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Competition in the presence of a lethal external inhibitor

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Abstract

The study considers two organisms competing for a nutrient in an open system in the presence of an inhibitor (or toxicant). The inhibitor is input at a constant rate and is lethal to one competitor while being taken up by the other without harm. This is in contrast to previous studies, where the inhibitor decreases the reproductive rate of one of the organisms. The mathematical result of the lethal effect, modeled by a mass action term, is that the system cannot be reduced to a monotone dynamical system of one order lower as is common with chemostat-like problems. The model is described by four non-linear, ordinary differential equations and we seek to describe the asymptotic behavior as a function of the parameters of the system. Several global exclusion results are presented with mathematical proofs. However, in the case of coexistence, oscillatory behavior is possible and the study proceeds with numerical examples. The model is relevant to bioremediation problems in nature and to laboratory bio-reactors. © 2000 Elsevier Science Inc. All rights reserved.

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1. Introduction

The chemostat is one of the standard models of an open system in ecology. It is quite natural then that it should be used as a model for studying detoxification problems. For this, we have in mind two (realistically more than two) organisms competing for a nutrient in the presence of an inhibitor (toxicant). The inhibitor is detrimental to one of the organisms while the other can take

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it up with no deleterious effect. Thus, we think of the second organism as detoxifying the environment. From the standpoint of competition, the question is whether the detoxifying organism survives. The detoxification question is the level of the inhibitor left in the environment. Mathematically, both are questions of omega limit sets of a system of differential equations. The pioneering study in this direction is that of Lenski and Hattings [1]. A mathematical analysis of this was presented in [2]. We refer to this class of problems as external inhibitor problems. Although we have posed the biological question in terms of bioremediation, this problem is also relevant to biotechnology, where the chemostat is a laboratory model of a bioreactor and where the competitors may be plasmid-bearing (genetically altered) and plasmid-free organisms. The plasmid directs the manufacture of a product but it can be lost in reproduction creating a better competitor (one which does not carry the metabolic load imposed by the plasmid). To counter this, the plasmid can also be coded for antibiotic resistance and an antibiotic added to the nutrient input of the reactor. The basic assumption is that the inhibitor reduces the growth of the affected organism (which, in the chemostat, is assumed to be proportional to the nutrient uptake). Hsu et al. [3] have studied a model of competition between plasmid-bearing and plasmid-free organisms in the chemostat with an external inhibitor.

Competition between plasmid-bearing and plasmid-free organisms is a subject of considerable interest. The theoretical literature includes Hsu et al. [4], Lu and Haderler [5], Levin [6], Hsu and Luo [7], Macken et al. [8], Ryder and DiBiaso [9] and Stephanopoulos and Lapidus [10].

An alternative problem is where one competitor produces the inhibitor at some cost to its own growth. The biological evidence of this can be found in [6,11]. This problem was analyzed in [12] in the context of competition between plasmid-bearing and plasmid-free organisms. This is then called the internal inhibitor problem. It is not a detoxification problem.

Although the assumption that the inhibitor interferes with growth is realistic, it can also be the case that the inhibitor is lethal. Although this change seems slight from the biological perspective (increased death rather than decreased growth), it turns out to be mathematically significant. It precludes the use of one of the basic tools, a reduction of order through a conservation principle, to a monotone system. Moreover, mass action terms, quadratic terms, are more difficult to handle than the usual Michaelis–Menten responses of the standard chemostat. The internal inhibitor problem with a lethal inhibitor was treated by Hsu and Waltman [13].

Finally, there remains the case where the inhibitor is from an external source but is lethal to one competitor and not to the other which can take it up without harm. This problem is the subject of the current paper.

The goal, as with all such problems, is to determine the asymptotic behavior as a function of the parameters. While we are able to do that in a large portion of the parameter space, we cannot do it in all of it, and in a few cases, we resort to numerical simulations. Of these, the most interesting is the case of oscillatory behavior.

In Section 2, we present the model and discuss it in heuristic terms. In Section 3, we deal with preliminary material such as boundedness of solutions, the existence and stability of rest points, and the behavior of trajectories on certain lower-dimensional subspaces. The basic exclusion theorems are stated in Section 4. Section 5 deals with numerical simulations of cases with an interior equilibrium, where global results have not been rigorously established. The most interesting part is the existence of apparently periodic solutions. Section 6 contains a brief discussion of the results. The more demanding proofs are deferred to Appendix A.

2. The basic equations

We use the standard chemostat notation [14]. Let $S(t)$ denote the concentration of the nutrient at time t ; let $x(t)$ and $y(t)$ denote the concentrations of the competitors; finally, let $P(t)$ denote the concentration of the inhibitor. We will always let x denote the competitor affected by the inhibitor and y the competitor, which detoxifies the inhibitor. In the case where the inhibitor acts on the growth rate with a degree of inhibition $f(P)$, the model took the form

$$\begin{aligned} S' &= (S^{(0)} - S)D - \frac{x}{\beta_1} \frac{m_1 S}{a_1 + S} f(P) - \frac{y}{\beta_2} \frac{m_2 S}{a_2 + S}, \\ x' &= x \left(\frac{m_1 S}{a_1 + S} f(P) - D \right), \\ y' &= y \left(\frac{m_2 S}{a_2 + S} - D \right), \\ P' &= (P^{(0)} - P)D - \frac{\delta y P}{K + P}, \end{aligned} \tag{2.1}$$

$$S(0) \geq 0, \quad x(0) > 0, \quad y(0) > 0, \quad P(0) \geq 0.$$

$S^{(0)}$ is the input concentration of the nutrient, and $P^{(0)}$ is the input concentration of the inhibitor, both of which are assumed to be constant. D is the dilution rate of the chemostat. m_i, a_i , $i = 1, 2$ are the maximal growth rates of the competitors (without an inhibitor) and the Michaelis–Menten (or half saturation) constants, respectively, and β_i represent yield constants. These parameters, inherent properties of the organism, are measurable in the laboratory. δ and K play similar roles for the inhibitor, δ being the uptake by y and K being a half-saturation parameter. The function $f(P)$ represents the degree of inhibition of P on the growth rate (or uptake rate) of x .

Analysis of this model (essentially that of [1]) was the problem studied in [2]. To introduce a lethal inhibitor, the function f , which represents the effect of the inhibitor on growth (as written, on consumption, but growth and consumption are assumed proportional in the chemostat) is replaced by a mass action term involving the concentration of the inhibitor and the concentration of the x competitor. The constant of proportionality will be γ and all other parameters are as above. The mass action term is used typically to represent interactions that depend jointly on the concentrations. It is standard, for example, in the Lotka–Volterra models of predator prey interactions and was used by Levin [6] to model the lethal effect of a toxin on an organism. The model of the chemostat with a lethal inhibitor, which is the subject of this paper, then takes the form

$$\begin{aligned} S' &= (S^{(0)} - S)D - \frac{x}{\beta_1} \frac{m_1 S}{a_1 + S} - \frac{y}{\beta_2} \frac{m_2 S}{a_2 + S}, \\ x' &= x \left[\frac{m_1 S}{a_1 + S} - D - \gamma P \right], \\ y' &= y \left[\frac{m_2 S}{a_2 + S} - D \right], \\ P' &= (P^0 - P)D - \frac{\delta P}{K + P} y, \end{aligned} \tag{2.2}$$

$$S(0) \geq 0, \quad x(0) > 0, \quad y(0) > 0, \quad P(0) \geq 0.$$

It is convenient to scale the variables. Let $\bar{S} = S/S^0$, $\bar{x} = x/\beta_1 S^0$, $\bar{y} = y/(\beta_2 S^0)$, $\bar{P} = (P/P^0)$, $\bar{\delta} = \beta_2 S^0 \delta / DP^0$, $\bar{\gamma} = (P^0 \gamma) / D$, $\bar{m}_i = (m_i / D)$, $\bar{a}_i = (a_i / S^{(0)})$, $i = 1, 2$, $\bar{K} = K / P^0$, and $\bar{t} = Dt$. Making these changes and then dropping the bars yields the non-dimensional model

$$\begin{aligned}
 S' &= 1 - S - \frac{m_1 S}{a_1 + S} x - \frac{m_2 S}{a_2 + S} y, \\
 x' &= x \left[\frac{m_1 S}{a_1 + S} - 1 - \gamma P \right], \\
 y' &= y \left[\frac{m_2 S}{a_2 + S} - 1 \right], \\
 P' &= 1 - P - \frac{\delta P}{K + P} y.
 \end{aligned}
 \tag{2.3}$$

Eq. (2.3) is the model to be analyzed here.

