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Competition in the Chemostat when One Competitor Produces a Toxin*

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The usual models of the chemostat assume that the competition is purely exploitative, the competition is only through the consumption of the nutrient. However, it is known that microorganisms can produce toxins against its competitors. The basic experiments are due to Chao and Levin. In this work, we consider a model of competition in the chemostat of two competitors for a single nutrient where one of the competitors can produce a toxin against its opponent at some cost to its reproductive abilities. We give a complete characterization of the outcome of this competition in terms of the relevant parameters in hyperbolic cases. In three of four cases, the asymptotic results are global.

Key words: competition, chemostat, global stability, Lyapunov function

1. Introduction

The basic chemostat is a standard example of an open system with purely exploitative competition. It consists, essentially, of three vessels. The first contains the nutrient which is pumped at a constant rate into the second vessel, the culture vessel. This vessel is charged with micro-organisms which compete, in a purely exploitative manner, for the nutrient. The contents of the second vessel is pumped, at a constant rate, into the third or overflow vessel. The key assumptions are that the culture vessel is well stirred, that temperature, pH, etc., are kept constant and that the turnover of the vessel is sufficiently fast that no wall growth occurs and that there is no buildup of metabolic products. In ecology the chemostat is a model of a simple lake but in chemical engineering it also serves as a laboratory model of a bio-reactor used to manufacture products with genetically altered organisms. In more complicated situations, it is often the starting point for construction of models in waste water treatment, Schuler and Kargi [14], or of the mammalian large intestine, Freter [4]. Early analyses can be found in the articles of Levin and Stewart [13], Hsu, Hubbell and Waltman [8], Fredrickson and Stephanopoulos [3]. The recent monograph of Smith and Waltman [15], provides a detailed description

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of the chemostat and its properties.

The models assume that no toxins are produced by one organism to inhibit the other thus making for purely exploitative competition. However, in nature it is known that micro-organisms produce inhibitors against their rivals. In a fundamental paper, Chao and Levin [1], provided basic experiments on anti-bacterial toxins. The focus of our study will be on the case where one competitor produces a toxin which destroys the other. The model is described in the next section and the goal of the paper is to describe the global asymptotic behavior of the model in terms of the system parameters (the operating parameters of the chemostat and the parameters of the organisms.) The utility of this information will be illustrated in the discussion section. To put this into perspective, we comment on some other models of inhibitors in the chemostat.

Lenski and Hattingh [11] produced a model of the chemostat with an external inhibitor and provided numerical experiments to illustrate the behavior of solutions. The introduction of an inhibitor produces a selective medium. The model of Lenski and Hattingh is appropriate for detoxification problems in that the external inhibitor interferes with the growth of one competitor while being taken up without ill effect by the other. The model proposed by Lenski and Hattingh was analyzed by Hsu and Waltman [6] where the possible outcomes were classified in terms of the parameters of the system and the global asymptotic behavior of the system determined. See also Luo and Hsu [9] for another approach. This is important in bio-reactors because inhibitors are used to suppress the competitors of the organism manufacturing a product.

If a competitor produces the inhibitor (the toxin) it also produces a selective medium in the same sense as the external inhibitor only "naturally". A question which we answer is whether a substance that inhibits growth produces different qualitative behavior than one that destroys the cell.

A model for toxins in the chemostat was given by Levin [12]. He provided numerical evidence of the presence of bi-stable attractors. See, in particular, Figure 1 of the above cited paper. In this case, the winner of the competition is determined by the initial conditions.

A mathematical analysis of the chemostat with an internally produced selective medium can be found in Hsu and Waltman [7]. In this approach, the inhibitor reduces the growth of the competitor rather than being lethal. The models there focused on the effect of plasmid loss to create the competitor. In the models of Lenski and Hattingh [11], Hsu and Waltman [6], the inhibitor affected the nutrient uptake – and consequently the growth – of the sensitive cell.

Following Chao and Levin [1], we model the effect of the inhibitor destroying its competitor by a mass action term. The mathematical consequences of this are severe. The "usual" reduction of the system to a monotone (competitive) system of one order lower through the "conservation of nutrient" principle is lost. The monotonicity of the resulting differential equations has been a principal tool of the analysis of chemostat-like systems; see Smith and Waltman [15] for examples.

The difference between our model and the one of Levin cited above [12], is that

we allocate a direct cost to the production of the inhibitor by redirecting a portion of the consumed nutrient to the production of the inhibitor. This is discussed more fully after the presentation of the model in Section 2. The principal difference centers around the parameter k in the model, the fraction of nutrient uptake directed to producing a toxin. The conservation principle does not apply and the resulting dynamical system is not monotone. We seek to describe the global asymptotic behavior of the model in terms of the parameters of the system. The results are given in four theorems, which cover all cases, three of which yield global results. In the case of bi-stable attractors, we are not able to rule out the possibility that the attractor includes limit cycles, etc., although our computer simulations have not demonstrated any. This possibility remains an open question. The techniques are those of Liapunov functions which, unfortunately but also typically, make the proofs computation intensive. For this reason, we have deferred the presentation of the proofs until the fourth section of the paper. We first present the model and some simplifications, state the results in terms of a key parameter, and then present the proofs. The interpretation and the potential applications are discussed in the concluding section.

2. The Model

At time t, let $S(t)$ denote the concentration of nutrient in the vessel, $x(t)$, the concentration of the toxin sensitive microorganism, $y(t)$, the toxin producing organism and $P(t)$, the concentration of toxin present. The model takes the form

$$\begin{aligned} S' &= (S^{(0)} - S)D - \frac{m_1 S}{a_1 + S}\frac{x}{\gamma_1} - \frac{m_2 S}{a_2 + S}\frac{y}{\gamma_2} \\ x' &= x\left[\frac{m_1 S}{a_1 + S} - D - \gamma P\right] \\ y' &= y\left[(1-k)\frac{m_2 S}{a_2 + S} - D\right] \\ P' &= k\frac{m_2 S y}{a_2 + S} - DP \end{aligned} \tag{2.1}$$

$S^{(0)}$ is the input concentration of nutrient, D is the washout rate, m_i, the maximal growth rates, a_i, the Michaelis-Menten constants and γ_i, $i = 1, 2$, the yield constants. This is usually called the Monod Model or the model with Michaelis Menten dynamics. The constant k represents the fraction of potential growth devoted to producing the toxin. Some resources are needed to account for the added metabolic burden and this must come at some cost to the organism's reproductive abilities. $k = 0$ produces a system asymptotic to the standard chemostat and $k = 1$ represents all efforts devoted to producing the toxin and results in no growth and thus extinction. These two extremes help to delineate the meaning of k. For this study we assume the k is constant.

