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A survey of mathematical models of competition with an inhibitor

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Abstract

Mathematical models of the effect of inhibitors on microbial competition are surveyed. The term inhibitor is used in a broad sense and includes toxins, contaminants, allelopathic agents, etc. This includes both detoxification where the inhibitor is viewed as a pollutant and control where the inhibitor is viewed as an aid to controlling a bioreactor. The inhibitor may be supplied externally or may be created as an anti-competitor toxin. This includes plasmid-bearing, plasmid-free competition. The literature is spread across journals in different disciplines and with different notation. The survey attempts to present the mathematical models and the results of the corresponding analysis within a common framework and notation. Detailed mathematical proofs are not given but the methods of proof are indicated, references cited, and the results presented in tables. Open problems are indicated where there is a gap in the theory.

Keywords: Inhibitors; Detoxification; Anti-competitor toxins; Allelopathic agent; Plasmid; Mathematical models

1. Introduction

The chemostat is one of the standard models of an open system and is used extensively in ecological problems. The basic model of competition is described with three ordinary (non-linear) differential equations and it is one place in ecology where the mathematics is tractable, the experiments can be performed, and the two are in agreement [1]. It is quite natural then to use it as a

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beginning for a model of inhibitor problems. For this, one has two (realistically more than two) organisms competing for a nutrient in the presence of an inhibitor. The inhibitor is detrimental to one of the organisms while the other can take it up with no deleterious effect. Thus, in ecological terms, we think of the second organism as detoxifying the environment (removing the toxicant or pollutant). From the standpoint of competition, the question is whether the detoxifying organism survives. The success of the detoxification is the level of the inhibitor left in the environment. Mathematically, the question is the structure of the omega limit sets of a system of differential equations. The original model in this direction is that of Lenski and Hattingh [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 represents a laboratory model of a bioreactor. An organism is genetically altered to manufacture a product by the insertion of a plasmid, a piece of genetic material. Thus the competitors are 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. If the plasmid is lost, the organism is sensitive to the antibiotic. In this view, the inhibitor is helpful for the desired outcome. Plasmid models have been developed, in particular Ryder and DiBiasio [3], Stephanopoulos and Lapidus [4], and studied from the mathematical viewpoint in Hsu and Luo [5], Hsu et al. [6], Hsu et al. [7], Hsu and Waltman [8], Lu and Hadeler [9], and Macken et al. [10]. Simonsen, [11] discusses both theory and experiments.

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 the classic paper of Chao and Levin [12] and in Levin [13]. This produces a very different model although also one where the determining the structure of the omega limit sets is the desired mathematical conclusion. This problem has been studied in a general context of competition and in the context of competition between plasmid-bearing and plasmid-free organisms and both will be reviewed below. This is then called the internal inhibitor problem, and it is not a detoxification problem. This also has implications for biotechnology since supplying the inhibitor (antibiotic, in this case) from an external source is an added expense and may itself carry environmental costs.

Most of literature assumes that the inhibitor interferes with the reproduction of the organism. Although this assumption 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, common in chemostat problems, of a reduction of order through a conservation principle, to a monotone system. The theory of monotone dynamical systems is given in Smith [14]. Moreover, mass action terms, standard for modeling an interaction that involves two concentration are quadratic terms, and are more difficult to handle than the usual Michaelis–Menten responses of the standard chemostat. Both the internal and external inhibitor problem with a lethal inhibitor have been studied and will be reviewed below.

The goal, as with all such problems, is to determine the asymptotic behavior as a function of the parameters. While this can often be done in a large portion of the parameter space, it usually cannot be done in all of it. In these cases, we present numerical simulations.

Table 1

Inhibition source	Effect
Internal	Inhibits growth
External	Lethal

The papers which consider these problems have been studied with different notation, different mathematical techniques, and the results have been published in a variety of journals, some mathematical, some biological, and some engineering. The purpose of this survey is put these studies together in one place and to present the results in a unified manner with a common notation. We also illustrate the more interesting or unusual results with numerical solutions.

We begin with a description of the basic model. In the succeeding sections we modify this model to account for the source and the effect of the inhibitor. In Table 1, we list the choices where a selection may be made from each column.

The case of plasmid-bearing plasmid-free competition is of special interest in reactor theory. On the one hand the problem should be easier because the organisms are essentially the same but on the other hand the change of one organism into another complicates the dynamics. The potential loss of the plasmid means that there can be no stable steady state consisting of only plasmid-bearing organisms. After cases given by the above table have been completed, we survey plasmid-free plasmid-bearing competition. Global results for these models are less complete and several open problems remain.

In this survey we do not give rigorous mathematical proofs of the results but refer the reader to the literature. In the first case considered, Section 3, we provide more detail to give the reader an understanding of the steps involved. In later sections we simply collect the results in tables or give informal explanations. We sometimes give proofs of simple statements or give simple indications of the nature of proofs. For example, we show the Liapunov function when one is used in the proof but do not carry out the calculations.

2. The basic chemostat

The chemostat is a piece of laboratory apparatus that captures the essentials of exploitative competition in an open system. Basically, it consists of three vessels connected by pumps. The first is called the feed bottle and contains all of the nutrients essential for growth of microorganisms with one, hereafter called the nutrient, is short supply. The contents of the feed bottle are pumped at constant rate into the second vessel, the reaction chamber which will be charged with microorganisms and which is well mixed. The contents of the reaction vessel are pumped at the same constant rate into the final vessel, called the overflow vessel. Thus the volume of the reaction vessel is constant, an important assumption. Other names in use are continuous culture, CSTR (continuously stirred tank reactor) and bioreactor. In ecology this is a laboratory model of a simple lake while in biotechnology this is the laboratory model of a commercial reactor, perhaps manufacturing a product with genetically altered organisms.

A derivation of the chemostat equations can be found in almost any bioengineering text, for example [15] or [16], or in [17]. We give here a hueristic description and the reader is referred to

one of the above references for a more detailed description. Let $S(t)$ denote the concentration of the nutrient in the reaction vessel at time t, $S^{(0)}$, the concentration of the nutrient in the feed bottle, F, the flow rate (determined by the pump speed), V, the volume of the reaction vessel and define the parameter D, called the dilution rate, by $D = F/V$. If there were no microorganisms, the rate of change of the concentration of the nutrient in the reaction vessel would be given by

$$\frac{\mathrm{d}S(t)}{\mathrm{d}t} = (S^{(0)} - S(t))D,$$

the simple statement that change in concentration is proportional to the difference between the incoming concentration and the resident concentration. If organisms are consuming the nutrient then this needs to be corrected for the consumption and the consumed nutrient converted to growth of the organism. A basic assumption is that growth is proportional to consumption. Nutrient uptake (consumption) is usually taken to be of the Monod (or Michaelis–Menten) form

$$\frac{mxS}{a+S},$$

where m is called the maximal growth rate and a is called the Michaelis–Menten constant. Thus, if $x(t)$ denotes the concentration of a microorganism at time t, the equations take the form (suppressing the t dependence in the independent variables)

$$S' = (S^{(0)} - S)D - \frac{x}{\gamma}\frac{mS}{a+S},$$

$$x' = x\left(\frac{mS}{a+S} - D\right).$$

The constant γ is a yield constant and represents the conversion of nutrient to organism. $S^{(0)}$ and D are controlled by the experimenter and can be thought of as environmental variables while m, a, and γ are properties of the organism, to be measured in the laboratory. There is also an underlying assumption that all other effects are controlled and constant, temperature and pH, in particular.

With two competitors and the same assumptions, the equations become

$$\begin{aligned} S' &= (S^{(0)} - S)D - \frac{x}{\gamma_1}\frac{m_1 S}{a_1+S} - \frac{y}{\gamma_2}\frac{m_2 S}{a_2+S}, \\ x' &= x\left(\frac{m_1 S}{a_1+S} - D\right), \\ y' &= y\left(\frac{m_2 S}{a_2+S} - D\right). \end{aligned} \tag{1}$$

These equations are the starting point for our construction of inhibitor models.

Two parameters determine the outcome of the competition. Define λ_1 and λ_2 as solutions of the following equations:

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

$$\frac{m_2\lambda_2}{a_2+\lambda_2} = D.$$

These parameters represent 'break-even' concentrations, values of the nutrient where the derivative of x or y, respectively, are zero. The basic result [18–21], which we state for two competitors, is:

If $0 < \lambda_1 < \lambda_2 < S^{(0)}$, then

$$\lim_{t\to\infty} S(t) = \lambda_1,$$

$$\lim_{t\to\infty} x(t) = S^{(0)} - \lambda_1,$$

$$\lim_{t\to\infty} y(t) = 0.$$

Competitive exclusion holds; only one competitor survives.

In what follows similar parameters will be defined and limiting behavior expressed as a function of the ordering of the parameters. Although the equations defining the parameters could be easily solved explicitly, we choose to leave them in the equation form to make comparisons easier both among parameters and among different cases.

3. The external inhibitor

Lenski and Hattingh [2], considered a model for competition for a limiting resource in a chemostat between two populations in the presence of an external inhibitor for one of the populations. The mathematical analysis of their model was provided by Hsu and Waltman [22] and this section follows that presentation. We consider this problem in detail to set the basic scenario, and then modify it in the later sections to account for other effects. Two types of microorganisms were considered, one of which is resistant to an agent which is being input into the chemostat. The model is that of the basic chemostat model described above but with an additional variable, $p(t)$ the concentration of the inhibitor (or toxicant or pollutant) added. The effect of the inhibitor is to retard growth (and hence, uptake, since one of the basic chemostat assumptions is that these are proportional). The Monod type function is also used to model the uptake of the inhibitor. The equations take the form

$$\begin{aligned}
S' &= (S^{(0)} - S)D - \frac{x}{\gamma_1}\frac{m_1 S}{a_1 + S}e^{-\mu p} - \frac{y}{\gamma_2}\frac{m_2 S}{a_2 + S},\\
x' &= x\left(\frac{m_1 S}{a_1 + S}e^{-\mu p} - D\right),\\
y' &= y\left(\frac{m_2 S}{a_2 + S} - D\right),\\
p' &= (p^{(0)} - p)D - \delta\frac{yp}{K + p}.
\end{aligned} \tag{2}$$

$$S(0) \geqslant 0, \quad x(0) > 0,$$

$$y(0) > 0, \quad p(0) \geqslant 0.$$

The variables may be scaled to non-dimensional form. This will be done throughout the paper, but we present the scaling in detail only here. We scale the dependent variables, the parameters, and time: $\hat{S} = \frac{S}{S^{(0)}}$, $\hat{x} = \frac{x}{\gamma_1 S^{(0)}}$, $\hat{y} = \frac{y}{\gamma_2 S^{(0)}}$, $\hat{m}_i = \frac{m_i}{D}$, $\hat{a}_i = \frac{a_i}{S^{(0)}}$, $\hat{p} = \frac{p}{p^{(0)}}$, $\hat{K} = \frac{K}{p^{(0)}}$, $\hat{\delta} = \frac{S^{(0)}\gamma_2\delta}{Dp^{(0)}}$, $\hat{\mu} = \mu p^{(0)}$, $\hat{t} = Dt$. Then, making the changes and dropping all of the hats, one has the system in non-dimensional form

$$\begin{aligned} S' &= 1 - S - \frac{m_1 x S}{a_1 + S} e^{-\mu p} - \frac{m_2 y S}{a_2 + S}, \\ x' &= x\left(\frac{m_1 S}{a_1 + S} e^{-\mu p} - 1\right), \\ y' &= y\left(\frac{m_2 S}{a_2 + S} - 1\right), \\ p' &= 1 - p - \delta \frac{yp}{K + p}. \end{aligned} \tag{3}$$

Although the exponential was used to model the effect of the inhibitor on the growth rate, one can replace the exponential form of the effect of the inhibitor by an arbitrary function $f'(p)$ where

(i) $f(p) \geqslant 0, \quad f(0) = 1,$

(ii) $f(p) < 0, \quad p > 0,$

without added difficulty. The exponential form is convenient for specific computations.

