

The chemostat with lateral gene transfer

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Abstract

We investigate the standard chemostat model when lateral gene transfer is taken into account. We will show that when the different genotypes have growth rate functions that are sufficiently close to a common growth rate function, and when the yields of the genotypes are sufficiently close to a common value, then the population evolves to a globally stable steady state, at which all genotypes coexist. These results can explain why the antibiotic resistant strains persist in the pathogen population.

1 Introduction

Antibiotic resistance is a growing problem worldwide. In many hospitals the prevalence of multi-strain resistant bacteria is increasing and the costs of the antibiotic resistance both in human life and expense of the treatment is skyrocketing.

The rapid evolution of antibiotic resistance is a very complex process, and we are only beginning to understand some of its causes. Many pathogens lack some of the DNA damage detection and repair mechanisms of eukaryotes, and consequently their mutation rates are higher. Coupled with the fast inter-generational time this provides bacteria with means of rapidly sampling the available DNA sequence space. In this context, the frequent use of antibiotics supplies the evolutionary pressure for development of antibiotic resistance. An additional factor that speeds up this process is the ability of many pathogens to acquire resistance genes through lateral (horizontal) gene transfer (LGT) [3, 10, 8]. For example, it has been estimated that up to 17% of the genome of the bacterium *Synechocystis* PCC6803 has been acquired through LGT, and this is an underestimate, since older gene transfers could not be detected [10].

LGT can occur via *transformation*, *transduction* and *conjugation*. Transformation refers to the process where naked DNA is picked up from the environment. In transduction, a replicating bacteriophage packages some donor genetic information and transfers this information upon infection to the new host. Finally, conjugation refers to the process where two cells come into contact with each other, and genetic material is exchanged. These mechanisms are illustrated in Figure 1.

In this paper we model competition in a chemostat for a single limiting resource S between different strains of the same pathogen in the presence of LGT. The strains will differ in their growth rate functions, which are arbitrary non-linear increasing functions of S , and the effectiveness of the resource utilization. Because of the genetic diversity we view pathogen population as a finite collection of genetically closely related strains. If one of these strains acquires resistance either by *de novo* mutation or by LGT it will gain selective advantage in the presence of antibiotics and can quickly dominate the population. On the other hand the plasmid with the resistance gene imparts metabolic cost associated with the transcription and the translation of the resistance gene(s) to its carrier. Therefore in the absence of the antibiotic the resistance carrying strain will be in competitive disadvantage with the other strains in the population. Since the antibiotic treatment is in general a rare treatment, why does the resistant strain persist in the population? The celebrated competitive exclusion principle [5, 12], although not applicable in complete generality [7, 6, 17, 18], implies that the resistant strain should quickly vanish from the population in the regular environment, being out competed by its more fit cousins.

To probe the effect of LTG on persistence of the resistant strains in the population we introduce a lateral transfer operator T . The (i, j) element of T specifies the rate of transformation of the clone j to clone i .

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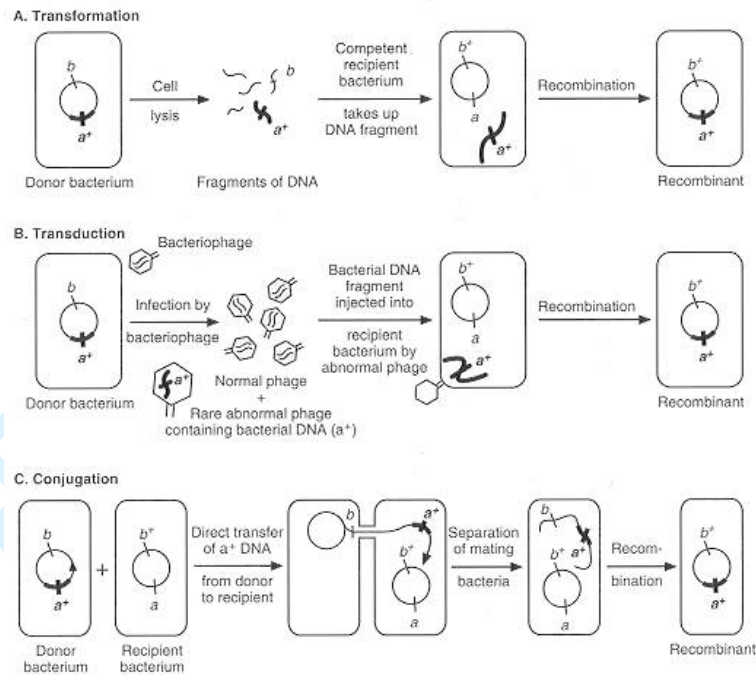


Figure 1: Mechanisms of lateral gene transfer.

Taken from http://bacteriology.suite101.com/article.cfm/bacteria_horizontal_gene_transfer

The transfer matrix is similar to a mutation matrix, but it also has significant differences. Unlike mutation rates, the transfer rates can be quite large in the presence of the antibiotic [9, 15, 16] and can increase as a result of the SOS response [1].