Several parameters will be of interest. Define $\lambda_1, \lambda_2, \hat{\lambda}_1, \lambda_p$ as solutions of

$$\frac{m_1 \lambda_1}{a_1 + \lambda_1} = 1,
 \tag{2.4}$$

$$\frac{m_2 \lambda_2}{a_2 + \lambda_2} = 1,
 \tag{2.5}$$

$$\frac{m_1 \hat{\lambda}_1}{a_1 + \hat{\lambda}_1} = 1 + \gamma,
 \tag{2.6}$$

$$\frac{m_1 \lambda_p}{a_1 + \lambda_p} = 1 + \gamma P^*,
 \tag{2.7}$$

and, P^* as the positive root of

$$(1 - z)(K + z) = \delta z(1 - \lambda_2).
 \tag{2.8}$$

These parameters reflect break-even concentrations. λ_1 and λ_2 are the usual chemostat parameters reflecting the break-even concentrations of x and y without an inhibitor present. $\hat{\lambda}_1$ and λ_p represent the break-even concentrations of x at what we will show to be the maximum (limiting) behavior of the inhibitor and the minimum (limiting) behavior of the inhibitor, respectively. Three of the parameters are ordered,

$$\lambda_1 < \lambda_p < \hat{\lambda}_1.$$

Our results may be summarized by the claim that where λ_2 falls in this ordering will determine the outcome of the competition.

The break-even concentration of y does not depend on the inhibitor. Hence, the value of λ_2 has same meaning that it has in the usual chemostat. The three values that correspond to x represent its effectiveness as a competitor for three levels of inhibition – the new parameters λ_p and $\hat{\lambda}_1$ representing effectiveness at the minimal and maximal levels of inhibition. Thus, the usual intuitive interpretation of the comparison of λ -values (the lower value represents a better competitor)

remains but has been adjusted for the corresponding level of inhibition. For the chemostat with the inhibitor, coexistence is possible without having equal λ -values, a departure from the ordinary chemostat, where competitive exclusion prevails unless the λ -parameters are equal.

Since a conservation law reflecting the representation of (2.3) as nutrient equivalent is almost part of the definition of a chemostat, one may wonder what is different here? Actually, the conservation is present; it is just that all of the variables are not represented. Let the variables be the same as above, but label x as x_1 . Then, let x_2 denote the concentration of the “killed” (non-reproducing) organism. Model (2.3) takes the form

$$\begin{aligned} S' &= 1 - S - \frac{m_1 S}{a_1 + S}x - \frac{m_2 S}{a_2 + S}y, \\ x_1' &= x_1 \left[\frac{m_1 S}{a_1 + S} - 1 - \gamma P \right], \\ x_2' &= \gamma P x_1 - x_2, \\ y' &= y \left[\frac{m_2 S}{a_2 + S} - 1 \right], \\ P' &= 1 - P - \frac{\delta P}{K + P}y, \end{aligned} \tag{2.9}$$

(2.3) results by dropping the equation for x_2 since it does not affect the other variables. ($x_2(t)$ can be recovered by a quadrature.) In the tradition of the chemostat literature, one can define $z(t) = 1 - S(t) - x_1(t) - x_2(t) - y(t)$ to obtain

$$z'(t) = -z(t),$$

or $\lim_{t \rightarrow \infty} z(t) = 0$. Using the theory of asymptotically autonomous systems [15,16] (there is a trivial hypothesis to be checked), one obtains an equivalent model

$$\begin{aligned} x_1' &= x_1 \left[\frac{m_1(1 - x_1 - x_2 - y)}{a_1 + 1 - x_1 - x_2 - y} - 1 - \gamma P \right], \\ x_2' &= \gamma P x_1 - x_2, \\ y' &= y \left[\frac{m_2(1 - x_1 - x_2 - y)}{a_2 + 1 - x_1 - x_2 - y} - 1 \right], \\ P' &= 1 - P - \frac{\delta P}{K + P}y. \end{aligned} \tag{2.10}$$

Although (2.10) could be used in some of the proofs, we use only model (2.3). The general techniques of monotone dynamical systems [17] do not apply to either model.

3. Preliminary results

The form of the equations for x and y allows one to conclude that for positive initial conditions, a trajectory remains positive for all finite time. At $S = 0$, $S' = 1$, and at $P = 0$, $P' = 1$. Therefore, the positive cone in R^4 is positively invariant for (2.3).

Adding the first three equations yields

$$S' + x' + y' \leq 1 - S - x - y,$$

or, using a comparison theorem,

$$S(t) + x(t) + y(t) \leq 1 + ce^{-t}.$$

Thus, all three concentrations are bounded since each element of the sum is positive. Moreover, the coordinates of any omega limit point must satisfy $S + x + y \leq 1$.

Since $P(t)$ satisfies

$$P'(t) \leq 1 - P(t),$$

then

$$\limsup_{t \rightarrow \infty} P(t) \leq 1.$$

As a consequence, the right-hand side of (2.3) is bounded, so when one can show that the limit as t tends to infinity of a variable exists, then the limit of the time derivative is zero. This is used repeatedly in the arguments that follow.

One also has

$$\liminf_{t \rightarrow \infty} P(t) \geq P^*.$$

To see this, suppose that $\liminf_{t \rightarrow \infty} P(t) < P^*$. If $\lim_{t \rightarrow \infty} y(t)$ exists, then $\lim_{t \rightarrow \infty} S(t) = \lambda_2$, and the restriction of the coordinates of omega limit points requires that $\lim_{t \rightarrow \infty} y(t) \leq 1 - \lambda_2$. If $\lim_{t \rightarrow \infty} y(t)$ does not exist, then there exists τ_n such that $y'(\tau_n) = 0$ and $\lim_{n \rightarrow \infty} y(\tau_n) = \limsup_{t \rightarrow \infty} y(t)$. Then, $S(\tau_n) = \lambda_2$, and, as above, $\lim_{n \rightarrow \infty} y(\tau_n) \leq 1 - \lambda_2$.

Next, we show that $\liminf_{t \rightarrow \infty} P(t) \geq P^*$. If $\lim_{t \rightarrow \infty} P(t)$ exists, then from $\lim_{t \rightarrow \infty} P'(t) = 0$, it follows that $\lim_{t \rightarrow \infty} y(t)$ exists and $\lim_{t \rightarrow \infty} y(t) \leq 1 - \lambda_2$. From the definition of P^* , it follows that $\lim_{t \rightarrow \infty} P(t) \geq P^*$. If $\lim_{t \rightarrow \infty} P(t)$ does not exist, then there exists a sequence $\{t_n\}$ such that $P'(t_n) = 0$, and $\lim_{n \rightarrow \infty} P(t_n) = \liminf_{t \rightarrow \infty} P(t) = P_*$. Then, $((1 - P_*)(K + P_*))/\delta P_* = y(t_n) \leq 1 - \lambda_2$, for t large, so $P_* \geq P^*$ by the definition of P^* .

In particular, for any $\epsilon > 0$, $P^* - \epsilon \leq P(t) \leq 1 + \epsilon$ if t is sufficiently large.

The above arguments are sufficient to show that any trajectory is in the region Q defined by

$$Q = \{0 \leq S \leq 1, 0 \leq x \leq 1, 0 \leq y \leq 1, P^* - \epsilon \leq P \leq 1 + \epsilon\}$$

for any $\epsilon > 0$ and for t sufficiently large.

