A feedback perspective for chemostat models with crowding effects

Patrick De Leenheer[1], David Angeli[2], and Eduardo D. Sontag[3]

[1] Department of Mathematics and Statistics, Arizona State University, Tempe, AZ 85287, USA leenheer@math.la.asu.edu
[2] Dip. di Sistemi e Informatica Universitá di Firenze, Via di S. Marta 3, 50139 Firenze, Italy, angeli@dsi.unifi.it
[3] Department of Mathematics, Rutgers University, New Brunswick, NJ 08903, USA http://www.math.rutgers.edu/~sontag, sontag@control.rutgers.edu

Abstract. This paper deals with an almost global stability result for a chemostat model with including effects. The proof relies on a particular small-gain theorem which has recently been developed for feedback interconnections of monotone systems.

1 Introduction

The chemostat is a well-known model used to describe the interaction between microbial species which are competing for a single nutrient, see [12] for a review. One of the prominent results in this area is the so-called 'competitive exclusion principle' which states roughly that in the long run only one of the species survives. This is in contrast to what is observed in nature where several species seem to coexist. This discrepancy has lead to modifications of the model to try and bring theory and practice in better accordance; see [14, 3, 9, 7]. Recently the chemostat has been *made* coexistent by means of feedback control of the dilution rate [4].

In this paper we propose another modification of the chemostat model:

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

where $i = 1,\ 2,\ ...,\ n$, x_i is the concentration of species i and S is the nutrient concentration. The positive parameters D_i are the sum of the (natural) death rates of species i and the dilution rate, while the positive parameters a_i give rise to death rates $a_i x_i$ which are due to crowding effects.

Throughout this paper we will assume the following:

$f_i : \mathbb{R}_+ \to \mathbb{R}_+$ is continuously differentiable Moreover the functions f_i are globally Lipschitz continuous on $\mathbb{R}_+$ with Lipschitz constants L_i.

The classical Monod function $f(S) = MS/(b+S)$ with $b,\, M > 0$ satisfies these assumptions with global Lipschitz constant M/b.

The only difference with the classical chemostat model [12] is that here crowding effects -modeled by the a_i- are taken into consideration.

Our main result is the following:

Theorem 1. *If*

$$n\,.\,\max_i\,(\frac{L_i}{a_i}).\max_i\,(f_i(1)) \;<\; 1 \tag{2}$$

then there exists an equilibrium point E^* *of system* (1) *such that every solution* $\xi(t) = (x_1(t),\, x_2(t),\, ..., x_n(t),\, S(t))^T$ *starting in* $\{(x_1,\, x_2,\, ...,\, x_n,\, S)^T \in \mathbb{R}_+^{n+1} |\; x_i > 0,\; \forall\, i = 1,\, ...,\, n\}$ *converges to* E^*.

Notice that our main result does not guarantee coexistence since the equilibrium point E^* could belong to the boundary of $\mathbb{R}_+^{n+1}$ and correspond to the absence of one of the species. However, in the sequel we will provide conditions that do imply coexistence.

The proof of our main result is based on the observation that system (1) can be written as a *negative feedback interconnection* of *monotone subsystems* and the availability of a particular *small-gain theorem* for such feedback systems. To see this, let us first introduce some notation. Define $x = (x_1,\, x_2,\, ...,\, x_n)^T$, $f(S) = (f_1(S),\, f_2(S),\, ...,\, f_n(S))^T$, $D = (D_1,\, D_2,\, ...,\, D_n)^T$ and $a = (a_1,\, a_2,\, ...,\, a_n)^T$. System (1) can then be compactly rewritten as follows:

$$\dot{S} = 1 - S + f^T(S)u_1,\; y_1 = S \tag{3}$$

$$\dot{x} = \text{diag}(x)(f(u_2) - D - \text{diag}(a)x),\; y_2 = x \tag{4}$$

$$u_1 = -y_2,\;\; u_2 = y_1 \tag{5}$$

System $(3)-(5)$ is a negative feedback system consisting of two input/output (I/O) subsystems (3) and (4) with inputs u_1, respectively u_2 and outputs y_1, respectively y_2.