Mutation usually creates a closely related individual and rarely induces substantial changes in the genome. Therefore a mutation matrix can be assumed to be near diagonal. In contrast, lateral gene transfer can cause large changes in the genome and we do not place any structural assumption on the matrix T . We do, however, assume that the matrix T does not depend on the substrate level S . In contrast, since the mutations happen during the duplication of DNA and hence are conditioned on the growth of the population, the mutation rates do, in general, depend on the growth rate and thus indirectly on the substrate level concentration [4].

We find that with lateral gene transfer all the strains will ultimately coexist at a globally stable steady state provided that the substrate influx is sufficiently high. Below the critical rate of substrate influx, the entire population disappears. The coexistence result shows that lateral gene transfer allows the population to keep the resistance gene. This mechanism avoids penalizing a single carrier strain which would lead to its extinction and loss of the gene from the entire population. Our persistence result only requires that all transfer rates are non-negative and that the matrix T is irreducible. That means that there is no lower bound on the rate of transfer from strain i to some other strain j , perhaps by passing via a sequence of other strains first.

Throughout the paper we will consider the following system on \mathbb{R}_+^{n+1} :

$$\dot{x} = [M(S) - I_n + T]x \quad (1)$$

$$\dot{S} = 1 - S - \mu^T(S) \text{diag}^{-1}(Y)x, \quad (2)$$

where

$$\mu^T(S) = (\mu_1(S) \mu_2(S) \dots \mu_n(S)) \text{ and } M(S) = \text{diag}(\mu(S)),$$

and I_n is the identity matrix.

The vector $\mu(S)$ contains the growth rate functions of the various cell types and the $Y_i \in (0, 1]$ are the respective yield constants. Each growth rate function μ_i is smooth, zero at zero, with $\mu'_i(S) > 0$ for $S > 0$.

The matrix T contains the rates at which the strains convert from one type to another. It is assumed to be quasi-positive (i.e. all its off-diagonal entries are non-negative) and irreducible. Then it has a real dominant eigenvalue by a generalization of the Perron-Frobenius Theorem [2], and we assume that that eigenvalue is

zero. To clarify the latter assumption, assume that the strains would not grow, nor wash out or die. In that case equation (1) would be linear: $\dot{x} = Tx$ and only describe the movement of strains between the various genotypes. Since growth and washout/death are neglected, the total amount of biomass is conserved. This can only happen if the dominant eigenvalue of T is zero. If it would be negative, then all solutions would converge to zero, whereas they would diverge if it were positive.

The Perron-Frobenius Theorem also implies that there is some positive vector w^T corresponding to the zero eigenvalue: $w^T T = 0$. A particular consequence is that the diagonal entries of T must be negative, for if this were not the case, then $v^T T$ could not be zero for any positive vector v , implying that zero is not the dominant eigenvalue, which in turn would violate the conservation of biomass described above.

We claim that without loss of generality we can assume that $w^T = (1 \ 1 \ \dots \ 1)$, which implies that T is in fact compartmental (i.e. it is quasi-positive and all its column sums are zero). To see this, we re-scale x as follows. Let $z = Wx$, where $W = \text{diag}(w)$. Then (1) – (2) is transformed to

$$\begin{aligned}\dot{z} &= [M(S) - I_n + \tilde{T}]z \\ \dot{S} &= 1 - S - \mu^T(S) \text{diag}^{-1}(Y)W^{-1}z,\end{aligned}$$

where $\tilde{T} = WTW^{-1}$ is still quasi-positive and irreducible, and clearly $1^T \tilde{T} = 0$. If necessary, the transformed yield coefficients can be chosen to satisfy $Y_i w_i \leq 1$ by rescaling w in the transformation $z = Wx$ by a sufficiently small positive scaling factor.

Thus, throughout the rest of the paper we assume that:

T is compartmental and irreducible.

In this case the matrix T represents the lateral gene transfer matrix, and each off-diagonal entry T_{ij} represents the rate of conversion of genotype j to genotype i .

The main result of this paper is as follows.

Theorem 1. *Let $\mu_0(S)$ be smooth, zero at zero with $\mu'_0(S) > 0$ for $S > 0$, and let $Y_0 > 0$. If $\mu_0(1) > 1$, then there exist $\varepsilon^* > 0$ such that if $\|\mu_i - \mu_0\|_{C^0} < \varepsilon^*$, $|Y_i - Y_0| < \varepsilon^*$, then system (1) – (2) has a unique positive steady state (x^*, S^*) which is globally asymptotically stable with respect to initial conditions satisfying $x(0) \neq 0$. Here, the norm $\|\cdot\|_{C^0}$ denotes the usual sup norm for bounded continuous functions.*

In Section 2 we will state and prove several general properties of system (1) – (2), including an extinction result and a uniform persistence property. In Section 3 we first specialize system (1) – (2) to the case where all growth rate functions μ_i are the same, and equal to a common function μ_0 , and where all yields Y_i are equal to some common value Y_0 . For this case we will be able to prove a global stability result. This in turn allows Theorem 1 to be proved by means of a perturbation result in the last subsection of Section 3.

2 Some general properties of the model

2.1 Uniform boundedness

We start by establishing that all solutions are ultimately bounded by the same bound.

