Feedback control for a chemostat with two organisms

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Abstract

It is shown that a chemostat with two organisms can be made coexistent by means of feedback control of the dilution rate.

1 Introduction

The chemostat model is a benchmark model in mathematical biology, used to model competition of several organisms for a single nutrient source. For exmaple, it has been used to study lakes, waste-treatment and reactors for commercial production of genetically altered organisms. A classical result is the 'competitive exclusion principle' [4], stating that in the long run only one organism survives while the others die out. For the mentioned production process it may lead to a loss of the altered organism which should of course be prevented by all means. To achieve this we propose to consider the dilution rate as a feedback variable, although different approaches are available, see e.g. [4, 3]. We will show that if the dilution rate depends affinely on the concentrations of the competing organisms, coexistence may be achieved.
Unfortunately we show that coexistence is not achievable by means of feedback control for chemostats with more than two competitors.

2 Model of the chemostat

The model of a chemostat is given by the following set of differential equations:

$$\begin{aligned} \dot{S} &= D(S^0 - S) - \sum_{i=1}^{2} \frac{x_i}{\gamma_i} f_i(S) \\ \dot{x}_i &= x_i(f_i(S) - D),\ i = 1, 2 \end{aligned} \tag{2.1}$$

where $S(t)$ is the concentration of nutrient and $x_i(t)$ is the concentration of organism i in the chemostat at time t. The *dilution rate* of the chemostat is denoted as D and S^0 is the concentration of the input nutrient. The constants γ_i are *yield constants*. The functions $f_i : \mathbb{R}_+ \to \mathbb{R}_+$ with $f_i(0) = 0$ are called *uptake functions*, are assumed to be continuously differentiable and monotonically increasing (i.e. $f_i' > 0$ for all $S \in \mathbb{R}_+$).
A minimal requirement for any model of a chemostat is that the state components S, x_1 and x_2 only take non-negative values for all times $t \geq 0$. It can be shown that system (2.1) satisfies this requirement. It is sometimes convenient to pass to non-dimensional variables $\bar{S} := S/S^0$,

$\bar{x} := x/(\gamma_i S^0)$. After dropping the bars and writing $f_i(S)$ instead of $f_i(S^0 S)$ we obtain:

$$\begin{aligned} \dot{S} &= D(1-S) - \sum_{i=1}^{2} x_i f_i(S) \\ \dot{x}_i &= x_i(f_i(S) - D),\ i = 1,2 \end{aligned} \tag{2.2}$$

The equilibrium points of system (2.2) are:

$$E_0 := (1,\, 0,\, 0),\ E_1 := (\lambda_1,\, 1-\lambda_1,\, 0) \text{ and } E_2 := (\lambda_2,\, 0,\, 1-\lambda_2) \tag{2.3}$$

where the λ_i - which are assumed to be different throughout the rest of this paper - are implicitly defined as follows: $f_i(\lambda_i) = D,\ i = 1,2$.
The principal result concerning the chemostat is the so-called 'exclusion principle', see [4]:

Theorem 2.1. *If $0 < \lambda_1 < 1$ and if $\lambda_1 < \lambda_2$ then E_1 is a globally asymptotically stable equilibrium point of system (2.2) with respect to all initial conditions in the set $\{(S,\, x_1,\, x_2) \in \mathbb{R}^3_+ \,|\, x_i > 0,\ i = 1,2\}$.*

3 The dilution rate as a feedback variable

In view of the exclusion principle, one might wonder whether it is possible to change the long term behavior of the chemostat and make the organisms coexist. The obvious parameters that are manipulable are the dilution rate D and the input nutrient concentration S^0. In this paper we will assume that S^0 is fixed and D is manipulable. We will assume throughout the rest of this paper that the uptake functions satisfy the following standing hypothesis (see Figure 1):
H The graphs of the functions f_1 and f_2 intersect once at $\tilde{S}$:

$$f_1(\tilde{S}) = f_2(\tilde{S}) = \tilde{D} \tag{3.4}$$

where $\tilde{S} \in (0,1)$. If $S \in (0,\, \tilde{S})$ then $f_1(S) > f_2(S)$, while for all $S > \tilde{S}$ holds that $f_1(S) < f_2(S)$.
It follows from Theorem 2.1 that for low values of the dilution rate ($D < \tilde{D}$), organism 1 wins the competition while organism 2 wins if $D > \tilde{D}$. To achieve coexistence we propose to choose dilution rate as a feedback variable:

$$D \equiv D(S,\, x_1,\, x_2) \tag{3.5}$$

where $D(S,\, x_1,\, x_2)$ is some function defined on $\mathbb{R}^3_+$. Of course this function should only take non-negative values for obvious physical reasons (dilution rates cannot be negative).
Next we define the concept of coexistence for so-called positive systems (i.e. systems for which $\mathbb{R}^n_+$ is a forward invariant set). A positive system $\dot{x} = f(x)$ is *coexistent* if there exists a compact set K, $K \subset \text{int}(\mathbb{R}^n_+)$, which attracts all solutions starting in $\text{int}(\mathbb{R}^n_+)$, i.e. $\forall x_0 \in \text{int}(\mathbb{R}^n_+), \exists T(x_0) :\ x(t, x_0) \in K,\ \forall t \geq T(x_0)$. Coexistence might come in different forms. The simplest manifestation occurs if a positive system possesses an equilibrium point in $\text{int}(\mathbb{R}^n_+)$ which is globally asymptotically stable with respect to initial conditions in $\text{int}(\mathbb{R}^n_+)$.

