniform lower semi-continuity of ψ on compact sets), it follows that there exists an open set W_z containing z such that for all $z' \in W_z$, it holds that

$$\psi(\phi(t, z') > \psi(\phi(t, z)) - \epsilon, \quad \forall t \in [0, T]. \tag{27}$$

Since

$$\langle \psi(\phi(T, z)) \rangle = \epsilon + h,$$

it follows from (27) that for all $z' \in W_z$,

$$\langle \psi(\phi(T, z')) \rangle > h,$$

and thus $W_z \subset U_h$, establishing our claim.

Step 3. Define $T_h \colon U_h \to [\tau, +\infty)$ as

$$T_h(z) := \inf\{T > \tau | \langle \psi(\phi(T, z)) \rangle > h\}.$$

We claim that T_h is upper semi-continuous. Let $z \in U_h$ and let $\epsilon' > 0$ be given. Then, there is some $T > \tau$ such that

$$\langle \psi(\phi(T, z)) \rangle > h,$$

which implies that

$$T < T_h(z) + \epsilon'. \tag{28}$$

By the argument in Step 2, there is some open set W_z containing z such that for all $z' \in W_z$, it holds that

$$\langle \psi(\phi(T, z')) \rangle > h,$$

and thus that for all $z' \in W_z$,

$$T_h(z') \leqslant T. \tag{29}$$

Our claim follows by combining (28) and (29).

Step 4. The nested family $\{U_h\}_{h>0}$ is decreasing (under set inclusion), and forms an open cover of K_0. Hence, there is some $\bar{h}$ so that $U_{\bar{h}}$ covers K_0. Since $\tilde{K} := K \setminus U_{\bar{h}}$ is compact and Π is continuous, Π attains its minimal value $m > 0$ on $\tilde{K}$. Choose $p \in (0, m)$ and define

$$I_p := \{z \in K | \Pi(z) \in (0, p]\} \subset U_{\bar{h}}.$$

Step 5. We claim that every forward solution starting in I_p eventually leaves I_p, that is,

$$\forall z \in I_p, \quad \exists t_z > 0 \colon \phi(t_z, z) \notin I_p.$$

By contradiction, if $\phi(t, z) \in I_p$ for all $t \geqslant 0$, then $\phi(t, z) \in U_{\bar{h}}$ for all $t \geqslant 0$, and thus,

$$\exists\, T_t \geqslant \tau \colon \frac{1}{T_t} \int_t^{t+T_t} \psi(\phi(s, z))\mathrm{d}s > \bar{h}.$$

Integrating equation (25) from t to $t + T$, we find that

$$\ln\left(\frac{\Pi(\phi(t + T_t, z))}{\Pi(\phi(t, z))}\right) > \bar{h} T_t,$$

which implies that

$$\Pi(\phi(t + T_t, z)) > e^{\bar{h} T_t} \Pi(\phi(t, z)). \tag{30}$$

Set $t_0 = 0$ and $t_k = t_{k-1} + T_{t_{k-1}}$ for $k = 1, 2, \ldots$. Since each $T_{t_k} \geqslant \tau > 0$, it follows that $t_k \to \infty$. Then, by (30) and since $t_k \geqslant \tau$ for all k, we have that

$$\Pi(\phi(t_k, z)) > e^{\bar{h} T_{t_{k-1}}} \Pi(\phi(t_{k-1}, z)) > e^{k\tau} \Pi(z),$$

so that $\Pi(\phi(t_k, z)) \to \infty$ as $k \to \infty$. This contradicts the boundedness of Π on the compact set K.
Step 6. Let

$$\tilde{I}_p = I_p \cup K_0.$$

We will show that there is some $q \in (0, p)$ so that forward solutions starting outside $\tilde{I}_p$ never reach I_q, that is,

$$\exists\, q \in (0, p) \colon z \notin \tilde{I}_p \Rightarrow \phi(t, z) \notin I_q, \quad \forall t \geqslant 0.$$

Consider a forward solution $\phi(t, z)$ with $z \notin \tilde{I}_p$. If $\phi(t, z) \notin \tilde{I}_p$ for all $t \geqslant 0$, then we are done since $\tilde{I}_q \subset \tilde{I}_p$, so let us assume that for some $t_z > 0 \Rightarrow \phi(t_z, z) \in \tilde{I}_p$. Denote the first time this happens by t_0:

$$t_0 = \min\{t > 0 | \phi(t, z) \in \tilde{I}_p\}.$$

Set $z^* = \phi(t_0, z)$ and note that $\Pi(z^*) = p$. Denote $\inf_{z \in K_0} \psi(z)$ by m'. If $m' \geqslant 0$, then (25) implies that $\Pi(\phi(t, z^*)) \geqslant \Pi(z^*) = p$ for all $t \geqslant 0$, so that we are done. If on the the other hand $m' < 0$, we first define

$$\bar{T} = \max_{z \in \tilde{I}_p} T_h(z) \quad (\geqslant \tau > 0).$$

Note that this maximum is indeed achieved on the compact set $\tilde{I}_p$ since T_h is upper semi-continuous. Now, we define

$$q = p\, e^{m'\bar{T}},$$

and note that q is independent of the chosen solution $z(t)$. We will show that for this choice of q, our claim follows. Indeed, we have that

$$\forall t \in (0, \bar{T}): \frac{1}{t}\int_0^t \psi(\phi(s, z^*))\mathrm{d}s \geqslant m',$$

and thus by (25) that

$$\forall t \in (0, \bar{T}): \Pi(\phi(t, z^*)) \geqslant \Pi(z^*)e^{m't} > q, \tag{31}$$

which implies that during the time interval $(0, \bar{T})$, the solution $\phi(t, z^*)$ has not reached I_q. On the other hand, during that same time interval $(0, \bar{T})$, the solution $\phi(t, z^*)$ must have left $\tilde{I}_p$. If this were not the case, then by the argument in Step 5, there would be some $T^* \in [\tau, \bar{T})$ such that

$$\Pi(\phi(T^*, z^*)) \geqslant \Pi(z^*)e^{\bar{h}T} > p$$

and thus that $\phi(T^*, z^*) \notin \tilde{I}_p$, a contradiction to our assumption. This process can be repeated iteratively to show that the forward solution $\phi(t, z)$ that did not start in $\tilde{I}_p$ will never reach I_q.

So far we have shown that for any solution $\phi(t, x) \notin K_0$, inequality $\Pi(\phi(t, x)) \geqslant q > 0$ holds for all sufficiently large t. The sets $K_0 = \Pi^{-1}(\{0\})$ and $\Pi^{-1}([q, +\infty)) \cap K$ are compact and disjoint. Therefore, there exists a $\delta > 0$ such that $d(\phi(t, x), K_0) \geqslant \delta$ for all $x \notin K_0$ and all sufficiently large t.   □

4.2 Global stability for small $\mu > 0$

The following lemmas will be used to prove the global stability of the positive equilibrium for small $\mu > 0$.

LEMMA 4 Let $a: \mathbb{R}^m \to \mathbb{R}^n$ be continuous and let $b \in \mathrm{int}(\mathbb{R}_+^n)$. Let $f: \mathbb{R}^m \times (\mathbb{R}_+^n \setminus \{0\}) \to \mathbb{R}$ be defined as

$$f(x, y) := \frac{a'(x)y}{b'y}.$$

Then,

$$\liminf_{x \to x_0, y \to 0+} f(x, y) = \min_{i \in \{1,\dots,n\}} \frac{a_i(x_0)}{b_i}; \tag{32}$$

furthermore, if we define $f(x, 0) = \min_{i \in \{1,\dots,n\}} \frac{a_i(x)}{b_i}$, then $f(x, y)$ becomes a lower semi-continuous function on $\mathbb{R}^m \times \mathbb{R}_+^n$ whose restriction on $\mathbb{R}^m \times \{0\}$ is continuous.

Proof. Extending the function $f(x, y)$ by defining $f(x_0, 0) = \liminf_{x \to x_0, y \to 0+} f(x, y)$ clearly produces a lower semi-continuous function. Furthermore, since $a(x)$ is continuous, the function $\min_{i \in \{1,\dots,n\}} \frac{a_i(x)}{b_i}$ is continuous as well. So it remains to show that (32) holds.

Without loss of generality, we may assume that $\min_{i \in \{1,\dots,n\}} \frac{a_i(x_0)}{b_i} = \frac{a_1(x_0)}{b_1}$. Setting $x = x_0$ and $y_2 = y_3 = \cdots = y_n = 0$ and letting $y_1 \to 0^+$, we find that $f(x_0, y_1, 0, \dots, 0) \to \frac{a_1(x_0)}{b_1}$. Hence, $\liminf_{x \to x_0, y \to 0+} f(x, y) \leqslant \frac{a_1(x_0)}{b_1}$. We also observe that as long as $y \in \mathbb{R}_+^n \setminus \{0\}$, the value

$$\frac{a'(x)y}{b'y} = \sum_{i=1}^{n} \frac{a_i(x)}{b_i} \frac{b_i y_i}{b_1 y_1 + \cdots + b_n y_n}$$

is a convex linear combination of the values $\frac{a_i(x)}{b_i}$, $i = 1, \dots, n$. By continuity of $a(x)$, for any $\varepsilon > 0$, there exists a $\delta > 0$ such that $\forall i \in \{1, \dots, n\}$ and $\forall x \in B_\delta(x_0)$, we have $a_i(x) > a_i(x_0) - \varepsilon b_i$. Hence, for all $x \in B_\delta(x_0)$ and for all $y \in \mathbb{R}_+^n \setminus \{0\}$, $f(x, y) \geqslant \frac{a_1(x_0)}{b_1} - \varepsilon$. We have established that

$$\frac{a_1(x_0)}{b_1} \geqslant \liminf_{x \to x_0, y \to 0+} f(x, y) \geqslant \frac{a_1(x_0)}{b_1} - \varepsilon.$$

Since $\varepsilon > 0$ is arbitrary, (32) follows. □

LEMMA 5 Suppose that (8) holds. Then, there exist $\eta, \mu_0 > 0$ such that

$$\liminf_{t \to \infty} 1'V(t) \geqslant \eta > 0$$

for any $\mu \in [0, \mu_0]$ and for any solution of (10–12) and (13–15) with $1'V(t) > 0$.