The development of a theory for monotone I/O systems has recently been initiated in [1]. One of its purposes is to extend the rich theory of monotone dynamical systems developed by Hirsch [8], see [11] for a review and [11, 1, 6, 10] for applications in biology. For biological applications of monotone I/O systems see [5] and the use of small-gain theorems in biology see [13].

2 Preliminaries and proofs

2.1 Monotone I/O systems and a small-gain theorem

The material in this section can be found in a far more general setting in [1, 2]. We restrict to a framework that serves our purposes, namely I/O systems described by differential equations. Consider the following I/O system:

$$\dot{x} = f(x, u), \quad y = h(x) \tag{6}$$

where $x \in \mathbb{R}^n$ is the state, $u \in U \subset \mathbb{R}^m$ the input and $y \in Y \subset \mathbb{R}^p$ the output. It is assumed that f and g are smooth (say continuously differentiable) and that the input signals $u(t) : \mathbb{R} \to U$ are Lebesgue measurable functions and locally essentially bounded (i.e. for every compact time interval $[T_m, T_M]$, there is some compact set C such that $u(t) \in C$ for almost all $t \in [T_m, T_M]$). This implies that solutions with initial states $x_0 \in \mathbb{R}^n$ are defined for all inputs $u(.)$ and will be denoted by $x(t, x_0, u(.))$, $t \in \mathcal{I}$ where $\mathcal{I}$ is the maximal interval of existence for this solution. From now on we will assume that a fixed set $X \subset \mathbb{R}^n$ is given which is forward invariant, i.e. for all inputs $u(.)$ and for every $x_0 \in X$ it holds that $x(t, x_0, u(.)) \in X$, for all $t \in \mathcal{I} \cap \mathbb{R}_+$. Henceforth initial conditions are restricted to this set X. For our purposes X will be $\mathbb{R}^n_+$ or $\mathbb{R}_+$ and U will be $\mathbb{R}_+$ or $-\mathbb{R}^n_+$.

We denote the usual partial order on $\mathbb{R}^n$ by $\preceq$, i.e. for $x, y \in \mathbb{R}^n$, $x \preceq y$ means that $x_i \leq y_i$ for $i = 1, ..., n$. The state space X (input space U, output space Y) inherits the partial order from $\mathbb{R}^n$ ($\mathbb{R}^m$, $\mathbb{R}^p$) as the former sets are subsets of the latter ones. Similarly, the partial order on $\mathbb{R}^m$ carries over to the set of input signals in a natural way (hence we use the same notation for the partial order on this latter set): $u(.) \preceq v(.)$ if $u(t) \preceq v(t)$ for almost all $t \geq 0$. The next definition introduces the concept of a monotone I/O system which, loosely speaking means that ordered initial conditions and input signals lead to subsequent ordered solutions.

Definition 1. *The I/O system* (6) *is monotone (with respect to the usual partial orders) if the following conditions hold:*

$$x_1 \preceq x_2,\ u(.) \preceq v(.) \Rightarrow x(t, x_1, u(.)) \preceq x(t, x_2, v(.)),\ \forall\, t \in (\mathcal{I}_1 \cap \mathcal{I}_2) \cap \mathbb{R}_+. \tag{7}$$

and

$$h \text{ is a monotone map, i.e. } x_1 \preceq x_2 \Rightarrow h(x_1) \preceq h(x_2). \tag{8}$$

Of particular interest is how an I/O system behaves when it is supplied with a *constant* input. Next we introduce a notion which implies that this behavior is fairly simple [2].