Lemma 1. *The solutions of (1) – (2) are uniformly bounded. More precisely, there is some $m^* > 0$ such that for every solution $(x(t), S(t))$, there is a τ such that*

$$(x(t), S(t)) \in L, \text{ for all } t \geq \tau,$$

where

$$L := \{(x, S) \in \mathbb{R}_+^{n+1} \mid 1^T x + S \leq m^*\}.$$

Proof. First note that \mathbb{R}_+^{n+1} is forward invariant because T is quasi-positive. Define $y := (Y_1^{-1} \ \dots \ Y_n^{-1})^T$. Since all $Y_i \in (0, 1]$ it follows that $y - 1 \geq 0$. Let us consider the evolution of the variable:

$$m = S + 1^T x,$$

along an arbitrary solution $(x(t), S(t))$ of (1) – (2). Observe that:

$$\dot{m}(t) = 1 - m(t) - [y - 1]^T M(S(t))x(t) \leq 1 - m(t).$$

The conclusion follows by setting $m^* = 1.1$. □

2.2 Steady states

Here we show that system (1) – (2) always has a washout steady state, and we discuss its stability properties. We also show that the system can have a second coexistence steady state.

In order not to complicate the notation too much, we define for all $S \geq 0$ the following matrix:

$$B(S) = M(S) - I_n + T,$$

and notice that it is quasi-positive and irreducible. By the Perron-Frobenius Theorem, for every $S \geq 0$, the matrix $B(S)$ has a real, dominant eigenvalue $\lambda(B(S))$ which is simple and has a corresponding positive eigenvector. Except for this positive eigenvector (and all its scalar multiples with a positive scalar), there are no other non-negative eigenvectors.

We also have the following property.

Lemma 2. *The eigenvalue $\lambda(B(S))$ is a continuous and increasing function of S , with $\lambda(B(0)) = -1$.*

Proof. Continuity is obvious. Since T is compartmental and irreducible, its dominant eigenvalue $\lambda(T)$ is 0, and hence $\lambda(B(0)) = \lambda(T) - 1 = -1$. Since each $\mu_i(S)$ is increasing, it follows that $\lambda(B(S)) = \lambda(B(0) + M(S))$ is increasing as well by Corollary (1.5)(b) in [2] (i.e. $S_1 < S_2$ implies that $\lambda(B(S_1)) < \lambda(B(S_2))$). \square

Lemma 3. *The washout state $(0, 0, \dots, 0, 1)^T$ is always a steady state of (1) – (2).*

There are no other steady states on the boundary of \mathbb{R}_+^{n+1} .

If $\lambda(B(1)) \leq 0$, then the washout steady state is the only steady state of (1) – (2), and if $\lambda(B(1)) < 0$, then the washout steady state is hyperbolic and locally asymptotically stable.

If $\lambda(B(1)) > 0$, then the washout steady state is unstable, and (1) – (2) has a unique positive steady state (x^, S^*) . Here, S^* is the unique positive number for which $\lambda(B(S^*)) = 0$, and the vector x^* is the unique positive vector satisfying $B(S^*)x^* = 0$ and $x^{*T} \text{diag}^{-1}(Y)\mu(S^*) = 1 - S^*$.*

Proof. Steady states are (non-negative) solutions (x^*, S^*) of

$$B(S^*)x^* = 0 \tag{3}$$

$$x^{*T} \text{diag}^{-1}(Y)\mu(S^*) = 1 - S^* \tag{4}$$

By (4), no steady state can have $S^* = 0$, and so we can assume without loss of generality that $S^* > 0$ from now on.

The first assertion is trivial. Linearization at the washout steady state yields the following Jacobian matrix:

$$\begin{pmatrix} B(1) & 0 \\ -\mu^T(1)\text{diag}^{-1}(Y) & -1 \end{pmatrix},$$

hence all assertions regarding hyperbolicity and local asymptotic stability or instability of the washout steady state follow immediately.

Let us now focus on finding steady states (x^*, S^*) with (non-negative) $x^* \neq 0$. Equation (3) implies that x^* must be an eigenvector corresponding to the eigenvalue 0. But if x^* is non-negative, it must be an eigenvector corresponding to the dominant eigenvalue by the Perron-Frobenius Theorem. Hence, if a steady state (x^*, S^*) exists with $x^* \neq 0$, then it is such that $\lambda(B(S^*)) = 0$ and moreover x^* must be a positive vector (rather than only non-negative).

If $\lambda(B(1)) > 0$, since $\lambda(B(S))$ is increasing by Lemma 2 and $\lambda(B(0)) = -1$, there is a unique $S^* \in (0, 1)$ such that $\lambda(B(S^*)) = 0$. It follows from (3) that x^* is simply a positive eigenvector corresponding to $\lambda(B(S^*)) = 0$. Of course, this vector is only determined up to multiplication by some positive scalar, but (4) determines that scalar uniquely.

Finally, if $\lambda(B(1)) \leq 0$, then $\lambda(B(S^*)) = 0$ may be solvable for S^* , but then $S^* \geq 1$, again using monotonicity of $\lambda(B(S))$ established in Lemma 2. But then there cannot exist a corresponding positive vector x^* that satisfies (3) and (4). Thus, in this case, the washout steady state is the only steady state of (1) – (2). \square

2.3 Extinction

We show that system (1) – (2) has the following extinction property.