We turn now to the equilibrium or rest points of the system. To be meaningful, the coordinates of a rest point need to be non-negative. In what follows, when we say ‘exists’ we intend ‘exists and is meaningful’. The equilibrium $\bar{E}_0 \equiv (1, 0, 0, 1)$ always exists. In addition, the equilibria $\bar{E}_1 \equiv (\hat{\lambda}_1, \hat{x}, 0, 1)$ and $\bar{E}_2 \equiv (\lambda_2, 0, 1 - \lambda_2, P^*)$ exist whenever $\hat{\lambda}_1 < 1$ and $\lambda_2 < 1$, respectively, where

$$\hat{x} = \frac{1 - \hat{\lambda}_1}{1 + \gamma}.$$

By calculating the variational matrix of system (2.3) and evaluating it at each equilibrium, the local stability of the equilibria is obtained.

Lemma 3.1.

- The equilibrium \bar{E}_0 is locally stable if $\hat{\lambda}_1 > 1$ and $\lambda_2 > 1$. It is unstable if either inequality is reversed.
- The equilibrium \bar{E}_1 is locally stable if \bar{E}_1 exists and $\hat{\lambda}_1 < \lambda_2$. It is unstable if the inequality is reversed.
- The equilibrium \bar{E}_2 is locally stable if \bar{E}_2 exists and $\lambda_2 < \lambda_p$. It is unstable if the inequality is reversed.

The proof is a straight-forward computation, which we defer to Appendix A. An interior equilibrium is also possible.

Theorem 3.1. *If $\lambda_2 < 1$, λ_p exists, and either*

- (1) $\lambda_p < \lambda_2$, $\hat{\lambda}_1$ does not exist, or
- (2) $\lambda_p < \lambda_2 < \hat{\lambda}_1$

holds, then the equilibrium $\bar{E}_c \equiv (\lambda_2, \bar{x}_c, \bar{y}_c, \bar{P}_c)$ exists, where

$$\begin{aligned} \bar{P}_c &\equiv \frac{1}{\gamma} \left(\frac{m_1 \lambda_2}{a_1 + \lambda_2} - 1 \right), \\ \bar{y}_c &\equiv \frac{(1 - \bar{P}_c)(K + \bar{P}_c)}{\delta \bar{P}_c}, \\ \bar{x}_c &\equiv \frac{1 - \lambda_2 - \bar{y}_c}{1 + \gamma \bar{P}_c}. \end{aligned} \tag{3.1}$$

These conditions require that \bar{E}_1 and \bar{E}_2 exist, \bar{E}_0 repels, and \bar{E}_1 and \bar{E}_2 are unstable. The necessary computations are given in Appendix A. The stability of E_c , when it exists, is a key factor in our analysis for it determines if the system oscillates. The approach is through the Route–Hurwitz criterion.

To state a precise result, we need to introduce the variational matrix for (2.3) evaluated at E_c . Write \bar{M}_c as

$$\bar{M}_c \equiv \begin{bmatrix} m_{11} & m_{12} & -1 & 0 \\ m_{21} & 0 & 0 & m_{24} \\ m_{31} & 0 & 0 & 0 \\ 0 & 0 & m_{43} & m_{44} \end{bmatrix},$$

where

$$m_{11} = -1 - \frac{m_1 a_1}{(a_1 + \lambda_2)^2} \bar{x}_c - \frac{m_2 a_2}{(a_2 + \lambda_2)^2} \bar{y}_c,$$

$$m_{12} = -\frac{m_1 \lambda_2}{a_1 + \lambda_2},$$

$$m_{21} = \frac{m_1 a_1}{(a_1 + \lambda_2)^2} \bar{x}_c,$$

$$m_{24} = -\gamma \bar{x}_c,$$

$$m_{31} = \frac{m_2 a_2}{(a_2 + \lambda_2)^2} \bar{y}_c,$$

$$m_{43} = -\frac{\delta \bar{P}_c}{K + \bar{P}_c},$$

$$m_{44} = -1 - \frac{\delta K}{(K + \bar{P}_c)^2} \bar{y}_c.$$

Obviously m_{11} , m_{12} , m_{24} , m_{43} , m_{44} are negative; m_{21} and m_{31} are positive. To determine the local stability, we apply the Routh–Hurwitz criterion; a direct application of Coppel [18, p. 158], yields the following criteria:

Lemma 3.2. \bar{E}_c is locally asymptotic stable if and only if

$$\begin{aligned} A_4 > 0, \quad A_2 > 0, \quad A_1 > 0, \\ A_3(A_1 A_2 - A_3) > A_1^2 A_4, \end{aligned} \tag{3.2}$$

where the characteristic polynomial of \bar{M}_c is

$$f(\lambda) = \lambda^4 + A_1 \lambda^3 + A_2 \lambda^2 + A_3 \lambda + A_4,$$

with

$$\begin{aligned} A_1 &= -m_{11} - m_{44}, \\ A_2 &= m_{31} - m_{12} m_{21} + m_{11} m_{44}, \\ A_3 &= m_{44} (m_{12} m_{21} - m_{31}), \\ A_4 &= -m_{12} m_{24} m_{43} m_{31}. \end{aligned} \tag{3.3}$$

Proof. The first three inequalities in (3.2) are trivial; for the last, a simple computation shows that

$$A_3(A_1 A_2 - A_3) = -m_{11} A_3 (A_2 + m_{44}^2) > 0.$$

If this quantity is $> A_1^2 A_4$, then the rest point is locally asymptotically stable. If it is $< A_1^2 A_4$, then the rest point is unstable. Both cases occur and we give examples in Section 5.

There are two invariant subspaces given by $x = 0$ and $y = 0$. We consider the dynamical systems generated by (2.3) restricted to these sets.

Consider the set $y \equiv 0$. System (2.3) becomes

$$\begin{aligned} \dot{S} &= 1 - S - \frac{m_1 S}{a_1 + S} x, \\ \dot{x} &= \left[\frac{m_1 S}{a_1 + S} - 1 - \gamma P \right] x, \\ \dot{P} &= 1 - P. \end{aligned} \tag{3.4}$$

Clearly, $\lim_{t \rightarrow \infty} P(t) = 1$, so we consider the limiting system

$$\begin{aligned}\dot{S} &= 1 - S - \frac{m_1 S}{a_1 + S} x, \\ \dot{x} &= \left[x \frac{m_1 S}{a_1 + S} - 1 - \gamma \right].\end{aligned}\tag{3.5}$$

If $\hat{\lambda}_1 < 1$, then it follows from [19] that

$$\lim_{t \rightarrow \infty} S(t) = \hat{\lambda}_1 \quad \text{and} \quad \lim_{t \rightarrow \infty} x(t) = \hat{x}.$$

Using the theory of asymptotic autonomous systems, [14, Appendix F] and [15,16], we obtain

$$\lim_{t \rightarrow \infty} (S(t), x(t), P(t)) = (\hat{\lambda}_1, \hat{x}, 1).$$

In a similar way, for $x = 0$, we obtain

$$\lim_{t \rightarrow \infty} (S(t), y(t), P(t)) = (\lambda_2, 1 - \lambda_2, P^*)$$

if $\lambda_2 < 1$.

When one is able to establish that $\lim_{t \rightarrow \infty} x(t) = 0$ or $\lim_{t \rightarrow \infty} y(t) = 0$ for (2.3), then trajectories of the full system will be attracted to these rest points by the theory cited above.

It was noted above that for the interior equilibrium to exist, E_0 , E_1 and E_2 were unstable. In this case, the stable manifold of E_0 is the two-dimensional set, $(S, 0, 0, P)$; for E_1 and E_2 it is the respective three-dimensional sets given by $x = 0$ or $y = 0$. In each case, the unstable manifold has points in the interior of the positive cone and by the Butler–Magehee Lemma (using the boundedness of the omega limit set), no trajectory in the interior has such rest points as omega limit points. Moreover, the stable manifolds described above preclude a cyclic orbit on the boundary. This is a key hypothesis in the general theory of persistence. See the survey articles [20,21] or the research articles [22–25]. In particular, the results of Thieme [25] allow one to conclude that system (2.3) is uniformly persistent under these conditions. The nature of the limit set is explored in Section 5.