Let $\Sigma = 1 - S - x - y$. Then the system may be replaced by

$$\Sigma' = -\Sigma,$$

$$x' = x\left(\frac{m_1(1 - \Sigma - x - y)}{a_1 + 1 - \Sigma - x - y} f(p) - 1\right),$$

$$y' = y\left(\frac{m_2(1 - \Sigma - x - y)}{a_2 + 1 - \Sigma - x - y} - 1\right),$$

$$p' = 1 - p - \frac{\delta yp}{K + p}.$$

Clearly, $\lim_{t\to\infty} \Sigma(t) = 0$. Hence, using the theory of asymptotically autonomous systems one studies the limiting system

$$\begin{aligned} x' &= x\left(\frac{m_1(1 - x - y)}{1 + a_1 - x - y} f(p) - 1\right), \\ y' &= y\left(\frac{m_2(1 - x - y)}{1 + a_2 - x - y} - 1\right), \\ p' &= 1 - p - \frac{\delta yp}{K + p}. \end{aligned} \tag{4}$$

$$x(0) > 0, \quad y(0) > 0, \quad p(0) \geqslant 0,$$

$$x(0) + y(0) < 1.$$

There are simple (in this case) hypotheses to be checked before one can conclude that the dynamics of the original system and that of the asymptotic limiting equations are the same. The original result on asymptotically autonomous systems is Markus [23] and the current state of the theory is given by Thieme [24]. A special case is sufficient here, see [17], Appendix F. The important hypothesis is the lack of a cyclic connection for orbits on the boundary, and we comment on this since it is an important hypothesis for uniform persistence, discussed below, as well. We describe only the simple case of rest points.

Let $A_1, A_2, \ldots, A_n$ be a finite set of rest points for a system of differential equations

$$x' = F(x),$$

A_1 is said to be chained to A_2 if there exists an orbit, γ, of the above system such that the omega limit set of γ is A_2 and the alpha limit set is A_1. This is written $A_1 \to A_2$. Note than an orbit can be chained to itself. If $A_1 \to A_2 \to \cdots \to A_n \to A_1$, the set of rest points is said to form a cycle. If no subset of the rest point set forms a cycle, the set is said to be acyclic. We shall see below that the stability of the rest points for (4) (and for other problems considered here) proves that the set is acyclic. The concept exists in a much more general setting.

An important consideration is that (4) has a special property which limits the possible attractors. A system

$$x' = F(x), \tag{5}$$

$x \in R^n$, is said to be competitive if

$$\frac{\partial F_i}{\partial x_j} \leqslant 0, \quad i \neq j,$$

(4) has this property in the open, positive octant. A two dimensional competitive system has no periodic orbits and a three dimensional system with an irreducible Jacobian matrix satisfies a Poincaré–Bendixson type theorem. See Hirsch [25] and Smith [26].

Let the two basic parameters of the chemostat λ_1 and λ_2 be as above. As noted in the discussion of the chemostat, these are break-even concentrations and, in the simple chemostat, $\lambda_1 < \lambda_2$ implies that $\lim_{t\to\infty} y(t) = 0$. Two other parameters, break-even concentrations for special situations, are needed to describe the asymptotic behavior of the system. Similar parameters will be needed for other situations which follow. To unify the notation and to reflect the fact that these are break-even concentrations, it is better to define them as the roots of appropriate equations. In this case, define

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

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

$$\frac{m_1\lambda^+}{a_1 + \lambda^+} f(1) = 1,$$

$$\frac{m_1\lambda^-}{a_1+\lambda^-}f(p^*)=1,$$

where p^* is the positive root of

$$(1-z)(K+z)-\delta(1-\lambda_2)z=0,$$

λ_1, λ^+, λ^- involve only the parameters for the x-population and are related:

$$\lambda_1<\lambda^-<\lambda^+.$$

The global outcome will be determined by where λ_2 falls in this ordering and this is a unifying theme in the models to follow.

We will assume that $m_1>1$, $m_2>1$, or the problem is not interesting since $m_i<1$ implies (using simple inequalities) that the corresponding population washes out of the chemostat (ecologically, becomes extinct, mathematically, that $\lim_{t\to\infty}x(t)=0$ or that $\lim_{t\to\infty}y(t)=0$).

There are three potential rest points on the boundary which we label

$$E_0=(0,0,1),$$

$$E_1=(1-\lambda^+,0,1),$$

$$E_2=(0,1-\lambda_2,p^*).$$

These correspond respectively, to both populations washing out of the chemostat, the y-population washing out, and the x-population washing out. In the chemostat without an inhibitor, this is all that can happen. With an inhibitor, a richer set of limits is possible as we shall see below. The local stability of each rest point can be determined by computing the eigenvalues of the Jacobian of (4) around that point. The end result of this computation (see [22] for details) is shown in Table 2.

These rest points correspond to the absence of one or both competitors and thus represent extinction states. They are reflections of eigenvalue computations. If one of the inequalities in line one of the table is reversed, then E_0 repels in the corresponding direction. Moreover, when E_1 or E_2 exist, they have a two dimensional stable manifold with eigenvectors lying in the planes $y=0$ or $x=0$ respectively. Thus the stability of these points is determined by one eigenvalue. The problem is to determine when the rest points are global attractors with respect to the interior of the positive cone.

Before presenting these extinction results we note a consequence of these remarks and competitiveness of (4). Note first that the sets $\{(x,y,p)|x>0,y=0,p>0\}$ and $\{(x,y,p)|x=0,y>0,p>0\}$ are positively invariant sets. Since they are planar, the Poincaré–Bendixson theorem applies. If E_1 exists then it is the global attractor of the first, and if E_2 exists it is the global

Table 2

	Exists	Locally asymptotically stable if
E_0	Always	$\lambda_1>1$, $\lambda_2>1$
E_1	$0<\lambda^+<1$	$0<\lambda^+<\lambda_2$
E_2	$\lambda_2<1$	$0<\lambda_2<\lambda^-$

Table 3
Extinction theorems

Global attractor	Condition
E_0	$\lambda_1 > 1,\ \lambda_2 > 1$
E_2	$\lambda_2 < \lambda_1 < \lambda^- < \lambda^+$
E_2	$\lambda_1 < \lambda_2 < \lambda^- < \lambda^+$
E_1	$\lambda_1 < \lambda^- < \lambda^+ < \lambda_2$

attractor of the second. They are the only rest points in these sets and competitive two dimensional systems do not have limit cycles. Thus the Poincaré–Bendixson Theorem completes the proof of convergence for initial conditions in these sets. Table 3 summarizes the extinction results. Each line entry represents an extinction theorem and the proofs can be found in [22].

The above table contains all of the conditions except the case where

$$\lambda_1 < \lambda^- < \lambda_2 < \lambda^+. \tag{6}$$

This is the most interesting case for then an interior equilibrium exists.
It takes the form $E_c = (x_c, y_c, p_c)$ where

$$p_c = f^{-1}\left(\frac{a_1 + \lambda_2}{m_1 \lambda_2}\right),$$

$$y_c = \frac{(1 - p_c)(K + p_c)}{\delta p_c},$$

$$x_c = 1 - y_c - \lambda_2.$$

p_c exists since $\lambda^- < \lambda_2 < \lambda^+$, $\lambda_2 < 1$, and $f(0) = 1$. This makes $p_c < p^*$ and hence $y_c < 1 - \lambda_2$. The rest point is unique since p_c is unique from the monotonicity of f.

The existence of E_c is related to uniform persistence. Let

$$x' = F(x), \tag{7}$$

where $x = (x_1, x_2, \ldots, x_n)$. Then (7) is said to be uniformly persistent if there exists a number $\eta > 0$ such that

$$\liminf_{t\to\infty} x_i(t) > \eta > 0, \quad i = 1, 2, \ldots, n.$$

From the form of the equations, it is clear that such an η exists for S and p, so the point of establishing uniform persistence is that both populations survive and are bounded away from zero. There exists a separate literature on persistence; see [27–34] for examples or see the survey articles [35,36]. To obtain uniform persistence for (4), under the condition (6), it is most direct to use the results of Thieme [31]. Since E_2 is globally stable in the set $x = 0$, there are no cyclic orbits on the boundary of the positive cone in R^3. Since we have already observed that the system is uniformly bounded, uniform persistence has the consequence that there is a global attractor interior to the positive cone. The structure of this attractor is to be determined.

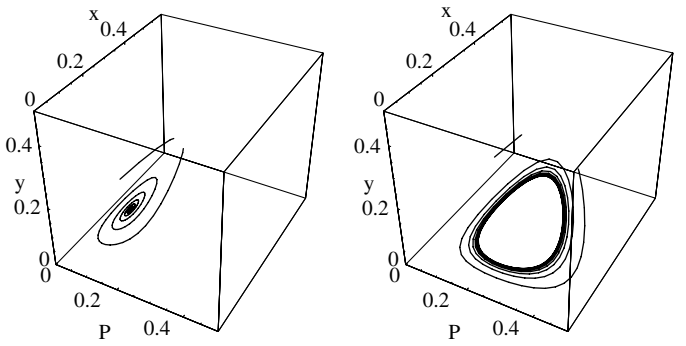

Fig. 1. Parameters: $a_1 = 0.5$, $a_2 = 3.5$, $m_1 = 5.0$, $m_2 = 6.0$, $\delta = 50$, $K = 0.1$, (a) $\mu = 13.0$, (b) $\mu = 5.0$.

Theorem 1. *If* $\lambda_2 < 1$ *and* (6) *holds, then* (4) *is uniformly persistent.*

The next step is to compute the stability of the interior rest point. This can be done by applying the Routh–Hurwitz criterion [37], to the variational matrix but this is a very complicated computation. The end result [22] is that the rest point will be asymptotically stable if and only if

$$\left(1+\frac{\delta K y_c}{(K+p_c)^2}+\frac{a_1 x_c}{(a_1+\lambda_2)\lambda_2}+\frac{a_2 y_c}{(a_2+\lambda_2)\lambda_2}\right)\left(1+\frac{\delta K y_c}{(K+p_c)^2}\right)\left(\frac{a_1 x_c}{(a_1+\lambda_2)\lambda_2}+\frac{a_2 y_c}{(a_2+\lambda_2)\lambda_2}\right)$$
$$> -\frac{f'(p_c)}{f(p_c)}\frac{a_2}{(a_1+\lambda_2)\lambda_2}\frac{\delta p_c}{K+p_c}x_c y_c. \tag{8}$$

The stability of E_c can be determined by (8) in any given case, but the question of the existence of unstable limit cycles or of multiple limit cycles is not known for these problems. In the special case that $f(p) = e^{-\mu p}$ we show that both stability and instability of the interior rest point is possible. Let $a_1 = 0.5$, $a_2 = 3.5$, $m_1 = 5.0$, $m_2 = 6.0$, $\delta = 50$, $K = 0.1$. $\mu = 13.0$ produces a stable spiral while $\mu = 5.0$ produces a limit cycle. The respective trajectories are shown in Fig. 1.

Hopf bifurcation has occurred and, as noted above, the general results of [25,26], provide a proof that it is indeed a limit cycle. This phenomenon cannot occur in the basic chemostat without an inhibitor.