Theorem 2. *Suppose that $\lambda := \lambda(B(1)) < 0$. Then every solution $(x(t), S(t))$ of (1) – (2) is such that*

$$\lim_{t \rightarrow \infty} (x^T(t), S(t)) = (0, 0, \dots, 0, 1),$$

where $(0, 0, \dots, 0, 1)$ is the washout steady state.

Proof. We see that Lemma 1 is still valid if $m^* = 1 + \epsilon$ for all $\epsilon > 0$ by re-examining its proof. Fix $\epsilon > 0$ such that $\tilde{\lambda} := \lambda(B(1 + \epsilon)) < 0$ (this is possible since eigenvalues of a matrix are continuous in the entries of the matrix). Let $(x(t), S(t))$ be a solution of (1) – (2). Then by Lemma 1, there is some $\tau > 0$ such that $S(t) \leq 1 + \epsilon$ for all $t \geq \tau$. Then

$$\dot{x}(t) \leq B(1 + \epsilon)x(t), \text{ for all } t \geq \tau. \quad (5)$$

Consider the function $V(x, S) = v^T x$ where v^T is a positive left eigenvector of $B(1 + \epsilon)$ corresponding to $\tilde{\lambda}$: $v^T B(1 + \epsilon) = \tilde{\lambda} v^T$. Then along the solution $(x(t), S(t))$, we have that for all $t \geq \tau$:

$$\dot{V}(x(t), S(t)) = v^T \dot{x}(t) \leq v^T B(1 + \epsilon)x(t) = \tilde{\lambda} v^T x(t) = \tilde{\lambda} V(x(t), S(t)) \leq 0,$$

where we used (5) to establish the inequality. LaSalle's invariance principle (see e.g. [12]) implies that $(x(t), S(t))$ converges to the largest invariant set contained in the set $\Omega = \{(x, S) \in \mathbb{R}_+^{n+1} \mid v^T x = 0\} = \{(x, S) \in \mathbb{R}_+^{n+1} \mid x = 0\}$, the non-negative S -axis. Clearly, the largest invariant set contained in Ω is $\{(0, 0, \dots, 0, 1)\}$, which concludes the proof. \square

2.4 Uniform persistence

Reversing the inequality in the condition of Theorem 2 implies that system (1) – (2) has the following persistence property. We shall give two proofs of this fact.

Theorem 3. *Suppose that $\lambda := \lambda(B(1)) > 0$. Then there exists $\Delta > 0$ such that*

$$\liminf_{t \rightarrow +\infty} 1^T x(t) \geq \Delta$$

for all solutions $(x(t), S(t))$ of the system (1) – (2) with $1^T x(0) > 0$.

Proof. Define $y := (Y_1^{-1} \dots Y_n^{-1})^T$, and let $\alpha > 0$ be large enough such that $\alpha 1 \geq y$. By continuity of $\mu_i(\cdot)$, $i = 1, 2, \dots, n$, there exists $\delta \in (0, 1)$ such that $\mu_i(1 - z) - \mu_i(1) \geq -\frac{\lambda}{2}$ for all $z \in [0, \delta]$ and for all $i = 1, 2, \dots, n$. Define the auxiliary function $m(t) := S(t) + \alpha 1^T x(t)$. It follows that

$$\dot{m}(t) = 1 - S(t) - \alpha 1^T x(t) + (\alpha 1 - y)^T M(S(t))x(t) \geq 1 - m(t),$$

hence for every solution of (1) – (2), there exists $\tau > 0$ such that $m(t) \geq 1 - \frac{\delta}{2}$ for all $t \geq \tau$. By shifting time, if necessary, we may assume that $\tau = 0$. Hence we have,

$$S(t) \geq 1 - \frac{\delta}{2} - \alpha 1^T x(t), \quad \forall t \geq 0.$$

Let v^T be a positive left eigenvector of $B(1)$ corresponding to λ : $v^T B(1) = \lambda v^T$. Consider the set

$$D := \left\{ (x, S) \mid S \geq 0, 0 < v^T x < \frac{\delta}{2\alpha} \min_i v_i \right\}.$$

If $(x(t), S(t)) \in D$, we have that

$$\alpha 1^T x(t) < \frac{\alpha}{\min_i v_i} v^T x(t) < \frac{\delta}{2},$$

hence the following inequality holds:

$$\begin{aligned} \dot{x}(t) &\geq \left(M \left(1 - \frac{\delta}{2} - \alpha 1^T x(t) \right) - I + T \right) x(t) \\ &= B(1)x(t) + \left(M \left(1 - \frac{\delta}{2} - \alpha 1^T x(t) \right) - M(1) \right) x(t) \\ &\geq B(1)x(t) - \frac{\lambda}{2} x(t), \end{aligned}$$

by the choice of δ and since $\alpha 1^T x(t) < \frac{\delta}{2}$ in D . Multiplying the above inequality by v^T on the left, we find that

$$v^T \dot{x}(t) \geq v^T B(1)x(t) - \frac{\lambda}{2} v^T x(t) = \lambda v^T x(t) - \frac{\lambda}{2} v^T x(t) = \frac{\lambda}{2} v^T x(t).$$