We perform the usual scaling for the chemostat. Specifically, let

$$\overline{S} = \frac{S}{S^{(0)}}, \quad \overline{x} = \frac{x}{\gamma_1 S^{(0)}}, \quad \overline{y} = \frac{y}{\gamma_2 S^{(0)}}, \quad \overline{P} = \frac{P}{\gamma_2 S^{(0)}},$$
$$\tau = Dt, \quad \overline{m}_i = \frac{m_i}{D}, \quad \overline{a}_i = \frac{a_i}{S^{(0)}},$$
$$\overline{\gamma} = \frac{\gamma_2 \gamma S^{(0)}}{D}, \quad ' = \frac{d}{d\tau}.$$

(2.1) becomes

$$\begin{aligned}
\overline{S}' &= 1 - \overline{S} - \frac{\overline{m}_1 \overline{S} \overline{x}}{\overline{a}_1 + \overline{S}} - \frac{m_2 \overline{S} \overline{y}}{\overline{a}_2 + \overline{S}} \\
\overline{x}' &= \overline{x} \left[\frac{\overline{m}_1 \overline{S}}{\overline{a}_1 + \overline{S}} - 1 - \overline{\gamma} \overline{P} \right] \\
\overline{y}' &= \overline{y} \left[(1-k) \frac{\overline{m}_2 \overline{S}}{\overline{a}_2 + \overline{S}} - 1 \right] \\
\overline{P}' &= k \frac{\overline{m}_2 \overline{S} \overline{y}}{\overline{a}_2 + \overline{S}} - \overline{P}
\end{aligned}$$

Dropping the bars yields the model of interest:

$$\begin{aligned}
S' &= 1 - S - \frac{m_1 S}{a_1 + S} x - \frac{m_2 S}{a_2 + S} y \\
x' &= x \left[\frac{m_1 S}{a_1 + S} - 1 - \gamma P \right] \\
y' &= y \left[(1-k) \frac{m_2 S}{a_2 + S} - 1 \right] \\
P' &= k \frac{m_2 S}{a_2 + S} y - P.
\end{aligned} \tag{2.2}$$

The parameters have been scaled by the operating environment of the chemostat, determined by $S^{(0)}$ and D. The variables are non-dimensional and the parameters are scaled relative to this environment.

The interaction between the toxin and the sensitive micro-organism is taken to be of mass action form, $-\gamma P x$. A fraction, k, of the nutrient consumption has been allocated to the production of the toxin and the growth rate corresponding reduced. These equations differ in this respect from those of Levin [12].

In the same scaling as above the model proposed by Levin, with Monod dynamics, takes the form

$$\begin{aligned}
S' &= 1 - S - \frac{m_1 S}{a_1 + S} x - \frac{m_1 S}{a_1 + S} y(1-\alpha) \\
x' &= x \left[\frac{m_1 S}{a_1 + S} - 1 - \gamma P \right]
\end{aligned}$$

$$\begin{aligned} y' &= y\left[(1-\alpha)\frac{m_1 S}{a_1+S} - 1\right] \\ P' &= \beta y - P. \end{aligned} \tag{2.3}$$

α is interpreted as a selection coefficient. If one sets $m_2 = (1-\alpha)m_1$, this can be written as

$$\begin{aligned} S' &= 1 - S - \frac{m_1 S}{a_1+S}x - \frac{m_2 S}{a_1+S}y \\ x' &= x\left[\frac{m_1 S}{a_1+S} - 1 - \gamma P\right] \\ y' &= y\left[\frac{m_2 S}{a_1+S} - 1\right] \\ P' &= \beta y - P \end{aligned} \tag{2.4}$$

and the difference between (2.2) and (2.4) is apparent. (2.2) takes a portion of the growth and uses it to generate the toxin. (2.4) has the toxin produced proportional to the amount of the competitor y that is present and at no cost. A cost can be inferred if the parameter α is positive. We believe, but cannot prove, that (2.2) and (2.4) have the same asymptotic behavior, and believe that (2.2) represents a more adequate model.

We note that 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 $\Sigma = S + x + y + P$. Then

$$\begin{aligned} \Sigma' &= 1 - S - x - y - P - \gamma x P \\ &\leq 1 - \Sigma \end{aligned}$$

or

$$\limsup_{t\to\infty} \Sigma(t) \leq 1.$$

Since each component is non-negative, the system (2.2) is dissipative and thus, has a compact, global attractor. To simplify (2.2), let $z = P - \frac{ky}{1-k}$. This change of dependent variables yields the system

$$\begin{aligned} z' &= -z \\ S' &= 1 - S - \frac{m_1 S x}{a_1+S} - \frac{m_2 S y}{a_2+S} \\ x' &= x\left[\frac{m_1 S}{a_1+S} - 1 - \gamma z - \frac{\gamma k y}{1-k}\right] \\ y' &= y\left[\frac{(1-k)m_2 S}{a_2+S} - 1\right] \end{aligned} \tag{2.5}$$

Clearly, $z(t) \to 0$, so (2.5) may be viewed as an asymptotically autonomous system with limiting system

$$\begin{aligned} S' &= 1 - S - \frac{m_1 S x}{a_1 + S} - \frac{m_2 S y}{a_2 + S} \\ x' &= x\left[\frac{m_1 S}{a_1 + S} - 1 - \frac{k\gamma}{1-k} y\right] \\ y' &= y\left[(1-k)\frac{m_2 S}{a_2 + S} - 1\right] \end{aligned} \tag{2.6}$$

Again, the form of the equations guarantees that the positive cone is positively invariant and that the faces $x = 0$ and $y = 0$ are invariant sets. Dissipativeness is inherited from (2.5) (or one can prove it directly). As a consequence, the global attractor of (2.5) lies in the set $z = 0$ where (2.6) is satisfied. When the analysis of (2.6) is completed, the work of Thieme [17], relates the corresponding dynamics of (2.5) and (2.6), and hence of (2.2). We will show that all solutions of (2.6) tend to rest points and hence, using Thieme [16], so do those of (2.2).