4. Extinction

We now turn to results on extinction. The results presented are global in the sense that all solutions of (2.3) tend to an equilibrium state. The first theorem deals with cases where one competitor is not viable in the environment. The first part of the theorem excludes y . This means that the environment is not detoxified, a negative result. The second part excludes x , and detoxifies the environment to the maximal extent possible.

Theorem 4.1.

- (i) If $\lambda_2 > 1$, then $\lim_{t \rightarrow \infty} y(t) = 0$. Moreover, if $\hat{\lambda}_1 < 1$, \bar{E}_1 is globally asymptotically stable.
- (ii) If $\lambda_1 > 1$ then $\lim_{t \rightarrow \infty} x(t) = 0$. Moreover, if $\lambda_2 < 1$, \bar{E}_2 is globally asymptotically stable.

The proof of Theorem 4.1 is referred to Appendix A.

The next theorem provides sufficient conditions to exclude x and detoxify the environment in the case that both competitors are viable in an inhibitor-free environment.

Theorem 4.2. *If $\lambda_2 < 1$ and either*

- (i) $\lambda_p > 1$, or
- (ii) $\lambda_2 < \lambda_p < 1 < \hat{\lambda}_1$, or
- (iii) $\lambda_2 < \lambda_p < \hat{\lambda}_1 < 1$,

then \bar{E}_2 is globally asymptotically stable.

In condition (i), x is not viable at the minimal level of the inhibitor (λ_p does not exist), in (ii), x is viable at the minimal level of the inhibitor, but not at the maximal level (λ_p exists but $\hat{\lambda}_1$ does not) and in (iii), x is viable at the maximal level (λ_p and $\hat{\lambda}_1$ exist).

In (i), y is viable ($\lambda_2 < 1$); in (ii) and (iii), y is not only viable, but is a better competitor. The proof which uses a Liapunov argument is deferred to Appendix A.

When $\lambda_p < \lambda_2$ and $\hat{\lambda}_1$ does not exist, and for $\lambda_p < \lambda_2 < \hat{\lambda}_1$, an interior equilibrium exists (Theorem 3.2), so there can be no extinction result. One anticipates that if $\lambda_2 > \hat{\lambda}_1$, that $\lim_{t \rightarrow \infty} y(t) = 0$ (y becomes extinct). The following theorem is slightly less than that. We note that in the proof, $\lambda_2 > \hat{\lambda}_1 + (\gamma/1 + \gamma)$ is used only to prove that the limit exists. For that reason, we divide the proof, deferred to Appendix A, into three lemmas.

Theorem 4.3. *If $1 > \lambda_2 > \hat{\lambda}_1 + \gamma/(1 + \gamma)$, then $\lim_{t \rightarrow \infty} y(t) = 0$.*

5. Behavior of trajectories with an interior rest point

As noted earlier, there can be an interior rest point and when this occurs, the system is uniformly persistent. The stability of the rest point can be obtained with a somewhat complicated computation, (3.2). We present here three examples to show the complexity of the behavior of the system. In the sense of a detoxification problem, the existence of an interior rest point represents a discouraging outcome, but may be the best obtainable. All of the computations in this section were performed with Mathematica.

The first example is of damped oscillations. In this case, the rest point is stable. The computations indicate that it is globally stable but we do not have a rigorous proof of this. The relevant parameters are: $a_1 = 0.06$, $a_2 = 1.0$, $m_1 = 4.0$, $m_2 = 5.0$, $\gamma = 4.0$, $K = 1.3$, $\delta = 5.0$. The parameters are chosen to illustrate the phenomena and are not meant to be relevant to any meaningful problem. The interior rest point has coordinates $(S, x, y, P) = (0.25, 0.149, 0.216, 0.643)$ and the computation in (3.2) indicates that it is stable.

The time course is shown in Fig. 1. Next, we plot the trajectories in (S, x, y) coordinates in Fig. 2. Since $\lim_{t \rightarrow \infty} P(t)$ exists, this can be thought of as the plot of an asymptotically limiting system.

If the rest point becomes unstable, then the orbit must leave a neighborhood of the rest point, but because of the uniform persistence, must remain in the interior of the positive cone. Since the system is four-dimensional, the orbits could be very complicated. However, our simulations show simple limit cycles. The parameters are as above except that $a_1 = 0.03$. The coordinates of the interior rest point are (in the same order) $(0.25, 0.140, 0.296, 0.556)$. The plot sequence is as above,

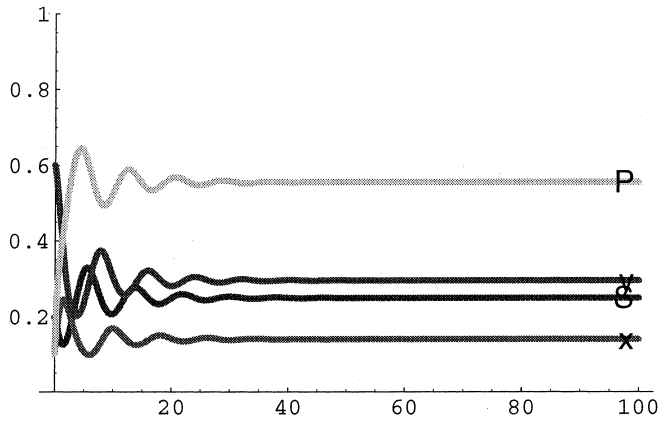


Fig. 1. Time course.

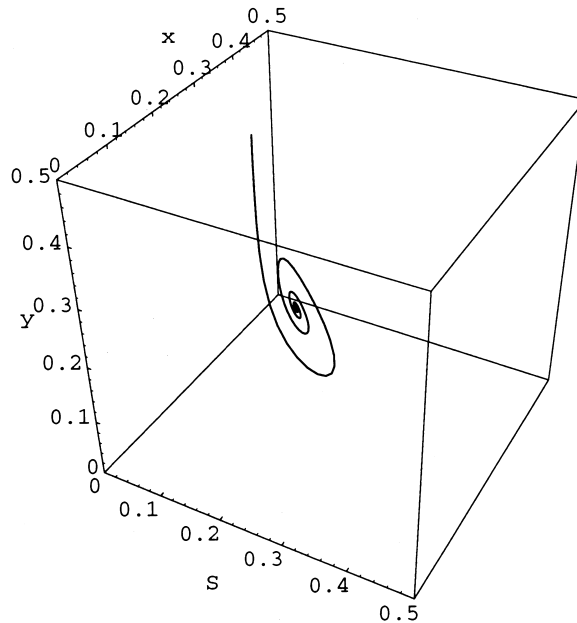


Fig. 2. Location of the spiral in three dimensions.

the time course in Fig. 3, followed by the location in (S, x, y) space, Fig. 4. The orbit is shown in R^3 even though this is not an invariant set since $P(t)$ is oscillatory.

The interior rest point has lost its stability and a Hopf bifurcation has occurred. The parameter that we have chosen to vary for illustrative purposes is convenient but not the most meaningful one. In the laboratory model, the experimenter can vary D , S^0 or P^0 . In Section 6, we vary two of these to present an operating diagram which could be used to determine the operating parameters of the system. The global stability question remains open.

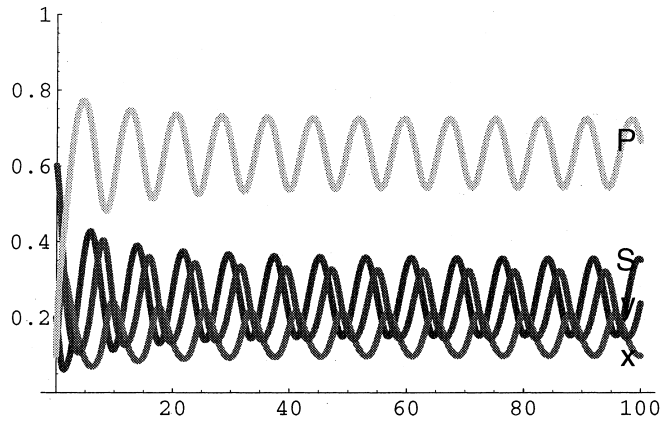


Fig. 3. Time course.