Proof. We will prove the claim for system (10–12) (the proof for (13–15) is similar). The proof consists of two parts. We first show that there exist $\eta_0, \mu_0 > 0$ such that $\liminf_{t \to \infty} 1'(T^*(t) + V(t)) \geqslant \eta_0 > 0$ for all solutions with $T^*(t), V(t) \neq 0$.

We choose n positive numbers $\tilde{N}_i$ so that $\frac{\gamma_i}{k_i T_0} < \tilde{N}_i < N_i$ for all $1 \leqslant i \leqslant n$. This is possible since we assume $\bar{T}_i = \frac{\gamma_i}{k_i N_i} < T_0$. Let $\upsilon = (\tilde{N}, 1)$. It follows that

$$\upsilon' \begin{pmatrix} -B & K T_0 \\ \hat{N} B & -\Gamma \end{pmatrix} = (b_1(N_1 - \tilde{N}_1), \dots, b_n(N_n - \tilde{N}_n), k_1 T_0 \tilde{N}_1 - \gamma_1, \dots, k_n T_0 \tilde{N}_n - \gamma_n)$$

is a positive vector. By continuity, there exists a $\mu_0 > 0$ such that

$$\upsilon' M(T_0, \mu), \quad \text{where } M(T, \mu) := \begin{pmatrix} -B & P(\mu) K T_0 \\ \hat{N} B & -\Gamma \end{pmatrix}$$

is a positive vector for all $\mu \in [0, \mu_0]$.

Consider a system

$$\dot{T} = f(T) - k'VT, \quad T \in \mathbb{R}_+, \tag{33}$$

$$\dot{T}^* = P(\mu)KVT - BT^*, \quad T^* \in \mathbb{R}_+^n, \tag{34}$$

$$\dot{V} = \hat{N}BT^* - \Gamma V, \quad V \in \mathbb{R}_+^n, \tag{35}$$

$$\dot{\mu} = 0, \quad \mu \in [0, \mu_0]. \tag{36}$$

Let K' be the forward-invariant compact set for (10–12) established in Lemma 1 and define $K = K' \times [0, \mu_0]$. It is clear that K is compact and forward invariant under (33–36). The set

$$K_0 := ([0, T_0] \times \{0\} \times \{0\} \times [0, \mu_0]) \cap K$$

is clearly a compact forward-invariant subset of K.

Let $\Pi(T^*, V) := v'(T^*, V)$. The function Π is clearly smooth and zero on K_0 and positive on $K \setminus K_0$. Furthermore,

$$\frac{\dot{\Pi}}{\Pi} = \psi := \frac{v' M(T, \mu)(T^*, V)}{v'(T^*, V)}$$

is lower semi-continuous on K by Lemma 4 once we define the value of ψ on K_0 as

$$\psi(T, \mu) = \min_{i=1,\ldots,n} \frac{v' M(T, \mu)_i}{v_i}.$$

We note that the function $\psi(T, \mu)$ is continuous in (T, μ). Since all solutions of (33–36) in K_0 have the property that $\lim_{t \to \infty} T(t) = T_0$, it follows that $\psi(T(t), \mu) > 0$ for all sufficiently large t. Hence, by Theorem 3, the set K_0 is a uniform strong repeller in K. If we use the L^1-norm of (T^*, V) as the distance function to K_0, we find that there exists an $\eta_0 > 0$ such that

$$\liminf_{t \to \infty} 1'(T^* + V) \geqslant \eta_0$$

for all solutions of (33–36) in $K \setminus K_0$.

To complete the proof, we need to show that there exists an $\eta > 0$ such that $\liminf_{t \to \infty} 1'V(t) \geqslant \eta > 0$ for all solutions with $1'V(t) > 0$. Observe that $1'V(t) > 0$ implies that $1'T^*(t) > 0$. Hence, by the result of part one, we have that $\liminf_{t \to \infty} 1'(T^*(t) + V(t)) \geqslant \eta_0 > 0$ or, equivalently, $1'T^*(t) > \eta_0/2 - 1'V(t)$ for all sufficiently large t. We substitute this inequality into (12) and find that

$$1'\dot{V} \geqslant A_0 \left(\frac{\eta_0}{2} - 1'V(t) \right) - A_1 1'V(t), \quad A_0 := \min_i(N_i \beta_i) > 0, \ A_1 := \max_i(\gamma_i) > 0$$

holds for large t. It follows immediately that

$$\liminf_{t \to \infty} 1'V(t) \geqslant \eta = \frac{\eta_0 A_0}{2(A_0 + A_1)} > 0.$$

$\square$

LEMMA 6 Let

$$\sigma(x, y, z) := x + y + \frac{z}{xy} - 3z^{\frac{1}{3}}.$$

Then, for any $z_0, M > 0$, there exists a $\delta > 0$ such that $\sigma(x, y, z) > M$ for all $0 < x < \delta$, all $y > 0$ and all $z > z_0$.

Proof. Observe that the minimum of the function $\sigma(x, \cdot, z)$ on the set $y \in (0, +\infty)$ is achieved at $y = \sqrt{z/x}$. Hence, for all $y > 0$, it holds that

$$f(x, y, z) \geqslant f\left(x, \sqrt{\frac{z}{x}}, z\right) = x + 2\sqrt{\frac{z}{x}} - 3z^{\frac{1}{3}}.$$

Let $z_0 > 0$ and define

$$\delta := \frac{4z_0}{\left(M + 3z_0^{\frac{1}{3}}\right)^2}.$$

Then for all $0 < x < \delta$, all $y > 0$, and all $z > z_0$, it holds that

$$f(x, y, z) \geqslant 2\sqrt{\frac{z}{x}} - 3z^{\frac{1}{3}} = z^{\frac{1}{2}}\left(\frac{2}{x^{\frac{1}{2}}} - 3z^{-\frac{1}{6}}\right) > z_0^{\frac{1}{2}}\left(\frac{2}{\delta^{\frac{1}{2}}} - 3z_0^{-\frac{1}{6}}\right) = M.$$

$\square$

THEOREM 4 Let K be the absorbing compact set established in Lemma 1, and let

$$U = \{(T, T^*, V) \in \mathbb{R}_+^{2n+1} | T, T_1^*, V_1 > 0\}.$$

Suppose that (C) holds with $\bar{T}^1$ instead of $\bar{T}$. Then, there exist a $\mu_1 > 0$ and a compact set $K_\delta \subset U$ such that for any $\mu \in [0, \mu_1]$ and for any solution of (10–12) or (13–15) in U, there exists a $t_0 > 0$ such that $(T(t), T^*(t), V(t)) \in K_\delta$ for all $t > t_0$.

Proof. Both for system (10–12) and (13–15), the proof will be based on the same Lyapunov function

$$W = \int_{\bar{T}^1}^T \left(1 - \frac{\bar{T}^1}{\tau}\right) d\tau + \int_{\bar{T}_1^*}^{T_1^*} \left(1 - \frac{\bar{T}_1^*}{\tau}\right) d\tau + \frac{1}{N_1}\int_{\bar{V}_1}^{V_1} \left(1 - \frac{\bar{V}_1}{\tau}\right) d\tau + \sum_{i>1} T_i^* + \frac{1}{N_i}V_i$$

that we used to show competitive exclusion with $\mu = 0$.

Case 1. System (10–12).

Computing $\dot{W}$ for system (10–12), we obtain after some simplifications

$$\dot{W} = (f(T) - f(\bar{T}^1))\left(1 - \frac{\bar{T}^1}{T}\right) - \beta_1\bar{T}_1^*\left[\frac{\bar{T}^1}{T} + \frac{\bar{T}_1^*V_1T}{T_1^*\bar{V}_1\bar{T}^1} + \frac{\bar{V}_1T_1^*}{V_1\bar{T}_1^*} - 3\right]$$

$$- \sum_{i=2}^n k_iV_i(\bar{T}^i - \bar{T}^1) + \frac{T_1^* - \bar{T}_1^*}{T_1^*}\mu\sum_{j=1}^n q_{1j}k_jV_jT + \mu\sum_{i=2}^n\sum_{j=1}^n q_{ij}k_jV_jT.$$

Recombining the terms, we further obtain

$$\dot{W} = (f(T) - f(\bar{T}^1))\left(1 - \frac{\bar{T}^1}{T}\right) - \beta_1\bar{T}_1^*\left[\frac{\bar{T}^1}{T} + \frac{\bar{T}_1^*V_1T}{T_1^*\bar{V}_1\bar{T}^1} + \frac{\bar{V}_1T_1^*}{V_1\bar{T}_1^*} - 3\right]$$

$$- \sum_{i=2}^n k_iV_i(\bar{T}^i - \bar{T}^1) - \frac{\bar{T}_1^*}{T_1^*}\mu\sum_{j=1}^n q_{1j}k_jV_jT + \mu\sum_{i=1}^n\sum_{j=1}^n q_{ij}k_jV_jT.$$

We note that

$$\sum_{i=1}^n\sum_{j=1}^n q_{ij}k_jV_jT = \sum_{j=1}^n\left(\sum_{i=1}^n q_{ij}\right)k_jV_jT = 0$$

since all column sums of Q are zero. Hence,

$$\dot{W} = (f(T) - f(\bar{T}^1))\left(1 - \frac{\bar{T}^1}{T}\right) - \beta_1 \bar{T}_1^* \left[\frac{\bar{T}^1}{T} + \frac{\bar{T}_1^* V_1 T}{T_1^* \bar{V}_1 \bar{T}^1} + \frac{\bar{V}_1 T_1^*}{V_1 \bar{T}_1^*} - 3\right]$$

$$- \sum_{i=2}^{n} k_i V_i(\bar{T}^i - \bar{T}^1) - \frac{\bar{T}_1^*}{T_1^*} \mu q_{11} k_1 V_1 T - \frac{\bar{T}_1^*}{T_1^*} \mu \sum_{j=2}^{n} q_{1j} k_j V_j T.$$