This implies that the set D is (i) invariant in reverse time and (ii) that all solutions of (1) – (2) leave D in forward time. It follows immediately that

$$\liminf_{t \rightarrow +\infty} v^T x(t) \geq \frac{\delta}{2\alpha} \min_i v_i,$$

and thus

$$\liminf_{t \rightarrow +\infty} 1^T x(t) \geq \frac{\delta}{2\alpha} \frac{\min_i v_i}{\max_i v_i} =: \Delta > 0,$$

for all solutions of (1) – (2) with $1^T x(0) > 0$. This concludes the proof. \square

Remark 1. We also provide an alternative proof of Theorem 3. It is based on the fluctuation method, coupled with the results from [11] which demonstrate when uniform weak repellers are uniform strong repellers. First we introduce some notation: For a scalar function $x(t)$, $t \in \mathbb{R}_+$, we denote the (extended) real numbers $\limsup_{t \rightarrow \infty} x(t)$ and $\liminf_{t \rightarrow \infty} x(t)$ as x^∞ and x_∞ respectively.

By continuity of eigenvalues of a matrix and since $\lambda = \lambda(B(1)) > 0$, there exists an $\epsilon > 0$ such that $\lambda(B(1 - \epsilon)) > 0$ as well.

Assume that the quantity $1^T x$ is not uniformly weakly persistent for (1) – (2).

Then there is some solution $(x(t), S(t))$ with $x(0) \neq 0$ such that

$$(1^T x(t))^\infty \leq \frac{\epsilon}{2\gamma}, \quad (6)$$

where $\gamma := \max_i Y_i^{-1} \mu_i(1)$. Equation (2) implies that $S_\infty \leq 1$. From Corollary 2.4 in [11] (this is a consequence of the famous fluctuation lemma) it follows that

$$\begin{aligned} 0 &\geq \liminf_{t \rightarrow \infty} (1 - S_\infty - y^T M(S_\infty)x(t)) \\ &\geq \liminf_{t \rightarrow \infty} (1 - S_\infty - y^T M(1)x(t)) \\ &\geq \liminf_{t \rightarrow \infty} (1 - S_\infty - \gamma(1^T x(t))) \\ &\geq 1 - S_\infty - \gamma(1^T x(t))^\infty \\ &\geq 1 - S_\infty - \frac{\epsilon}{2}, \end{aligned}$$

where we used (6) to establish the last inequality. Therefore $S_\infty \geq 1 - \epsilon/2$, and hence $S(t) \geq 1 - \epsilon$ for all sufficiently large t . Then (1) implies that for all sufficiently large t :

$$\dot{x}(t) \geq B(1 - \epsilon)x(t).$$

Since $\lambda(B(1 - \epsilon)) > 0$, all solutions of $\dot{z} = B(1 - \epsilon)z$ with $z(0) \neq 0$ and $z(0) \geq 0$ diverge as $t \rightarrow \infty$, and thus by a comparison argument the same is true for $x(t)$. This contradicts boundedness of $x(t)$, see Lemma 1.

We have established that $1^T x$ is uniformly weakly persistent, or using the terminology of [11], that $X_2 := \{(x, S) \in \mathbb{R}_+^{n+1} \mid 1^T x = 0\}$ is a uniform weak repeller for $X_1 := \{(x, S) \in \mathbb{R}_+^{n+1} \mid 1^T x > 0\}$. Using Lemma 1, it now follows from Theorem 1.4 of [11], that X_2 is in fact a uniform strong repeller for X_1 . This concludes the proof.

3 Specializing the model

In this section we will first specialize the model (1) – (2) to the case where all growth rate functions μ_i are equal to a given growth rate μ_0 , and all yield coefficients Y_i are equal to a given yield Y_0 . After that, we will be able to prove the main result of our paper, Theorem 1, using a particular perturbation result. The perturbation is measured in terms of how much the various growth rate functions μ_i deviate from μ_0 , and the yields coefficients Y_i deviate from Y_0 . Biologically, this means that our main result holds when the various genotypes are not too different in the way they consume nutrient and in how efficiently they convert it into new biomass.

3.1 Local and global stability when all μ_i are equal to μ_0 and all Y_i are Y_0 .

Specializing (1) – (2) to the case where $\mu_i(S) = \mu_0(S)$ and $Y_i = Y_0$ for all i , yields the following simplified equations:

$$\dot{x} = [(\mu_0(S) - 1)I_n + T]x \quad (7)$$

$$\dot{S} = 1 - S - \mu_0(S)Y_0^{-1}(1^T x). \quad (8)$$

In this case $\lambda(B(S)) = \mu_0(S) - 1$, and thus if $\lambda(B(1)) = \mu_0(1) - 1 > 0$, then system (7) – (8) has a unique positive steady state (x^*, S^*) by Lemma 3. We show next that it is asymptotically stable.