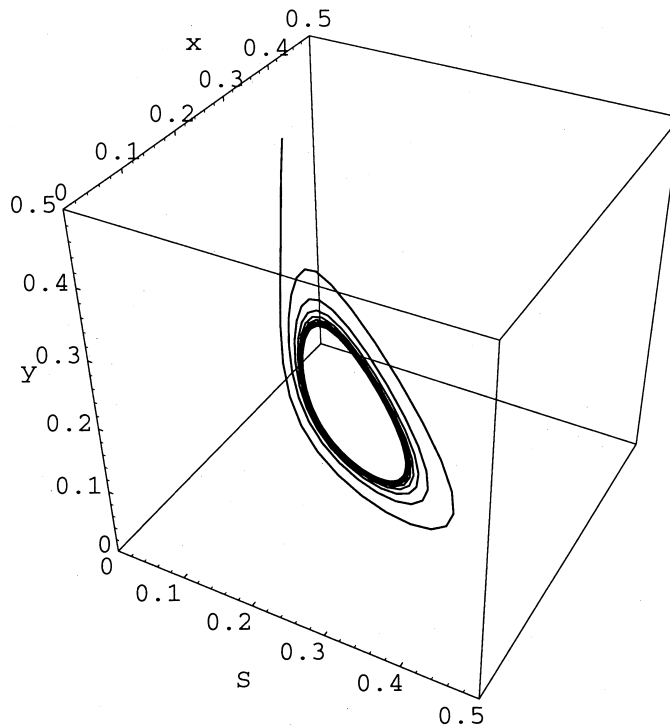


Fig. 4. Location of the limit cycle in three dimensions.

In the examples presented, the level of the inhibitor is relatively high. One might suspect that if there is an interior rest point, that is x is able to exist, that this will always be the case. We present the time course of a simple example with parameters as above except that $a_1 = 0.3$, $k = 0.3$ and $\delta = 3.0$. The inhibitor is reduced to about 20% of the input concentration even though x survives (Fig. 5).

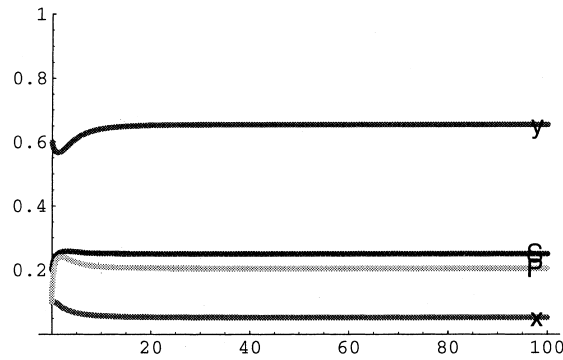


Fig. 5. Time course.

6. Discussion

We have considered competition in a chemostat, a model open system, in the presence of an inhibitor that affects one of the competitors but is removed by the other. The interesting case, of course, is where the stronger, natural competitor is the one affected by the inhibitor. This problem is important in ecology for the study of models of detoxification and in biotechnology, where inhibitors are used to control the effects of plasmid loss in genetically altered organisms (the plasmid-free organism is presumably the better competitor). The object of the study is to classify the outcomes of the competition in terms of the parameters of the system.

The basic model was scaled to make the concentrations non-dimensional and to change the nutrient and inhibitor input concentrations and the dilution rate to one, thereby reducing the number of parameters. This means that the results presented here are given in terms of a fixed environment. However, the system can be ‘unscaled’ to yield conditions in terms of the original parameters. The rest points were located and their (local) stability obtained by linearization. These can be summarized in Table 1.

The major mathematical results were extinction theorems, which provide conditions for the elimination of one of the competitors. The conclusions in this case were global and were obtained by dynamical system arguments (Table 2).

When the interior rest point existed, the system was shown to be uniformly persistent, which means that the competitors coexist. No information could be proved about the nature of the attractor. In this case, we used numerical simulations to study the model.

Table 1
Local stability of rest points

Point	Existence	Stability
E_0	Always	$\hat{\lambda}_1 > 1, \lambda_2 > 1$
E_1	$\hat{\lambda}_1 < 1$	$\hat{\lambda}_1 < \lambda_2$
E_2	$\lambda_2 < 1$	$\lambda_2 < \lambda_p$
E_c	$\lambda_p < \lambda_2 < 1$ and $\hat{\lambda}_1$ does not exist or $\lambda_2 < \hat{\lambda}_1$	Given by Routh–Hurwitz

Table 2
Global stability of boundary rest points (extinction)

Point	Conditon	Method of proof
E_0	$\hat{\lambda}_1 > 1, \lambda_2 > 1$	Comparison theorems
E_1	$\lambda_1 < \lambda_p < \hat{\lambda}_1 < 1 < \lambda_2$	Fluctuation analysis
	$1 > \lambda_2 > \hat{\lambda}_1 + (\gamma/(1 + \gamma))$	Fluctuation analysis
E_2	$\lambda_2 < 1, \lambda_1 > 1$	Fluctuation analysis
	$\lambda_2 < 1, \lambda_2 < \lambda_p < \hat{\lambda}_1$	Liapunov function

The most interesting case occurred when the interior rest point was unstable. The numerical studies showed clear evidence of an attracting limit cycle, created when the rest point changed from a stable to an unstable spiral point (a Hopf bifurcation). Rigorous mathematical analysis of this case remains open for further study. In the case of the bioreactor, knowledge of the competitive outcomes in terms of the original parameters is important because it can indicate where the reactor can be operated in order to achieve the desired outcome. For detoxification problems, it has predictive value for determining the effectiveness of a prescribed course of action. The selection of the organisms is, in mathematical terms, the selection the parameters m_i and a_i . For a bioreactor, the operator also controls the input concentrations and the dilution rate. To exhibit the potential usefulness of our results, we present an ‘operating diagram’. Fix all parameters except the input concentration of the inhibitor and the dilution rate (controlled by the pump speed). The theorems then separate the plane into regions of competitive exclusion and coexistence. The engineer can then choose to operate the reactor in a region that produces the desired outcome. Such a diagram is presented in Fig. 6. The results of course apply to the unscaled equations, (2.2). The parameters need to be reinterpreted but they still are break-even concentrations. In the unscaled model, these are solutions of the following equations:

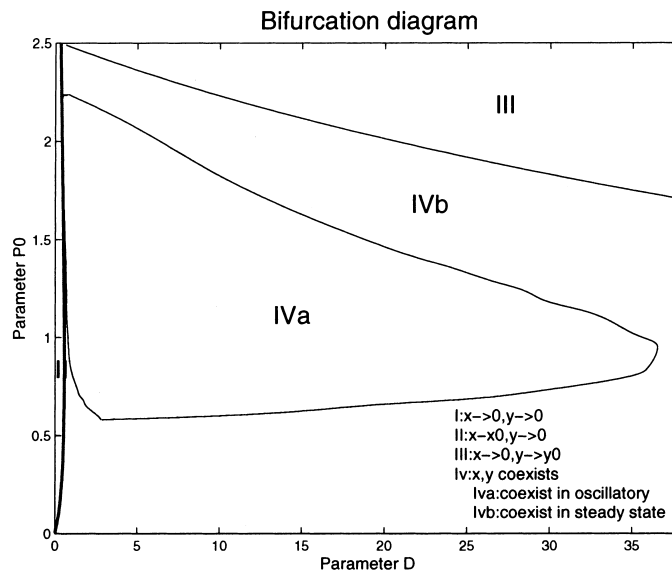


Fig. 6. Time course.

$$\frac{m_1 \lambda_1}{a_1 + \lambda_1} = D, \tag{6.1}$$

$$\frac{m_2 \lambda_2}{a_2 + \lambda_2} = D, \tag{6.2}$$

$$\frac{m_1 \hat{\lambda}_1}{a_1 + \hat{\lambda}_1} = D + \gamma, \tag{6.3}$$

$$\frac{m_1 \lambda_p}{a_1 + \lambda_p} = D + \gamma P^*, \tag{6.4}$$

where now P^* as the positive root of

$$(P^0 - z)(K + z)D = \delta z(1 - \lambda_2). \tag{6.5}$$

To expand the diagram, we have chosen $\beta_1 = \beta_2 = \beta = 10^2$. The major import of this is that applying the comparison theorem in Section 3 yields that

$$S(t) + \frac{x(t)}{\beta} + \frac{y(t)}{\beta} \leq 1 + ce^{-t}$$

and the coordinates of the rest points have changed. Locating the coordinates of P^0 and D in Fig. 6 yields the resulting asymptotic behavior.