We rewrite $\dot{W}$ as

$$\dot{W} = (f(T) - f(\bar{T}^1))\left(1 - \frac{\bar{T}^1}{T}\right) - \beta_1 \bar{T}_1^* \left[\frac{\bar{T}^1}{T} + (1 + q_{11}\mu)\frac{\bar{T}_1^* V_1 T}{T_1^* \bar{V}_1 \bar{T}^1} + \frac{\bar{V}_1 T_1^*}{V_1 \bar{T}_1^*} - 3(1 + q_{11}\mu)^{1/3}\right]$$

$$+ 3\beta_1 \bar{T}_1^*(1 - (1 + q_{11}\mu)^{1/3}) - \sum_{i=2}^{n} k_i V_i(\bar{T}^i - \bar{T}^1) - \frac{\bar{T}_1^*}{T_1^*} \mu \sum_{j=2}^{n} q_{1j} k_j V_j T.$$

Note that the last term of $\dot{W}$ is non-positive, hence[1]

$$\dot{W} \leqslant (f(T) - f(\bar{T}^1))\left(1 - \frac{\bar{T}^1}{T}\right) - \beta_1 \bar{T}_1^* \left[\frac{\bar{T}^1}{T} + (1 + q_{11}\mu)\frac{\bar{T}_1^* V_1 T}{T_1^* \bar{V}_1 \bar{T}^1} + \frac{\bar{V}_1 T_1^*}{V_1 \bar{T}_1^*} - 3(1 + q_{11}\mu)^{1/3}\right]$$

$$+ 3\beta_1 \bar{T}_1^*(1 - (1 + q_{11}\mu)^{1/3}) - \sum_{i=2}^{n} k_i V_i(\bar{T}^i - \bar{T}^1).$$

By Lemma 5, there exist $\eta, \mu_a > 0$ such that $1'V(t) > \eta$ for all $\mu \in [0, \mu_a]$ and all sufficiently large t. Let $\alpha = \min_{i \geqslant 2} k_i(\bar{T}^i - \bar{T}^1) > 0$, then

$$\sum_{i=2}^{n} k_i V_i(\bar{T}^i - \bar{T}^1) \geqslant \alpha \sum_{i=2}^{n} V_i \geqslant \alpha(\eta - V_1).$$

Thus, by shifting time forward if necessary, we have the inequality

$$\dot{W} \leqslant (f(T) - f(\bar{T}^1))\left(1 - \frac{\bar{T}^1}{T}\right) - \beta_1 \bar{T}_1^* \left[\frac{\bar{T}^1}{T} + (1 + q_{11}\mu)\frac{\bar{T}_1^* V_1 T}{T_1^* \bar{V}_1 \bar{T}^1} + \frac{\bar{V}_1 T_1^*}{V_1 \bar{T}_1^*} - 3(1 + q_{11}\mu)^{1/3}\right]$$

$$+ 3\beta_1 \bar{T}_1^*(1 - (1 + q_{11}\mu)^{1/3}) - \alpha\eta + \alpha V_1.$$

Let $\mu_b > 0$ be such that for all $\mu \in [0, \mu_b]$,

$$1 + q_{11}\mu \in \left[\frac{1}{2}, 1\right], \quad 3\beta_1 \bar{T}_1^*(1 - (1 + q_{11}\mu)^{1/3}) - \alpha\eta \leqslant -\frac{\alpha\eta}{2}.$$

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[1]Incidentally, if $q_{11} = 0$, we obtain global stability of the boundary equilibrium E_1 for all $\mu > 0$.

Let $\mu_1 = \min(\mu_a, \mu_b)$ and choose sufficiently large $L > 0$ so that

$$3\beta_1 \bar{T}_1^* (1 - (1 + q_{11}\mu)^{1/3}) - \alpha\eta + \alpha V_1 < L$$

for all solutions of (10–12) in K and all $\mu \in [0, \mu_1]$. For any $\mu \in [0, \mu_1]$, we have that

$$\dot{W} \leqslant (f(T) - f(\bar{T}^1))\left(1 - \frac{\bar{T}^1}{T}\right) - \beta_1 \bar{T}_1^* \left[\frac{\bar{T}^1}{T} + (1 + q_{11}\mu)\frac{\bar{T}_1^* V_1 T}{T_1^* \bar{V}_1 \bar{T}^1} + \frac{\bar{V}_1 T_1^*}{V_1 \bar{T}_1^*} - 3(1 + q_{11}\mu)^{1/3}\right]$$

$$-\frac{\alpha\eta}{2} + \alpha V_1,$$

where the first two terms are non-positive and $1 + q_{11}\mu \in \left[\frac{1}{2}, 1\right]$. Inspecting the first term in $\dot{W}$, we find that there exists a $\delta_0 > 0$ such that

$$(f(T) - f(\bar{T}^1))\left(1 - \frac{\bar{T}^1}{T}\right) < -(L + 1)$$

for all $T < \delta_0$ and all $\mu \in [0, \mu_1]$. Now, we inspect the the second term in $\dot{W}$. Using Lemma 6 with

$$x = \frac{\bar{V}_1 T_1^*}{V_1 \bar{T}_1^*}, \quad y = \frac{\bar{T}^1}{T}, \quad z = 1 + q_{11}\mu, \quad z_0 = \frac{1}{2},$$

we conclude that there exists a $\delta_1 > 0$ such that

$$-\beta_1 \bar{T}_1^* \left[\frac{\bar{T}^1}{T} + (1 + q_{11}\mu)\frac{\bar{T}_1^* V_1 T}{T_1^* \bar{V}_1 \bar{T}^1} + \frac{\bar{V}_1 T_1^*}{V_1 \bar{T}_1^*} - 3(1 + q_{11}\mu)^{1/3}\right] < -(L + 1)$$

for all $\frac{T_1^*}{V_1} < \delta_1$ and all $\mu \in [0, \mu_1]$. Finally, there exists a $\delta_2 > 0$ such that $-\frac{\alpha\eta}{2} + \alpha V_1 < -\frac{\alpha\eta}{4}$ for all $V_1 < \delta_2$ and all $\mu \in [0, \mu_1]$. Let

$$\hat{K}_\delta = \{(T, T^*, V) \in K \cap U | T \geqslant \delta_0, V_1 \geqslant \delta_2, T_1^* \geqslant \delta_1 V_1\}.$$

Consider $(T, T^*, V) \in (K \cap U) \backslash \hat{K}_\delta$ and let $\mu \in [0, \mu_1]$, then at least one of the following holds:

- $T < \delta_0$, in which case $\dot{W} \leqslant -(L + 1) + L \leqslant -1$;
- $T_1^*/V_1 < \delta_1$, in which case $\dot{W} \leqslant -(L + 1) + L \leqslant -1$;
- $V_1 < \delta_2$, in which case $\dot{W} \leqslant -\frac{\alpha\eta}{4}$.

Hence, for all $(T, T^*, V) \in (K \cap U) \backslash \hat{K}_\delta$ and all $\mu \in [0, \mu_1]$, we have

$$\dot{W} \leqslant -\min\left(1, \frac{\alpha\eta}{4}\right) < 0.$$

We postpone the rest of the proof until we have showed that a similar inequality holds for system (13–15).

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Case 2. System (13–15).

Computing $\dot{W}$ for system (13–15), we obtain after some simplifications

$$\dot{W} = (f(T) - f(\bar{T}^1))\left(1 - \frac{\bar{T}^1}{T}\right) - \beta_1 \bar{T}_1^*\left[\frac{\bar{T}^1}{T} + \frac{\bar{T}_1^* V_1 T}{T_1^* \bar{V}_1 \bar{T}^1} + \frac{\bar{V}_1 T_1^*}{V_1 \bar{T}_1^*} - 3\right]$$

$$- \sum_{i=2}^{n} k_i V_i(\bar{T}^i - \bar{T}^1) + \mu\left(\frac{V_1 - \bar{V}_1}{V_1}\right)\sum_{j=1}^{n} q_{1j}\frac{N_j}{N_1}\beta_j T_j^* + \mu\sum_{i=2}^{n}\sum_{j=1}^{n} q_{ij}\frac{N_j}{N_i}\beta_j T_j^*.$$

Note that the μ dependent terms can be rearranged as follows:

$$\mu\left(\sum_{i=1}^{n} q_{ii}\beta_i T_i^* - \frac{\bar{V}_1}{V_1}\sum_{j=2}^{n} q_{1j}\frac{N_j}{N_1}\beta_j T_j^*\right) + \mu\left(\sum_{j=2}^{n} q_{1j}\frac{N_j}{N_1}\beta_j T_j^* + \sum_{i=2}^{n}\sum_{j\neq i} q_{ij}\frac{N_j}{N_i}\beta_j T_j^*\right) - \mu\frac{\bar{V}_1}{V_1}q_{11}\beta_1 T_1^*.$$

In the above, the first term is non-positive and the second term can be rewritten as follows:

$$\mu\sum_{i=1}^{n} \alpha_i T_i^*,$$

for suitable $\alpha_i \geqslant 0$, and the third term will be absorbed in the square bracket $[\cdot]$ term in $\dot{W}$. We find that

$$\dot{W} \leqslant (f(T) - f(\bar{T}^1))\left(1 - \frac{\bar{T}^1}{T}\right) - \beta_1 \bar{T}_1^*\left[\frac{\bar{T}^1}{T} + \frac{\bar{T}_1^* V_1 T}{T_1^* \bar{V}_1 \bar{T}^1} + (1 + q_{11}\mu)\frac{\bar{V}_1 T_1^*}{V_1 \bar{T}_1^*} - 3(1 + q_{11}\mu)^{1/3}\right]$$

$$+ 3\beta_1 \bar{T}_1^*(1 - (1 + q_{11}\mu)^{1/3}) + \mu\sum_{i=1}^{n} \alpha_i T_i^* - \sum_{i=2}^{n} k_i V_i(\bar{T}^i - \bar{T}^1).$$

By Lemma 5, there exist $\eta, \mu_a > 0$ such that $1'V(t) > \eta$ for all $\mu \in [0, \mu_a]$ and all sufficiently large t. Let $\alpha = \min_{i\geqslant 2} k_i(\bar{T}^i - \bar{T}^1) > 0$, then

$$\sum_{i=2}^{n} k_i V_i(\bar{T}^i - \bar{T}^1) \geqslant \alpha\sum_{i=2}^{n} V_i \geqslant \alpha(\eta - V_1).$$