Definition 2. *Assume that X has positive (Lebesgue) measure. The I/O system* (6) *possesses an Input/State (I/S) quasi-characteristic $k : U \to X$ if for every constant input $u \in U$ (and using the same notation for the corresponding $u(.)$), there exists a set of (Lebesgue) measure zero $\mathcal{B}_u$ such that:*

$$\forall x_0 \in X \setminus \mathcal{B}_u : \lim_{t \to +\infty} x(t, x_0, u) = k(u) \tag{9}$$

If system (6) *possesses an I/S quasi-characteristic k then it also possesses an Input/Output (I/O) quasi-characteristic $g : U \to Y$ defined as $g := h \circ k$.*

Next we recall the main tool (see [2]) for proving our main result. In the following statement we use the concept of an *almost globally attractive equilibrium point* of an autonomous system, which means that there exists an equilibrium point of this system which attracts all solutions which are not initiated in a certain set of (Lebesgue) measure zero.

Theorem 2. *Consider the following two I/O systems:*

$$\dot{x}_1 = f_1(x_1, u_1), \quad y_1 = h_1(x_1) \tag{10}$$

$$\dot{x}_2 = f_2(x_2, u_2), \quad y_2 = h_2(x_2) \tag{11}$$

where $x_i \in X_i \subset \mathbb{R}^{n_i}$*,* $u_i \in U_i \subset \mathbb{R}^{m_i}$ *and* $y_i \in Y_i \subset \mathbb{R}^{p_i}$ *for* $i = 1, 2$*. Suppose that* $Y_1 = U_2$ *and* $Y_2 = -U_1$ *and that the I/O systems are interconnected through a (negative) feedback loop:*

$$u_2 = y_1, \;\; u_1 = -y_2 \tag{12}$$

Assume that:

1. *Both I/O systems* (10) *and* (11) *are monotone.*
2. *Both I/O systems* (10) *and* (11) *possess continuous I/S quasi-characteristics* k_1 *and* k_2 *respectively (and thus also I/O quasi-characteristics* g_1 *and* g_2*).*
3. *All forward solutions of the feedback system* $(10) - (12)$ *are bounded.*

Then the feedback system possesses an almost globally attractive equilibrium point $(\bar{x}_1, \bar{x}_2) \in X_1 \times X_2$ *if the following discrete-time system, defined on* U_2*:*

$$u_{k+1} = (g_1 \circ (-g_2))(u_k) \tag{13}$$

possesses a globally attractive fixed point $\bar{u} \in U_2$*. In that case* $(\bar{x}_1, \bar{x}_2) = ((k_1 \circ (-k_2))(\bar{u}),\, k_2(\bar{u}))$*.*

In the sequel we will refer to this result as a *small-gain theorem* and to the last condition as a *small-gain condition*.

2.2 Properties of the full system and both subsystems

Lemma 1. $\mathbb{R}_+^{n+1}$ *is a forward invariant set for system* (1) *and the solutions initiated in this set remain bounded.*

(Sketch of proof) The first claim follows from e.g. Theorem 3 in [1]. The second claim follows from the fact that for $V(x,\,S) = S + \sum_{i=1}^n x_i$, we have $\dot{V} \leq 1 - D^* V$ with $D^* = \min(1,\, D_1,\, ...,\, D_n)$ and hence $V(t) \leq V(0)\,\mathrm{e}^{-D^* t} + 1/D^*$.

Next we investigate the I/O-properties of the subsystems (3) and (4) which have the following input, state and output spaces.

$$\begin{aligned} \dot{S} &= 1 - S + f^T(S) u_1 \\ y_1 &= S \end{aligned} \tag{14}$$

where $S \in X_1 := \mathbb{R}_+$ denotes the state, $u_1 \in U_1 := -\mathbb{R}^n_+$ denotes the input and $y_1 \in Y_1 := \mathbb{R}_+$ denotes the output. The input signals $u_1(t) : \mathbb{R} \to U_1$ are assumed to Lebesgue be measurable and essentially locally bounded, ensuring existence and uniqueness of solutions as discussed in the previous subsection.

Similarly consider

$$\begin{aligned} \dot{x} &= \mathrm{diag}(x)(f(u_2) - D - \mathrm{diag}(a)x) \\ y_2 &= x \end{aligned} \tag{15}$$

where $x \in X_2 := \mathbb{R}^n_+$ denotes the state, $u_2 \in U_2 := \mathbb{R}_+$ denotes the input and $y_2 \in Y_2 := \mathbb{R}^n_+$ denotes the output. As before, input signals $u_2(t) : \mathbb{R} \to U_2$ are Lebesgue measurable and essentially locally bounded.