Appendix A. Proofs and computations

Proof of Lemma 3.1. The variational matrices at \bar{E}_0 , \bar{E}_1 and \bar{E}_2 are

$$\bar{M}_0 \equiv \begin{bmatrix} -1 & -\frac{m_1}{a_1 + 1} & -\frac{m_2}{a_1 + 1} & 0 \\ 0 & \frac{m_1}{a_1 + 1} - 1 - \gamma & 0 & 0 \\ 0 & 0 & \frac{m_2}{a_2 + 1} - 1 & 0 \\ 0 & 0 & \frac{-\delta}{K + 1} & -1 \end{bmatrix},$$

$$\bar{M}_1 \equiv \begin{bmatrix} -1 - \frac{m_1 a_1}{(a_1 + \hat{\lambda}_1)^2} \hat{x} & -1 - \gamma & \frac{-m_2 \hat{\lambda}_1}{a_2 + \hat{\lambda}_1} & 0 \\ \frac{m_1 a_1}{(a_1 + \hat{\lambda}_1)^2} \hat{x} & 0 & 0 & -\gamma \hat{x} \\ 0 & 0 & \frac{m_2 \hat{\lambda}_1}{a_2 + \hat{\lambda}_1} - 1 & 0 \\ 0 & 0 & \frac{-\delta}{K + 1} & -1 \end{bmatrix},$$

and

$$\bar{M}_2 \equiv \begin{bmatrix} -1 - \frac{m_2 a_2 (1 - \lambda_2)}{(a_2 + \lambda_2)^2} & -\frac{m_1 \lambda_2}{a_1 + \lambda_2} & -1 & 0 \\ 0 & \frac{m_1 \lambda_2}{a_1 + \lambda_2} - 1 - \gamma P^* & 0 & 0 \\ \frac{m_2 a_2}{(a_2 + \lambda_2)^2} (1 - \lambda_2) & 0 & 0 & 0 \\ 0 & 0 & -\frac{\delta P^*}{K + P^*} - 1 & -\frac{\delta K}{(K + P^*)^2} (1 - \lambda_2) \end{bmatrix}.$$

The corresponding eigenvalues are

$$-1, \quad -1, \quad \frac{m_1}{a_1 + 1} - 1 - \gamma \quad \text{and} \quad \frac{m_2}{a_2 + 1} - 1$$

for \bar{M}_0 ;

$$-1, \quad \frac{m_2 \hat{\lambda}_1}{a_2 + \hat{\lambda}_1} - 1$$

and

$$-\frac{1}{2} - \frac{m_1 a_1}{2(a_1 + \hat{\lambda}_1)^2} \hat{x} \pm \frac{1}{2} \left[\left(1 + \frac{m_1 a_1}{(a_1 + \hat{\lambda}_1)^2} \hat{x} \right)^2 - \frac{4m_1 a_1 (1 + \gamma)}{(a_1 + \hat{\lambda}_1)^2} \hat{x} \right]^{1/2}$$

for \bar{M}_1 ;

$$-1, \quad -1 - \frac{\delta K (1 - \lambda_2)}{(K + P^*)^2}, \quad \frac{m_1 \lambda_2}{a_1 + \lambda_2} - 1 - \gamma P^*, \quad \text{and} \quad -\frac{m_2 a_2 (1 - \lambda_2)}{(a_2 + \lambda_2)^2}$$

for \bar{M}_2 , respectively. Hence, the Lemma follows.

Proof of Theorem 3.1. First, consider the case (1). Since

$$\frac{m_1 \lambda_2}{a_1 + \lambda_2} < \frac{m_1}{a_1 + 1} < 1 + \gamma,$$

$\bar{P}_c < 1$, and therefore one has that $y_c > 0$. From

$$\lambda_2 > \lambda_p, \quad \frac{m_1 \lambda_2}{a_1 + \lambda_2} > 1 + \gamma P^*,$$

$\bar{P}_c > P^*$ follows. This implies that

$$\bar{y}_c \equiv \frac{1 - \bar{P}_c}{\delta \bar{P}_c / (K + \bar{P}_c)} < \frac{1 - P^*}{\delta P^* / (K + P^*)} = 1 - \lambda_2.$$

Then $\bar{x}_c > 0$. And it is easy to verify that

$$\begin{aligned} \lambda_2 + \bar{x}_c + \bar{y}_c &= \lambda_2 + \frac{1 - \lambda_2 - \bar{y}_c}{1 + \gamma \bar{P}_c} + \bar{y}_c \\ &= \frac{1 + \gamma \bar{P}_c (\lambda_2 + \bar{y}_c)}{1 + \gamma \bar{P}_c} \\ &\leq \frac{1 + \gamma \bar{P}_c \cdot 1}{1 + \gamma \bar{P}_c} = 1. \end{aligned}$$

Now, consider case (2). Since

$$\begin{aligned} \lambda_2 &< \hat{\lambda}_1, \\ \frac{m_1 \lambda_2}{a_1 + \lambda_2} &< \frac{m_1 \hat{\lambda}_1}{a_1 + \hat{\lambda}_1} = 1 + \gamma, \end{aligned}$$

we have $\bar{P}_c < 1$. The others can be obtained in similar way.

Proof of Theorem 4.1. (i) If $\lim_{t \rightarrow \infty} y(t)$ exists and is not zero, then $\lim_{t \rightarrow \infty} S(t) = \lambda_2$, which is a contradiction since $\lambda_2 > 1$. Suppose $\liminf_{t \rightarrow \infty} y(t) < \limsup_{t \rightarrow \infty} y(t)$. Since $y(t)$ is not monotone and is smooth, there is a sequence $\{t_k\}$, $t_k \rightarrow \infty$ as $k \rightarrow \infty$ such that $y'(t_k) = 0$, and $\lim_{t \rightarrow \infty} y(t_k) = \limsup_{t \rightarrow \infty} y(t) > 0$. (This is sometimes called the fluctuation lemma.) Then, $\lim_{k \rightarrow \infty} [m_2 S(t_k)/(a_2 + S(t_k)) - 1] = 0$, or $\lim_{k \rightarrow \infty} S(t_k) = \lambda_2 > 1$, a contradiction since no omega limit point of (2.3) can have an S -component greater than one. Thus, the omega limit set lies in the plane $y = 0$.