Thus, by shifting time forward if necessary, we have the inequality

$$\dot{W} \leqslant (f(T) - f(\bar{T}^1))\left(1 - \frac{\bar{T}^1}{T}\right) - \beta_1 \bar{T}_1^*\left[\frac{\bar{T}^1}{T} + \frac{\bar{T}_1^* V_1 T}{T_1^* \bar{V}_1 \bar{T}^1} + (1 + q_{11}\mu)\frac{\bar{V}_1 T_1^*}{V_1 \bar{T}_1^*} - 3(1 + q_{11}\mu)^{1/3}\right]$$

$$+ 3\beta_1 \bar{T}_1^*(1 - (1 + q_{11}\mu)^{1/3}) + \mu\sum_{i=1}^{n} \alpha_i T_i^* - \alpha\eta + \alpha V_1.$$

Since solutions are in the compact set K for sufficiently large times, there is some $\mu_a' > 0$ such that

$$\mu\sum_{i=1}^{n} \alpha_i T_i^* \leqslant \frac{\alpha\eta}{2}, \quad \forall \mu \in [0, \mu_a'],$$

and therefore,

$$\dot{W} \leqslant (f(T) - f(\bar{T}^1))\left(1 - \frac{\bar{T}^1}{T}\right) - \beta_1 \bar{T}_1^* \left[\frac{\bar{T}^1}{T} + \frac{\bar{T}_1^* V_1 T}{T_1^* \bar{V}_1 \bar{T}^1} + (1 + q_{11}\mu)\frac{\bar{V}_1 T_1^*}{V_1 \bar{T}_1^*} - 3(1 + q_{11}\mu)^{1/3}\right]$$

$$+ 3\beta_1 \bar{T}_1^*(1 - (1 + q_{11}\mu)^{1/3}) - \frac{\alpha \eta}{2} + \alpha V_1.$$

Let $\mu_b > 0$ be such that for all $\mu \in [0, \mu_b]$,

$$1 + q_{11}\mu \in \left[\frac{1}{2}, 1\right], \quad 3\beta_1 \bar{T}_1^*(1 - (1 + q_{11}\mu)^{1/3}) - \frac{\alpha \eta}{2} \leqslant -\frac{\alpha \eta}{4}.$$

Let $\mu_1 = \min(\mu_a, \mu_a', \mu_b)$ and choose sufficiently large $L > 0$ so that

$$3\beta_1 \bar{T}_1^*(1 - (1 + q_{11}\mu)^{1/3}) - \alpha \eta + \alpha V_1 < L$$

for all solutions of (13–15) in K and all $\mu \in [0, \mu_1]$. For any $\mu \in [0, \mu_1]$, we have that

$$\dot{W} \leqslant (f(T) - f(\bar{T}^1))\left(1 - \frac{\bar{T}^1}{T}\right) - \beta_1 \bar{T}_1^* \left[\frac{\bar{T}^1}{T} + \frac{\bar{T}_1^* V_1 T}{T_1^* \bar{V}_1 \bar{T}^1} + (1 + q_{11}\mu)\frac{\bar{V}_1 T_1^*}{V_1 \bar{T}_1^*} - 3(1 + q_{11}\mu)^{1/3}\right]$$

$$- \frac{\alpha \eta}{4} + \alpha V_1,$$

where the first two terms are non-positive and $1 + q_{11}\mu \in \left[\frac{1}{2}, 1\right]$. Inspecting the first term in $\dot{W}$, we find that there exists a $\delta_0 > 0$ such that

$$(f(T) - f(\bar{T}^1))\left(1 - \frac{\bar{T}^1}{T}\right) < -(L + 1)$$

for all $T < \delta_0$ and all $\mu \in [0, \mu_1]$. Inspecting the second term in $\dot{W}$, we use Lemma 6 with

$$x = (1 + q_{11}\mu)\frac{\bar{V}_1 T_1^*}{V_1 \bar{T}_1^*}, \quad y = \frac{\bar{T}^1}{T}, \quad z = 1 + q_{11}\mu, \quad z_0 = \frac{1}{2}$$

and conclude that there exists a $\delta_1 > 0$ such that

$$-\beta_1 \bar{T}_1^* \left[\frac{\bar{T}^1}{T} + \frac{\bar{T}_1^* V_1 T}{T_1^* \bar{V}_1 \bar{T}^1} + (1 + q_{11}\mu)\frac{\bar{V}_1 T_1^*}{V_1 \bar{T}_1^*} - 3(1 + q_{11}\mu)^{1/3}\right] < -(L + 1)$$

for all $\frac{T_1^*}{V_1} < \delta_1$ and all $\mu \in [0, \mu_1]$. Finally, there exists a $\delta_2 > 0$ such that $-\frac{\alpha \eta}{4} + \alpha V_1 < -\frac{\alpha \eta}{8}$ for all $V_1 < \delta_2$ and all $\mu \in [0, \mu_1]$. Let

$$\hat{K}_\delta = \{(T, T^*, V) \in K \cap U | T \geqslant \delta_0, V_1 \geqslant \delta_2, T_1^* \geqslant \delta_1 V_1\}.$$

Consider $(T, T^*, V) \in (K \cap U) \backslash \hat{K}_\delta$ and let $\mu \in [0, \mu_1]$, then at least one of the following holds:

- $T < \delta_0$, in which case $\dot{W} \leqslant -(L + 1) + L \leqslant -1$;

- $T_1^*/V_1 < \delta_1$, in which case $\dot{W} \leqslant -(L + 1) + L \leqslant -1$;

- $V_1 < \delta_2$, in which case $\dot{W} \leqslant -\frac{\alpha\eta}{8}$.

Hence, for all $(T, T^*, V) \in (K \cap U) \backslash \hat{K}_\delta$ and all $\mu \in [0, \mu_1]$, we have

$$\dot{W} \leqslant -\min\left(1, \frac{\alpha\eta}{8}\right) < 0.$$

The remainder of the proof is the same for both the above two cases and presented next.

The non-negative function $W(T, T^*, V, \mu)$ is continuous and bounded from above on the set $\hat{K}_\delta \times [0, \mu_1]$ because T, T_1^*, V_1 are bounded away from zero. Hence, it attains a finite positive maximum

$$w := \max_{\hat{K}_\delta \times [0, \mu_1]} W(T, T^*, V, \mu) > 0.$$

Define a new set

$$K_\delta = \{(T, T^*, V) \in K \cap U \,|\, W(T, T^*, V, \mu) \leqslant w, \forall \mu \in [0, \mu_1]\}.$$

By construction, we have that $\hat{K}_\delta \subset K_\delta \subset K \cap U$. The continuity of W implies that K_δ is closed, and therefore compact in U.

It remains to show that all the solutions of (10–12) in U enter and remain in K_δ for all sufficiently large times. Since $K \cap U$ is an absorbing set for all $\mu \geqslant 0$ (Lemma 1), without loss of generality we need to prove this for all solutions in $K \cap U$.

Let $\Phi(t) = (T(t), T^*(t), V(t)) \in K \cap U$ be a solution of (10–12) for some fixed $\mu \in [0, \mu_1]$. Observe that in the set $(K \cap U) \backslash \hat{K}_\delta$, the inequality $\dot{W} \leqslant -\min\left(1, \frac{\alpha\eta}{8}\right) < 0$ holds. Since $W \geqslant 0$, there exists a $t_0 \geqslant 0$ such that $\Phi(t_0) \in \hat{K}_\delta \subset K_\delta$. We will show that $\Phi(t) \in K_\delta$ for all $t \geqslant t_0$. For the sake of contradiction, let us suppose that there exists a $t_1 > t_0$ such that $\Phi(t_1) \notin K_\delta$. Then there exists a $t_2 \in [t_0, t_1)$ such that $\Phi(t_2) \in K_\delta$ and $\Phi(t) \notin K_\delta$ for all $t \in (t_2, t_1]$. On the one hand, we have that

$$W(\Phi(t_2), \mu) \leqslant w < W(\Phi(t_1), \mu)$$

by definition of K_δ. On the other hand, for all $t \in (t_2, t_1]$, we have $\Phi(t) \notin K_\delta$ and consequently $\Phi(t) \notin \hat{K}_\delta$ so that $\frac{d}{dt} W(\Phi(t), \mu) = \dot{W} < 0$. This contradiction shows that $\Phi(t) \in K_\delta$ for all $t \geqslant t_0$ and concludes the proof of the theorem. $\qquad\square$

THEOREM 5 Let the assumptions of Lemma 2 hold, let U be the set from Theorem 4 and define

$$U' = \{(T, T^*, V) \in \mathbb{R}_+^{2n+1} \,|\, T_1^* + V_1 > 0\} \supset U.$$

Then, there exist a $\mu_0 > 0$ and a continuous map $E: [0, \mu_0] \to U$ such that the following holds:

1. $E(0) = E_1$ (where E_1 is the same as in Lemma 2), and $E(\mu)$ is an equilibrium of (10–12) or of (13–15) for all $\mu \in [0, \mu_0]$;

2. for each $\mu \in [0, \mu_0]$, $E(\mu)$ is a globally asymptotically stable equilibrium of (10–12) or (13–15) in U'.

Proof. To prove the first assertion, we begin by noting that for $\mu = 0$, E_1 is a stable hyperbolic equilibrium of (10–12) or (13–15) by Lemma 2. Since the vector field of (10–12) and (13–15) is linear in μ, by the implicit function theorem there exist a $h > 0$ and a continuous map $E: (-h, h) \to \mathbb{R}^{2n+1}$ such that $E(\mu)$ is an equilibrium of (10–12) or (13–15) for all $\mu \in (-h, h)$. The fact that $E(\mu) \in U$ for all $\mu \in [0, h)$ follows from Proposition 2 and the fact that $\bar{T}_1 < \bar{T}_i$, $i \geqslant 2$. Note that for $\mu > 0$, $E(\mu)$ may be positive (if Q is irreducible) or non-negative (if Q is reducible). Nevertheless, in both cases, $\mu > 0$ implies $E(\mu) \in U$.

