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Abstract: In this paper we consider a control problem for an uncertain chemostat model with a general monotone growth function. This uncertainty affects the model (growth function) as well as the outputs (measurements of substrate). Despite this lack of information, an upper bound and a lower bound for those uncertainties are assumed to be known a priori.

We are able to build a family of feedback control laws on the dilution rate, giving a guaranteed estimation on the unmeasured variable (biomass), and stabilizing asymptotically the two variables in a rectangular set, around a reference value of the substrate. This could be implemented in a real chemostat, keeping a high level of substrate, avoiding the washout of the bioreactor.

Key-words: Chemostat, Uncertain biological models, Feedback control,Competitive systems

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Contrôle robuste pour un modèle incertain du chemostat

Résumé : Dans cet article, nous considérons un problème de contrôle pour un modèle incertain du chemostat avec une fonction de croissance monotone. Cette incertitude affecte tant le modèle (fonction de croissance) que la sortie (la mesure du substrat). Malgré ce manque d'information, on connait *a priori* des bornes supérieures et inférieures pour les incertitudes.

Nous construisons une famille de lois de contrôle en boucle fermée sur le taux de dilution, permettant de donner des estimations pour la variable non mesurée (biomasse) et stabilisant asymptotiquement les deux variables dans un ensemble rectangulaire autour d'une consigne pour le substrat. Cette loi de contrôle pourrait être appliquée dans un chemostat réel, permettant un niveau élevé de substrat tout en évitant le lessivage du chemostat.

Mots-clés : Chemostat, Modèle biologique incertain, Contrôle en boucle fermée, Système dynamique compétitif

1 Introduction

The chemostat is a laboratory apparatus used to culture microorganisms in concentration x which consume a substrat s to grow. Mathematical modeling of chemostat has been extensively developed, mainly using ordinary differential equations and several results have been validated experimentally. See [1, Chapt.9],[17] for a review of mathematical results on the theory of chemostat.

Feedback control of biological models has been a focus of intensive research [2],[7],[11]; the problem we investigate in this paper deals with the feedback control and estimation of an *uncertain* chemostat model. In this control context, uncertainty must be understood in two basic types:

(1) *Internal*: Some parts of the model are not precisely known; for example the functions that describe the kinetic reactions or some parameters.

(2) *External*: The measure of the variables is susceptible to having different kinds of noise such as unknown additive or multiplicative disturbances.

There are several theoretical approaches for the feedback control and estimation of uncertain biological models: Robust deterministic control, Adaptive control [13], Fuzzy Logic [8], Neural Networks [11, Chapt.7], among others. Although much research has been devoted to control of uncertain biological systems, few results considering simultaneously internal and external sources of uncertainty are available. In fact, motivated by the work of [15],[16], we will follow the deterministic approach in order to study an uncertain chemostat in this paper: we will consider internal and external uncertainties as deterministic disturbances with bounds assumed to be known a priori. Moreover, given those bounds on the uncertainties, we will build a family of feedback control laws that gives dynamic bounds on the unmeasured variables and makes possible the stabilization of the system in a compact set whose bounds will be related to the uncertainties bounds. Our technics are also similar to the approach in [6], where the problem is to obtain coexistence for two competing species.

Our application concerns the stabilization of the chemostat at a high level of nutrient.Chemostat has been used currently in marine laboratories (see for example [4]) to simulate in vitro the growth of unicellular phytoplanktonic algae in marine ecosystems, where the phytoplankton feeds on limiting substrate (for example nitrate, iron, phosphorus, silicon, inorganic carbon, etc.) supplied at a constant rate. As it is easy to see, the standard equilibrium point in a chemostat with a monotone classical growth functions as the Monod function correspond to a low level of substrate, for realistic values of the parameters (see [3],[20]): it comes from the fact that the growth function has a large slope at the origin, attaining very fast its maximum. In fact, experimentally, the value of the substrate at the equilibrium is often so small that is not measurable with the usual apparatus.

To reproduce growth conditions with a high level of nutrient in vitro, we wish to be able to maintain a high level of substrate at the equilibrium. At the level, the risk of washout (loss of biomass) is very high if there are uncertainties in the model. Therefore we need a control to stabilize the chemostat and avoid washout.

This paper is organized as follows: In section 2 we recall some facts of the chemostat model and state the assumptions about uncertainty. Section 3 presents the robust regulation/estimation problem in full detail. The main result and its proof is given in section 4. The application and simulations are given in section 5 and 6.

2 Modeling of an uncertain chemostat

Let us recall the chemostat equations (see, for example [17, Chapt.1]):

$$\begin{aligned} \dot{s} &= D(s_{in} - s) - \alpha x f(s), \\ \dot{x} &= x(f(s) - D), \\ s(0) &\in (0, s_{in}), \quad x(0) > 0. \end{aligned} \tag{1}$$

Where $s(t)$ and $x(t)$ are the concentration of the nutrient and the density of biomass at time t, $s_{in} > 0$ denotes the input concentration of nutrient, $D > 0$ is the dilution rate, $\alpha > 0$ is a growth yield constant. The function $f: \mathbb{R}_+ \mapsto \mathbb{R}_+$ represents the per capita growth rate of nutrient of the biomass.