4. The lethal external inhibitor

We now change the above model only slightly. We suppose that instead of interfering with reproduction, the inhibitor is lethal to the organism. From the biological standpoint this is, apparently, a relatively minor change, an increased death rate rather than a slower growth rate. To describe the interaction between the inhibitor and the organisms we use mass action to reflect the effect as being proportional to the concentration of each. This introduces a new parameter γ and removes the function $f(p)$. The variables are the same and the equations corresponding to (2) become

$$
\begin{aligned}
S' &= (S^0 - S)D - \frac{m_1 S}{a_1 + S}x - \frac{m_2 S}{a_2 + S}y,\\
x' &= x\left(\frac{m_1 S}{a_1 + S} - D - \gamma p\right),\\
y' &= y\left(\frac{m_2 S}{a_2 + S} - D\right),\\
p' &= (p^0 - p)D - \frac{\delta p}{K + p}y,
\end{aligned}
\tag{9}
$$

$$S(0) \geqslant 0, \quad x(0) > 0, \quad y(0) > 0, \quad p(0) \geqslant 0.$$

Although the system of equations appears to be very similar to (2), we shall see that it is mathematically very different. The presentation follows that of [38]. As above, we seek to scale the equations and reduce the number of parameters. With the same scaling that produced (3) and with $\hat{\gamma} = \frac{\gamma p^0}{D}$, (9) becomes

$$
\begin{aligned}
S' &= 1 - S - \frac{m_1 S}{a_1 + S}x - \frac{m_2 S}{a_2 + S}y,\\
x' &= x\left(\frac{m_1 S}{a_1 + S} - 1 - \gamma p\right),\\
y' &= y\left(\frac{m_2 S}{a_2 + S} - 1\right),\\
p' &= 1 - p - \frac{\delta p}{K + p}y.
\end{aligned}
\tag{10}
$$

The same parameters will be of interest although the mathematical definitions are slightly different. We define four parameters, λ_1, λ_2, λ^+, λ^-, break-even concentrations, as solutions of

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

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

$$\frac{m_1 \lambda^+}{a_1 + \lambda^+} = 1 + \gamma,$$

$$\frac{m_1 \lambda^-}{a_1 + \lambda^-} = 1 + \gamma p^*,$$

where p^*, is the positive root of

$$(1 - z)(K + z) = \delta z(1 - \lambda_2).$$

The λ-parameters have the same meaning as before. λ_1 and λ_2 are the break even concentrations for x and y in the simple chemostat without an inhibitor; λ^+ and λ^- are the break-even concentrations for x at the maximum level of the inhibitor ($p = 1$ in the scaled system) and the minimum level ($p = p^*$) respectively. One must prove, of course, that this is the minimal attainable level of the

inhibitor. As before, three of the λ-parameters are defined using only the parameters associated with the x variable and thus they are ordered. We tacitly assume that they are different and one has

$$\lambda_1 < \lambda^- < \lambda^+.$$

The behavior of the solutions will be determined will by where λ_2 falls in the ordering.

If the equations are added it becomes evident that there is no reduction in order (the addition trick fails.) The system is not competitive and all of the tools provided by the results of Hirsch [25] and Smith [26], used in the non-lethal case, are lost. This will keep us from concluding rigorously that the oscillatory solutions illustrated below are, in fact, periodic. We will be able to show that the system has essentially the same behavior as (3) but the proofs will be very different. We do not get as far with rigorous arguments and must resort to numerical indications. We begin, however, by noting which conclusions are possible by arguments similar to those in the previous section.

Simple differential inequality arguments show that any trajectory is eventually in the region Q defined by

$$Q = \{0 \leqslant S \leqslant 1, 0 \leqslant x \leqslant 1, 0 \leqslant y \leqslant 1, p^* - \epsilon \leqslant p \leqslant 1 + \epsilon\}.$$

This bounds the right hand side of (10), at least for t large. Thus when limits exist, one also knows that the limit of the time derivative of the corresponding variable is zero.

There are three potential rest points on the boundary which we label

$$E_0 \equiv (1, 0, 0, 1),$$

$$E_1 \equiv (\lambda^+, \hat{x}, 0, 1),$$

$$E_2 \equiv (\lambda_2, 0, 1 - \lambda_2, p^*),$$

where $\hat{x}$ is given by

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

An interior equilibrium $E_c \equiv (\lambda_2, \bar{x}_c, \bar{y}_c, \bar{p}_c)$ is also possible where the coordinates are

$$\bar{p}_c \equiv \frac{1}{\gamma}\left(\frac{m_1\lambda_2}{a_1 + \lambda_2} - 1\right),$$

$$\bar{y}_c \equiv \frac{(1 - \bar{p}_c)(K + \bar{p}_c)}{\delta\bar{p}_c},$$

and

$$\bar{x}_c \equiv \frac{1 - \lambda_2 - \bar{y}_c}{1 + \gamma\bar{p}_c}.$$

The local stability of the rest point is determined by the eigenvalues of the variational matrix for (10) evaluated at the rest point. The local stability is summarized in the Table 4; the entry 'Routh–Hurwitz indicates that the Routh–Hurwitz condition, see [37], a very complicated formula, involving the parameters of the system, determines the stability. It is, however, precise and the details of the computation may be found in [38].

Table 4
Local stability of rest points

Point	Existence	Stability condition
E_0	Always	$\lambda^+ > 1$, $\lambda_2 > 1$
E_1	$\lambda^+ < 1$	$\lambda^+ < \lambda_2$
E_2	$\lambda_2 < 1$	$\lambda_2 < \lambda^-$
E_c	$\lambda^- < \lambda_2 < 1$, and λ^+ does not exist or $\lambda_2 < \lambda^+$	Routh–Hurwitz

The next step is to determine the conditions for the global stability of the rest points. The proofs are very different from those in the previous section since the system is no longer competitive and the theory for three dimensional competitive systems is no longer available. The results, however, match those of the preceding section very well. The global stability of the boundary rest points represent extinction theorems, one or both of the competitors do not survive. The arguments are such that the dynamical system on the invariant sets $x = 0$ and $y = 0$ play a key role. Consider the set $y \equiv 0$. The system (10) becomes

$$\begin{aligned} S' &= 1 - S - \frac{m_1 S}{a_1 + S}x, \\ x' &= \left[\frac{m_1 S}{a_1 + S} - 1 - \gamma p\right]x, \\ p' &= 1 - p. \end{aligned} \tag{11}$$

Clearly, $\lim_{t\to\infty} p(t) = 1$, so, using the theory of asymptotically autonomous systems, we consider the limiting system

$$\begin{aligned} S' &= 1 - S - \frac{m_1 S}{a_1 + S}x, \\ x' &= x\left[\frac{m_1 S}{a_1 + S} - 1 - \gamma\right]. \end{aligned} \tag{12}$$

If $\lambda^+ < 1$, it follows from Hsu [39] that

$$\lim_{t\to\infty} S(t) = \lambda^+ \quad \text{and} \quad \lim_{t\to\infty} x(t) = \hat{x}.$$

Returning to the original system, one has

$$\lim_{t\to\infty}(S(t), x(t), p(t)) = (\lambda^+, \hat{x}, 1).$$

In a similar way, for $x = 0$, one has

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

if $\lambda_2 < 1$. The stability of these rest points preclude the existence of a cyclic connection between them, an important hypothesis for applying the theory of uniform persistence. Another consequence is that when one is able to establish that $\lim_{t\to\infty} x(t) = 0$ or $\lim_{t\to\infty} y(t) = 0$ for all nontrivial solutions of (10), then trajectories of the full system will be attracted to the corresponding boundary rest points.

Table 5

Point	Condition	Proof
E_0	$\lambda^+ > 1$, $\lambda_2 > 1$	Comparison
E_1	$\lambda_1 < \lambda^- < \lambda^+ < 1 < \lambda_2$	Fluctuations
	$1 > \lambda_2 > \lambda^+ + \frac{\gamma}{1+\gamma}$	Fluctuations
E_2	$\lambda_2 < 1$, $\lambda_1 > 1$	Fluctuations
	$\lambda_2 < 1$, $\lambda_2 < \lambda^- < \lambda^+$	Liapunov

The very existence of an interior rest point indicates the potential for coexistence, either as a globally stable rest point or as some other attractor. The results for global stability of all of the rest points are shown in Table 5. In the indication of a proof the term fluctuations indicates a technical argument involving limsup or liminf of trajectories. We will illustrate one such argument. The term Liapunov indicates an argument by a Liapunov function. The function will be given below but the computations are long and tedious and the interested reader is referred to [38].

When the interior rest points exists, the system is uniformly persistent. The proof follows from the general theory since we have already noted that there is no cyclic connection of rest points on the boundary.

When E_0 is globally asymptotically stable, both organisms wash out of the system and the environment is not detoxified. When E_2 is globally asymptotically stable, the x competitor is removed from the system and the environment is detoxified to the maximum possible extent with this organism. This is the most desirable conclusion. When E_1 is globally asymptotically stable, the detoxifying agent is excluded from the system and no detoxification results. This is the worst possible case. Finally, when E_c exists, both organisms remain in the system. If E_c is globally asymptotically stable, the extent of detoxification is the value p_c. If E_c is unstable, there is a more complicated interior attractor. Our computations indicate that it is a limit cycle. The interior rest point may be stable or unstable and both case are illustrated below.

The Liapunov function used to establish the global stability of E_2 was

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

where c is a positive number to be chosen in the argument. See [38].

Before proceeding to the numerical computations, we give one proof using the fluctuation type arguments.

If $\lambda_2 > 1$, then $\lim_{t\to\infty} y(t) = 0$. Moreover, if $\lambda^+ < 1$, E_1 is globally asymptotically stable.

Proof. If $\lim_{t\to\infty} y(t)$ exists and is not zero, then $\lim_{t\to\infty} S(t) = \lambda_2$ which is a contradiction since $\lambda_2 > 1$. Suppose $\liminf_{t\to\infty} y(t) < \limsup_{t\to\infty} y(t)$. Since $y(t)$ is not monotone and is smooth, there is a sequence $\{t_k\}$, $t_k \to \infty$ as $k \to \infty$ such that $y'(t_k) = 0$, and $\lim_{t\to\infty} y(t_k) = \limsup_{t\to\infty} y(t) > 0$. (This is sometimes called the fluctuation lemma.) Then $\lim_{k\to\infty} \left[\frac{m_2 S(t_k)}{a_2 + S(t_k)} - 1\right] = 0$, or $\lim_{k\to\infty} S(t_k) = \lambda_2 > 1$, a contradiction since no omega limit point of (10) can have an S-component greater than one. Thus the omega limit set lies in the plane $y = 0$.

If, in addition, $\lambda^+ < 1$, it follows that $\lim_{t\to\infty}(S(t), x(t), p(t)) = (\lambda^+, \hat{x}, 1)$ for all trajectories in the invariant set $y = 0$. □

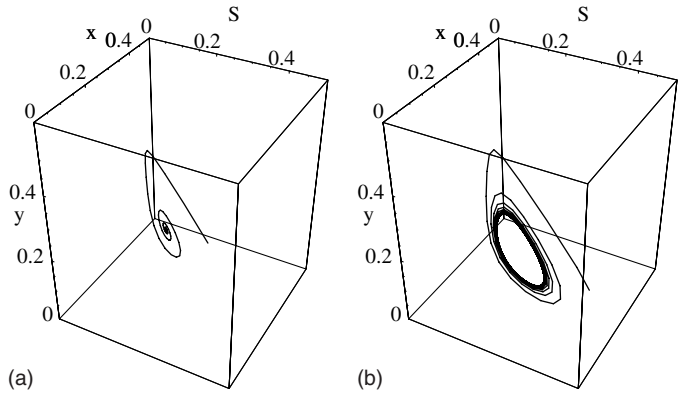

Fig. 2. The parameters are $a_2 = 1.0$, $m_1 = 4.0$, $m_2 = 5.0$, $\gamma = 4.0$, $K = 1.3$, $\delta = 5.0$, (a) $a_1 = 0.06$, (b) $a_1 = 0.03$.

The interior rest point E_c can be locally stable or locally unstable and this can be determined using the Routh–Hurwitz criterion. Choose the parameters to be: $a_2 = 1.0$, $m_1 = 4.0$, $m_2 = 5.0$, $\gamma = 4.0$, $K = 1.3$, $\delta = 5.0$. The parameters are chosen to illustrate the phenomena and are not biologically motivated. If $a_1 = 0.06$ the interior rest point has coordinates $(S, x, y, p) = (0.25, 0.149, 0.216, 0.643)$ and the Routh–Hurwitz criterion indicates that it is stable. A typical trajectory is shown in Fig. 2(a) in (S, x, y) coordinates. Since $\lim_{t\to\infty} p(t)$ exists, this can be thought of as the plot of an asymptotically limiting system. The computations indicate that the rest point is globally asymptotically stable but this has not been rigorously established.

If the rest point becomes unstable, then the orbit leaves a neighborhood of the rest point, but because of the uniform persistence, it must remain in the interior of the positive cone. Since the system is four dimensional strange attractors are theoretically possible. However, the simulations show a simple, globally asymptotically stable limit cycle. The parameters are as above except that $a_1 = 0.03$. The coordinates of the interior rest point become (0.25, 0.140, 0.296, 0.556). We show the plot in (S, x, y)-space in Fig. 2(b). The orbit is shown in R^3, but the reader is reminded that $p(t)$, the coordinate not shown, is oscillatory.

The final results are essentially the same as in the preceding section where the inhibitor was not lethal and the major interesting outcomes were a stable limit cycle or a stable spiral point. However, the mathematical tools needed were very different. While the limit cycle shown in Fig. 1 was rigorously established, only uniform persistence was established for Fig. 2. That the attractor is a limit cycle and, if it is, that it is unique, has not been established and these remain open mathematical questions.