The proof of the second assertion is based on the result of Smith & Waltman (1999, Proposition 2.3). We have already established the fact that $E(0)$ is a stable hyperbolic equilibrium of (10–12) or (13–15). By Theorem 2, $E(0)$ is globally asymptotically stable in U' for $\mu = 0$. In addition, by Theorem 4, there exist a $\mu_0 > 0$ and a compact set $K_\delta \subset U$ such that for each $\mu \in [0, \mu_0]$ and each solution $(T(t), T^*(t), V(t))$ of (10–12) or (13–15) in U, there exists a $t_0 > 0$ such that $(T(t), T^*(t), V(t)) \in K_\delta$ for all $t > t_0$. Hence, the condition (H1) of Proposition 2.3 in Smith & Waltman (1999) holds. Proposition 2.3 itself then implies the global stability of $E(\mu)$ in U for all sufficiently small $\mu \geqslant 0$. Finally, solutions of (10–12) or (13–15) starting in U enter U' instantaneously, hence global stability of $E(\mu)$ in U' follows as well. □

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Appendix A. Inclusion of loss of virus in the model

A.1 *Single strain*

If we explicitly account for the loss of the free virions upon infection, model (1) becomes

$$\dot{T} = f(T) - kVT,$$

$$\dot{T}^* = kVT - \beta T^*,$$

$$\dot{V} = N\beta T^* - \gamma V - kVT. \tag{A.1}$$

We still assume that the growth rate of the healthy cell population is given by (2), hence $E_0 = (T_0, 0, 0)$ is still an equilibrium of (A.1). A positive equilibrium exists if the following quantities are positive:

$$\bar{T} = \frac{\gamma}{k(N-1)}, \quad \bar{T}^* = \frac{f(\bar{T})}{\beta}, \quad \bar{V} = \frac{f(\bar{T})}{k\bar{T}}. \tag{A.2}$$

Note that this is the case when $N > 1$ and $f\left(\frac{\gamma}{k(N-1)}\right) > 0$ or (equivalently by (2)) when $\bar{T} = \frac{\gamma}{k(N-1)} < T_0$. In terms of the basic reproduction number

$$\mathcal{R}^0 := \frac{k(N-1)}{\gamma} T_0 = \frac{T_0}{\bar{T}},$$

existence of a positive equilibrium is therefore equivalent to $\mathcal{R}^0 > 1$. Assuming that $\mathcal{R}^0 > 1$, we will still denote this disease steady state by $E = (\bar{T}, \bar{T}^*, \bar{V})$. We introduce the following condition:

$$(\text{C}') \quad f'(c) + \frac{k}{\gamma} f(\bar{T}) \leqslant 0, \quad \text{for all } c \in [0, T_0].$$

Note that this condition is satisfied when $f(T)$ is a decreasing function with a sufficiently large negative derivative.

THEOREM A1 Let (C') hold. Then, the positive equilibrium E is globally asymptotically stable for (A.1) with respect to the initial conditions satisfying $T^*(0) + V(0) > 0$.

Proof. Consider the following function on $int(\mathbb{R}^3_+)$:

$$W = (N-1) \int_{\bar{T}}^{T} \left(1 - \frac{\bar{T}}{\tau}\right) d\tau + N \int_{\bar{T}^*}^{T^*} \left(1 - \frac{\bar{T}^*}{\tau}\right) d\tau + \int_{\bar{V}}^{V} \left(1 - \frac{\bar{V}}{\tau}\right) d\tau.$$

Then,

$$\dot{W} = (N-1)(f(T) - kVT)\left(1 - \frac{\bar{T}}{T}\right) + N(kVT - \beta T^*)\left(1 - \frac{\bar{T}^*}{T^*}\right)$$

$$+ (N\beta T^* - \gamma V - kVT)\left(1 - \frac{\bar{V}}{V}\right)$$

$$= (N-1)f(T)\left(1 - \frac{\bar{T}}{T}\right) - NkVT\frac{\bar{T}^*}{T^*} + N\beta\bar{T}^* - N\beta T^*\frac{\bar{V}}{V} + \gamma\bar{V} + k\bar{V}T$$

$$= (N-1)(f(T) - f(\bar{T}))\left(1 - \frac{\bar{T}}{T}\right) + (N-1)f(\bar{T})\left(1 - \frac{\bar{T}}{T}\right)$$

$$+ N\beta\bar{T}^*\left[2 - \frac{VT\bar{T}^*}{\bar{V}\bar{T}T^*} - \frac{T^*\bar{V}}{\bar{T}^*V}\right] - \beta\bar{T}^* + \beta\bar{T}^*\frac{T}{\bar{T}}$$

$$= (N-1)(f(T) - f(\bar{T}))\left(1 - \frac{\bar{T}}{T}\right) + (N-1)\beta\bar{T}^*\left(1 - \frac{\bar{T}}{T}\right)$$

$$+ N\beta\bar{T}^*\left[2 - \frac{VT\bar{T}^*}{\bar{V}\bar{T}T^*} - \frac{T^*\bar{V}}{\bar{T}^*V}\right] - \beta\bar{T}^* + \beta\bar{T}^*\frac{T}{\bar{T}}$$

$$= (N-1)(f(T) - f(\bar{T}))\left(1 - \frac{\bar{T}}{T}\right) + \beta\bar{T}^*\left(-2 + \frac{\bar{T}}{T} + \frac{T}{\bar{T}}\right)$$

$$+ N\beta\bar{T}^*\left[3 - \frac{VT\bar{T}^*}{\bar{V}\bar{T}T^*} - \frac{T^*\bar{V}}{\bar{T}^*V} - \frac{\bar{T}}{T}\right]$$

$$= [(N-1)(f(T) - f(\bar{T}))\bar{T} + \beta\bar{T}^*(T - \bar{T})]\frac{(T - \bar{T})}{T\bar{T}} + N\beta\bar{T}^*\left[3 - \frac{VT\bar{T}^*}{\bar{V}\bar{T}T^*} - \frac{T^*\bar{V}}{\bar{T}^*V} - \frac{\bar{T}}{T}\right],$$

where we used (A.2) repeatedly; in particular, in the second, third and fourth lines. By the mean value theorem, there exists some $c \in (T, \bar{T})$ or $(\bar{T}, T)$ such that

$$f(T) - f(\bar{T}) = f'(c)(T - \bar{T}),$$

hence using (A.2) once more, we obtain

$$\dot{W} = (N-1)\left[f'(c) + \frac{k}{\gamma}f(\bar{T})\right]\frac{(T - \bar{T})^2}{T} + N\beta\bar{T}^*\left[3 - \frac{VT\bar{T}^*}{\bar{V}\bar{T}T^*} - \frac{T^*\bar{V}}{\bar{T}^*V} - \frac{\bar{T}}{T}\right].$$

The first term is non-positive by (C′) and because we can assume that $T \leqslant T_0$ by dissipativity (see Lemma A1 later). The second term is non-positive as well since the geometric mean of three non-negative numbers does not exceed the arithmetic mean of these numbers. We conclude that $\dot{W} \leqslant 0$ in $\mathrm{int}(\mathbb{R}^3_+)$, hence local stability of E follows. Note that $\dot{W}$ equals zero if and only if both the first term and the second term are zero. This occurs at points where

$$\frac{\bar{T}}{T} = 1 \quad \text{and} \quad \frac{\bar{T}^* V}{T^* \bar{V}} = 1.$$

Then, LaSalle's invariance principle implies that all bounded solutions (and as before, solutions are easily shown to be bounded, see also Lemma A1 later) in $\mathrm{int}(\mathbb{R}^3_+)$ converge to the largest invariant set in

$$M = \left\{ (T, T^*, V) \in \mathrm{int}(\mathbb{R}^3_+) \,\bigg|\, \frac{\bar{T}}{T} = 1, \, \frac{\bar{T}^* V}{T^* \bar{V}} = 1 \right\}.$$

It is clear that the largest invariant set in M is the singleton $\{E\}$. Finally, note that forward solutions starting on the boundary of $\mathbb{R}^3_+$ with either $T_1(0)$ or $V_1(0)$ positive enter $\mathrm{int}(\mathbb{R}^3_+)$ instantaneously. This concludes the proof.   □

A.2 *Competitive exclusion*

Now, we modify the multistrain model (4–6) to

$$\dot{T} = f(T) - kVT, \quad T \in \mathbb{R}_+, \tag{A.3}$$

$$\dot{T}^* = KVT - BT^*, \quad T^* \in \mathbb{R}^n_+, \tag{A.4}$$

$$\dot{V} = \hat{N}BT^* - \Gamma V - KVT, \quad V \in \mathbb{R}^n_+, \tag{A.5}$$

where $k = (k_1, \ldots, k_n)$, $K = \mathrm{diag}(k_1, \ldots, k_n)$, $B = \mathrm{diag}(\beta_1, \ldots, \beta_n)$, $\hat{N} = \mathrm{diag}(N_1, \ldots, N_n)$, and $\Gamma = \mathrm{diag}(\gamma_1, \ldots, \gamma_n)$. Suppose that each strain is capable to persist at steady state by itself, that is, $N_i > 1$ and $\bar{T}_i = \frac{\gamma_i}{k_i(N_i - 1)} < T_0$, and denote the corresponding equilibria also by $E_1, \ldots, E_n$. Assume that

$$0 < \bar{T}_1 \leqslant \bar{T}_2 \leqslant \cdots \leqslant \bar{T}_n < T_0. \tag{A.6}$$

In addition, suppose that (C′) holds with $\bar{T} = \bar{T}_1$. Then, we have the following theorem.

THEOREM A2 The single-strain equilibrium E_1 is globally asymptotically stable for (A.3–A.5) with respect to the initial conditions satisfying $T_1^*(0) + V_1(0) > 0$.