From this point, to save notation, we write $f_i(S) = \frac{m_i S}{a_i + S}$, $i = 1, 2$.

The equilibrium point

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

always exists. If $f_1(1) > 1$, then there is an equilibrium of (2.6) of the form

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

where λ_1 is the unique value of S such that $f_1(\lambda_1) = 1$. Similarly, if $f_2(1) > 1/(1-k)$, there is an equilibrium of the form

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

where λ_2 is the unique value of S such that $f_2(\lambda_2) = 1/(1-k)$ or $\lambda_2 = \frac{a_2}{(1-k)m_2 - 1}$. The stability of these rest points is critical to the analysis, but before beginning the computations, we look at the flows on the invariant faces noted above, $x = 0$ and $y = 0$.

The dynamical system on the two dimensional faces, $x = 0$ or $y = 0$, is important for later discussions. On the face $y = 0$, the problem takes the form

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

These are the equations of a simple chemostat with rest points (1,0) and $(\lambda_1, 1-\lambda_1)$ if $f_1(1) > 1$ and $f_1(\lambda_1) = 1$. If $f_1(1) < 1$, (1,0) is globally asymptotically stable.

If $f_1(1) > 1$, $(\lambda_1, 1 - \lambda_1)$ is globally asymptotically stable; in particular, when E_1 (above) exists, it will always have at least a two dimensional stable manifold.

Similarly, on the face $x = 0$, the dynamical system takes the form

$$\begin{aligned} S' &= 1 - S - f_2(S)y \\ y' &= y[(1-k)f_2(S) - 1] \end{aligned}$$

There is a rest point (1,0) which is globally asymptotically stable if $f_2(1) < (1-k)^{-1}$. If $f_2(1) > (1-k)^{-1}$, there is a rest point $(\lambda_2, (1-k)(1-\lambda_2))$ where $f_2(\lambda_2) = (1-k)^{-1}$. Let $g(S) = (1-k)f_2(S)$ and $z = y(1-k)^{-1}$. The system becomes

$$\begin{aligned} S' &= 1 - S - g(S)z \\ z' &= z[g(S) - 1] \end{aligned}$$

which is again a chemostat with rest point $(\lambda_2, 1-\lambda_2)$ which is globally asymptotically stable. Returning to (S, y) this is $(\lambda_2, (1-k)(1-\lambda_2))$.

Again, when E_2 exists, it has at least a two dimensional stable manifold. The point of this discussion is that the stability of the rest points of (2.6), E_1, and E_2, will depend on a single eigenvalue.

LEMMA 2.1. (i) *E_0 always exists. It is globally asymptotically stable if $f_1(1) < 1$ and $f_2(1) < (1-k)^{-1}$. It is unstable if either inequality is reversed.*

(ii) *E_1 exists if and only if $f_1(1) > 1$. If it exists, it has at least a two dimensional stable manifold (the plane $y = 0$) and is locally asymptotically stable if $f_2(\lambda_1) < (1-k)^{-1}$ and unstable if the inequality is reversed.*

(iii) *E_2 exists if and only if $f_2(1) > (1-k)^{-1}$. If it exists, it has at least a two dimensional stable manifold (the plane $x = 0$) and is locally asymptotically stable if $f_1(\lambda_2) - 1 - \gamma k(1-\lambda_2) < 1$ and unstable if this inequality is reversed.*

Proof. Except for (i), all of the claims are local and proved by a linearization. We provide some of the details. The variational matrix of (2.6) takes the form

$$\begin{bmatrix} -1 - f_1'(S)x - f_2'(S)y & -f_1(S) & -f_2(S) \\ xf_1'(S) & f_1(S) - 1 - \dfrac{k\gamma}{1-k}y & -\dfrac{\gamma k x}{1-k} \\ (1-k)yf_2'(S) & 0 & (1-k)f_2(S) - 1 \end{bmatrix}.$$

At $(1,0,0)$ this is

$$\begin{bmatrix} -1 & -f_1(1) & -f_2(1) \\ 0 & f_1(1) - 1 & 0 \\ 0 & 0 & (1-k)f_2(1) - 1 \end{bmatrix}.$$

The eigenvalues are on the diagonal and $E_0 = (1,0,0)$ will be locally asymptotically stable if $f_1(1) < 1$ and $f_2(1) < (1-k)^{-1}$. In this case, the rest points E_1 and E_2 do not exist.

At $E_1 = (\lambda_1, 1-\lambda_1, 0)$ the variational matrix takes the form

$$\begin{bmatrix} -1 - f_1'(\lambda_1)(1-\lambda_1) & -1 & -f_2(\lambda_1) \\ (1-\lambda_1)f_1'(\lambda_1) & 0 & 0 \\ 0 & 0 & (1-k)f_2(\lambda_1) - 1 \end{bmatrix}.$$

E_1 is locally asymptotically stable if $f_2(\lambda_1) < (1-k)^{-1}$. A similar argument shows that E_2 is locally asymptotically stable if $f_1(\lambda_2) - 1 - \gamma k(1-\lambda_2) < 1$ and unstable if this inequality is reversed. The statements about the stable manifolds have already been established.

The global statements of (i) are established by comparison theorems using (2.6) and the flow on each of the faces $x = 0$ and $y = 0$. The same comparison argument and the Butler-McGehee Theorem, (see Smith and Waltman [15], p.12) shows that if only one of E_1 or E_2 exists, that rest point is globally asymptotically stable.