Lemma 4. *Let $\mu_0(S)$ be smooth, zero at zero, with $\mu'_0(S) > 0$ for $S > 0$, and let $Y_0 \in (0, 1]$. If $\mu_0(1) - 1 > 0$, then the steady state (x^*, S^*) is hyperbolic and locally asymptotically stable for (7) – (8).*

Proof. In this particular case, the positive steady state (x^*, S^*) satisfies:

$$B(S^*)x^* = 0 \quad (9)$$

$$\mu_0(S^*)(1^T x^*) = Y_0(1 - S^*) \quad (10)$$

The first equation implies that $\lambda(B(S^*)) = 0$, and thus that:

$$\mu_0(S^*) = 1.$$

Therefore, the equations (9) – (10) simplify to:

$$Tx^* = 0 \quad (11)$$

$$1^T x^* = Y_0(1 - S^*) \quad (12)$$

Linearization of (7) – (8) at (x^*, S^*) yields the following block-matrix:

$$\begin{pmatrix} T & \mu'_0(S^*)x^* \\ -Y_0^{-1}1^T & -1 - \mu'_0(S^*)(1 - S^*) \end{pmatrix}$$

where we used (12). We decompose this matrix as follows:

$$A + kbc^T := \begin{pmatrix} T & 0 \\ -Y_0^{-1}1^T & -1 \end{pmatrix} + \mu'_0(S^*) \begin{pmatrix} x^* \\ -(1 - S^*) \end{pmatrix} \begin{pmatrix} 0 & 0 & \dots & 0 & 1 \end{pmatrix}.$$

Notice that the spectrum of the $(n + 1) \times (n + 1)$ matrix A is given by

$$\sigma(A) = \sigma(T) \cup \{-1\},$$

and thus all eigenvalues of A have negative real part, except for a simple eigenvalue at 0 (because T is compartmental and irreducible). Also notice that the parameter

$$k = \mu'_0(S^*)$$

is positive. We will show that for all $k > 0$, the eigenvalues of $A + kbc^T$ have negative real part. To see this we perform a similarity transformation as follows. Let

$$P = \begin{pmatrix} b & v_1 & v_2 & \dots & v_n \end{pmatrix},$$

where v_1, \dots, v_n are chosen arbitrarily such that

$$\text{span}\{b\} \oplus \text{span}\{v_1, v_2, \dots, v_n\} = \mathbb{R}^{n+1}$$

Then using (11) – (12) it follows that:

$$P^{-1}AP + kP^{-1}bc^T P = \begin{pmatrix} 0 & * \\ 0 & \tilde{A} \end{pmatrix} + k \begin{pmatrix} -(1 - S^*) & * \\ 0 & 0 \end{pmatrix},$$

where the *'s do not matter for our purposes, and the eigenvalues of the $n \times n$ matrix \tilde{A} are -1 and the $n - 1$ eigenvalues of the matrix T that belong to the open left-half plane (Indeed, this follows from similarity which implies that $\sigma(A) = \{0\} \cup \sigma(\tilde{A})$, and since $\sigma(A) = \sigma(T) \cup \{-1\}$). It follows that the eigenvalues of $A + kbc^T$ are given by

$$-k(1 - S^*),$$

which is negative because $k > 0$ and $1 - S^* > 0$ by (12), and by the eigenvalues of \tilde{A} , all of which have negative real part. This concludes the proof. \square

Remark 2. The argument in the proof of Lemma 4 is routinely used in control theory [14]. The problem amounts to showing that the following output feedback system

$$\begin{aligned}\dot{x} &= Ax + bu, \quad y = c^T x \\ u &= ky\end{aligned}$$

is asymptotically stable for arbitrary $k > 0$, or equivalently, that all eigenvalues of $A + kbc^T$ have negative real part.

It is easy to see that the controllability matrix of this system:

$$\mathcal{R}(A, b) := [b \quad Ab \quad A^2b \quad \dots \quad A^{n-1}b] = [b \quad 0 \quad 0 \quad \dots \quad 0],$$

(we used (11) – (12) here) has a one-dimensional column space $\text{span}\{b\}$. Thus the feedback system has a single controllable mode at 0 (notice that b is an eigenvector of A corresponding to eigenvalue 0 because $Ab = 0$), and n uncontrollable modes (the $n - 1$ eigenvalues of T having negative real part, and -1). The linear coordinate transformation:

$$x = Pz,$$

yields the (Kalman) controllable canonical form

$$\begin{aligned}\dot{z} &= \begin{pmatrix} 0 & * \\ 0 & \tilde{A} \end{pmatrix} z + \begin{pmatrix} b_1 \\ 0 \end{pmatrix} u, \quad y = c^T Pz \\ u &= ky\end{aligned}$$

where the scalar $b_1 \neq 0$, which shows that the only mode of the open loop system that can be shifted by output feedback is the zero mode, while none of the uncontrollable modes can be changed by output feedback (or even by state feedback). The rest of the proof of Lemma 4 shows that output feedback shifts the zero mode in the right direction for all $k > 0$, namely into the open left half-plane of the complex plane.

Theorem 4. *Let $\mu_0(S)$ be smooth, zero at zero, with $\mu_0'(S) > 0$ for $S > 0$, and let $Y_0 \in (0, 1]$. If $\mu_0(1) - 1 > 0$, then the steady state (x^*, S^*) is globally asymptotically stable for (7) – (8) with respect to initial conditions satisfying $x(0) \neq 0$.*

Proof. By Lemma 1 and Theorem 3, all solutions of (7) – (8) with $x(0) \neq 0$ eventually enter the compact forward invariant set

$$D := L \cap \{(x, S) \in \mathbb{R}_+^{n+1} \mid 1^T x \geq \Delta\}.$$

Thus, without loss of generality, we henceforth restrict initial conditions to D .