We formulate the main problem of this paper:

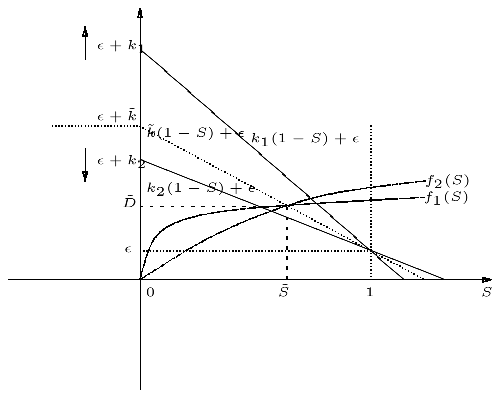

Figure 1: Bound for k_1 and k_2

Coexistence Problem: Find -if possible- a feedback $D : \mathbb{R}^3_+ \to \mathbb{R}_+$ such that the following system:

$$\begin{aligned} \dot{S} &= D(x)(1-S) - \sum_{i=1}^{2} x_i f_i(S) \\ \dot{x}_i &= x_i(f_i(S) - D(x)),\ i = 1, 2 \end{aligned} \tag{3.6}$$

where $x := (S,\, x_1,\, x_2)^T$, is coexistent.

Our main result is then the following.

Theorem 3.1. *Pick any ϵ in the interval $(0,\, \tilde{D})$. Then the coexistence problem is solvable by means of the following affine feedback:*

$$D(x) = k_1 x_1 + k_2 x_2 + \epsilon \tag{3.7}$$

if the gains $k_i > 0$, $i = 1, 2$ satisfy the following inequalities:

$$k_1 > \tilde{k} \text{ and } k_2 < \tilde{k} \tag{3.8}$$

where $\tilde{k} := \frac{\tilde{D} - \epsilon}{1 - \tilde{S}}$, see Figure 1.

Remark 3.1. *Although it is not clear from the statement of Theorem 3.1, the coexistence of the system (3.6) with feedback (3.7) takes the form of an equilibrium point $(S^e,\, x_1^e,\, x_2^e)$ in $\mathrm{int}(\mathbb{R}^n_+)$ which is globally asymptotically stable with respect to initial conditions in $\mathrm{int}(\mathbb{R}^n_+)$. Since the constraints (3.8) on the feedback gains stail entail some freedom for the feedback law (3.7), one might wonder whether it is possible to modify a particular performance index, the ratio of the values of both organisms at the interior equilibrium point. The proof of Theorem 3.1 will reveal that this ratio is given by:*

$$\frac{x_1^e}{x_2^e} = \frac{\tilde{k} - k_2}{k_1 - \tilde{k}} \tag{3.9}$$

showing that any value can be assigned to it without violating the gain constraints (3.8)*. This ratio is of interest for chemostats which are used for commercial production of genetically altered organisms in continuous culture, see e.g. [2].*

Remark 3.2. *Unfortunately the result on coexistence does not carry over to the case of more than two competitors due to a topological obstruction. A coexistent chemostat should possess at least one equilibrium point in the interior of the positive orthant [1]. But no matter what feedback law is chosen, chemostats with more than two competing species (generically) cannot satisfy this constraint. To see this, consider a chemostat with $n \geq 3$ competitors:*

$$\begin{aligned} \dot{S} &= D(x)(1-S) - \sum_{i=1}^{n} x_i f_i(S) \\ \dot{x}_i &= x_i(f_i(S) - D(x)),\ i = 1, ..., n \end{aligned} \tag{3.10}$$

with the same assumptions for the uptake functions as in the case of a chemostat with two competitors. Then the graphs of the uptake functions in general do not have a nontrivial common intersection point, unless in cases which are no generic and thus coexistence is not achievable.

4 Proofs

We start by proving that all solutions of a chemostat controlled by an affine feedback converge to a particular subset in $\mathbb{R}^3_+$.