We sketch one argument in the case that $f_1(1) < 1$ and $f_2(1) < (1-k)^{-1}$. Let $(S(t), x(t), y(t))$ be a solution of (2.6). By adding the equations one has that

$$\begin{aligned} \left(S + x + \frac{y}{1-k}\right)' &= 1 - \left(S + x + \frac{y}{1-k}\right) - \frac{k\gamma}{1-k}xy \\ &\leq 1 - \left(S + x + \frac{y}{1-k}\right). \end{aligned}$$

We may assume that $S + x + \frac{y}{1-k} \leq 1$ for t sufficiently large. Then

$$x'(t) \leq x(t)\left[f_1(1 - x(t)) - 1\right].$$

Let $\widehat{x}(t)$ be the solution of

$$\begin{aligned} \widehat{x}(t) &= \widehat{x}(t)\left[f_1(1 - \widehat{x}(t)) - 1\right] \\ \widehat{x}(t_o) &= x(t_o). \end{aligned}$$

From this, it follows that $0 < x(t) \leq \widehat{x}(t)$; however, $\lim_{t\to\infty} \widehat{x}(t) = 0$.

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

3. Statement of Results

From the standpoint of the operation of the bio-reactor, if E_0 or E_1 is a globally asymptotically stable rest point, the reactor is not functioning as desired. Conversely, if E_2 is at least locally asymptotically stable, y survives and is manufacturing the desired product. The theorems given in this section give a complete characterization (of the hyperbolic cases) in terms of the system parameters of the operation of the bio-reactor. The proofs are given in Section 4.

The following theorem is a direct consequence of the discussion in Section 2. By "globally" we intend with respect to the open positive octant in R^3.

THEOREM 3.1. *If* $f_1(1) < 1$ *and* $f_2(1) < (1-k)^{-1}$, *then* E_0 *is globally asymptotically stable.*

If $f_1(1) > 1$ *and* $f_2(1) < (1-k)^{-1}$, *then* E_1 *is globally asymptotically stable.*

If $f_1(1) < 1$ *and* $f_2(1) > (1-k)^{-1}$, *then* E_2 *is globally asymptotically stable.*

The only interesting cases are where $f_1(1) > 1$ and $f_2(1) > (1-k)^{-1}$. Recall that the parameters λ_1 and λ_2 were defined as the unique value where $f_1(\lambda_1) = 1$ and $f_2(\lambda_2) = (1-k)^{-1}$.

THEOREM 3.2. *If* $\lambda_2 < \lambda_1$, *then* E_2 *is globally asymptotically stable.*

We introduce an additional parameter $\widehat{\lambda}$. Define

$$g(x) = f_1(x) - 1 - \gamma k(1-x) \tag{3.1}$$

Clearly, $g'(x) > 0$ for $x > 0$. Furthermore, $g(0) = -1-\gamma k < 0$ and $g(1) = f_1(1)-1 > 0$. Thus, $g(x)$ has a unique zero on $(0,1)$ which we denote by $\widehat{\lambda}$. Furthermore, since $g(\lambda_1) = -\gamma k(1-\lambda_1) < 0$, one has that $0 < \lambda_1 < \widehat{\lambda}$. The relationship of λ_2 to this ordering determines the outcome of the competition.

THEOREM 3.3. *If* $\lambda_1 < \lambda_2 < \widehat{\lambda}$, *then there exists a unique interior equilibrium,* $E_c = (S^*, x^*, y^*)$ *which has a one dimensional unstable manifold and a two dimensional stable manifold while* E_1 *and* E_2 *are locally asymptotically stable.*

This is the case of bistable attractors noted in particular in Figure 1 of Levin [12]. In this case, the outcome of the competition is determined by the initial conditions.

THEOREM 3.4. *If* $\lambda_2 > \widehat{\lambda}$, *then* E_1 *is globally asymptotically stable.*

It is important to note that an interior, asymptotically stable equilibrium does not exists. (The reasons become clear in the proofs). For viable competitors (i.e., the case where λ_1 and λ_2 exist), the following table summarizes the situation.

CONDITION	ATTRACTOR
$\lambda_2 < \lambda_1 < \widehat{\lambda}$	E_2
$\lambda_1 < \lambda_2 < \widehat{\lambda}$	Bistable Attractors
$\lambda_1 < \widehat{\lambda} < \lambda_2$	E_1

In the bistable case, we are not able to assert that all ω-limit sets consist of the corresponding rest point. Limit cycles (or more complicated invariant sets) have not been ruled out. They did not occur in any of our simulations. Eliminating this possibility remains an interesting open question.

4. Proofs

The remaining proofs are given in this section. Two of these use the LaSalle corollary to the Liapunov stability theorem. Since our Liapunov functions are not necessarily continuous on the closure of the region, we note the extension used by Wolkowicz and Lu [18], and make use of it in our proofs. Specifically, (Wolkowicz and Lu) V is a Liapunov function for a system $\frac{dx}{dt} = f(x)$ in a region $G \subset \overline{G}$ if

i) V is continuous on G

ii) V is not continuous at a point $\overline{x} \in \overline{G}$ implies $\lim_{\substack{x \to \overline{x} \\ x \in G}} V(x) = \infty$

iii) $V' = \nabla V \cdot f \leq 0$ on G

Proof of Theorem 3.2.

Theorem 3.2 is proved with a Liapunov function argument. Let

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

where c_1 and c_2 are to be chosen below and where, to simplify notation, we have used $y^* = (1-k)(1-\lambda_2)$. Then

$$\begin{aligned} V' &= \frac{S-\lambda_2}{S}[1 - S - f_2(S)y - f_1(S)x] \\ &\quad + c_1(y - y^*)[(1-k)f_2(S) - 1] + c_2 x\left[f_1(S) - 1 - \frac{\gamma k}{1-k}y\right] \\ &= \left[\left(\frac{S-\lambda_2}{S}\right)(1 - S - f_2(S)y) + c_1(y - y^*)((1-k)f_2(S) - 1)\right] \\ &\quad - c_2\frac{\gamma k}{1-k}xy + c_2 x(f_1(\lambda_2) - 1) \\ &\quad + x\left[c_2(f_1(S) - f_1(\lambda_2)) - \frac{(S-\lambda_2)}{S}f_1(S)\right] \\ &= A + B + C + D. \end{aligned}$$

We analyze each of the four parts separately making use, when necessary, of the explicit form of $f_i(S)$ and λ_2.

$$\begin{aligned} A &= \left[\frac{(S-\lambda_2)}{S}(1-S) - c_1 y^*((1-k)f_2(S) - 1)\right] \\ &\quad + \left[-\left(\frac{S-\lambda_2}{S}\right) y f_2(S) + y\,[c_1((1-k)f_2(S) - 1)]\right] \\ &= A_1 + A_2 \end{aligned}$$