Define the variable

$$m = S + Y_0^{-1}(1^T x),$$

and note that

$$\dot{m} = 1 - m,$$

and hence that $m(t) \rightarrow 1$ as $t \rightarrow \infty$. Consequently, we replace S by $1 - Y_0^{-1}(1^T x)$ in (7) – (8), and study the limiting system:

$$\dot{x} = [(\mu_0(1 - Y_0^{-1}(1^T x)) - 1)I_n + T]x, \quad (13)$$

which evolves on the forward invariant set

$$\Omega = \{x \in \mathbb{R}_+^n \mid \Delta \leq (1^T x) \leq Y_0\}.$$

Consider the following function on Ω :

$$V(x) = \frac{1}{2} (Y_0^{-1}(1^T x) - (1 - S^*))^2.$$

Then its time-derivative along solutions of (13) is:

$$\dot{V} = (Y_0^{-1}(1^T x) - (1 - S^*))Y_0^{-1}(1^T \dot{x}) = Y_0^{-1}(1^T x)(Y_0^{-1}(1^T x) - (1 - S^*))(\mu_0(1 - Y_0^{-1}(1^T x)) - 1)$$

Notice that in Ω ,

$$\begin{aligned} Y_1^{-1}(1^T x) - (1 - S^*) &> \text{(or } <) & 0 &\Leftrightarrow \\ S^* &> \text{(or } <) & 1 - Y_0^{-1}(1^T x) &\Leftrightarrow \\ \mu_0(S^*) &> \text{(or } <) & \mu_0(1 - Y_0^{-1}(1^T x)) &\Leftrightarrow \\ \mu_0(S^*) - 1 &> \text{(or } <) & \mu_0(1 - Y_0^{-1}(1^T x)) - 1 &\Leftrightarrow \\ 0 &> \text{(or } <) & \mu_0(1 - Y_0^{-1}(1^T x)) - 1, \end{aligned}$$

where we have used that μ_0 is monotonically increasing in the third line, and that $\mu_0(S^*) = 1$ (this follows from multiplying $[(\mu_0(S^*) - 1)I_n + T]x^* = 0$ by 1^T on the left, and using that $1^T T = 0$ and that $1^T x^* > 0$) in the last line. Therefore, since the first factor in \dot{V} is always non-negative in Ω , it follows that:

$$\dot{V} \leq 0.$$

By LaSalle's invariance principle all solutions of (13) converge to the largest invariant set contained in $\mathcal{S} := \{x \in \Omega \mid 1 - Y_0^{-1}(1^T x) = S^*\}$. We claim that this set is the singleton $\{x^*\}$. To see this, first notice that the set \mathcal{S} is a forward invariant set for (13), that \mathcal{S} contains the unique steady state x^* , and the that dynamics on \mathcal{S} are given by:

$$\dot{x} = B(S^*)x, \quad x \in \mathcal{S} \quad (14)$$

Now, consider the linear system:

$$\dot{z} = B(S^*)z, \quad z \in \mathbb{R}^n. \quad (15)$$

Clearly, every solution of (14) coincides with a solution of (15). We examine the dynamics of (15). Since $\lambda(B(S^*)) = 0$, the state space \mathbb{R}^n of (15) is foliated by invariant hyperplanes (generated by the $(n - 1)$ -dimensional vector space which is given by the direct sum of all generalized eigenspaces that correspond to eigenvalues with negative real part), and all forward solutions of (15) converge to a unique steady state in each hyperplane (each steady state is an eigenvector corresponding to the eigenvalue $\lambda(B(S^*)) = 0$). In backward time on the other hand, all non-equilibrium solutions of (15) starting in \mathbb{R}_+^n , leave \mathbb{R}_+^n in finite time. In particular, this happens to non-equilibrium solutions of (15) starting in the set \mathcal{S} . Consequently, the largest invariant set of (13) contained in \mathcal{S} is the steady state x^* . Summarizing, we have established that all solutions of (13) in Ω with converge to x^* .

Finally, in order to return from the behavior of (13) to the original system (7) – (8) we will use a limiting theorem applied to the asymptotically autonomous system

$$\dot{m} = 1 - m \quad (16)$$

$$\dot{x} = [(\mu_0(m - Y_0^{-1}(1^T x)) - 1)I_n + T]x, \quad (17)$$

evolving on $D' = \{(m, x) \in \mathbb{R}_+^{n+1} \mid m \leq m^*, 1^T x \geq \Delta\}$, which is equivalent to the original system (7) – (8) on D .

Notice that (13) has a unique steady state x^* which is hyperbolic and locally asymptotically stable by Lemma 4. Moreover, we have shown that all solutions of (13) converge to x^* , and clearly x^* cannot be chained to itself. Now it follows from Theorem F.1 in [12] that all solutions of (16) – (17) in D' converge to $(1, x^*)$. This in turn implies that all solutions of (7) – (8) in D converge to (x^*, S^*) . \square

3.2 A persistence property, uniform in model parameters

We strengthen the persistence result of Theorem 3 as follows: If system (1) – (2) deviates only slightly from a system where all species have the same growth rate function $\mu_0(S)$ and the same yield Y_0 , then the total population ultimately persists above a level which is both independent of the initial population composition, and of the growth rate functions and yield coefficients.