Proof. Consider the function W defined on $U := \{(T, T^*, V) \in \mathbb{R}^{2n+1} | T, T_1^*, V_1 > 0\}$ as

$$W = (N_1 - 1) \int_{\bar{T}_1}^T \left(1 - \frac{\bar{T}_1}{\tau}\right) d\tau + N_1 \int_{\bar{T}_1^*}^{T_1^*} \left(1 - \frac{\bar{T}_1^*}{\tau}\right) d\tau + \int_{\bar{V}_1}^{V_1} \left(1 - \frac{\bar{V}_1}{\tau}\right) d\tau$$

$$+ \sum_{i=2}^n \frac{N_1 - 1}{N_i - 1}(N_i T_i^* + V_i).$$

Computing $\dot{W}$, we find that

$$\dot{W} = (N_1 - 1)\left[f'(c) + \frac{k}{\gamma}f(\bar{T}_1)\right]\frac{(T - \bar{T}_1)^2}{T} + N_1\beta_1\bar{T}_1^*\left[3 - \frac{V_1 T \bar{T}_1^*}{\bar{V}_1 \bar{T}_1 T_1^*} - \frac{T_1^* \bar{V}_1}{\bar{T}_1^* V_1} - \frac{\bar{T}_1}{T}\right]$$

$$+ \sum_{i=2}^{n}\left(-k_i V_i(T - \bar{T}_1) + \frac{(N_1 - 1)}{N_i - 1}(N_i k_i V_i T - N_i \beta_i T_i^* + N_i \beta_i T_i^* - \gamma_i - k_i V_i T)\right).$$

After simplifications, we have

$$\dot{W} = (N_1 - 1)\left[f'(c) + \frac{k}{\gamma}f(\bar{T}_1)\right]\frac{(T - \bar{T}_1)^2}{T} + N_1\beta_1\bar{T}_1^*\left[3 - \frac{V_1 T \bar{T}_1^*}{\bar{V}_1 \bar{T}_1 T_1^*} - \frac{T_1^* \bar{V}_1}{\bar{T}_1^* V_1} - \frac{\bar{T}_1}{T}\right]$$

$$-(N_1 - 1)\sum_{i=2}^{n} k_i V_i(\bar{T}_i - \bar{T}_1).$$

The first term is non-positive since (C′) with $\bar{T} = \bar{T}_1$ holds and because $T \leqslant T_0$ by dissipativity (see Lemma A1 later). The second term is non-positive as well and so is the third by (A.6). Thus, $\dot{W} \leqslant 0$ which already implies that E_1 is stable. An application of LaSalle's invariance principle shows that all the bounded solutions in U (boundedness follows from Lemma A1 which is proved later) converge to the largest invariant set in

$$\left\{(T, T_1^*, \ldots, T_n^*, V_1, \ldots, V_n) \in U \,\bigg|\, \frac{\bar{T}^1}{T} = 1, \frac{\bar{T}_1^* V_1}{T_1^* \bar{V}_1} = 1, V_i = 0, i > 2\right\},$$

which is easily shown to be the singleton $\{E_1\}$. Finally, solutions on the boundary of U with $T_1^*(0) + V_1(0) > 0$ enter U instantaneously, which concludes the proof. □

A.3 Adding mutations

We modify the model (A.3–A.5) to account for mutations. Again, we consider two alternative models:

$$\dot{T} = f(T) - kVT, \quad T \in \mathbb{R}_+,$$

$$\dot{T}^* = P(\mu)KVT - BT^*, \quad T^* \in \mathbb{R}_+^n,$$

$$\dot{V} = \hat{N}BT^* - \Gamma V - KVT, \quad V \in \mathbb{R}_+^n, \tag{A.7}$$

and

$$\dot{T} = f(T) - kVT, \quad T \in \mathbb{R}_+,$$

$$\dot{T}^* = KVT - BT^*, \quad T^* \in \mathbb{R}_+^n,$$

$$\dot{V} = P(\mu)\hat{N}BT^* - \Gamma V - KVT, \quad V \in \mathbb{R}_+^n, \tag{A.8}$$

where k, K, B, $\hat{N}$ and Γ are the same as before, $P(\mu) = I + \mu Q$ and Q is a stochastic matrix with non-negative off-diagonal entries.

LEMMA A1 Both systems (A.7) and (A.8) are dissipative, i.e. there is some compact set K such that every solution eventually enters K and remains in K forever after.

Proof. The proof is similar to the proof of Lemma 1 and will be omitted.   □

LEMMA A2 For $\mu = 0$, let all the single-strain equilibria $E_1, E_2, \ldots, E_n$ exist for either (A.7) or (A.8), and assume that

$$\bar{T}^1 < \bar{T}^2 < \cdots < \bar{T}^n < \bar{T}^{n+1} := T_0 \tag{A.9}$$

and

$$f'(\bar{T}^j) \leqslant 0, \quad \text{for all } j = 1, \ldots, n+1. \tag{A.10}$$

Then, the Jacobian matrices of (A.7) or (A.8), evaluated at any of the E_is, $i = 1, \ldots, n+1$ (where $E_{n+1} := E_0$) have the following properties: $J(E_i)$ has $i-1$ eigenvalues (counting multiplicities) in the open right half-plane and $2(n+1) - i$ eigenvalues in the open left half-plane. In particular, $J(E_1)$ is Hurwitz.

Proof. The proof is similar to that of Lemma 2. The only difference is that the entries of the Jacobian matrices change. In particular, the $(3, 1)$- and $(3, 3)$-entry of A_1^i now become $-k_i \bar{V}_i$ and $-\gamma_i - k\bar{T}^i$, respectively, but by (A.9) and Lemma 3.4 in De Leenheer & Smith (2003), A_1^i is still Hurwitz.   □

To study the equilibria of systems (A.7) and (A.8), we introduce the matrix

$$A(\mu) = \Gamma^{-1}(\hat{N}P(\mu) - I)K, \tag{A.11}$$

which has non-negative off-diagonal entries for $\mu > 0$ and

$$A(0) = \text{diag}\left(\frac{k_1(N_1 - 1)}{\gamma_1}, \ldots, \frac{k_n(N_n - 1)}{\gamma_n}\right) = \text{diag}\left(\frac{1}{\bar{T}_1}, \ldots, \frac{1}{\bar{T}_n}\right).$$

Clearly, Proposition 1 holds with $A(\mu)$ given by (A.11). Hence, we have the following proposition.

PROPOSITION A1 Let the assumptions of Lemma A2 hold and suppose that the strains are renumbered so that $A(\mu)$ has the form (23). Let $E_j(\mu) = (\hat{T}_j(\mu), \hat{T}_j^*(\mu), \hat{V}_j(\mu))$ denote the non-trivial equilibria of both (A.7) and (A.8) for small $\mu > 0$. Then,

1. $E_j(\mu)$ is positive if and only if $\frac{1}{\hat{T}_j(\mu)}$ is an eigenvalue of $A(\mu)$ with a positive eigenvector V_j;

2. $E_j(\mu)$ is non-negative if and only if $\frac{1}{\hat{T}_j(\mu)}$ is an eigenvalue of $A(\mu)$ with a non-negative eigenvector V_j;

3. $E_j(\mu) \notin \mathbb{R}_+^{2n+1}$ if and only if $\frac{1}{\hat{T}_j(\mu)}$ is an eigenvalue of $A(\mu)$ with eigenvector V_j which is not sign definite.

Proof. We will prove the proposition only for system (A.7) (the proof for (A.8) is similar). Observe that at equilibrium, $\hat{T}_j^*(\mu) = (\hat{N}B)^{-1}(\Gamma + K\hat{T}_j(\mu))\hat{V}_j(\mu)$. Hence, the signs of the corresponding components of $\hat{T}_j^*(\mu)$ and $\hat{V}_j(\mu)$ are the same. Substituting the above expression into (A.7), we find that $\hat{V}_j(\mu)$ must satisfy

$$\left[\Gamma^{-1}(\hat{N}P(\mu) - I)K - \frac{1}{\hat{T}_j(\mu)}I\right]\hat{V}_j(\mu) = \left[A(\mu) - \frac{1}{\hat{T}_j(\mu)}I\right]\hat{V}_j(\mu) = 0.$$

Thus, for each non-trivial equilibrium $E_j(\mu)$, the quantity $\frac{1}{\hat{T}_j(\mu)}$ must be an eigenvalue of $A(\mu)$ and $\hat{V}_j(\mu)$ must be a multiple of the corresponding eigenvector V_j. If V_j is not sign definite, it follows that $E_j(\mu) \notin \mathbb{R}_+^{2n+1}$. For all $V_j \geqslant 0$, the components of $E_j(\mu)$ are uniquely determined via

$$\hat{V}_j(\mu) = \frac{f(\hat{T}_j(\mu))}{\hat{T}_j(\mu)k'V_j} V_j, \quad \hat{T}_j^*(\mu) = (\hat{N}B)^{-1}(\Gamma + K\hat{T}_j(\mu))\hat{V}_j(\mu).$$

Hence, $E_j(\mu)$ is positive (non-negative) if and only if V_j is positive (non-negative). $\qquad\square$

A.4 *Lower bounds*

LEMMA A3 Suppose that (A.9) holds. Then, there exist $\eta, \mu_0 > 0$ such that

$$\liminf_{t \to \infty} 1'V(t) \geqslant \eta > 0$$

for any $\mu \in [0, \mu_0]$ and for any solution of (A.7) and (A.8) with $1'V(t) > 0$.

Proof. We will prove the claim for system (A.7) (the proof for (A.8) is similar). The proof consists of two parts. We first show that there exist $\eta_0, \mu_0 > 0$ such that $\liminf_{t \to \infty} 1'(T^*(t) + V(t)) \geqslant \eta_0 > 0$ for all solutions with $T^*(t), V(t) \neq 0$. We choose n positive numbers $\tilde{N}_i$ so that $\frac{\gamma_i + k_i T_0}{k_i T_0} < \tilde{N}_i < N_i$ for all $1 \leqslant i \leqslant n$. This is possible since we assume $\bar{T}_i = \frac{\gamma_i}{k_i(N_i - 1)} < T_0$ which is equivalent to $N_i > \frac{\gamma_i + k_i T_0}{k_i T_0}$. Let $\upsilon = (\tilde{N}, 1)$. It follows that

$$\upsilon' \begin{pmatrix} -B & KT_0 \\ \hat{N}B & -\Gamma - KT_0 \end{pmatrix} = (b_1(N_1 - \tilde{N}_1), \ldots, b_n(N_n - \tilde{N}_n), k_1 T_0 \tilde{N}_1$$

$$- (\gamma_1 + k_1 T_0), \ldots, k_n T_0 \tilde{N}_n - (\gamma_n + k_n T_0))$$

is a positive vector. By continuity, there exists a $\mu_0 > 0$ such that

$$\upsilon' M(T_0, \mu), \quad \text{where } M(T, \mu) := \begin{pmatrix} -B & P(\mu)KT \\ \hat{N}B & -\Gamma - KT \end{pmatrix},$$

is a positive vector for all $\mu \in [0, \mu_0]$.