Choose $c_1 = m_2/((1-k)m_2 - 1)$. Note that $f_2(1) > (1-k)^{-1}$ implies that $(1-k)m_2 - 1 > a_2$, so c_1 is positive. Since

$$\begin{aligned} (1-k)f_2(S) - 1 &= \frac{(1-k)m_2 S}{a_2 + S} - 1 \\ &= \frac{(1-k)m_2 - 1}{a_2 + S}(S - \lambda_2), \end{aligned}$$

then

$$\begin{aligned} A_2 &= \frac{(S-\lambda_2)y}{a_2+S}\left[c_1((1-k)m_2-1)-m_2\right] \\ &= 0. \end{aligned}$$

It follows that

$$A_1 = (S-\lambda_2)\left[\frac{1-S}{S} - \frac{m_2 y^*}{a_2+S}\right].$$

If one writes y^* as

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

then

$$\begin{aligned} A_1 &= (S-\lambda_2)\left[\frac{(1-S)(a_2+S)\lambda_2 - (1-\lambda_2)(a_2+\lambda_2)S}{\lambda_2 S(a_2+S)}\right] \\ &= -(S-\lambda_2)^2\left[\frac{a_2+S\lambda_2}{\lambda_2 S(a_2+S)}\right] \leq 0 \end{aligned}$$

If $c_2 > 0$, then $B \leq 0$. By hypothesis, $\lambda_2 < \lambda_1$ so $f_1(\lambda_2) < f_1(\lambda_1) = 1$ and $C \leq 0$. We choose c_2 so that $D = 0$. To see that this is possible

$$\begin{aligned} D &= x\left[c_2\left(\frac{m_1 S}{a_1+S} - \frac{m_1\lambda_2}{a_1+\lambda_2}\right) - \frac{(S-\lambda_2)m_1}{a_1+S}\right] \\ &= \left[\frac{c_2 a_1 m_1(S-\lambda_2)}{(a_1+S)(a_1+\lambda_2)} - \frac{m_1(S-\lambda_2)}{a_1+S}\right]x \\ &= \frac{m_1(S-\lambda_2)}{a_1+S}\left[\frac{c_2 a_1}{a_1+\lambda_2} - 1\right]x. \end{aligned}$$

Hence, if $c_2 = \frac{a_1+\lambda_2}{a_1} > 0$, $D = 0$ and $V' \leq 0$. By the LaSalle corollary to the Liapunov Theorem, all trajectories tend to the largest invariant set in $M = \{(S,x,y) \mid V' = 0\}$. This requires $S \equiv \lambda_2$ and $x \equiv 0$.

To make $\{S \mid S = \lambda_2\}$ invariant, under the condition $x = 0$ requires

$$S' = 1 - \lambda_2 - (1-k)^{-1}y = 0$$

(recall that $f_2(\lambda_2) = (1-k)^{-1}$). One must take $y = (1-\lambda_2)(1-k)$. Therefore $\{E_2\}$ is the unique invariant set in M.

Proof of Theorem 3.3.

We first determine the existence and stability of the interior rest point. From the equation for y one has directly that $S_c = \lambda_2$. From the equation for x it follows that

$$y_c = \frac{1-k}{k\gamma}\left[f_1(\lambda_2) - 1\right].$$

Since $\lambda_2 > \lambda_1 = f_1^{-1}(1)$, $y_c > 0$. The equation for S then yields

$$\begin{aligned}\frac{m_1\lambda_2}{a_1+\lambda_2}x_c &= 1-\lambda_2-f_2(\lambda_2)y_c \\ &= 1-\lambda_2-\frac{1}{\gamma k}(f_1(\lambda_2)-1).\end{aligned}$$

The last quantity is positive in this case since $g(\lambda_2) < 0$ if and only if $\lambda_2 < \widehat{\lambda}$ (γ and k are positive), as noted in the previous section. Thus, E_c exists and is uniquely determined under the hypothesis of the theorem.

To determine the stability of E_c, we investigate the eigenvalues of the Jacobian matrix,

$$M = \begin{bmatrix} m_{11} & m_{12} & m_{13} \\ m_{21} & m_{22} & m_{23} \\ m_{31} & m_{32} & m_{33} \end{bmatrix}$$

where

$$\begin{aligned} m_{11} &= -1-f_1'(\lambda_2)x_c - f_2'(\lambda_2)y_c \\ m_{12} &= -f_1(\lambda_2) \\ m_{13} &= -f_2(\lambda_2) \\ m_{21} &= -f_1'(\lambda_2)x_c \\ m_{22} &= 0 \\ m_{23} &= -\frac{\gamma k}{1-k}x_c \\ m_{31} &= (1-k)f_2'(\lambda_2)y_c \\ m_{32} &= 0 \\ m_{33} &= 0 \end{aligned}$$

Note first that $\det(M) = m_{12}m_{23}m_{31} > 0$, so E_c is unstable, either a repeller or unstable with a two dimensional stable manifold. Since the trace is negative ($= m_{11}$), the first alternative can not hold. Thus, E_c is unstable with a two dimensional stable manifold. The local stability of E_1 and E_2 was established in Lemma 2.1.

Proof of Theorem 3.4.

The proof is via a Liapunov argument. Before beginning, we remind the reader that the basic hypothesis $\lambda_2 > \widehat{\lambda}$ holds if and only if $g(\lambda_2) > 0$ or $f_1(\lambda_2) - 1 > \gamma k(1-\lambda_2)$. We already know in this case that E_1 is (locally) asymptotically stable and E_2 is unstable. Since we have shown that $\limsup_{t\to\infty}(S(t)+x(t)+\frac{y(t)}{1-k}) \leq 1$ for t sufficiently large and all of the quantities are non-negative, it follows that $\limsup_{t\to\infty} S(t) \leq 1$. Except for the washout case, this also means that $0 < S(t) < 1$ for t sufficiently large. Define

$$V(S,x,y) = \int_{\lambda_1}^{S} \frac{x^*(f_1(\xi)-1)}{1-\xi}d\xi + \int_{x^*}^{x} \frac{\xi-x^*}{\xi}d\xi + cy$$