5. Internal inhibition

Sections 3 and 4 discussed competition in the chemostat with an inhibitor that was introduced into the system from the feed bottle to create a selective medium. An alternative would be to use a medium where the selective pressure is generated within the system itself, for example, where one of the competitors produces a toxin against the other.

In a fundamental paper, Chao and Levin [12] demonstrated the presence of anti-bacterial toxins. A model for such toxins in the chemostat was given by Levin [13]. Such toxins affect the medium in the same way as the external model discussed above except now the concentration of the inhibitor is determined by the abundance of the competitor producing it. The resources used to produce the inhibitor must be taken from the resources that would otherwise be used for growth. As with the external inhibitor, we divide the problem in to the case where the inhibitor interferes with growth of, and the case where it is lethal to, the organism.

In this section we consider the first case and assume that the inhibitor reduces the growth of the organism. The case of the lethal inhibitor will be considered in Section 6. Since the proportionality of growth to consumption is one of the basic assumptions of the chemostat, this, in effect, says that the inhibitor interferes with the cells ability to take up the nutrient.

We continue the convention that x represents the organism affected by the inhibitor and thus y represents the organism producing the inhibitor. The parameter k represents the fraction of the consumption devoted to producing the inhibitor. The other parameters – basic chemostat parameters – have the same meaning as before.

The equations take the form

$$\begin{aligned} S' &= (S^{(0)} - S)D - x\mathrm{e}^{-\mu p}\frac{1}{\gamma_1}\frac{m_1 S}{a_1 + S} - y\frac{1}{\gamma_2}\frac{m_2 S}{a_2 + S}, \\ x' &= x\left[\frac{m_1 S}{a_1 + S}\mathrm{e}^{-\mu p} - D\right], \\ y' &= y\left[(1-k)\frac{m_2 S}{a_2 + S} - D\right], \\ p' &= ky\frac{m_2 S}{a_2 + S} - Dp. \end{aligned} \tag{13}$$

As before, the variables are first scaled to non-dimensional ones in the same manner as above and the equations take the form

$$\begin{aligned} S' &= 1 - S - x\frac{m_1 S}{a_1 + S}\mathrm{e}^{-\mu p} - y\frac{m_2 S}{a_2 + S}, \\ x' &= x\left[\frac{m_1 S}{a_1 + S}\mathrm{e}^{-\mu p} - 1\right], \\ y' &= y\left[(1-k)\frac{m_2 S}{a_2 + S} - 1\right], \\ p' &= ky\frac{m_2 S}{a_2 + S} - p. \end{aligned} \tag{14}$$

If the new variable $\Sigma = 1 - S - x - y - p$ is introduced, then $\Sigma' = -\Sigma$. Rewriting the system in terms of Σ, x, y, p and applying the theory of asymptotically autonomous systems, produces the limiting system

$$x' = x\left[\frac{m_1(1-x-y-p)}{a_1 + 1 - x - y - p}\mathrm{e}^{-\mu p} - 1\right],$$

$$\begin{aligned} y' &= y\left[(1-k)\frac{m_2(1-x-y-p)}{a_2+1-x-y-p}-1\right], \\ p' &= ky\frac{m_2(1-x-y-p)}{a_2+1-x-y-p}-p. \end{aligned} \tag{15}$$

The no cycle condition, required to use the asymptotically autonomous theory, will become clear after we analyze the stability of the rest points. One further reduction is possible. Introduce the new variable $\Gamma = p - cy$, $c = \frac{k}{1-k}$, in (15). Then, since $\Gamma' = -\Gamma$, the limiting equation for (15) becomes

$$\begin{aligned} x' &= x\left[\frac{m_1(1-x-(1+c)y)}{a_1+1-x-(1+c)y}\mathrm{e}^{-c\mu y}-1\right], \\ y' &= y\left[(1-k)\frac{m_2(1-(1+c)y-x)}{a_2+1-x-(1+c)y}-1\right]. \end{aligned} \tag{16}$$

The variables are constrained to be in

$$\Omega = \{(x,y)|x \geqslant 0, y \geqslant 0, (1+c)y + x \leqslant 1, c = k/1-k\}.$$

The asymptotic behavior of the system (16) will be determined. The region Ω is positively invariant under the solution map for (16). The theory of asymptotically autonomous systems allows one to draw the same conclusions for the original system.

As before, certain break-even concentrations will be important. Define λ_1, λ_2, and λ_2^+ as solutions of

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

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

$$\frac{m_2\lambda_2^+}{a_2+\lambda_2^+} = \frac{1}{1-k}.$$

There is no minimum value for the level of the inhibitor since if the y-populations washes out of the chemostat, no inhibitor is produced. Clearly, $\lambda_2 < \lambda_2^+$.

There are three potential rest points on the boundary which we label

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

$$E_1 = (1-\lambda_1, 0),$$

$$E_2 = (0, (1-\lambda_2^+)(1-k)).$$

These correspond respectively, to both populations washing out of the chemostat, the x-population washing out, and the y-population washing out. The local stability of each rest point can be found by computing the eigenvalues of the variational matrix evaluated at each of the rest point listed above. The computations are standard and we summarize the results in Table 6. Note that $\lambda_2^+ < \lambda_1$ is sufficient for the stability of E_2.

Table 6

Point	Existence	Locally asymptotically stable if
E_0	Always	$\lambda_1 > 1$, $\lambda_2^+ > 1$
E_1	$0 < \lambda_1 < 1$	$0 < \lambda_1 < \lambda_2^+$
E_2	$\lambda_2^+ < 1$	$\frac{m_1\lambda_2^+}{a_1+\lambda_2^+}e^{-k\mu(1-\lambda_2^+)} < 1$

The location and the stability of an interior rest point is a more delicate matter. The equations for the rest point take the form

$$\frac{m_1(1-x-(1+c)y)}{a_1+1-x-(1+c)y}e^{-c\mu y}-1=0,$$

$$(1-k)\frac{m_2(1-(1+c)y-x)}{a_2+1-x-(1+c)y}-1=0.$$

The variables are constrained to be in Ω. From the second equation one has that any interior rest point must lie on the line

$$(1+c)y+x=1-\lambda_2^+, \quad (x,y)\epsilon\mathring{\Omega},$$

and hence that

$$\frac{m_1\lambda_2^+}{a_1+\lambda_2^+}e^{-c\mu y}=1. \tag{17}$$

Thus to have an interior rest point it must be the case that $\lambda_1 < \lambda_2^+$. One can solve this equation for the y coordinate of the rest point to obtain that

$$y_c=-\frac{1}{c\mu}\ln\left(\frac{a_1+\lambda_2^+}{m_1\lambda_2^+}\right).$$

This will be a positive number if $\lambda_2^+ > \lambda_1$ and it will be less than one for μ sufficiently large, say $\mu > \mu_0$. Then $x_c = 1-\lambda_2^+-(1+c)y_c$. This will be positive if μ is sufficiently large, and we can take μ_0 to be this critical value of μ where both conditions are satisfied.

Since the system is two dimensional and smooth, the Poincaré–Bendixson Theorem applies. For example, if E_c does not exist, the only omega limits sets are E_1 and E_2. As noted above, $0 < \lambda_1 < \lambda_2^+$, required for the existence of E_c makes E_1 locally asymptotically stable. If E_c exists, then (17) makes E_2 locally asymptotically stable. Moreover (16) is a competitive system and there are no limit cycles. Thus, E_c, when it exists, that is, for μ sufficiently large, is unstable and both E_1 and E_2 are locally stable. The basins of attraction of E_1 and E_2 are open sets, and, since the interior rest point is unstable, these rest points attract all trajectories except for the stable manifold of E_c. This means that the outcome of the competition depends on the initial conditions.

The global results, which follow directly from the Poincaré–Bendixson Theorem and the absence of limit cycles, are summarized in Table 7.

The case of bistable attractors is the most interesting and the trajectories for a variety of initial conditions for such a case are plotted in Fig. 3. As noted above the interpretation of bistable attractors on the boundaries is that competitive exclusion holds but the winner is determined by the initial conditions.

Table 7

$\lambda_2^+ > 1$	$\lambda_1 > 1$		E_0 is a global attractor
	$\lambda_1 < 1$		E_1 is a global attractor
$\lambda_2^+ < 1$	$\lambda_2^+ < \lambda_1$		E_2 is a global attractor
	$\lambda_1 < \lambda_2^+$	$\mu < \mu_0$	E_1 is a global attractor
		$\mu > \mu_0$	Bistable attractors

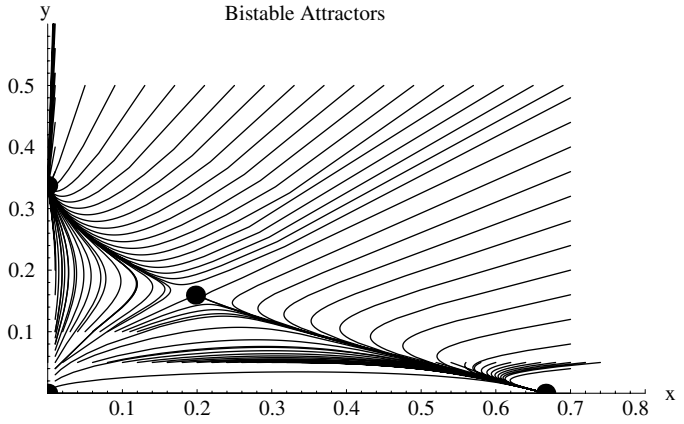

Fig. 3. Bistable attractors.

6. Lethal internal inhibitors

We turn now to the case that the inhibitor is produced by one of the competitors and is lethal to the other. As in the external case, the change from inhibited growth to increased death is not great from a biological standpoint but does introduced serious mathematical complications. Our presentation of this problem follows the pattern of the previous sections.

Chao and Levin [12], demonstrated the presence of anti-bacterial toxins. In their experiments, the winner of the competition was determined by the initial conditions. See, in particular, Fig. 1 of the above cited paper of Levin. In the model the inhibitor 'kills' the organism; this effect is modeled by a mass action term. As with the external inhibitor, presence of the mass action term takes away many of the tools normally used in the analysis on chemostat models; in particular, the monotonicity of the resulting differential equations is lost.

The only difference between the model discussed here and the one of Levin cited above, is that we attribute a cost to the production of the inhibitor. We again seek to describe the global asymptotic behavior of the model in terms of the parameters of the system. In the case of bistable attractors, we are not able to rule out the possibility of other than steady state attractors although our computer simulations have not demonstrated any. This possibility remains an open question. The techniques are those of Liapunov functions. The full details and the proofs can be found in [40].

The model takes the form

$$\begin{aligned} S' &= (S^{(0)} - S)D - \frac{m_1 S}{a_1 + S}\frac{x}{\gamma_1} - \frac{m_2 S}{a_2 + S}\frac{y}{\gamma_2}, \\ x' &= x\left[\frac{m_1 S}{a_1 + S} - D - \gamma p\right], \\ y' &= y\left[(1-k)\frac{m_2 S}{a_2 + S} - D\right], \\ p' &= k\frac{m_2 S y}{a_2 + S} - Dp. \end{aligned} \tag{18}$$

The variables and parameters are as before; $0 \leqslant k < 1$ represents the fraction of potential growth allocated to producing the toxin. We scale to non-dimensional variables to obtain

$$\begin{aligned} S' &= 1 - S - \frac{m_1 S}{a_1 + S}x - \frac{m_2 S}{a_2 + S}y, \\ x' &= x\left[\frac{m_1 S}{a_1 + S} - 1 - \gamma p\right], \\ y' &= y\left[(1-k)\frac{m_2 S}{a_2 + S} - 1\right], \\ p' &= k\frac{m_2 S}{a_2 + S}y - p. \end{aligned} \tag{19}$$

The interaction between the toxin and the sensitive microorganisms is taken to be of mass action form, $-\gamma p x$. A portion of the nutrient consumption has been allocated to the production of the toxin and the growth rate correspondingly debited. The form of the equations are such that positive initial conditions at $t = 0$ result in positive solutions for $t > 0$. (The positive cone is positively invariant.) Let $\Sigma = S + x + y + p$. The boundedness of solutions is obtained by a simple inequality. Since

$$\Sigma' = 1 - S - x - y - p - \gamma x p \leqslant 1 - \Sigma,$$

then $\limsup_{t\to\infty} \Sigma(t) \leqslant 1$. Since each component is non-negative, the system is dissipative and thus, has a compact, global attractor.