Lemma 2. *X_1, respectively X_2, is forward invariant for system* (14)*, respectively system* (15)*.*

Proof. The proof follows from an application of Theorem 3 in [1].

Lemma 3. *Systems* (14) *and* (15) *are monotone.*

Proof. This follows from an application of Proposition 3.3 in [1].

The next result is the key to proving the main theorem and reveals that both subsystems possess I/S quasi-characteristics with certain smoothness properties.

Lemma 4. *System* (14) *possesses a continuously differentiable I/S quasi-characteristic $k_1 : U_1 \to X_1$. Moreover, k_1 is globally Lipschitz with Lipschitz constant $L_1^* := n \, . \, \max_{i=1,\dots,n} f_i(1)$, i.e.*

$$\forall\, u_1^a,\, u_1^b \in U_1 :\ |k_1(u_1^a) - k_1(u_1^b)| \,\leq\, L_1^* \, ||u_1^a - u_1^b||_{\max} \tag{16}$$

where $||.||_{\max}$ denotes the max-norm on $\mathbb{R}^n$, i.e. $||z||_{\max} = \max_{i=1,\dots,n} |z_i|$ when $z \in \mathbb{R}^n$.

System (15) *possesses a globally Lipschitz continuous I/S quasi-characteristic $k_2 : U_2 \to X_2$ with Lipschitz constant $L_2^* := \max_{i=1,\dots,n} L_i/a_i$, i.e.*

$$\forall\, u_2^a,\, u_2^b \in U_2 :\ ||k_2(u_2^a) - k_2(u_2^b)||_{\max} \leq L_2^* \, |u_2^a - u_2^b| \tag{17}$$

Proof. Due to space limitations we leave out the proof of this result. It will be included in an extended version of this paper.

Remark 1. Notice that the output spaces Y_1, Y_2 of systems (14) and (15) are identical to their respective state spaces X_1, X_2 and that the output mappings h_1 and h_2 are just the identity mappings. Therefore the I/O quasi-characteristics g_1 and g_2 of these systems equal their respective I/S quasi-characteristics and possess the same smoothness properties.

2.3 Proof of the main result

Consider system (1) or its equivalent feedback representation (3) – (5). We will show that the three conditions and the small-gain condition in theorem 2 are satisfied. The first, second and third conditions follow from respectively lemma 3, lemma 4 and lemma 1. To see that small-gain condition is satisfied, recall from lemma 4 and remark 1 that $g_1 = k_1$ and $g_2 = k_2$ are globally Lipschitz with Lipschitz constants L_1^*, respectively L_2^*. This implies that for all u^a, $u^b \in U_2$, the composition $g := g_1 \circ (-g_2)$ satisfies the following:

$$|g(u^a) - g(u^b)| \leq L_1^* ||(-g_2)(u^a) - (-g_2)(u^b)||_{\max} \leq L_1^* L_2^* |u^a - u^b|$$

which by the definitions of L_1^* and L_2^* (see lemma 4) and condition (2) shows that g is a contraction mapping on the complete metric space $U_2 = \mathbb{R}_+$. Then a contraction mapping argument shows the small-gain condition is indeed satisfied, which concludes the proof of this theorem.

3 Coexistence for 2 species

In this section we provide a coexistence result for system (1) with $n = 2$. A coexistence result in case of n species is deferred to an extended version of this paper.

Definition 3. *System* (1) *with* $n = 2$ *is coexistent if there exists some* $\epsilon > 0$ *such that for* $i = 1, 2$ *holds:*

$$\liminf_{t \to \infty} x_i(t) > \epsilon \text{ whenever } x_1(0) > 0 \text{ and } x_2(0) > 0$$

where $(x_1(t), x_2(t), S(t))^T$ *denotes the solution of system* (1) *with initial condition* $(x_1(0), x_2(0), S(0))^T \in \mathbb{R}^3_+$.