where $c > 0$ is to be chosen and we have written x^* for $1 - \lambda_1$ to conserve notation. It follows that

$$\begin{aligned} V' &= \frac{x^*(f_1(S)-1)}{1-S}[1 - S - f_1(S)x - f_2(S)y] \\ &\quad + (x - x^*)\left[f_1(S) - 1 - \frac{\gamma k}{1-k}y\right] + cy[(1-k)f_2(S) - 1] \\ &= x\left[(f_1(S)-1)\left(1 - \frac{x^* f_1(S)}{1-S}\right)\right] - \frac{\gamma k}{1-k}xy \\ &\quad + y\left[-f_2(S)\frac{x^*(f_1(S)-1)}{1-S} + \frac{\gamma k x^*}{1-k} + c(1-k)(f_2(S) - f_2(\lambda_2))\right] \end{aligned}$$

where we have used the fact that $f_2(\lambda_2) = \frac{1}{1-k}$. We write

$$V' = A + B + C.$$

Clearly, $B \leq 0$ since $k < 1$ and $x \geq 0$ and $y \geq 0$. If $f_1(S) > 1$, then $S > \lambda_1$, so

$$\frac{x^* f_1(S)}{1-S} > \frac{x^*}{1-\lambda_1} = \frac{x^*}{x^*} = 1$$

or the second factor in A is negative. If $f_1(S) < 1$, then $S < \lambda_1$ so the first factor of A is positive and the second is negative. The principal difficulty in the argument is to show that $C \leq 0$. Think of C as $C = y\Delta(S)$ and we will work with $\Delta(S)$. Then,

$$\begin{aligned} \Delta(S) &= (f_2(S) - f_2(\lambda_2))c(1-k) - \left[\frac{x^* f_2(S)(f_1(S)-1)}{1-S} - \frac{\gamma k}{1-k}x^*\right] \\ &= [f_2(S) - f_2(\lambda_2)]\left(\frac{x^*}{1-k}\right)\left[\alpha - \frac{f_2(S)(1-k)\frac{f_1(S)-1}{1-S} - \gamma k}{f_2(S) - f_2(\lambda_2)}\right] \end{aligned}$$

where $\alpha = \frac{c(1-k)^2}{x^*}$. Choosing a positive α is equivalent to choosing a positive c. The object is to choose α so that if $S < \lambda_2$, the last square bracket is positive and if $S > \lambda_2$, it is negative. That this is possible is the crux of the argument.

Consider the function

$$\begin{aligned} h(S) &= \frac{f_2(S)(1-k)\dfrac{f_1(S)-1}{1-S} - \gamma k}{f_2(S) - f_2(\lambda_2)} \\ &= \frac{f_2(S)(1-k)(f_1(S)-1) - \gamma k(1-S)}{(1-S)(f_2(S) - f_2(\lambda_2))} \\ &= \frac{v(S)}{(1-S)(f_2(S) - f_2(\lambda_2))}. \end{aligned} \tag{4.1}$$

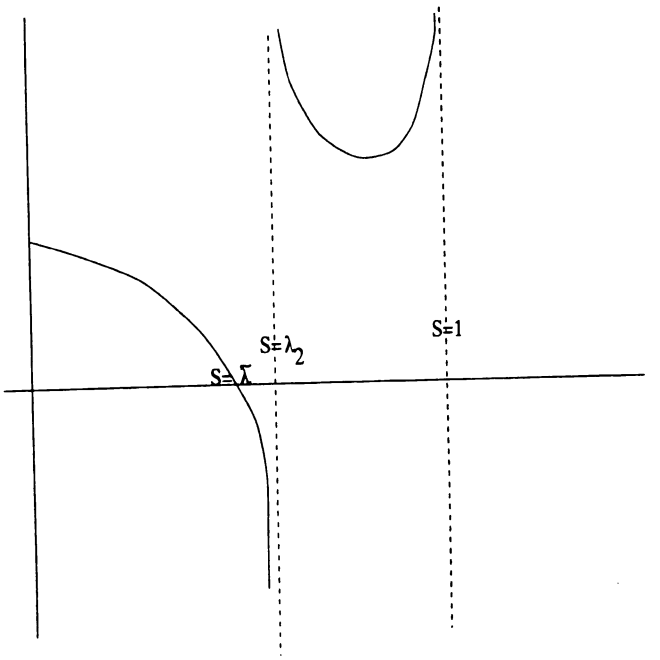

Fig. 4.1. Graph of $h(S)$

The numerator is positive for S close to λ_2 since $f_2(\lambda_2)(1-k) = 1$ and $g(\lambda_2) > 0$; hence,

$$\lim_{S\to\lambda_2^-} h(S) = -\infty$$
$$\lim_{S\to\lambda_2^+} h(S) = +\infty.$$

Moreover,

$$\lim_{S\to 1^-} h(S) = \infty \quad \text{and} \quad h(0) > 0.$$

This establishes that the asymptotics are as shown in Figure 4.1. If one could choose α so that

$$\sup_{0<S<\lambda_2} h(S) \le \alpha \le \inf_{\lambda_2<S<1} h(S) \tag{4.2}$$

the Liapunov argument would be complete since $\{E_1\}$ is the only invariant set in M where $M = \{(S,x,y) \mid V'(S,x,y) = 0\}$.

LEMMA 4.1. *There exists a positive number α such that* (4.2) *holds for* $S > \lambda_1$.

Proof. We first examine the numerator $v(S)$ in (4.1). It has already been noted that this quantity is positive at $S = \lambda_2$. It is negative at $0 < S < \lambda_1$, and for $S > \lambda_1$

$$\begin{aligned} v'(S) &= f_2'(S)(1-k)(f_1(S)-1) + f_2(S)(1-k)f_1'(S) + \gamma k \\ &> 0. \end{aligned}$$

Hence, $v(S)$ has a unique zero $\tilde{\lambda} < \lambda_2$ Thus, for $S > \lambda_2$, $h(S) > 0$ as shown in Figure 4.1 (compare with Figure 1 of Wolkowicz and Lu) and (4.2) can be weakened to showing

$$\sup_{0<S<\tilde{\lambda}} h(S) < \inf_{\lambda_2<S<1} h(S). \tag{4.3}$$

We seek to apply the technique of Wolkowicz and Lu [18], Corollary 2.4, by considering the function

$$w(S) = h(S)\frac{S-\lambda_2}{S-\tilde{\lambda}}.$$

$(S-\lambda_2)$ in the numerator removes the pole in $h(S)$ and $(S-\tilde{\lambda})$ in the denominator removes the zero.