The order of the system may be reduced by one dimension (in contrast to two above). To reduce the order of the model let $z = p - \frac{ky}{1-k}$, and note that $z' = -z$. Clearly, $z(t) \to 0$, so the theory of asymptotically autonomous systems yields the limiting system

$$\begin{aligned} S' &= 1 - S - \frac{m_1 S x}{a_1 + S} - \frac{m_2 S y}{a_2 + S}, \\ x' &= x\left[\frac{m_1 S}{a_1 + S} - 1 - \frac{k\gamma}{1-k}y\right], \\ y' &= y\left[(1-k)\frac{m_2 S}{a_2 + S} - 1\right]. \end{aligned} \tag{20}$$

The work of Thieme [24], (or see [17], Appendix F) relates the corresponding dynamics. (As always, there are some simple hypotheses to verify before claiming that the two dynamical systems have the same asymptotic behavior.)

Only three parameters are required to characterize the classes of asymptotic behavior. Define λ_1, λ_2^+, $\hat{\lambda}$, as solutions of

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

$$\frac{m_2\lambda_2^+}{a_2+\lambda_2^+}=\frac{1}{1-k},$$

$$\frac{m_1\hat{\lambda}}{a_1+\hat{\lambda}}=1+\gamma k(1-\hat{\lambda}),$$

We tacitly assume that they are different. Clearly, $\lambda_1<\hat{\lambda}$. The eventual behavior is determined by where λ_2 falls in the ordering.

There are three potential rest points on the boundary which we label

$$E_0=(1,0,0),$$

$$E_1=(\lambda_1,1-\lambda_1,0),$$

$$E_2=(\lambda_2^+,0,(1-k)(1-\lambda_2^+)).$$

There also can be a (unique, if it exists) interior rest point, $E_c=(S_c,x_c,y_c)$. Clearly, for such a point to exist, $S_c=\lambda_2^+$. It follows then that $y_c=\frac{1-k}{k\gamma}\left[\frac{m_1\lambda_2^+}{a_1+\lambda_2^+}-1\right]$ provided this quantity is positive which will be the case if $\lambda_2^+>\lambda_1$. Finally, the sign of x_c is the sign of $1-\lambda_2^+-\frac{1}{\gamma k}\left(\frac{m_1\lambda_2^+}{a_1+\lambda_2^+}\right)$. This will be positive if $\lambda_2^+<\hat{\lambda}$. See [40] for the details. Stability of the rest points is given in Table 8.

The first three entries in Table 8 correspond to the absence of one or both competitors. The proof of the claims in the table rest with a linear stability analysis around the respective rest points. As a consequence, if an inequality for stability is reversed, the rest point is unstable. (E_c is unstable if it exists but has a non-empty stable manifold.) Note that E_c exists if E_1 and E_2 are both stable.

The conditions for local stability are in fact global. This is summarized in Table 9.

Table 8

	Exists	Asymptotic stability
E_0	Always	$\lambda_1>1,\lambda_2^+>1$
E_1	$0<\lambda_1<1$	$0<\hat{\lambda}<\lambda_2^+$
E_2	$\lambda_2^+<1$	$0<\lambda_2^+<\hat{\lambda}$
E_c	$\lambda_1<\lambda_2^+<\hat{\lambda}<1$	Unstable

Table 9

Condition	Attractor
$\lambda_2^+<\lambda_1<\hat{\lambda}$	E_2
$\lambda_1<\lambda_2^+<\hat{\lambda}$	Bistable attractors
$\lambda_1<\hat{\lambda}<\lambda_2^+$	E_1

The proof of global stability for E_0 is quite simple as is the instability of E_c when it exists. The global stability of E_1 and E_2 require Liapunov function type arguments. For E_2 one uses

$$V(S,x,y) = \int_{\lambda_2^+}^{S} \frac{\eta - \lambda_2^+}{\eta}\,\mathrm{d}\eta + c_1 \int_{y_c}^{y} \frac{\eta - y_c}{\eta}\,\mathrm{d}\eta + c_2 x.$$

where c_1 and c_2 are determined in the course of the proof.

For the global stability of E_1, the function used was of the form

$$V(S,x,y) = \int_{\lambda_1}^{S} \frac{x_c\left(\frac{m_1\xi}{a_1+\xi} - 1\right)}{1-\xi}\,\mathrm{d}\xi + \int_{x_c}^{x} \frac{\xi - x_c}{\xi}\,\mathrm{d}\xi + cy,$$

where again $c > 0$ is determined in the argument. The computations are long and make use of the approach of Wolkowicz and Lu [41].

Mathematically, one can intuitively think of the significant parameter λ_2^+ as being a function of k. When $k = 0$, y is the weaker competitor and washes out of the system; when $k = 1$, all energy is devoted to toxin production, so there is no growth and y washes out of the system. For values of k, where the interior, unstable rest point exists, the stable manifold of that rest point separates the space into two basins of attraction. Where the initial conditions lie, determines which attractor the trajectory approaches. This intuition is, of course, more than was rigorously proved in [40].

A plot of a variety of trajectories for a case of bistable attractors is shown in Fig. 4; this is similar to Fig. 3 except that it is in three dimensions.

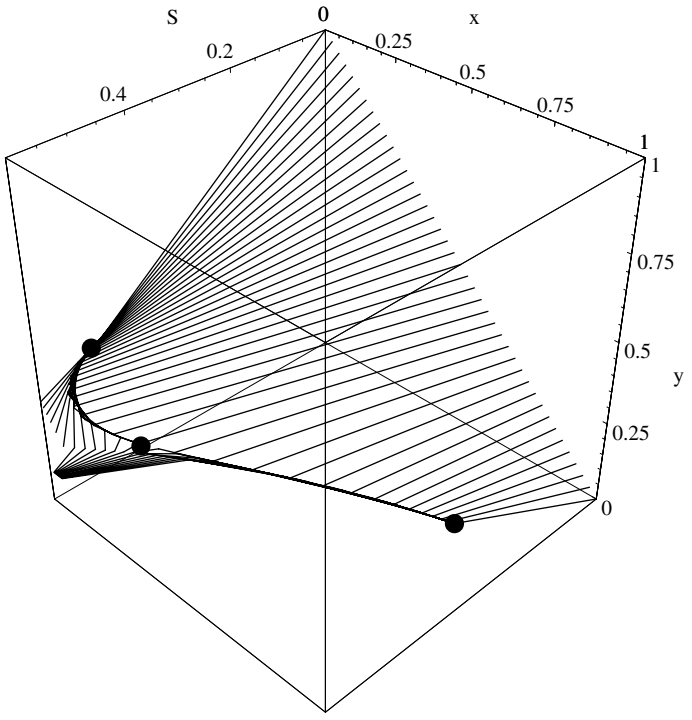

Fig. 4. Bistable attractors in three dimensions.

In the model the effort devoted to the production of the inhibitor was a constant. A more natural assumption might be that the effort devoted to inhibitor production be a function of the state of the system, that is, modify the k in the model to become $k(x,y)$. The inhibitor production can be adjusted to reflect the state of the competition, that is, it can be allocated dynamically. For example, if there is no competition, there is no need to devote the constant fraction to inhibitor production. More explicitly, replace the system (18) by

$$\begin{aligned} S' &= (S^{(0)} - S)D - \frac{m_1 S}{a_1 + S}\frac{x}{\gamma_1} - \frac{m_2 S}{a_2 + S}\frac{y}{\gamma_2}, \\ x' &= x\left[\frac{m_1 S}{a_1 + S} - D - \gamma p\right], \\ y' &= y\left[(1 - k(x,y))\frac{m_2 S}{a_2 + S} - D\right], \\ p' &= k(x,y)\frac{m_2 S y}{a_2 + S} - Dp. \end{aligned} \tag{21}$$

It is convenient to assume that the yield constants are equal, $\hat{\gamma} = \gamma_1 = \gamma_2$. Without this assumption, one has an additional parameter, the ratio of the yield constants. With this assumption, we perform the same scaling as before to obtain

$$\begin{aligned} S' &= 1 - S - \frac{m_1 S}{a_1 + S}x - \frac{m_2 S}{a_2 + S}y, \\ x' &= x\left[\frac{m_1 S}{a_1 + S} - 1 - \gamma p\right], \\ y' &= y\left[(1 - k(x,y))\frac{m_2 S}{a_2 + S} - 1\right], \\ p' &= k(x,y)\frac{m_2 S}{a_2 + S}y - p. \end{aligned} \tag{22}$$

This system was investigated in [42]. Since the level of inhibitor production depends on the organism being able to sense the state of the system, one must first answer as to a possible mechanism. This is possibly provided, although not yet established experimentally in this case, by the mechanism of quorum sensing. See Bassler [43] for a review. [42] considers two special cases that represent the extremes for reasonable functions

$$k(x,y) = \frac{\alpha y}{\beta + x + y}, \tag{23}$$

$$k(x,y) = \frac{\alpha x}{\beta + x + y}, \tag{24}$$

(23) is monotone increasing in y while (24) is monotone increasing in x. These are two opposite strategies. For the first, a large y causes the organism to devote more of its resources to producing the toxin for it can afford to do so. This guards against invasion. In (24) if x is large, y increases the toxin production. Since it is already losing the competition this represents a desperation strategy. One advantage of this strategy is that if there is no competition, no resource is wasted on toxin

production. Both can produce interior attractors. A mixture of the two would be possible and one can conceive of many other strategies that could be investigated.

In principle the same dynamical systems techniques used for (18) could be applied but the complications become apparent immediately. For example, while the boundary rest points can be analyzed directly, the interior rest points require the solution of a fifth order polynomial. Thus the analysis in [42] proceeds by numerical computation using a general Mathematica notebook. The numerical examples show that a wide variety of dynamical systems can be achieved. The most interesting examples are bistable attractors where one attractor is interior, in contrast to the constant case where the only attractors are on the boundary. We reproduce two tables and graphs from [42] as illustrations.

Let

$$k(x,y)=\frac{\alpha y}{\beta+x+y},$$

and let $m_1=1.17$, $m_2=1.17$, $a_1=0.017$, $a_2=0.025$, $\alpha=0.6$, $\beta=0.01$, and $\gamma=20$. The rest points and their stability are shown in Table 10 where the boundary rest points have numerical subscripts and the interior ones have capital letter subscripts.

The dynamical systems has (apparently, as no proofs have been constructed) an interior, stable limit cycle, and a stable boundary rest point. A plot of trajectories, projected onto the x–y–S-space, is shown in Fig. 5.

We turn now to the choice

$$k(x,y)=\frac{\alpha x}{\beta+x+y}, \tag{25}$$

with parameters $m_1=1.1$, $m_2=1.1$, $a_1=0.0567$, $a_2=0.06$, $\alpha=0.2$, $\beta=1.0$, and $\gamma=6$. There are two interior rest points; the coordinates and the eigenvalues of all rest points given in Table 11.

Trajectories of the differential equations were computed with these parameters and the results, projected onto two dimensions, are shown in Fig. 6.

With constant inhibitor production, E_1 stable, and E_2 unstable, the y-population lost the competition. In this case, the inhibitor was sufficiently effective that, for an open region in the parameter space, coexistence occurred.

The obvious significance from an ecological standpoint is that by producing a toxin against its competitor, even with some degradation of its growth rate (fitness) a population can survive when it would otherwise be excluded. For reactor technology, which will be discussed below when plasmids are considered, this is relevant to the possibility of using internally produced inhibitors rather than externally provided ones.