Consider a system

$$\dot{T} = f(T) - k'VT, \quad T \in \mathbb{R}_+, \tag{A.12}$$

$$\dot{T}^* = P(\mu)KVT - BT^*, \quad T^* \in \mathbb{R}_+^n, \tag{A.13}$$

$$\dot{V} = \hat{N}BT^* - \Gamma V - KVT, \quad V \in \mathbb{R}_+^n, \tag{A.14}$$

$$\dot{\mu} = 0, \quad \mu \in [0, \mu_0]. \tag{A.15}$$

Let K' be the forward-invariant compact set for (A.7) established in Lemma A1 and define $K = K' \times [0, \mu_0]$. It is clear that K is compact and forward invariant under (A.12–A.15). The set $K_0 = ([0, T_0] \times 0 \times 0 \times [0, \mu_0]) \cap K$ is clearly a compact forward-invariant subset of K.

Let $\Pi(T^*, V) := v'(T^*, V)$. The function Π is clearly smooth and zero on K_0 and positive on $K \setminus K_0$. Furthermore,

$$\frac{\dot{\Pi}}{\Pi} = \psi := \frac{v'M(T, \mu)(T^*, V)}{v'(T^*, V)}$$

is lower semi-continuous on K by Lemma 4 once we define the value of ψ on K_0 as

$$\psi(T, \mu) = \min_{i=1,\dots,n} \frac{v'M(T, \mu)_i}{v_i}.$$

We note that the function $\psi(T, \mu)$ is continuous in (T, μ). Since all solutions of (A.12–A.15) in K_0 have the property that $\lim_{t \to \infty} T(t) = T_0$, it implies that $\psi(T(t), \mu) > 0$ for all sufficiently large t. Hence, by Theorem 3, the set K_0 is a uniform strong repellor in K. If we use the L^1-norm of (T^*, V) as the distance function to K_0, we find that there exists an $\eta_0 > 0$ such that

$$\liminf_{t \to \infty} 1'(T^* + V) \geqslant \eta_0$$

for all solutions of (A.12–A.15) in $K \setminus K_0$.

To complete the proof, we need to show that there exists an $\eta > 0$ such that $\liminf_{t \to \infty} 1'V(t) \geqslant \eta > 0$ for all solutions with $1'V(t) > 0$. Observe that $1'V(t) > 0$ implies that $1'T^*(t) > 0$. Hence, by the result of part one, we have that $\liminf_{t \to \infty} 1'(T^*(t) + V(t)) \geqslant \eta_0 > 0$ or, equivalently, $1'T^*(t) > \eta_0/2 - 1'V(t)$ for all sufficiently large t. From (A.14), we have that

$$1'\dot{V} \geqslant \sum_{i=1}^{n} N_i \beta_i T_i^* - \sum_{i=1}^{n} (\gamma_i + k_i T) V_i \geqslant \sum_{i=1}^{n} N_i \beta_i T_i^* - \sum_{i=1}^{n} (\gamma_i + k_i T_0) V_i.$$

Hence,

$$1'\dot{V} \geqslant A_0 \left(\frac{\eta_0}{2} - 1'V(t) \right) - A_1 1'V(t), \quad A_0 := \min_i (N_i \beta_i) > 0, \quad A_1 := \max_i (\gamma_i + k_i T_0) > 0,$$

holds for large t. It follows immediately that

$$\liminf_{t \to \infty} 1'V(t) \geqslant \eta = \frac{\eta_0 A_0}{2(A_0 + A_1)} > 0.$$

$\square$

A.5   *Existence of an absorbing compact set for small $\mu > 0$*

THEOREM A3   Let K be the absorbing compact set established in Lemma A1, and let

$$U = \{(T, T^*, V) \in \mathbb{R}_+^{2n+1} | T, T_1^*, V_1 > 0\}.$$

Suppose that there exists an $\epsilon > 0$ such that

$$(C_\epsilon) \quad f'(c) + \frac{k_1}{\gamma_1} f(\bar{T}_1) \leqslant -\epsilon < 0, \quad \text{for all } c \in [0, T_0].$$

Then, there exist a $\mu_1 > 0$ and a compact set $K_\delta \subset U$ such that for any $\mu \in [0, \mu_1]$ and for any solution of system (A.7) in U, there exists a $t_0 > 0$ such that $(T(t), T^*(t), V(t)) \in K_\delta$ for all $t > t_0$. An identical statement holds for system (A.8).

Proof.

(a) We first prove the statement for system (A.7). Consider the function

$$W = (N_1 - 1) \int_{\bar{T}_1}^{T} \left(1 - \frac{\bar{T}_1}{\tau}\right) d\tau + N_1 \int_{\bar{T}_1^*}^{T_1^*} \left(1 - \frac{\bar{T}_1^*}{\tau}\right) d\tau + \int_{\bar{V}_1}^{V_1} \left(1 - \frac{\bar{V}_1}{\tau}\right) d\tau$$

$$+ \sum_{i=2}^{n} \frac{N_1 - 1}{N_i - 1}(N_i T_i^* + V_i).$$

Computing $\dot{W}$ for the system (A.7), we obtain

$$\dot{W} = (N_1 - 1)\left[f'(c) + \frac{k}{\gamma}f(\bar{T}_1)\right]\frac{(T - \bar{T}_1)^2}{T} + N_1\beta_1\bar{T}_1^*\left[3 - \frac{V_1 T \bar{T}_1^*}{\bar{V}_1\bar{T}_1 T_1^*} - \frac{T_1^* \bar{V}_1}{\bar{T}_1^* V_1} - \frac{\bar{T}_1}{T}\right]$$

$$-(N_1 - 1)\sum_{i=2}^{n} k_i V_i(\bar{T}_i - \bar{T}_1) + \mu N_1 \frac{T_1^* - \bar{T}_1^*}{T_1^*}$$

$$\times \sum_{j=1}^{n} q_{1j}k_j V_j T + \mu(N_1 - 1)\sum_{i=2}^{n} \frac{N_i}{N_i - 1}\sum_{j=1}^{n} q_{ij}k_j V_j T.$$

Recombining the terms, we find that

$$\dot{W} = (N_1 - 1)\left[f'(c) + \frac{k}{\gamma}f(\bar{T}_1)\right]\frac{(T - \bar{T}_1)^2}{T} + N_1\beta_1\bar{T}_1^*\left[3 - \frac{V_1 T \bar{T}_1^*}{\bar{V}_1\bar{T}_1 T_1^*} - \frac{T_1^* \bar{V}_1}{\bar{T}_1^* V_1} - \frac{\bar{T}_1}{T}\right]$$

$$-(N_1 - 1)\sum_{i=2}^{n} k_i V_i(\bar{T}_i - \bar{T}_1) + \mu(N_1 - 1)\sum_{i=1}^{n} \frac{N_i}{N_i - 1}\sum_{j=1}^{n} q_{ij}k_j V_j T$$

$$-\mu N_1 q_{11}\frac{\bar{T}_1^* V_1 T}{T_1^*} - \mu N_1 \frac{\bar{T}_1^*}{T_1^*}\sum_{j=1}^{n} q_{1j}k_j V_j T,$$

where the last term is clearly non-positive. Let

$$\alpha = (N_1 - 1)\min_{i \geqslant 2} k_i(\bar{T}_i - \bar{T}_1) > 0,$$

$$L = \sup_{K}(N_1 - 1)\sum_{i=1}^{n} \frac{N_i}{N_i - 1}\sum_{j=1}^{n} q_{ij}k_j V_j T \geqslant 0.$$

By Lemma A3, there exist $\eta, \mu_a > 0$ such that $1'V(t) > \eta$ for all $\mu \in [0, \mu_a]$ and all sufficiently large t. Hence, by shifting time forward if necessary, we have the inequality

$$\dot{W} \leqslant -\epsilon(N_1 - 1)\frac{(T - \bar{T}_1)^2}{T} + N_1\beta_1\bar{T}_1^* \left[3 - \frac{V_1 T \bar{T}_1^*}{\bar{V}_1 \bar{T}_1 T_1^*} - \frac{T_1^* \bar{V}_1}{\bar{T}_1^* V_1} - \frac{\bar{T}_1}{T} \right]$$

$$-\alpha(\eta - V_1) + \mu L - \mu N_1 q_{11}\frac{\bar{T}_1^* V_1 T}{T_1^*},$$

which holds in K for all $\mu \in [0, \mu_a]$. We combine the second and the last terms to obtain

$$\dot{W} \leqslant -\epsilon(N_1 - 1)\frac{(T - \bar{T}_1)^2}{T} + N_1\beta_1\bar{T}_1^* \left[3 - (1 + q_{11}\mu)\frac{V_1 T \bar{T}_1^*}{\bar{V}_1 \bar{T}_1 T_1^*} - \frac{T_1^* \bar{V}_1}{\bar{T}_1^* V_1} - \frac{\bar{T}_1}{T} \right]$$

$$-\alpha(\eta - V_1) + \mu L.$$

Further, we rewrite the above inequality as

$$\dot{W} \leqslant -\epsilon(N_1 - 1)\frac{(T - \bar{T}_1)^2}{T} + N_1\beta_1\bar{T}_1^* \left[3(1 + q_{11}\mu)^{1/3} - (1 + q_{11}\mu)\frac{V_1 T \bar{T}_1^*}{\bar{V}_1 \bar{T}_1 T_1^*} - \frac{T_1^* \bar{V}_1}{\bar{T}_1^* V_1} - \frac{\bar{T}_1}{T} \right]$$

$$-\alpha(\eta - V_1) + \mu L + 3N_1\beta_1\bar{T}_1^*[1 - (1 + q_{11}\mu)^{1/3}].$$