We show that $w(S)$ is monotone increasing. From this, (4.3) will follow since

$$\sup_{0<S<\tilde{\lambda}} \frac{S-\tilde{\lambda}}{S-\lambda_2} < \inf_{\lambda_2<S<1} \frac{S-\tilde{\lambda}}{S-\lambda_2}$$

because $\frac{\tilde{\lambda}}{\lambda_2} < \frac{1-\tilde{\lambda}}{1-\lambda_2}$ and the monotonicity of the function $\frac{S-\tilde{\lambda}}{S-\lambda_2}$. Thus Lemma 4.1 (and consequently the theorem) is established by showing that $w(S)$ is monotone increasing.

First write

$$\begin{aligned} w(S) &= h(S)\frac{S-\lambda_2}{S-\tilde{\lambda}} \\ &= \frac{f_2(S)(1-k)(f_1(S)-1) - \gamma k(1-S)}{(1-S)(S-\tilde{\lambda})}\frac{S-\lambda_2}{f_2(S)-f_2(\lambda_2)} \end{aligned}$$

and consider each factor separately.

The second factor simplifies easily:

$$\frac{S-\lambda_2}{\frac{m_2 S}{a_2+S} - \frac{m_2\lambda_2}{a_2+\lambda_2}} = \frac{(S-\lambda_2)(a_2+S)(a_2+\lambda)}{m_2 a_2(S-\lambda_2)} = \frac{(a_2+\lambda_2)(a_2+S)}{m_2 a_2}.$$

The numerator of the first factor has a zero at $\tilde{\lambda}$ and hence may be factored as $(S-\tilde{\lambda})Q(S)$. We seek to determine $Q(S)$.

$$(S-\tilde{\lambda})Q(S) = f_2(S)(1-k)(f_1(S)-1) - \gamma k(1-S)$$

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

$$= \frac{1}{(a_2+S)}\left[\frac{(1-k)m_2 S(m_1-1)(S-\lambda_1)}{a_1+S} - \gamma k(1-S)(a_2+S)\right]$$

$$= \frac{\gamma k}{(a_2+S)(a_1+S)}\left[\frac{1-k}{\gamma k}m_2(m_1-1)S(S-\lambda_1)\right.$$

$$\left. - (1-S)(a_2+S)(a_1+S)\right]$$

$$= \frac{\gamma k}{(a_2+S)(a_1+S)}\left[S^3 + c_2 S^2 + c_1 S - a_1 a_2\right].$$

Thus

$$Q(S) = \frac{\gamma k}{(a_2+S)(a_1+S)}\left[S^2 + AS + \frac{a_1 a_2}{\tilde{\lambda}}\right],$$

where, by comparing coefficients one has that

$$A = \frac{1-k}{\gamma k}m_2(m_1-1) + a_1 + a_2 - 1 + \tilde{\lambda}.$$

If we return to the original factorization of $w(S)$, we have

$$w(S) = \left[\frac{a_2+\lambda_2}{m_2 a_2}\gamma k\right]\left[\frac{S^2 + AS + \frac{a_1 a_2}{\tilde{\lambda}}}{(1-S)(a_1+S)}\right].$$

The first factor is a positive constant.

Using the identity

$$\frac{S^2 + AS + \frac{a_1 a_2}{\tilde{\lambda}}}{(1-S)(a_1+S)} = -1 + \frac{(A+1-a_1)S + \frac{a_1 a_2}{\tilde{\lambda}} + a_1}{(1-S)(a_1+S)}$$

$$= \frac{A_1 S + B_1}{a_1+S}\cdot\frac{1}{1-S} - 1,$$

where $A_1 = A + 1 - a_1$ and $B_1 = \frac{a_1 a_2}{\tilde{\lambda}} + a_1$, it is sufficient to show that

$$\frac{A_1 S + B_1}{a_1+S}$$

is increasing. From the definition of A, it follows that $A_1 > 0$.

We compute

$$\frac{d}{dS}\left(\frac{A_1 S + B_1}{a_1+S}\right) = \frac{a_1 A_1 - B_1}{(a_1+S)^2}.$$

This quantity is positive if and only if $A_1 > \frac{B_1}{a_1}$ which, in turn, is equivalent to $A - a_1 > \frac{a_2}{\widetilde{\lambda}}$. Using the definition of A, this inequality is

$$\frac{1-k}{\gamma k} m_2(m_1 - 1) + a_2 - 1 + \widetilde{\lambda} > \frac{a_2}{\widetilde{\lambda}}$$

which can be rewritten as

$$\frac{1-k}{\gamma k} m_2(m_1 - 1) > \left(\frac{a_2}{\widetilde{\lambda}} + 1\right)(1 - \widetilde{\lambda}),$$

or, using the definition of $\widetilde{\lambda}$, as

$$\frac{1-k}{\gamma k} m_2(m_1 - 1) > \left(\frac{a_2}{\widetilde{\lambda}} + 1\right) f_2(\widetilde{\lambda})(f_1(\widetilde{\lambda}) - 1)\left(\frac{1-k}{\gamma k}\right).$$

This simplifies to

$$m_2(m_1 - 1) > \frac{a_2 + \widetilde{\lambda}}{\widetilde{\lambda}} \frac{m_2 \widetilde{\lambda}}{a_2 + \widetilde{\lambda}} \left(\frac{m_1 \widetilde{\lambda}}{a_1 + \widetilde{\lambda}} - 1\right)$$

or, cancelling terms, to

$$m_1 > \frac{m_1 \widetilde{\lambda}}{a_1 + \widetilde{\lambda}}.$$

This inequality holds since $\frac{\widetilde{\lambda}}{a_1 + \widetilde{\lambda}} < 1$. This establishes the monotonicity of $w(s)$ and completes the proof.