Table 10

Rest point	Coordinates	Eigenvalues	Stability
E_0	(1, 0, 0, 0)	−1, −1, 0.14, 0.15	Unstable
E_1	(0.1, 0.9, 0, 0)	−1.3, −1.0, −1.0, −0.0064	Stable
E_2	(0.99, 0, 0.0026, 0.00036)	−1.0, −1.0, 0.14, −0.11	Unstable
E_A	(0.26, 0.60, 0.072, 0.0049)	−1.1, −0.92, −0.29, 0.087	Unstable
E_B	(0.68, 0.22, 0.055, 0.0070)	$-1.1, -1, 0.00020 \pm 0.10i$	Unstable

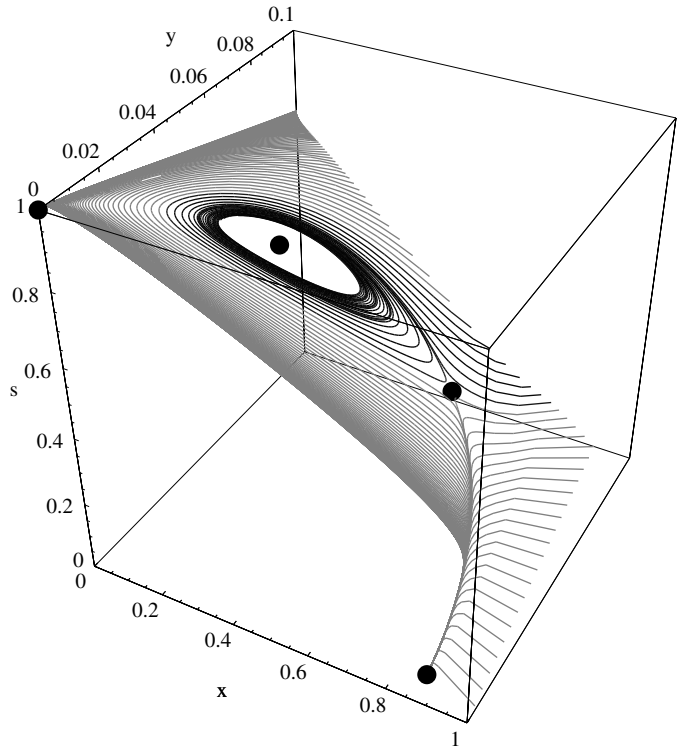

Fig. 5. A limit cycle for the model with dynamically allocated inhibitor production.

Table 11

Rest point	Coordinates	Eigenvalues	Stability
E_0	(1, 0, 0, 0)	−1, −1, 0.030, 0.037	Unstable
E_1	(0.57, 0.43, 0, 0)	−1.0, −1.0, −0.070, −0.066	Stable
E_2	(0.6, 0, 0.4, 0)	−1.0, −1.0, 0.061, −0.0051	Unstable
E_A	(0.63, 0.034, 0.33, 0.0016)	−1.00, −0.99, −0.056, −0.0025	Stable
E_B	(0.69, 0.077, 0.23, 0.0027)	−1.01, −0.98, −0.054, 0.038	Unstable

7. A model of plasmid-bearing, plasmid-free competition in the chemostat

The ability to manufacture products through genetically altered organisms is one of the modern developments in biotechnology. This genetic alteration commonly takes place through the insertion of a plasmid which codes for the production of the desired protein. Normally, the plasmid reproduces when the cell divides, but, with some probability, the plasmid is not passed to the daughter cell which introduces the plasmid-free organism into the process. Since the plasmid-free organism does not carry the added metabolic burden imposed by the plasmid, it is potentially a better competitor. The study of mathematical models for the competition between plasmid-free and plasmid-bearing populations has recently been a problem of considerable interest. We have

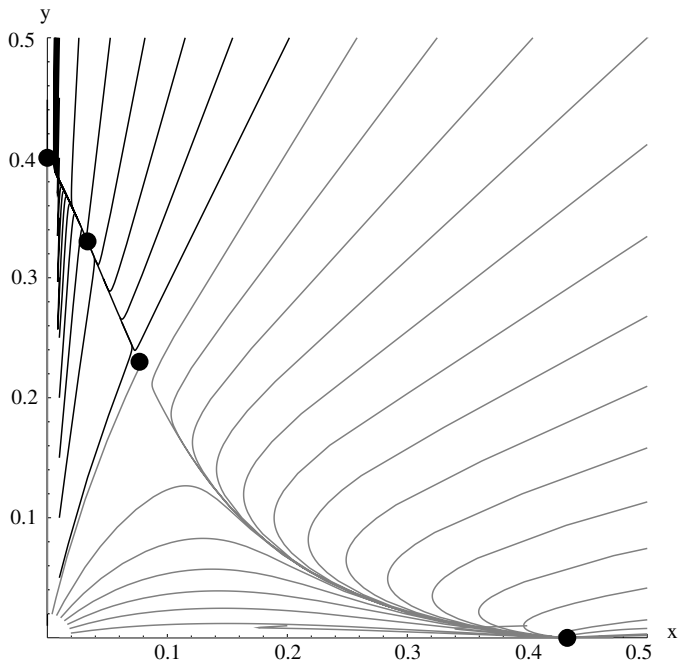

Fig. 6. Coexistence with E_2 unstable and E_1 stable.

already cited [3–13]. We begin with a detailed description of the basic model of competition between plasmid-bearing and plasmid-free organisms.

One begins with the basic chemostat equations, (1) and modifies them for the case that one organism, y, is plasmid-bearing but the plasmid can be lost in reproduction, resulting in a plasmid-free-organism x. It is also reasonable to assume that the yield constants for the two organism are the same since they are the same organism just with, and without, the plasmid. To keep continuity through the survey, we shall again assume that the uptake functions are of Monod form, $f_i(S) = \frac{m_i S}{a_i + S}$, but the known results for these equations are valid for much more general functions. The parameters have the same meaning as in the basic chemostat model except for the constant q which is the fraction of plasmids lost. The modified equations become

$$\begin{aligned} S' &= (S^{(0)} - S)D - \frac{x}{\gamma}\frac{m_1 S}{a_1 + S} - \frac{y}{\gamma}\frac{m_2 S}{a_2 + S}, \\ x' &= x\left(\frac{m_1 S}{a_1 + S} - D\right) + qy\frac{m_2 S}{a_2 + S}, \\ y' &= y\left(\frac{m_2 S}{a_2 + S}(1 - q) - D\right). \end{aligned} \tag{26}$$

These equations appear (more generally) in [4], and have been investigated mathematically in [7] where the system was first reduced to a plane autonomous system and then the Dulac criterion was used to show that there were no periodic orbits. Conditions were given for the existence and global stability of the rest points. We do not reproduce the results of [7] as they are contained (for the

Monod case) as special cases of the material presented below by choosing certain parameters (involving inhibitor production or introduction and the effect on the sensitive organism) to be zero. These equations will be modified to account for the inhibitor and its effect in the following sections.

8. Plasmid-bearing, plasmid-free competition with an external inhibitor

As noted above, the plasmid-free organism is expected to be a better competitor since it does not carry the added metabolic load. To avoid 'capture' of the process by the plasmid-free organism, selective media are used for the culture. The most obvious of these techniques is to induce antibiotic resistance into the cell on the same plasmid that codes for the production and to introduce an antibiotic (inhibitor) into the medium. Thus if the plasmid is lost, the organism is susceptible to the antibiotic. The case with the external inhibitor will be discussed in first in this section. It is a combination of the model of the chemostat with an external inhibitor discussed in Section 3 and the plasmid model discussed in Section 7. This model was proposed and analyzed in [6] and this section follows that development. The variables and parameters are as before, and the model, after scaling, takes the form

$$\begin{aligned} S' &= 1 - S - \mathrm{e}^{-\mu p}\frac{m_1 S}{a_1 + S}x - \frac{m_2 S}{a_2 + S}y,\\ x' &= x\left[\mathrm{e}^{-\mu p}\frac{m_1 S}{a_1 + S} - 1\right] + q\frac{m_2 S}{a_2 + S}y,\\ y' &= y\left[(1-q)\frac{m_2 S}{a_2 + S} - 1\right],\\ p' &= 1 - p - \frac{\delta p}{K + p}y. \end{aligned} \tag{27}$$

We will assume that $m_i > 1$, $i = 1, 2$; otherwise easy inequality arguments show that the corresponding population tends to zero as t tends to infinity. We follow the same reduction as before. Let $\Sigma(t) = 1 - x(t) - y(t) - S(t)$. Then, since $\Sigma' = -\Sigma$, or $\lim_{t\to\infty}\Sigma(t) = 0$, the limiting system may be written

$$\begin{aligned} x' &= x\left[\mathrm{e}^{-\mu p}\frac{m_1(1-x-y)}{a_1 + 1 - x - y} - 1\right] + qy\frac{m_2(1-x-y)}{a_2 + 1 - x - y},\\ y' &= y\left[(1-q)\frac{m_2(1-x-y)}{a_2 + 1 - x - y} - 1\right],\\ p' &= 1 - p - \frac{\delta p}{K + p}y. \end{aligned} \tag{28}$$

$$x(0) \geqslant 0, \quad y(0) \geqslant 0, \quad p(0) \geqslant 0, \quad 0 \leqslant x(0) + y(0) \leqslant 1.$$

Note that when $q = 0$, (27) is exactly (4) with $f(p) = \mathrm{e}^{-\mu p}$.

We define the four parameters that will determine the behavior of the system as solutions of the following equations:

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

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

$$\frac{m_1\lambda_1^+}{a_1+\lambda_1^+}=e^{\mu},$$

$$\frac{m_2\lambda_2^+}{a_2+\lambda_2^+}=\frac{1}{1-q},$$

λ_1 and λ_2 are the basic chemostat parameters but they will not play a crucial role here. The outcomes will be determined by the remaining two parameters. For λ_1^+ to be positive it is necessary that $m_1 > e^{\mu}$; for λ_2^+ to be positive it is necessary that $m_2(1-q) > 1$. To avoid needless repetition, we will assign the values $+\infty$ when the inequalities are violated. The intuition is that the function on the left hand side of the equality has a limit as the variable tends to infinity that is lower than the value on the right hand side of the defining equation.

There are two rest points on the boundary which we label

$$E_0 = (0,0,1), \quad \text{(the washout state)},$$

$$E_1 = (x^*,0,1), \quad \text{(the plasmid-free state)},$$

where x^* is a positive root of

$$e^{-\mu}\frac{m_1(1-z)}{a_1+1-z}=1$$

or

$$x^*=\frac{m_1e^{-\mu}-(1+a_1)}{m_1e^{-\mu}-1}.$$

These are obviously undesirable limits (omega limit sets) for the system as it is the plasmid-bearing organism that manufactures the product. E_0 always exists and $\lambda_1 < 1$ guarantees the existence of E_1; the reversal of the inequality precludes the existence of E_1. Note that in contrast to the models of Section 3, there is no rest point with $x = 0$, $y > 0$ since a positive plasmid-bearing state contributes input to the plasmid-free state.

An interior rest point is a solution of the algebraic system

$$x\left[e^{-\mu p}\frac{m_1(1-x-y)}{a_1+1-x-y}-1\right]+qy\frac{m_2(1-x-y)}{a_2+1-x-y}=0,$$

$$(1-q)\frac{m_2(1-x-y)}{a_2+1-x-y}-1=0,$$

$$1-p-\frac{\delta p}{K+p}y=0,$$

Straightforward algebra shows that, if $\lambda_2^+ < 1 < \lambda_1^+$ or if $\lambda_1^+ < 1$ and $1 > \lambda_1^+ > \lambda_2^+ > 0$, there will be a unique interior rest point. We label the positive equilibrium

$$E_c = (x_c, y_c, p_c).$$

The stability of E_0 and E_1 follows from standard linearization arguments. For E_c the calculation, though standard, is much more complicated and we turn again to the Routh–Hurwitz criterion.

The characteristic polynomial of the Jacobian

$$J = \begin{bmatrix} m_{11} & m_{12} & m_{13} \\ m_{21} & m_{22} & 0 \\ 0 & m_{32} & m_{33} \end{bmatrix}$$

at E_c takes the form

$$\lambda^3 + B_1\lambda_1^2 + B_2\lambda + B_3 = 0,$$

where

$$B_1 = -m_{11} - m_{22} - m_{33} > 0,$$

$$B_2 = m_{11}m_{22} - m_{12}m_{21} + m_{11}m_{33} + m_{22}m_{33} > 0,$$

$$B_3 = -m_{33}(m_{11}m_{22} - m_{12}m_{21}) - m_{13}m_{21}m_{32} > 0.$$

One may apply the Routh–Hurwitz criterion to conclude that all of roots have negative real part if and only if $B_1B_2 > B_3$. This is obviously a very complicated algebraic expression, but for fixed values of the parameters, is easy to check with any of the algebraic manipulation programs, Mathematica, for example. We summarize the local results in Table 12.