Let $\mu_b > 0$ be such that for all $\mu \in [0, \mu_b]$,

$$(1 + q_{11}\mu) \in \left[\frac{1}{2}, 1\right], \quad -\alpha\eta + \mu L + 3N_1\beta_1\bar{T}_1^*[1 - (1 + q_{11}\mu)^{1/3}] \leqslant -\frac{\alpha\eta}{2}.$$

Now, we let $\mu_1 = \min[\mu_a, \mu_b]$, so that for all $\mu \in [0, \mu_1]$ and all points in K,

$$\dot{W} \leqslant -\epsilon(N_1 - 1)\frac{(T - \bar{T}_1)^2}{T} + N_1\beta_1\bar{T}_1^* \left[3(1 + q_{11}\mu)^{1/3} - (1 + q_{11}\mu)\frac{V_1 T \bar{T}_1^*}{\bar{V}_1 \bar{T}_1 T_1^*} - \frac{T_1^* \bar{V}_1}{\bar{T}_1^* V_1} - \frac{\bar{T}_1}{T} \right]$$

$$-\frac{\alpha\eta}{2} + \alpha V_1.$$

Let $L_1 = \alpha \sup_K V_1$. Inspecting the first term in $\dot{W}$, we find that there exists a $\delta_0 > 0$ such that

$$-\epsilon(N_1 - 1)\frac{(T - \bar{T}_1)^2}{T} < -L_1$$

for all $T < \delta_0$. Similarly, inspecting the second term in $\dot{W}$ and using Lemma 6, we find that there exists a $\delta_1 > 0$ such that

$$N_1\beta_1\bar{T}_1^* \left[3(1 + q_{11}\mu)^{1/3} - (1 + q_{11}\mu)\frac{V_1 T \bar{T}_1^*}{\bar{V}_1 \bar{T}_1 T_1^*} - \frac{T_1^* \bar{V}_1}{\bar{T}_1^* V_1} - \frac{\bar{T}_1}{T} \right] < -L_1$$

for all $\frac{T_1^*}{V_1} < \delta_1$ and all $\mu \in [0, \mu_1]$. Finally, there exists a $\delta_2 > 0$ such that $-\frac{\alpha\eta}{2} + \alpha V_1 < -\frac{\alpha\eta}{4}$ for all $V_1 < \delta_2$. Let

$$\hat{K}_\delta = \{(T, T^*, V) \in K \cap U | T \geqslant \delta_0, V_1 \geqslant \delta_2, T_1^* \geqslant \delta_1 V_1\}.$$

Consider $(T, T^*, V) \in (K \cap U)\backslash\hat{K}_\delta$ and let $\mu \in [0, \mu_1]$, then at least one of the following holds:

- $T < \delta_0$, in which case $\dot{W} \leqslant -L_1 - \frac{\alpha\eta}{2} + L_1 \leqslant -\frac{\alpha\eta}{2}$;

- $T_1^*/V_1 < \delta_1$, in which case $\dot{W} \leqslant -L_1 - \frac{\alpha\eta}{2} + L_1 \leqslant -\frac{\alpha\eta}{2}$;

- $V_1 < \delta_2$, in which case $\dot{W} \leqslant -\frac{\alpha\eta}{4}$;

Hence, for all $(T, T^*, V) \in (K \cap U) \backslash \hat{K}_\delta$ and all $\mu \in [0, \mu_1]$, we have $\dot{W} \leqslant -\frac{\alpha\eta}{4} < 0$. From this point forward, the proof is identical to the proof of Theorem 4, so it will be omitted.

(b) Now, we consider system (A.8). Let W be the same as in part (a). Computing $\dot{W}$ for the system (A.8), we obtain

$$\dot{W} = (N_1 - 1)\left[f'(c) + \frac{k}{\gamma} f(\bar{T}_1) \right] \frac{(T - \bar{T}_1)^2}{T} + N_1 \beta_1 \bar{T}_1^* \left[3 - \frac{V_1 T \bar{T}_1^*}{\bar{V}_1 \bar{T}_1 T_1^*} - \frac{T_1^* \bar{V}_1}{\bar{T}_1^* V_1} - \frac{\bar{T}_1}{T} \right]$$

$$-(N_1 - 1)\sum_{i=2}^{n} k_i V_i (\bar{T}_i - \bar{T}_1) + \mu \frac{V_1 - \bar{V}_1}{V_1} \sum_{j=1}^{n} q_{1j} N_j \beta_j T_j^* + \mu \sum_{i=2}^{n} \frac{N_1 - 1}{N_i - 1} \sum_{j=1}^{n} q_{ij} N_j \beta_j T_j^*.$$

Recombining the terms, we find that

$$\dot{W} = (N_1 - 1)\left[f'(c) + \frac{k}{\gamma} f(\bar{T}_1) \right] \frac{(T - \bar{T}_1)^2}{T} + N_1 \beta_1 \bar{T}_1^* \left[3 - \frac{V_1 T \bar{T}_1^*}{\bar{V}_1 \bar{T}_1 T_1^*} - \frac{T_1^* \bar{V}_1}{\bar{T}_1^* V_1} - \frac{\bar{T}_1}{T} \right]$$

$$-(N_1 - 1)\sum_{i=2}^{n} k_i V_i (\bar{T}_i - \bar{T}_1) + \mu \sum_{i=1}^{n} \frac{N_1 - 1}{N_i - 1} \sum_{j=1}^{n} q_{ij} N_j \beta_j T_j^*$$

$$-\mu q_{11} \frac{\bar{V}_1 N_1 \beta_1 T_1^*}{V_1} - \mu \frac{\bar{V}_1}{V_1} \sum_{j=2}^{n} q_{1j} N_j \beta_j T_j^*,$$

where the last term is clearly non-positive. Let

$$\alpha = (N_1 - 1) \min_{i \geqslant 2} k_i (\bar{T}_i - \bar{T}_1) > 0,$$

$$L = \sup_{K} \sum_{i=1}^{n} \frac{N_1 - 1}{N_i - 1} \sum_{j=1}^{n} q_{ij} N_j \beta_j T_j^* \geqslant 0.$$

By Lemma A3, there exist $\eta, \mu_a > 0$ such that $1'V(t) > \eta$ for all $\mu \in [0, \mu_a]$ and all sufficiently large t. Hence, by shifting time forward if necessary, we have the inequality

$$\dot{W} \leqslant -\epsilon(N_1 - 1)\frac{(T - \bar{T}_1)^2}{T} + N_1 \beta_1 \bar{T}_1^* \left[3 - \frac{V_1 T \bar{T}_1^*}{\bar{V}_1 \bar{T}_1 T_1^*} - \frac{T_1^* \bar{V}_1}{\bar{T}_1^* V_1} - \frac{\bar{T}_1}{T} \right]$$

$$-\alpha(\eta - V_1) + \mu L - \mu q_{11} \frac{\bar{V}_1 N_1 \beta_1 T_1^*}{V_1},$$

which holds in K for all $\mu \in [0, \mu_a]$. We combine the second and the last terms to obtain

$$\dot{W} \leqslant -\epsilon (N_1 - 1)\frac{(T - \bar{T}_1)^2}{T} + N_1\beta_1\bar{T}_1^* \left[3 - \frac{V_1 T \bar{T}_1^*}{\bar{V}_1\bar{T}_1 T_1^*} - (1 + q_{11}\mu)\frac{T_1^*\bar{V}_1}{\bar{T}_1^* V_1} - \frac{\bar{T}_1}{T} \right]$$

$$-\alpha(\eta - V_1) + \mu L.$$

Further, we rewrite the above inequality as

$$\dot{W} \leqslant -\epsilon (N_1 - 1)\frac{(T - \bar{T}_1)^2}{T} + N_1\beta_1\bar{T}_1^* \left[3(1 + q_{11}\mu)^{1/3} - \frac{V_1 T \bar{T}_1^*}{\bar{V}_1\bar{T}_1 T_1^*} - (1 + q_{11}\mu)\frac{T_1^*\bar{V}_1}{\bar{T}_1^* V_1} - \frac{\bar{T}_1}{T} \right]$$

$$-\alpha(\eta - V_1) + \mu L + 3N_1\beta_1\bar{T}_1^*[1 - (1 + q_{11}\mu)^{1/3}].$$

Let $\mu_b > 0$ be such that for all $\mu \in [0, \mu_b]$,

$$(1 + q_{11}\mu) \in \left[\frac{1}{2}, 1 \right], \quad -\alpha\eta + \mu L + 3N_1\beta_1\bar{T}_1^*[1 - (1 + q_{11}\mu)^{1/3}] \leqslant -\frac{\alpha\eta}{2}.$$

Now, we let $\mu_1 = \min[\mu_a, \mu_b]$, so that for all $\mu \in [0, \mu_1]$ and all points in K,

$$\dot{W} \leqslant -\epsilon (N_1 - 1)\frac{(T - \bar{T}_1)^2}{T} + N_1\beta_1\bar{T}_1^* \left[3(1 + q_{11}\mu)^{1/3} - \frac{V_1 T \bar{T}_1^*}{\bar{V}_1\bar{T}_1 T_1^*} - (1 + q_{11}\mu)\frac{T_1^*\bar{V}_1}{\bar{T}_1^* V_1} - \frac{\bar{T}_1}{T} \right]$$

$$-\frac{\alpha\eta}{2} + \alpha V_1.$$

From this point forward, the proof is identical to the proof of part (a), so it will be omitted.

$\square$

THEOREM A4 Let the assumptions of Lemma A2 hold, let U be the set from Theorem A3 and define

$$U' = \{(T, T^*, V) \in \mathbb{R}_+^{2n+1}|T_1^* + V_1 > 0\} \supset U.$$

Then, there exist a $\mu_0 > 0$ and a continuous map $E: [0, \mu_0] \to U$ such that the following holds:

1. $E(0) = E_1$ (where E_1 is the same as in Lemma A2), and $E(\mu)$ is an equilibrium of (A.7) or (A.8) for all $\mu \in [0, \mu_0]$;

2. For each $\mu \in [0, \mu_0]$, $E(\mu)$ is a globally asymptotically stable equilibrium of (A.7) or (A.8) in U'.

Proof. The proof is similar to that of Theorem 5. $\square$