5. Discussion

The basic monotonicity properties of the chemostat model are lost if one organism produces a toxin against its competitors. To produce a toxin, the organism must devote a portion of its nutrient uptake to this end. This trade-off between the option of producing a toxin against a competitor or growing more is reflected in the parameter k. The experiments of Chao and Levin [1], showed that organisms do produce toxins against a competitor and the computations of Levin [12], showed the effect of varying the initial conditions in such a competitive situation.

In this study, we have shown how the asymptotic behavior of the model changes with the system parameters. We have shown the competitive exclusion holds although, for an open set of parameters, the outcome depends on the initial conditions. In our study, all of the parameter space is taken into account except for non-hyperbolic cases. Moreover, in three of the four cases, the asymptotic results are global, a rarity for a four-dimensional nonlinear system. The theorems are summarized in Table 1. The locally stable rest points are in bold type and the globally asymptotically stable rest points are in a box. The notation is that for the scaled system (2.6).

From the mathematical viewpoint, the "killing" of the organisms prohibits the reduction of the system to one where the techniques of monotone dynamical systems (which have been so successful in other chemostat problems) can be applied. The results were obtained through Liapunov techniques, which, unfortunately, do not give intuitive proofs.

In reactor technology, selective media are used to eliminate the genetically undesirable (i.e., non-producing) competitor. This can be done by introducing an inhibitor into the feed bottle. If the organism can be "engineered" to produce the toxin "naturally", the introduction of the inhibitor into the feed bottle could be eliminated. In such a case, our results show where the reactor must be operated.

To make this point clear we return to the unscaled model. The results presented in Table 2 where the notation is the same as Table 1 except that the variables, parameters and functions refer to the unscaled counterparts of Table 1. To emphasize this point we have used the notation $F_i(S)$ to represent the Monod function in its

Table 1. Outcomes in terms of scaled variables and parameters

Criterion	Equilibria
I $f_1(1) < 1,\ (1-k)f_2(1) < 1$	$\boldsymbol{E_0}$
II $f_1(1) > 1,\ (1-k)f_2(1) < 1$	$E_0,\ \boldsymbol{E_1}$
III $f_1(1) < 1,\ (1-k)f_2(1) > 1$	$E_0,\ \boldsymbol{E_2}$
IV $f_1(1) > 1,\ (1-k)f_2(1) > 1$ i) $f_1(\lambda_2) < 1$	$E_0,\ E_1,\ \boldsymbol{E_2}$
ii) $1 < f_1(\lambda_2) < 1 + \gamma k(1-\lambda_2)$	$E_0,\ \boldsymbol{E_1},\ \boldsymbol{E_2},\ E_c$
iii) $1 + \gamma k(1-\lambda_2) < f_1(\lambda_2)$	$E_0,\ \boldsymbol{E_1},\ E_2$

Table 2. Outcomes in terms of original variables and parameters

Criterion	Equilibria
I $F_1(S^{(0)}) < D,\ (1-k)F_2(S^{(0)}) < D$	$\boldsymbol{E_0}$
II $F_1(S^{(0)}) > D,\ (1-k)F_2(S^{(0)}) < D$	$E_0,\ \boldsymbol{E_1}$
III $F_1(S^{(0)}) < D,\ (1-k)F_2(S^{(0)}) > D$	$E_0,\ \boldsymbol{E_2}$
IV $F_1(S^{(0)}) > D,\ (1-k)F_2(S^{(0)}) > D$ i) $F_1(\Lambda_2) < D$	$E_0,\ E_1,\ \boldsymbol{E_2}$
ii) $D < F_1(\Lambda_2) < D + k\gamma_2\gamma(S^{(0)} - \Lambda_2)$	$E_0,\ \boldsymbol{E_1},\ \boldsymbol{E_2},\ E_c$
iii) $D + k\gamma_2\gamma(S^{(0)} - \Lambda_2) < F_1(\Lambda_2)$	$E_0,\ \boldsymbol{E_1},\ E_2$

unscaled form and Λ_i to denote the corresponding "break even" concentrations; specifically, in the table, $\Lambda_2 = S^{(0)}\lambda_2 = \frac{a_2 D}{(1-k)m_2 - D}$. k is dimensionless and represents the same value in both tables. (To return to (2.1), each rest point has a fourth coordinate which is zero if $y = 0$ and is either $\frac{k}{1-k}y^*$ or $(1 - \lambda_2)k$.)

To see how this might be useful in reactor technology we give a simple example. Suppose all of the parameters are fixed except the dilution rate D. This quantity is under the control of the reactor operator. Suppose, for example, that the region III (the most desirable from the standpoint of operation) of the table is not obtainable for any value of D; this occurs, for example, if $F_1(S^{(0)}) > (1-k)F_2(S^{(0)})$. One would like to choose D so that the desirable micro-organism persists. Clearly, the operating region IV is obtainable by letting D be sufficiently small since both quantities in the first column, to the left of the inequality sign, are positive. Note first that

$$\lim_{D\to 0_+} \frac{F_1(\Lambda_2)}{D} = \frac{m_1 a_2}{a_1(1-k)m_2}.$$

If this quantity is less than one IV(i) holds and otherwise it does not. If it does not, then the best that one could hope for would be IV(ii). To see that this is possible, note that $\lim_{D\to 0_+} \Lambda_2 = 0$, so that $\lim_{D\to 0_+} F_2(\Lambda_2) = 0$ while $\lim_{D\to 0_+} \left[D + k\gamma_2\gamma(S^{(0)} - \Lambda_2)\right] = \gamma\gamma_2 S^{(0)} > 0$. Hence it is possible to choose D so small that IV(ii) holds (E_2 is stable). If the initial conditions are appropriate, the desired organism will dominate the reactor.

We can also given an intuitive interpretation of the Theorems. In Theorem 3.2, the desirable organism is a better competitor without producing an inhibitor so the selective medium may not be important. In the parameter range where Theorem 3.4 applies, the desirable organism loses to its competition in spite of the ability to inhibit its opponent. If too much consumption is devoted to producing the inhibitor, λ_2 increases to the point that x wins in spite of the inhibition. For reactor technology, it is the circumstances of Theorem 3.3 that may be relevant. The inferior competitor can succeed by producing an inhibitor, but only if the initial conditions are suitable. Presumably, the quantity of the undesirable organism is small enough at the beginning for the system to be in the domain of the attraction of E_2.

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