Easy arguments using differential inequalities and comparison arguments show that E_0 is a global attractor if $\lambda_1^+ > 1$ and $\lambda_2^+ > 1$. A more difficult argument is required to show that if $0 < \lambda_1^+ < \lambda_2^+ < 1$, then E_1 is a global attractor (of the interior of the positive cone). The argument divides the positive cone into three disjoint pieces and then argues that all trajectories eventually (i.e., for large values of time) enter and remain in one of them. For trajectories in this region, the only possible omega limit set is E_1. The results are summarized in Table 13.

Note that the existence of E_c requires either the non-existence of E_1 or its instability. Easy arguments show that the existence of E_c makes the system uniformly persistent as for example in Theorem 1. This is an important remark for when E_c is unstable there must be an interior global attractor and it must be more complicated than a rest point. Ai [44] has provided conditions that

Table 12

	Exists	Locally asymptotically stable if
E_0	Always	$\lambda_1^+ > 1, \lambda_2^+ > 1$
E_1	$0 < \lambda_1^+ < 1$	$0 < \lambda_1^+ < \lambda_2^+$
E_c	$0 < \lambda_2^+ < \lambda_1^+ < 1$ or $\lambda_1^+ > 1$, $\lambda_2^+ < 1$	Routh–Hurwitz

Table 13

Conditions	$\lambda_1^+ > 1$	$\lambda_1^+ < 1$
$\lambda_2^+ > 1$	E_0 is a global attractor	E_1 is a global attractor
$\lambda_2^+ < 1$	E_c exists	$1 > \lambda_1^+ > \lambda_2^+ > 0$ – E_c exists
		$1 > \lambda_2^+ > \lambda_1^+ > 0$ – E_1 is a global attractor

establish the existence of a limit cycle. He has used a clever technique to follow trajectories through 'boxes' and has shown that they must return to the original box, allowing one to obtain a closed trajectory through the use of the Brouwer fixed point theorem.

If E_c is a global attractor for (4) (that is, (27) with $q = 0$), then [6] has shown that E_c is a global attractor for (27) if q is sufficiently small. For large q the problem remains open, awaiting, perhaps, the construction of an appropriate Liapunov function.

We now seek to change the effect of the external inhibitor to be lethal to the organism. The model then is a combination of the model of the chemostat with a lethal external inhibitor discussed in Section 4 and the plasmid model discussed in Section 7. This model was proposed and analyzed in [8] and the presentation here follows that development. The model, after scaling, and with equal yield constants, takes the form

$$\begin{aligned} S' &= 1 - S - \frac{m_1 S}{a_1 + S}x - \frac{m_2 S}{a_2 + S}y, \\ x' &= x\left(\frac{m_1 S}{a_1 + S} - 1 - \gamma p\right) + q\frac{m_2 S}{a_2 + S}y, \\ y' &= y\left((1-q)\frac{m_2 S}{a_2 + S} - 1\right), \\ p' &= 1 - p - \frac{\delta p}{K + p}y. \end{aligned} \tag{29}$$

where $S(0) \geqslant 0, x(0) > 0, y(0) > 0, p(0) \geqslant 0$. Of course, if $q = 0$ then (29) is contained in Section 4. Two parameters, λ_1^+, λ_2^+ are defined as solutions of the following equations:

$$\frac{m_1 \lambda_1^+}{a_1 + \lambda_1^+} = 1 + \gamma,$$

$$\frac{m_2 \lambda_2^+}{a_2 + \lambda_2^+} = \frac{1}{1-q}.$$

λ_1^+ is the λ^+ of Section 4 but the second parameter is different. Simple differential inequality arguments show that, for any $\epsilon > 0$, any trajectory of (29) will eventually enter the region

$$Q = \{(S, x, y, p) : 0 \leqslant S \leqslant 1, 0 \leqslant x \leqslant 1, 0 \leqslant y \leqslant 1, 0 \leqslant p \leqslant 1, 0 < S + x + y < 1 + \epsilon\}.$$

The boundary has two potential rest points given by

$$E_0 \equiv (1, 0, 0, 1),$$

$$E_1 \equiv (\lambda_1^+, x^*, 0, 1),$$

where x^* is defined by

$$x^* = \frac{1 - \lambda_1^+}{1 + \gamma}.$$

Note that if $q > 0$ there can be no rest point whose coordinates have $x = 0$. For $q = 0$ we have already noted that the theory of Section 4 applies.

The determination of the coordinates of a potential interior rest point is not as simple as it was in Section 4. Denote a potential interior rest point as $E_c = (S_c, x_c, y_c, p_c)$. Clearly one has $S_c = \lambda_2^+$. The remaining three coordinates satisfy the system

$$\begin{aligned} 1 - \lambda_2^+ &= \frac{m_1\lambda_2^+}{a_1 + \lambda_2^+}x_c + \frac{m_2\lambda_2^+}{a_2 + \lambda_2^+}y_c, \\ 1 - p_c &= \frac{\delta p_c}{K + p_c}y_c, \\ x_c\left(\frac{m_1\lambda_2^+}{a_1 + \lambda_2^+} - 1 - \gamma p_c\right) &+ q\frac{m_2\lambda_2^+}{a_2 + \lambda_2^+}y_c = 0. \end{aligned} \tag{30}$$

The algebra is quite complicated but the end result is that if $0 < \lambda_2^+ < \lambda_1^+ < 1$, there is an interior rest point and if the parameter ordering is reversed, there is not.

The (local) stability of E_1 can be computed directly from the variation equation and it is easily seen that it is asymptotically stable if $0 < \lambda_1^+ < \lambda_2^+ < 1$ and unstable if the parameter ordering is reversed. Such a computation is not possible for E_c since we do not have the explicit coordinates of the rest point.

However, when $q = 0$ this is exactly the case considered in Section 4. The local stability does not change for $q > 0$ and small, so the stability determined by the conditions expressed there (there are two cases), carry over to (29) when q is sufficiently small. The results of Section 4 depended on three parameters so the parameter λ_1^- defined there still plays a roll here. E_c can arise from two cases which, roughly speaking, can be thought of as the E_2 of Section 4 moving interior as q becomes positive or as arising from a perturbation of E_c.

The question of the global asymptotic stability of the interior rest point as well as questions of the existence of limit cycles remain open for future mathematical investigation.

9. Plasmid-bearing, plasmid-free competition with an internal inhibitor

We now turn to the case discussed in Sections 5 and 6 where the inhibitor is produced by one of the organisms. This would be accomplished by coding the plasmid for the production of the inhibitor, its immunity to it, and the manufacture of a product. We consider the non-lethal case first. The model then is a combination of the model of the chemostat with an internal inhibitor discussed in Section 5 and the plasmid model discussed in Section 7. This model was proposed and analyzed in [8] and the presentation follows that development. The model takes the form, after scaling and with equal yield constants,

$$\begin{aligned} S' &= 1 - S - x\frac{m_1 S}{a_1 + S}\mathrm{e}^{-\mu p} - y\frac{m_2 S}{a_2 + S}, \\ x' &= x\left[\frac{m_1 S}{a_1 + S}\mathrm{e}^{-\mu p} - 1\right] + q\frac{m_2 S}{a_2 + S}, \\ y' &= y\left[(1 - q - k)\frac{m_2 S}{a_2 + S} - 1\right], \\ p' &= ky\frac{m_2 S}{a_2 + S} - p, \end{aligned} \tag{31}$$

where $S(0) = S_0 \geqslant 0$, $x(0) = x_0 \geqslant 0$, $y(0) = y_0 \geqslant 0$, and $p(0) = p_0 \geqslant 0$. The reader is reminded that the parameters have changed their meaning. By what is now a familiar argument, the order of the system can be reduced by one. The change of variables $\Sigma = 1 - S - x - y - p$ yields $\Sigma' = -\Sigma$ or $\lim_{t\to\infty} \Sigma(t) = 0$, so the limiting equations become

$$x' = x\left[\frac{m_1(1-x-y-p)}{a_1+1-x-y-p}e^{-\mu p} - 1\right] + qy\frac{m_2(1-x-y-p)}{a_2+1-x-y-p},$$

$$y' = y\left[(1-q-k)\frac{m_2(1-x-y-p)}{a_2+1-x-y-p} - 1\right],$$

$$p' = ky\frac{m_2(1-x-y-p)}{a_2+1-x-y-p} - p,$$

making use of the theory of asymptotically autonomous systems.

The change of variable $\Gamma = p - cy$ where $c = \frac{k}{1-q-k}$ essentially reflects expressing the amount of inhibitor in terms of the amount of the inhibitor-producing organism. Since $\Gamma' = -\Gamma$ and $\lim_{t\to\infty} \Gamma(t) = 0$, the limiting system of equations becomes

$$\begin{aligned} x' &= x\left[\frac{m_1(1-x-(c+1)y)}{a_1+1-x-(c+1)y}e^{-\mu cy} - 1\right] + qy\frac{m_2(1-x-(c+1)y)}{a_2+1-x-(c+1)y}, \\ y' &= y\left[(1-q-k)\frac{m_2(1-x-(c+1)y)}{a_2+1-x-(c+1)y} - 1\right], \end{aligned} \tag{32}$$

where $x(0) \geqslant 0$, $y(0) \geqslant 0$, $x(0) + (c+1)y(0) \leqslant 0$. The variables are constrained to be in

$$\Omega = \{(x,y) | x \geqslant 0, y \geqslant 0, (1+c)y + x \leqslant 1, c = k/1-q-k\}.$$

This region is positively invariant under the solution map for (32).

The same break-even concentrations as in Section 6 will be important. λ_1, λ_2, and λ_2^+ are defined as solutions of

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

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

$$\frac{m_2\lambda_2^+}{a_2+\lambda_2^+} = \frac{1}{1-k-q}.$$

There are only two boundary rest points which we label as

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

$$E_1 = (\lambda_1, 0),$$

E_0 is a washout state and E_1 is a plasmid-free state; both are undesirable from the standpoint of a bioreactor. An interior rest point must satisfy the system

$$1 - x - (c+1)y = \lambda_2^+,$$

$$x\left[e^{-\mu cy}\frac{m_1\lambda_2^+}{a_1+\lambda_2^+}-1\right]+\frac{q}{1-k-q}y=0.$$

Thus one seeks a root of

$$F(y)=[1-\lambda_2^+-(c+1)y]\left[e^{-\mu cy}\frac{m_1\lambda_2^+}{a_1+\lambda_2^+}-1\right]+\frac{q}{1-k-q}y=0. \tag{33}$$

The analysis of the zeros of (33) is somewhat complicated and we refer the reader to [8] for the details and only state the results. If $0<\lambda_2<\lambda_1<1$ and $0<\lambda_2^+<1$, then there exists a unique interior rest point $E^*=(x^*,y^*)$. If $0<\lambda_1<\lambda_2<1$, and $0<\lambda_2^+<1$, there exists a unique number μ^* such that (i) if $\mu<\mu^*$, there are no interior rest points and (ii) if $\mu>\mu^*$, there are exactly two interior rest points, $E^*=(x^*,y^*)$ and $\hat{E}=(\hat{x},\hat{y})$. The case $0<\lambda_2<\lambda_1<1$ indicates that y is the better competitor, and while it cannot eliminate its competitor, it forces the existence of a coexistence state. In the case $0<\lambda_1<\lambda_2<1$, x is the better competitor and will eliminate y unless the effect of the toxin is sufficiently great, reflected in the conditions by $\mu>\mu^*$.

The eigenvalues of the variational matrix determine the local stability of the rest points. Table 14 summarizes the nature of the rest points [8].

The Dulac criterion can be used to show that there are no periodic orbits. When there are no periodic orbits, the Poincaré–Bendixson Theorem applies and all omega limit sets are rest points. This can be used to make local results global when there is a unique locally stable rest point. Table 15 summarizes the results of [8].

The last case represents bistable attractors, which we have seen earlier, and the outcome depends on the initial conditions, each rest point attracting an open set.