In fact we will prove the much stronger result that coexistence takes the form of a globally attracting interior equilibrium point. This contrasts the competitive exclusion principle which holds for the classical chemostat model. Since crowding effects are the only difference between the classical chemostat and the model presented here, this suggests they may be responsible for the observed coexistence of several species competing for a single nutrient.

We make the following additional -but fairly natural; see [12]- assumptions:

- **H1** $f_i(S_1) < f_i(S_2)$ if $S_1 < S_2$, where S_1, $S_2 \in \mathbb{R}_+$ and $i = 1, 2$.
- **H2** For $i = 1, 2$ there exist numbers $\lambda_i \in (0, 1)$ satisfying $f_i(\lambda_i) - D_i = 0$.

Notice that if **H1** holds, then the numbers λ_i, $i = 1, 2$ are unique. It is noteworthy that the numbers λ_i are independent of the a_i, $i = 1, 2$.

For $i = 1, 2$, we define the functions $F_i : \mathbb{R}_+ \to \mathbb{R}$ as follows:

$$F_i(S) = 1 - S - \frac{f_i(S) - D_i}{a_i} f_i(S) \text{ for } i = 1, 2$$

Obviously, both functions $F_i(S)$ are continuously differentiable.

Claim: If **H1** *and* **H2** *are satisfied, then there exist unique roots* $\lambda_i^* \in \mathbb{R}_+$ *such that* $F_i(\lambda_i^*) = 0$ *for* $i = 1, 2$. *In addition,* $\lambda_i^* \in (\lambda_i, 1)$ *for* $i = 1, 2$. (The proof of this claim is deferred to an extended version of this paper)

A final additional and non-trivial assumption is expressed in terms of these roots λ_i^*:

- **H3** $\max(\lambda_1, \lambda_2) < \min(\lambda_1^*, \lambda_2^*)$.

Later we will impose **H1**, **H2** and **H3** on system (1) with $n = 2$, so it is important to know whether these assumptions can be satisfied simultaneously. The next lemma shows that this can always be arranged by choosing the crowding effect parameters a_1 and a_2 large enough. The proof is left out and will be included in an extended version of this paper.

Lemma 5. *Assume that two uptake functions* f_1, f_2 *and two numbers* D_1 *and* D_2 *are given such that* **H1** *and* **H2** *hold. Interpret both* a_1 *and* a_2 *as variables in* $\text{int}(\mathbb{R}_+)$.

Then for $i = 1, 2$, *the* λ_i^* *are differentiable functions of* a_i *taking values in* $(\lambda_i, 1)$:

$$\lambda_i^* : \text{int}(\mathbb{R}_+) \to (\lambda_i, 1) \text{ and } \lim_{a_i \to \infty} \lambda_i^*(a_i) = 1$$

In particular, this implies that for a_i^* *large enough,* **H3** *is satisfied.*

Under the 3 additional assumptions it turns out that system (1) with $n = 2$, possesses 4 equilibria in $\mathbb{R}^3_+$. Exactly one of these equilibria lies in $\text{int}(\mathbb{R}^3_+)$ and is locally asymptotically stable as we show next. Again, the proof is deferred to an extended version of this paper.

Lemma 6. *If* **H1**, **H2** *and* **H3** *are satisfied, then system* (1) *with* $n = 2$ *possesses the following equilibria in* $\mathbb{R}^3_+$:

$$E_0 = (0, 0, 1)^T, \; E_1 = (x_1^*, 0, \lambda_1^*)^T, \; E_2 = (0, x_2^*, \lambda_2^*)^T \text{ and } E_e = (x_1^e, x_2^e, \lambda^e)^T$$

where x_1^*, x_2^*, x_1^e, x_2^e *and* λ_e *are positive numbers. The equilibrium point* E_e *is locally asymptotically stable.*