Proposition 4.1. *If $k_i > 0$, $i = 1, 2$, and $\epsilon > 0$ then all solutions of system* (3.6) *with feedback* (3.7) *starting in $\mathbb{R}^3_+$ are bounded. If $x(t) := (S(t), x_1(t), x_2(t))$ is a solution starting in $\mathbb{R}^3_+$, then*

$$\lim_{t \to +\infty} S(t) + x_1(t) + x_2(t) = 1 \tag{4.11}$$

Proof. The function $V(x) := \frac{1}{2}(S + x_1 + x_2 - 1)^2$ satisfies $\dot{V} = -2D(x)V(x)$ along solutions of (3.6) and thus $\dot{V} \leq 0$ for all $x \in \mathbb{R}^3_+$. Since V is radially unbounded in $\mathbb{R}^3_+$, the solutions of system (3.6) with feedback (3.7) are bounded. Lasalle's invariance principle implies that all solutions converge to the largest invariant set E contained in the set $M := \{x \in \mathbb{R}^3_+ \,|\, \dot{V} = 0\}$. This implies that (4.11) holds, concluding the proof. □

The proof of the previous result motivates the definition of the following invariant set:

$$\Omega := \{x \in \mathbb{R}^3_+ \,|\, S + x_1 + x_2 = 1\} \tag{4.12}$$

According to Proposition 4.1 the ω-limit set of every solution of system (3.6) and feedback (3.7) belongs to the set Ω. It may be conjectured that the asymptotic behavior of solutions on the set Ω also determines the asymptotic behavior of solutions of the original system. Although this is not true in general, it is true in this case as will be shown later.

Therefore we study the behavior of the original system restricted to the set Ω, which is governed by the following differential equation:

$$\begin{aligned} \dot{x}_1 &= x_1(f_1(1 - x_1 - x_2) - D(x)) \\ \dot{x}_2 &= x_2(f_2(1 - x_1 - x_2) - D(x)) \\ x_1(0) &\geq 0,\ x_2(0) \geq 0 \text{ and } x_1(0) + x_2(0) \leq 1 \end{aligned} \tag{4.13}$$

where $D(x) = k_1x_1 + k_2x_2 + \epsilon$ as before. Under condition (3.8), system (4.13) possesses four equilibrium points:

$$E_0 = (0,\, 0),\ E_1 = (1 - \lambda_1,\, 0),\ E_2 = (0,\, 1 - \lambda_2) \text{ and } E_3 = (x_1^e,\, x_2^e) \tag{4.14}$$

where λ_i and x_i^e, $i = 1, 2$ are given by: $f_i(\lambda_i) = k_i(1-\lambda_i)+\epsilon,\ i = 1, 2,\ x_1^e = \frac{1}{k_1-k_2}(\tilde{D}-(k_2(1-\tilde{S})+\epsilon))$ and $x_2^e = \frac{1}{k_1-k_2}((k_1(1 - \tilde{S}) + \epsilon) - \tilde{D})$

Proposition 4.2. *If $\epsilon \in (0,\, \tilde{D})$ and if the gains $k_i > 0,\ i = 1, 2$ satisfy the inequalities* (3.8)*, then E_3 is a globally asymptotically stable equilibrium point for system* (4.13) *with respect to initial conditions satisfying $x_1(0) > 0$, $x_2(0) > 0$ and $x_1(0) + x_2(0) \leq 1$.*

Proof. The proof is based on the Poincaré-Bendixson Theorem. Denote the Jacobian matrices of the equilibrium points $E_k,\ k = 0, ..., 3$ of system (4.13) by J_k and the spectrum of these matrices by $\sigma(J_k)$. Simple calculations leads to the following conclusions: $\sigma(J_0) = \{r_0^1,\, r_0^2\}$ with $r_0^j > 0,\ j = 1, 2$, $\sigma(J_1) = \{r_1^1,\, r_1^2\}$ with $r_1^1 > 0$ and $r_1^2 < 0$, $\sigma(J_2) = \{r_2^1,\, r_2^2\}$ with $r_2^1 > 0$ and $r_2^2 < 0$ and $\sigma(J_3) = \{r_3^1,\, r_3^2\}$ with $r_3^j < 0,\ j = 1, 2$. This means that E_0 is a repellor, E_3 is locally asymptotically stable and E_1 and E_2 are saddle points.
Consider a solution $(x_1(t),\ x_2(t))$ with $x_i(0) > 0,\ i = 1, 2$. If E_3 belongs to the ω-limit set of this solution, then it the ω-limit set because E_3 is asymptotically stable. A simple application of the Butler-McGehee theorem, see e.g. [4], shows that E_1 and E_2 cannot belong to the ω-limit set of this solution. The same is true for E_0 since it is a repellor. Notice that system (4.13) is a *competitive system*, i.e. the off-diagonal entries of the Jacobian matrix in all points are negative or zero, implying that the system does not exhibit periodic orbits, see [4]. Therefore the ω-limit set of $(x_1(t),\ x_2(t))$ must be the equilibrium point E_3, which concludes the proof. □