We now change the assumption that growth is inhibited to the assumption that the inhibitor produced by y is lethal to x. The system will no longer be reducible to a two dimension system where tools such as the Poincaré–Bendixson Theorem are so helpful. The basic model is

Table 14

Rest point	Existence	Local asymptotic stability
E_0	Always	$\lambda_1>1$, $\lambda_2^+>1$
E_1	$0<\lambda_1<1$	$\lambda_1<\lambda_2^+$
E^*	$0<\lambda_2<\lambda_1<1$, $0<\lambda_2^+<1$	Existence implies stability
$\hat{E}$ and E^*	$0<\lambda_1<\lambda_2<1$, $0<\lambda_2^+<1$, $\mu>\mu^*$	One of $\hat{E}$ or E^* is stable, E_1 is stable

Table 15

Conditions	Attractor
$\lambda_2^+>1$, $\lambda_1>1$	E_0
$\lambda_2^+>1$, $0<\lambda_1<1$	E_1
$\lambda_2^+<1$, $0<\lambda_1<\lambda_2<1$	E^*
$\lambda_2^+<1$, $0<\lambda_2<\lambda_1<1$, $\mu<\mu^*$	E_1
$\lambda_2^+<1$, $0<\lambda_2<\lambda_1<1$, $\mu>\mu^*$	E_1 and one of E^* or $\hat{E}$

$$
\begin{aligned}
S' &= (S^{(0)} - S)D - \frac{m_1 S}{a_1 + S}\frac{x}{\gamma_1} - \frac{m_2 S}{a_2 + S}\frac{y}{\gamma_2},\\
x' &= x\left[\frac{m_1 S}{a_1 + S} - D - \gamma p\right] + q\frac{m_2 S}{a_2 + S}y,\\
y' &= y\left[(1 - q - k)\frac{m_2 S}{a_2 + S} - D\right],\\
p' &= k\frac{m_2 S y}{a_2 + S} - Dp.
\end{aligned}
\tag{34}
$$

This model was investigated in [45] and the presentation here follows that work. Simple inequalities yield the boundedness of solutions. With the usual scaling, the assumption that $\gamma_1 = \gamma_2$, and one reduction of order using $z(t) = p(t) - \frac{k}{1-k-q}y(t)$, the non-dimensional, limiting system takes the form

$$
\begin{aligned}
S' &= 1 - S - \frac{m_1 S}{a_1 + S}x - \frac{m_2 S}{a_2 + S}y,\\
x' &= x\left[\frac{m_1 S}{a_1 + S} - 1 - \gamma\frac{k}{1 - k - q}y\right] + q\frac{m_2 S}{a_2 + S}y,\\
y' &= y\left[(1 - q - k)\frac{m_2 S}{a_2 + S} - 1\right].
\end{aligned}
\tag{35}
$$

Three parameters will be important for the system (35), λ_1, λ_2^+ and $\hat{\lambda}$. To emphasize its dependence on q we write $\lambda_2^+(q)$. These parameters are defined as solutions of the following equations.

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

$$\frac{m_2\lambda_2^+(q)}{a_2\lambda_2^+(q)} = \frac{1}{1 - k - q},$$

$$\frac{m_1\hat{\lambda}}{a_1 + \hat{\lambda}} - 1 - \gamma k(1 - \hat{\lambda}) = 0.$$

Clearly, $\lambda_1 < \hat{\lambda}$. There are two potential rest points on the boundary:

$$E_0 = (1, 0, 0), \tag{36}$$

$$E_1 = (\lambda_1, 1 - \lambda_1, 0). \tag{37}$$

The rest points in the interior are more complicated to determine. Let $E_c = (S_c, x_c, y_c)$ denote a potential interior rest point. From the equations for y in (35) one has at once that $S_c = \lambda_2^+(q)$. There remains then two equations to be satisfied:

$$1 - \lambda_2^+(q) - \frac{m_1\lambda_2^+(q)}{a_1 + \lambda_2^+(q)}x_c - \frac{m_2\lambda_2^+(q)}{a_2 + \lambda_2^+(q)}y_c = 0,$$

$$x_c\left[\frac{m_1\lambda_2^+(q)}{a_1+\lambda_2^+(q)}-1-\gamma\frac{k}{1-k-q}y_c\right]+q\frac{m_2\lambda_2^+(q)}{a_2+\lambda_2^+(q)}y_c=0.$$

From the first equation one can see that to have $x_c>0$, it must be the case that $0<y_c<(1-k-q)(1-\lambda_2^+(q))$ where use has been made of the definition of $\lambda_2^+(q)$. Combining the two equations, one has that y_c is a root of $H(z)=0$ where

$$H(z)=\frac{a_1+\lambda_2^+(q)}{m_1\lambda_2^+(q)}\left[1-\lambda_2^+(q)-\frac{1}{1-k-q}z\right]\left[\frac{m_1\lambda_2^+(q)}{a_1+\lambda_2^+(q)}-1-\frac{\gamma k}{1-k-q}z\right]+\frac{qz}{1-k-q}.$$

Since

$$H(0)<0 \quad \text{if } \lambda_2^+(q)<\lambda_1, \quad \text{and} \quad \lambda_2^+(q)<1,$$

$$H((1-k-q)(1-\lambda_2^+(q)))>0,$$

$H(z)$ has a zero between 0 and $(1-k-q)(1-\lambda_2^+(q))$. Moreover, $H(z)$ is a parabola with a positive z^2 coefficient, so this root is unique. We label this point as $E_{2c}(q)=(\lambda_2^+(q),x_{2c}(q),y_{2c}(q))$ and note that $\lim_{q\to 0}E_{2c}(q)=(\lambda_2^+,0,y_{2c}(0))$ which in the case of the internal inhibitor without plasmid components was labeled E_2.

However, if $0<\lambda_1<\lambda_2^+(q)<1$, then $H(0)>0$ and $H(1-k-q)(1-\lambda_2^+(q))>0$, so there are either no roots or two roots depending on where the minimum of $H(z)$ falls. Denote the location of the minimum by y^*. If $H(y^*)<0$, there are two roots, y_c and y_{2c} of $H(y)=0$ satisfying $0<y_c<y^*<y_{2c}<(1-\lambda_2^+(q))(1-k-q)$. Then there are two equilibria which we denote by $E_c=(\lambda_2^+(q),x_c,y_c)$ and $E_{2c}=(\lambda_2^+(q),x_{2c},y_{2c})$. If one of the two conditions

$$0<x^*<(1-\lambda_2^+(q)))(1-k-q), \tag{38}$$

$$H(x^*)<0 \tag{39}$$

fails, then there are no interior equilibria. When $q=0$, the condition that $H(x^*)<0$ is satisfied and the condition $\lambda_2^+(q)<x^*<(1-\lambda_2^+(0))(1-k)$ reduces to $\lambda_2^+(0)<\hat{\lambda}$. (See Section 6. This can form the basis of a perturbation argument.) The local stability is summarized in Table 16.

The question of the global asymptotic behavior is totally open. An approach would seem to be the construction of an appropriate Liapunov function and this construction is a challenge for some future investigator. However, when $q=0$, the system is well understood as demonstrated in Section 6. The parameter q is small and so perturbation techniques are useful. In particular the work on the perturbation of a globally stable steady state found in [46] can be applied. This

Table 16

λ_1	Condition	Rest points	Local attractors
$\lambda_1>1$	$\lambda_2^+(0)>1$	E_0	E_0
$\lambda_1<1$	$\lambda_2^+(0)>1$	E_0, E_1	E_1
	$0<\lambda_2^+(0)<\lambda_1$	E_0, E_1, E_{c2}	E_{c2}
	$0<\lambda_1<\lambda_2^+(0)$ conditions 38 and 39	E_0, E_1, E_{c2}, E_c	E_1, E_{2c}
	$0<\lambda_1<\lambda_2^+(0)$ one of conditions 38 and 39 fails	E_0, E_1	E_1

application is somewhat delicate and the reader is referred to [45] for the details. The results there take the form

Theorem 2. *For q suciently small*:

(*i*) *If* $\lambda_2^+(q) < \lambda_1$, *then* E_{c2} *is globally asymptotically stable*,
(*ii*) *If* $\lambda_1 < \lambda_2^+(q)$ *and one of* (38) *or* (39) *does not hold, then* E_1 *is globally asymptotically stable*.

Even for q small, there is more to be established.

10. Discussion

We have reviewed a collection of established models of the effect of a chemical agent on competing organisms in continuous culture. We have used the word 'inhibitor' to cover a variety of such agents, pollutants, antibiotics, allelopathic agents, etc. We distinguish two types of sources, either input directly into the system (the external inhibitor problem) or generated by one of the competitors as anti-competitor toxins (the internal inhibitor problem). The former is, in ecology, a detoxification problem; one organisms clears the inhibitor while the other undergoes an adverse reaction, but it also has a role in bioreactors to control the emergence of the wild type in genetically altered organisms. The effect of the inhibitor has been divided into two types, an agent which inhibits the growth of the organism and an agent which is lethal to the organism. The internal inhibitor often is the result of a plasmid and we have added plasmid dynamics to these models.

The models have been cast in standard chemostat terms, with the Monod (or Michaelis–Menten) form of the uptake, the chemostat being both the model of an open system in ecology and of a bioreactor in biotechnology. Various pieces of the problem have been studied in more generality but to distinguish the fine points of the generalization would bring us into a discussion of more mathematics than we think appropriate in a survey.

The survey illustrates that problems which are biological similar, and eventually are shown to have similar qualitative properties, require very different mathematical techniques. Small changes in the mathematical model require very different approaches. For example, in the models of the external inhibitor, retarding growth or being lethal provides similar phase portraits, but the mathematical techniques required are very different. Adding plasmid dynamics to the model, while complicating the mathematics, does not illustrate radically new behavior. On the other hand the difference in behavior between internal and external inhibitors is significant.

Although we have been concerned with mathematical models the experimental literature on these problems is vast. As a example of an agent which inhibits growth we note that Fig. 1(c) of Hansen and Hubbell [1] plots the effect of Nalidixic acid on the intrinsic rate of increase of two strains of *Escherichia coli*. Table 1 of this paper also presents realistic parameters for a chemostat experiment. Most of the research in biotechnology using chemostats and inhibitors is concerned with plasmid bearing organisms. The principal focus is on plasmid stabilty – the fraction of plasmid-bearing organisms that remain. A data set for the loss of the plasmid in a chemostat experiment, creating a plasmid-free organism, can be found in the text of Shuler and Kargi [16],

Table 13.4, where the table gives the fraction of plasmid-free cells indexed by time and the number of generations. For a more recent example, see Brigidi et al. [47], Fig. 1. Note that the graph plots the proportion of plasmid-free cells for three different plasmids.

Fig. 1 of Löser [48], also shows the fraction of plasmid-bearing cells surviving in a chemostat experiment. Then ampicillin was used to create the selective medium and seven chemostat experiments were performed using different ampicillin and nutrient concentrations. The results are presented in Figs. 2–4 of that paper. All of the results are of steady state type, and we are not aware of any experiments that produced the oscillatory behavior that the model shows is possible. A following paper by Löser and Ray [49] match these results with a mathematical model (slightly different than the one presented here). In the mathematical model the inhibitor is assumed to decrease the growth rate although not with the exponential factor used in [2]. Another set of experiments with two plasmids and ampicillin resistance can be found in Yazani and Mukherjee [50].

For the internal inhibitor, most of the information concerns bacteriocins, of which the colicins are an important part. The ecology and evolution of bacteriocins was reviewed by Riley and Gordon [51]. The classic experiments were those of Chao and Levin [12] who found the bistable attactors (they did not use this terminology) illustrated in Fig. 4. Riley and Wertz [52] note that colicin is 'primarily produced under times of stress', which motivates models requiring what we have called dynamic allocation at the end of Section 6, that is, a model that reflects the state of the competition. The function $k(x,y)$ used there would have to involve a threshold.

The basic model of Section 7 was applied by Patnaik [53] to experimental data on *S. cerevisiae* (from Cheng et al. [54] and on *E. coli* (from Morsrati et al. [55]). See also Patnaik [56].

These problems can be viewed as part of a larger class of interactions which can be classified as 'spiteful'. Iwasa et al. [57] define this to mean behaviors that reduce the fitness of other individuals, using energy, time or other resources. The internal inhibitor models here would fit this classification. They note that this behavior is found in group-living mammals and among terrestrial plants. They provide an alternate model with dynamics on a lattice (approximating colonies in agar) which in the completely mixed case yields Lotka–Volterra type equations. Another alternate model is that of Czaran et al. [58], which is based on cellular automaton.

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