Theorem 5. *Let $\mu_0(S)$ be smooth, $\mu_0(0) = 0$, $\mu'_0(S) > 0$ for $S > 0$, and $\mu_0(1) > 1$, and let $Y_0 \in (0, 1]$. Then there exist $\varepsilon > 0$, $\Delta > 0$, and a forward invariant set $K \subset \{(x, S) \mid x, S \geq 0, 1^T x \geq \Delta\}$, such that for any solution $(x(t), S(t))$ of the system (1) – (2) with $\|\mu_i - \mu_0\|_{C^0} < \varepsilon$, $|Y_i - Y_0| < \varepsilon$ and $1^T x > 0$, there exists $\tau > 0$ such that $(x(t), S(t)) \in K$ for all $t > \tau$.*

Proof. By continuity of $\mu_0(\cdot)$, there exist $\delta \in (0, 1)$ and $\tilde{\lambda} > 0$ such that $\mu_0(S) \geq 1 + 2\tilde{\lambda}$ for all $S \geq \delta$. If, in addition, $\|\mu_i - \mu_0\|_{C^0} < \tilde{\lambda}$, we have that $\mu_i(S) \geq 1 + \tilde{\lambda}$ for all $S \geq \delta$ and for all i . Since $\delta < 1$, there exist sufficiently small positive numbers β and Δ_0 such that

$$\frac{1}{1 + 2\beta} - \Delta_0 \geq \delta.$$

Finally, we let $\varepsilon > 0$ be sufficiently small, so that $\varepsilon < \tilde{\lambda}$ and so that if $|Y_i - Y_0| < \varepsilon$ for all i , then $\mu_i(S) \left(\frac{Y_0}{Y_i} - 1\right) < \beta$ for all values of $S \in [0, 2]$ and i . By shifting time, if necessary, we will assume that $S(t) \in [0, 2]$ for all $t \geq 0$.

Define the auxiliary function $m = S + \frac{1}{Y_0}(1^T x)$, and observe that

$$\dot{m}(t) = 1 - S(t) - \frac{1}{Y_0} \sum_i \left(1 + \mu_i(S(t)) \left(\frac{Y_0}{Y_i} - 1\right)\right) x_i(t).$$

Since $\mu_i(S) \left(\frac{Y_0}{Y_i} - 1\right) < \beta$ for all S and i , we have the inequality

$$\dot{m}(t) \geq 1 - S(t) - \frac{1}{Y_0}(1 + \beta)(1^T x(t)) \geq 1 - (1 + \beta)S(t) - \frac{1}{Y_0}(1 + \beta)(1^T x(t)) = 1 - (1 + \beta)m(t).$$

In particular, there exists a $T > 0$ such that $m(t) \geq \frac{1}{1 + 2\beta}$ for all $t \geq T$. Moreover, the set

$$K_0 := \{(x, S) \mid x, S \geq 0, S + \frac{1}{Y_0}(1^T x) \geq \frac{1}{1 + 2\beta}\}$$

is forward invariant. Let $K_1 := \{(x, S) \in K_0 \mid 0 < 1^T x < Y_0 \Delta_0\}$. For any solution $(x(t), S(t)) \in K_1$, we have the following estimates:

$$S(t) \geq \frac{1}{1 + 2\beta} - \frac{1}{Y_0}(1^T x(t)) > \frac{1}{1 + 2\beta} - \Delta_0 \geq \delta,$$

and thus $\mu_i(S(t)) \geq 1 + \tilde{\lambda}$, which implies that

$$\dot{x}(t) \geq (\tilde{\lambda}I + T)x(t).$$

Since $1^T T = 0$ (the matrix T is compartmental), the above inequality implies that for all solutions in K_1 the inequality

$$1^T \dot{x}(t) \geq \tilde{\lambda}1^T x(t)$$

holds. Thus, all solutions starting in K_1 enter the forward invariant complementary set $K = \{(x, S) \in K_0 \mid 1^T x \geq \Delta\}$, where $\Delta := Y_0 \Delta_0 > 0$. This concludes the proof. \square

3.3 Proof of Theorem 1.

The proof is an application of Theorem 2.2 in [13].

First notice that if all $\mu_i(S)$ equal $\mu_0(S)$, and all Y_i equal Y_0 , then system (1) – (2) has a unique positive steady state (x_0^*, S_0^*) by Lemma 3 which is hyperbolic and locally asymptotically stable by Lemma 4. Moreover, all solutions with $x(0) \neq 0$ converge to (x_0^*, S_0^*) by Theorem 4.

By Theorem 5 and Lemma 1, there exist $\varepsilon > 0$ and $\Delta > 0$ such that whenever $\|\mu_i - \mu_0\|_{C^0} < \varepsilon$ and $|Y_i - Y_0| < \varepsilon$, all solutions of (1) – (2) with $x(0) \neq 0$ eventually enter the compact invariant set

$$D = K \cap L.$$

The conclusion now follows immediately from Theorem 2.2 in [13].

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