If, in addition, $\hat{\lambda}_1 < 1$, it follows that $\lim_{t \rightarrow \infty} (S(t), x(t), P(t)) = (\hat{\lambda}_1, \hat{x}, 1)$ for all trajectories in the invariant set $y = 0$. (ii) Part (ii) is similar. Choose $\{t_k\}$ so that $x'(t_k) = 0$ and $\lim_{k \rightarrow \infty} x(t_k) = \limsup_{t \rightarrow \infty} x(t) > 0$. With arguments as above, we have that

$$1 + \gamma \lim_{k \rightarrow \infty} P(t_k) = \lim_{k \rightarrow \infty} \frac{m_1 S(t_k)}{a_1 + S(t_k)} \leq \frac{m_1}{1 + a_1} < 1,$$

a contradiction. Hence, $\lim_{t \rightarrow \infty} x(t) = 0$. Moreover, if $\lambda_2 < 1$, then

$$\lim_{t \rightarrow \infty} (S(t), y(t), P(t)) = (\lambda_2, 1 - \lambda_2, P^*).$$

Proof of Theorem 4.2. Consider the Liapunov function,

$$V(S, x, y, P) = \int_{\lambda_2}^S \left(1 - \frac{a_2 + \eta}{m_2 \eta} \right) d\eta + cx + \int_{1-\lambda_2}^y \frac{\eta - 1 - \lambda_2}{\eta} d\eta, \tag{A.1}$$

where c is a positive number to be chosen below. It is obvious that

$$V(S, x, y, P) \in C^1(\mathfrak{R}_+^4, \mathfrak{R}),$$

$$V(\lambda_2, 0, 1 - \lambda_2, P) = 0 \quad \text{for all } P$$

and that

$$V(S, x, y, P) > 0 \quad \text{for } (S, x, y, P) \in Q - \{\bar{E}_2\}.$$

We seek a positive number c such that $\dot{V} \leq 0$. Compute \dot{V} as

$$\begin{aligned} \dot{V} &= \left(1 - \frac{a_2 + S}{m_2 S}\right) \dot{S} + c\dot{x} + \frac{y - 1 + \lambda_2}{y} \dot{y} \\ &= \frac{(m_2 S / (a_2 + S)) - 1}{(m_2 S / (a_2 + S))} \left(1 - S - \frac{m_1 S}{a_1 + S} x - \frac{m_2 S}{a_2 + S} y\right) \\ &\quad + c \left(\frac{m_1 S}{a_1 + S} - 1 - \gamma P\right) x + (y - 1 + \lambda_2) \left(\frac{m_2 S}{a_2 + S} - 1\right) \\ &= \frac{(a_2 + S)(1 - S)}{m_2 S} \left(\frac{m_2 S}{a_2 + S} - 1\right) - \frac{m_1(a_2 + S)}{m_2(a_1 + S)} \left(\frac{m_2 S}{a_2 + S} - 1\right) x \\ &\quad + c \left(\frac{m_1 S}{a_1 + S} - 1 - \gamma P\right) x - (1 - \lambda_2) \left(\frac{m_2 S}{a_2 + S} - 1\right) \\ &= \left[\frac{(a_2 + S)(1 - S)}{m_2 S} \left(\frac{m_2 S}{a_2 + S} - 1\right) - (1 - \lambda_2) \left(\frac{m_2 S}{a_2 + S} - 1\right) \right] \\ &\quad + \left[c \left(\frac{m_1 S}{a_1 + S} - 1 - \gamma P\right) - \frac{m_1(a_2 + S)}{m_2(a_1 + S)} \left(\frac{m_2 S}{a_2 + S} - 1\right) \right] x, \end{aligned}$$

which we write as

$$\dot{V} = A(S) + B(S, P)x, \tag{A.2}$$

where

$$A(S) = \left(\frac{m_2 S}{a_2 + S} - 1\right) \left[\frac{(a_2 + S)(1 - S)}{m_2 S} - (1 - \lambda_2) \right],$$

and

$$B(S, P) = \left[c \left(\frac{m_1 S}{a_1 + S} - 1 - \gamma P\right) - \frac{m_1(a_2 + S)}{m_2(a_1 + S)} \left(\frac{m_2 S}{a_2 + S} - 1\right) \right].$$

We calculate the square bracket in $A(S)$, using the definition of λ_2 , as

$$\begin{aligned} &= \frac{(a_2 + S)(1 - S)}{m_2 S} - (1 - \lambda_2) \\ &= \frac{1}{m_2 S} [(a_2 + S)(1 - S) - (1 - \lambda_2)m_2 S] \\ &= \frac{(S + m_2 - 1)(\lambda_2 - S)}{m_2 S}. \end{aligned}$$

Since, for $S > \lambda_2$, $m_2 S / (a_2 + S) - 1 > 0$, so that

$$\frac{(S + m_2 - 1)(\lambda_2 - S)}{m_2 S} < 0,$$

and for $S < \lambda_2$, $m_2 S / (a_2 + S) - 1 < 0$, so that

$$\frac{(S + m_2 - 1)(\lambda_2 - S)}{m_2 S} > 0.$$

Hence,

$$A(S) \leq 0, \quad 0 \leq S \leq 1. \tag{A.3}$$

To estimate $B(S, P)$, we note that for any $\epsilon > 0$ and t sufficiently large,

$$B(S, P) \leq \hat{B}(S), \tag{A.4}$$

where

$$\hat{B}(S) = c \left(\frac{m_1 S}{a_1 + S} - 1 - \gamma P^* + \gamma \epsilon \right) - \frac{m_1(a_2 + S)}{m_2(a_1 + S)} \left(\frac{m_2 S}{a_2 + S} - 1 \right). \tag{A.5}$$

In case (i), choose ϵ such that

$$\epsilon < \frac{1}{\gamma} \left[1 + \gamma P^* - \frac{m_1}{a_1 + 1} \right].$$

Then,

$$\frac{m_1 S}{a_1 + S} - 1 - \gamma P^* + \gamma \epsilon < 0,$$

and it is sufficient to consider the case $S(t) \leq \lambda_2$ for $B(S) < 0$ for all c . Otherwise, the second factor is negative.

Let

$$U(S) = \frac{m_1(a_2 + S)}{m_2(a_1 + S)} \left(\frac{m_2 S}{a_2 + S} - 1 \right),$$

and we seek to find $\min_{0 \leq S \leq \lambda_2} U(S)$. Since

$$\begin{aligned} \dot{U}(S) &= \frac{m_1}{m_2} \cdot \frac{a_1 - a_2}{(a_1 + S)^2} \left(\frac{m_2 S}{a_2 + S} - 1 \right) + \frac{m_1(a_2 + S)}{m_2(a_1 + S)} \cdot \frac{m_2 a_2}{(a_2 + S)^2} \\ &= \frac{m_1}{m_2(a_1 + S)^2(a_2 + S)} [(a_1 - a_2)(m_2 S - a_2 - S) + m_2 a_2(a_1 + S)] \\ &= \frac{m_1}{m_2(a_1 + S)^2(a_2 + S)} [(m_2 - 1)a_1 + a_2] S + a_2^2 + a_1 a_2(m_2 - 1) \\ &> 0, \end{aligned}$$

we have

$$\min_{0 \leq S \leq \lambda_2} U(S) = U(0) = -\frac{m_1 a_2}{m_2 a_1}.$$

Therefore, the choice

$$c = \frac{m_1 a_2}{m_2 a_1 (1 + \gamma P^* - (m_1 / (a_1 + 1)) - \gamma \epsilon)},$$

yields

$$c \left(\frac{m_1 S}{a_1 + S} - 1 - \gamma P^* + \gamma \epsilon \right) \leq -\frac{m_1 a_2}{m_2 a_1} \leq U(S) \quad \text{for } 0 \leq S \leq \lambda_2.$$

Hence, $\hat{B}(S) \leq 0$ under condition (i). For (ii) and (iii), $\lambda_2 < \lambda_p$. Let

$$\begin{aligned} T(S) &= \frac{(m_1(a_2 + S)/m_2(a_1 + S))((m_2 S/(a_2 + S)) - 1)}{(m_1 S/(a_1 + S)) - 1 - \gamma P^* + \gamma \epsilon} \\ &= \frac{(m_1/m_2)(m_2 S - a_2 - S)}{m_1 S - (1 + \gamma P^* - \gamma \epsilon)(a_1 + S)}. \end{aligned}$$