The previous lemma and our main result suggest a mechanism to achieve coexistence for system (1) with $n = 2$: Suppose that it is possible to satisfy both the small-gain condition (2) and the three conditions expressed by **H1**, **H2** and **H3**. Then lemma 6 guarantees the existence of a locally asymptotically stable equilibrium point $E^e \in \text{int}(\mathbb{R}^3_+)$, while Theorem 1 ensures the existence of an equilibrium point for system (1) with $n = 2$ which attracts almost every solution initiated in $\mathbb{R}^3_+$. Obviously this equilibrium point must be E^e. It can be shown that the set of non-converging initial conditions (note that although they are not converging to E^e, they might be converging to other equilibria) is:

$$\mathcal{B} = \{(x_1, x_2, S)^T \in \mathbb{R}^3_+ | \; x_1 = 0 \text{ or } x_2 = 0\}$$

In particular, this implies that all solutions initiated in $\mathcal{P} := \{(x_1, x_2, S) \in \mathbb{R}^3_+ \,|\, x_1 > 0,\, x_2 > 0\}$ *do converge* to E^e and consequently that system (1) with $n = 2$ is coexistent.

The main problem is thus whether the small-gain condition (2) and **H1**, **H2** and **H3** can be satisfied simultaneously for system (1) with $n = 2$. But from lemma 5 and (2) is follows that this is possible if crowding effects are large enough. Combining theorem 1 and lemma 6 we conclude:

Theorem 3. *Assume that two uptake functions f_1, f_2, two numbers D_1 and D_2 are given such that* **H1** *and* **H2** *hold. Consider system* (1) *with* $n = 2$ *and interpret the a_i, $i = 1, 2$ as positive parameters.*

If the a_i are chosen large enough then **H3** *and* (2) *are satisfied. Then system* (1) *with $n = 2$ possesses an equilibrium point $E^e \in \mathrm{int}(\mathbb{R}^3_+)$ which is almost globally asymptotically stable with respect to initial conditions in $\mathbb{R}^3_+$. Moreover, every solution initiated in $\mathcal{P}$ converges to E^e implying that system* (1) *with $n = 2$ is coexistent.*

References

1. D. Angeli and E.D. Sontag, Monotone control systems, arXiv.org math.OC/0206133 and submitted (Prelim. version in proc. 41st CDC, 2002)
2. D. Angeli, P. De Leenheer and E.D. Sontag, A small-gain theorem for almost global convergence of monotone systems, in preparation.
3. G.J. Butler, S.B. Hsu, and P. Waltman, A mathematical model of the chemostat with periodic washout rate, SIAM J. Appl. Math. 45 (1985) 435-49.
4. P. De Leenheer and H.L. Smith, Feedback control for chemostat models, J. Math. Biol. 46, 48-70 (2003).
5. P. De Leenheer, D. Angeli and E.D. Sontag, On predator-prey systems and small-gain theorems, submitted.
6. P. De Leenheer and H.L. Smith, Virus dynamics: a global analysis, to appear in SIAM J. Appl. Math.
7. J.K. Hale and A.S. Somolinas, Competition for fluctuating nutrient, J. Math. Biol. 18 (1983) 255-80.
8. M.W. Hirsch, Systems of differential equations which are competitive or cooperative II: convergence almost everywhere. SIAM J. Math. Anal. 16, 423-439 (1985).
9. S.B. Hsu, A competition model for a seasonally fluctuating nutrient, J. Math. Biol. 9 (1980) 115-32.
10. M.Y. Li and J.S. Muldowney, Global stability for the SEIR model in epidemiology, Math. Biosci. 125, 155-164, 1995.
11. H.L. Smith, Monotone Dynamical Systems, AMS, Providence, 1995.
12. H.L. Smith and P. Waltman, The theory of the chemostat, Cambridge University Press, Cambridge, 1995.
13. E.D. Sontag, Asymptotic amplitudes and Cauchy gains: A small-gain principle and an application to inhibitory biological feedback, Systems Control Lett. 47, 167-179 (2002).
14. G. Stephanopoulos, A.G. Fredrickson, R. Aris, The growth of competing microbial populations in CSTR with periodically varying inputs, Amer. Instit. of Chem. Eng. J. 25 (1979) 863-72.