Proof of Theorem (3.1)
First introduce the variable $\Sigma := S + x_1 + x_2 - 1$ and consider system (3.6) with feedback (3.7):

$$\begin{aligned} \dot{x}_i &= x_i(f_i(1 - \Sigma - x_1 - x_2) - D(x)),\ i = 1, 2 \\ \dot{\Sigma} &= -D(x)\Sigma \end{aligned} \tag{4.15}$$

where $\Sigma(0) \geq -1$ and $x_i(0) \geq 0$. From Proposition (4.1) we obtain that $\lim_{t\to+\infty} \Sigma(t) = 0$ and that system (4.15) is uniformly bounded. On the set $\Omega := \{(x,\, \Sigma) \in \mathbb{R}_+^n \times [-1,\, +\infty) |\, \Sigma = 0\}$ the dynamics of system (4.15) is given by system (4.13).
Notice that system (4.15) takes the form of system (5.16) and system (4.13) the form of system (5.17) in the Appendix. Relying on Proposition 4.2 it can be checked that hypotheses **H1-H3** are true for system (4.13). Hypothesis **H4** holds since if system (4.13) would possess a cycle in Ω, only E_1 and/or E_2 could possibly belong to it. Indeed, it as been shown in the proof of Proposition 4.2 that E_0 is a repellor and E_3 is locally asymptotically stable and clearly these equilibrium points

cannot belong to a cycle. But since the stable manifolds of E_1 and E_2 are portions of the x_1-, respectively x_2-axis (and both axes are invariant sets for system (4.13)), they cannot be part of a cycle of equilibrium points either. Consequently Theorem 5.1 can be applied to system (4.15). In particular it follows that almost all solutions of this system converge to the equilibrium point $(E_3,\, 0)$ where E_3 is the asymptotically stable equilibrium point of system (4.13). The solutions which do not converge to this equilibrium point belong to the stable manifolds of the equilibrium points $(E_1,\, 0)$ and $(E_2,\, 0)$ (where E_2 and E_3 are the saddle points of system (4.13)), but these stable manifolds are subsets of the boundary faces $\{(x_1,\, x_2,\, \Sigma) \in \mathbb{R}^3 |\, x_2 = 0\}$, respectively $\{(x_1,\, x_2,\, \Sigma) \in \mathbb{R}^3 |\, x_1 = 0\}$, while we are only interested in solutions with initial condition satisfying $x_i(0) > 0$, $i = 1, 2$. These facts are easily rephrased for the original system (3.6), which concludes the proof.

5 Appendix

In this section we state a convergence theorem.
Consider the following system:

$$\begin{cases} \dot{x} = f(x, y),\; x \in \mathbb{R}^n \\ \dot{y} = -\gamma(x)y,\; y \in \mathbb{R} \end{cases} \tag{5.16}$$

where $f : \mathbb{R}^{n+1} \to \mathbb{R}^n$ and $\gamma : \mathbb{R}^n \to \mathbb{R}_+ \setminus \{0\}$ are sufficiently smooth (say at least of class C^1). We assume that D is a forward invariant set for system (5.16) and henceforth restrict initial conditions to D. Moreover it is assumed that solutions of system (5.16) are *uniformly bounded*, i.e. there exists a compact subset of D into which all solutions enter at some time and remain.
Next consider the following system:

$$\dot{x} = f(x, 0) \tag{5.17}$$

where $x \in \Omega := \{x \in \mathbb{R}^n |\, (x,\, 0) \in D\} \subset \mathbb{R}^n$ for which we introduce the following set of hypotheses:
H1 There are only a finite number, say p, equilibrium points in Ω, denoted as $x_1, ..., x_p$.
H2 The dimension of the stable manifold of x_j (which is denoted as $W^s(x_j)$) satisfies: $\dim(W^s(x_j)) = n$, $\forall j = 1, ..., r$ and $\dim(W^s(x_j)) < n$, $\forall j = r+1, ..., p$ for some $r \in \{1, 2, ..., p\}$.
H3 $\cup_{j=1}^{p} W^s(x_j) = \Omega$.
H4 There are no cycles of equilibrium points in Ω.
The following result is then only a slight modification of Theorem F.1 in [4].

Theorem 5.1. *If* **H1**-**H4** *are true, then for some* $i \in \{1, ..., p\}$*:*

$$\lim_{t\to+\infty} (x(t),\; y(t)) = (x_i,\; 0)$$

where $(x(t),\, y(t))$ *is a solution of system* (5.16) *in* D*. Moreover,* $\cup_{j=r+1}^{p} \tilde{W}^s(x_j,\, 0)$ *has Lebesgue measure zero, where* $\tilde{W}^s(x_j,\, 0)$ *is the stable manifold of* $(x_j,\, 0)$ *with respect to system* (5.16)*.*

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