Set $m_1 \hat{\lambda}_p / (a_1 + \hat{\lambda}_p) = 1 + \gamma P^* - \gamma \epsilon$, and choose ϵ small enough such that $\lambda_2 < \hat{\lambda}_p < \lambda_p$. It is clear that

$$T(\lambda_2) = 0, \quad \lim_{S \rightarrow \hat{\lambda}_p^+} T(S) = +\infty,$$

and that $T(S) > 0$ for $S > \hat{\lambda}_p$ and $S < \lambda_2$ and $T(S) < 0$ for $\lambda_2 < S < \hat{\lambda}_p$. Now, we show that there exists a positive number c such that

$$\max_{0 \leq S < \hat{\lambda}_p} T(S) \leq c \leq \min_{\hat{\lambda}_p < S \leq 1} T(S).$$

If c does exist, then there exists $\beta > 0$ such that the equation $T(S) = \beta$ has at least two distinct roots, α_1 and α_2 , satisfying $0 < \lambda_2 < \alpha_1 < \hat{\lambda}_p < \alpha_2 < 1$. Consider the functions

$$W(S) = \frac{m_1}{m_2} (m_2 S - a_2 - S) - \beta [m_1 S - (1 + \gamma P^* - \gamma \epsilon)(a_1 + S)].$$

Then, $W(S) = 0$ also has at least two distinct roots namely α_1 and α_2 in $[0, 1]$. But after some simplification,

$$W(S) = \left[\left(1 - \beta - \frac{1}{m_2} \right) m_1 + \beta (1 + \gamma P^* - \gamma \epsilon) \right] S + \left[-\frac{m_1 a_2}{m_2} + \beta (1 + \gamma P^* - \gamma \epsilon) a_1 \right]$$

is a polynomial of S with degree 1, and it cannot have two distinct roots. Hence, there exists a positive number c such that $\hat{\beta}(S) \leq 0$.

We now seek the maximum invariant region in the set $\{(S, x, y, P) | \dot{V} = 0\}$. Since $A(S) \leq 0$, $\hat{B}(S) \leq 0$ and \dot{V} is given by (A.2), it must be the case that $A(S) = 0$. Then, either $S = \lambda_2$ or S is a root of

$$\left[\frac{(a_2 + S)(1 - S)}{m_2 S} - (1 - \lambda_2) \right] = 0$$

or, equivalently, a root of

$$(S - \lambda_2) \left(S + \frac{a_2}{\lambda_2} \right) = 0.$$

Therefore, $S = \lambda_2$. Moreover, $B(\lambda_2, P) < 0$ (since $\lambda_2 < \lambda_p$), so $x = 0$. S and x constant, $S = \lambda_2$, $x = 0$, forces $y = 1 - \lambda_2$. The only invariant set in this region is the rest point $(\lambda_2, 0, 1 - \lambda_2, P^*)$. The LaSalle invariance principle completes the proof.

Proof of Theorem 4.3. The proof of Theorem 4.3 is contained in the following three lemmas.

Lemma A.1. *If $\lambda_2 > \hat{\lambda}_1$ and $\lim_{t \rightarrow \infty} y(t)$ exists, then $\lim_{t \rightarrow \infty} y(t) = 0$.*

Proof. If $\lim_{t \rightarrow \infty} y(t) = y^* > 0$, then $\lim_{t \rightarrow \infty} S(t) = \lambda_2$. The limiting equations for (2.3) (see the previous reference to asymptotically autonomous systems), contain the equation

$$\begin{aligned} x' &= x \left(\frac{m_1 \lambda_2}{a_1 + \lambda_2} - 1 - \gamma P(t) \right) \\ &\geq x \left(\frac{m_1 \lambda_2}{a_1 + \lambda_2} - 1 - \gamma \right). \end{aligned}$$

Since $\hat{\lambda}_1 < \lambda_2$, $x(t)$ grows without limit, a contradiction, since we have shown that $0 \leq x(t) \leq 1$.

Lemma A.2. *If $\lambda_2 > \hat{\lambda}_1$ and $\lim_{t \rightarrow \infty} x(t) = \xi > 0$, then $\lim_{t \rightarrow \infty} y(t) = 0$.*

If $y(t)$ does not tend to a limit, then the lim sup and the lim inf are different, i.e.,

$$0 \leq \liminf_{t \rightarrow \infty} y(t) < \limsup_{t \rightarrow \infty} y(t) = \eta.$$

Choose a sequence, $\{t_m\}$, such that $y'(t_m) = 0$ and $\lim_{m \rightarrow \infty} y(t_m) = \eta$. Since $x(t)$ tends to a positive limit by hypothesis, the limit of $x'(t)$ as t tends to infinity is zero; in particular $\lim_{t \rightarrow \infty} x'(t_m) = 0$. Thus

$$\begin{aligned} 0 &= \lim_{t \rightarrow \infty} \left[\frac{m_1 \lambda_2}{a_1 + \lambda_2} - 1 - \gamma x(t_n) p(t_n) \right] \\ &= \lim_{t \rightarrow \infty} \left[\frac{m_1 \lambda_2}{a_1 + \lambda_2} - 1 - \gamma + \gamma(1 - x(t_n) p(t_n)) \right]. \end{aligned}$$

Since $(m_1 \lambda_2 / a_1 + \lambda_2) - 1 - \gamma > 0$ and $x(t_n) p(t_n) < 1$, this is a contradiction. Thus, $y(t)$ tends to a limit as t tends to infinity, and, by the preceding lemma, this limit is zero.

Lemma A.3. *If $1 > \lambda_2 > \hat{\lambda}_1 + \gamma / (1 + \gamma)$, then $\lim_{t \rightarrow \infty} y(t)$ exists.*

Proof. In Section 3, we have already noted that

$$S(t) + x(t) + y(t) \leq 1 + c_2 e^{-t}.$$

In a very similar way, a lower bound can be obtained. Adding the equations yields

$$\begin{aligned} S'(t) + y'(t) + x'(t) &= 1 - S(t) - y(t) - x(t) - \gamma x(t) P(t) \\ &> 1 - S(t) - y(t) - x(t) - \gamma x(t) \\ &> 1 - (1 + \gamma)(S(t) + y(t) + x(t)). \end{aligned}$$

The standard comparison theorem yields that

$$S(t) + y(t) + x(t) > \frac{1}{1 + \gamma} + c_2 e^{-(1+\gamma)t}. \tag{A.6}$$

From the preceding lemmas, we may assume that $x(t)$ and $y(t)$ do not tend to limits as t tends to infinity. If these limits do not exist then, as above, then the \limsup and \liminf are different, i.e.,

$$0 \leq \liminf_{t \rightarrow \infty} y(t) < \limsup_{t \rightarrow \infty} y(t) = \eta$$

and

$$\liminf_{t \rightarrow \infty} x(t) = \xi < \limsup_{t \rightarrow \infty} x(t).$$

Choose a sequence, $\{t_m\}$, such that $y'(t_m) = 0$ and $\lim_{m \rightarrow \infty} y(t_m) = \eta$. Since $y(t_m) > 0$, $S(t_m) = \lambda_2$ and $\lambda_2 \leq 1 - \eta - \xi$ or $\xi + \eta \leq 1 - \lambda_2$. Now choose a sequence, $\{\tau_m\}$, such that $x'(\tau_m) = 0$ and $\lim_{m \rightarrow \infty} x(\tau_m) = \xi$. Since

$$\frac{m_1 S(\tau_m)}{a_1 + S(\tau_m)} - 1 - \gamma x(\tau_m) P(\tau_m) = 0,$$

$$\frac{m_1 S(\tau_m)}{a_1 + S(\tau_m)} - 1 - \gamma = -\gamma(1 - P(\tau_m)) \leq 0.$$

A consequence of this is that $S(\tau_m) \leq \hat{\lambda}_1$ or, using (A.6),

$$\frac{1}{1 + \gamma} - \hat{\lambda}_1 \leq \xi + \eta \leq 1 - \lambda_2,$$

which implies that

$$\frac{\gamma}{1 + \gamma} + \hat{\lambda}_1 \geq \lambda_2,$$

contrary to the hypothesis of the lemma.

This proof applies the techniques of Wolkowicz and Xia [26].

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