Notice that if $s(0) > s_{in}$ there exists $t_0 > 0$ such that $0 < s(t) < s_{in}$ for any $t > t_0$; hence, we consider only initial conditions $s(0) \in (0, s_{in})$.

Now, we make the assumptions about uncertainty of chemostat model:

(H1) The function f is unknown but locally Lipschitz and functionally bounded, *i.e.* there exist a couple of well known increasing continuous maps f^- and f^+ such that:

$$f^-(s) \leq f(s) \leq f^+(s), \quad \text{for any } s \geq 0 \text{ and } \quad f^-(0) = f^+(0) = 0.$$

(H2) The only output available takes the form:

$$y(t) = s(t)[1 + \Delta(t)]$$

where the function $\Delta: \mathbb{R}_+ \mapsto \mathbb{R}$ is bounded and measurable. Moreover, there exists two bounded and measurable functions: a negative function $\Delta^-(t)$ and a positive function $\Delta^+(t)$ such that:

$$\Delta^-(t) \leq \Delta(t) \leq \Delta^+(t) \quad \text{for any } t \geq 0.$$

Output $y(t)$ is known as a *deterministic multiplicative disturbance* (see for example [14]). Finally, we will denote by Δ^- and Δ^+ the minimum and maximum of functions $\Delta^-(t)$ and $\Delta^+(t)$ respectively.

Remark 1 (i) *Assumption* **(H1)** *follows from the fact that the explicit formulation of the function f is based on experimental evidence. Indeed, in several experiments it has been observed that the Monod function:*

$$f(s) = \frac{\mu_m s}{s + k_s}, \quad \mu_m, k_s > 0$$

provides a reasonable approximation for the experimental data. μ_m *is the maximum specific growth rate of limiting nutrient and* k_s *is the half-saturation constant (also called Monod's constant). Normally, there are uncertainty in the identification of these kinetic parameters (see for example* [2],[7, Chapt.3–5],[12]).
(ii) *Assumption* **(H2)** *is very common in the measure of biological variables: the information about the state variables is restricted and the available data are few and biased. Notice that there is not any statistical assumption for disturbance* $\Delta(t)$ *because every measurable function between* $[\Delta^-(t), \Delta^+(t)]$ *is considered to be as good as any other one. We need only deterministic bound on the uncertainties.*

Recall that **(H1)** and **(H2)** are assumed for the remainder of this paper.

3 Formulation of problem

In several bioprocesses, the goal is that the substrate reaches a neighborhood of level s^*; moreover it is important to produce an estimation -even during the transients of systems- for the unmeasured variable x: this task is made difficult by the uncertainty of the model. Motivated by this technical difficulty, we formulate the following problem:

Problem 1 (The robust regulation problem $\mathcal{P}$) *Given* $s^* \in (0, s_{in})$, *a set* $\Omega \subset (0, s_{in}) \times R_+$ *of initial conditions and considering* D *as a feedback control variable; find a family of positive feedback control laws* $D: \mathbb{R}_+ \times \Omega \mapsto \mathbb{R}_+ \setminus \{0\}$ *that renders the closed–loop system* (1) *with the following properties*:

(a) *There exist two bounded intervals, an upper one and a lower one, for the unmeasured variable* $x(t)$ *and* $s(t)$, *that means a couple of well known functions* $x^-, x^+ : \mathbb{R}_+ \mapsto \mathbb{R}_+$ *such that*:

$$x^-(t) \leq x(t) \leq x^+(t) \quad \text{and} \quad s^-(t) \leq s(t) \leq s^+(t) \quad \text{for any } t \geq 0.$$

Moreover, the box $[s^-(t), s^+(t)] \times [x^-(t), x^+(t)]$ *tends to a minimal area as the time is large.*

(b) *There exists a compact set* $K = [s^-, s^+] \times [x^-, x^+] \in \Omega$ *and* $T > 0$ *such that* $(s(t), x(t)) \in K$ *for any* $t > T$; *moreover* $s^* \in (s^-, s^+)$.

Although much research has been devoted to problems related to ($\mathcal{P}$) (see for example [2],[7],[9],[10],[15] and [16]), few results considering simultaneously **(H1)** and **(H2)** are available.

4 Main result

In this section, we give sufficient conditions to solve the problem ($\mathcal{P}$) summarized in Theorem 1. The key idea of the proof is to transform the closed–loop system (1) in a system that can be compared with *competitive* systems (see Def.1 in Appendix). Planar competitive systems theory (see Appendix) will be the main tool employed.

Theorem 1 *The problem $(\mathcal{P})$ is solvable by the following family of feedback control laws:*

$$D(y(t)) = g(s^* - y(t)) \tag{2}$$

where g satisfies the following assumptions:
(G1) *$g\colon \mathbb{R} \mapsto \mathbb{R}_+$ is Lipschitz, bounded and nondecreasing.*
(G2) $f^-(s^*) \leq g(-s^*\Delta^-)$ and $g(-s^*\Delta^+) \leq f^+(s^*)$.
(G3) *The constants s^*, s_{in} and Δ^- satisfy:*

$$-1 < \Delta^- \quad \text{and} \quad g(s^* - s_{in}[1 + \Delta^-]) < f^-(s_{in}).$$

Remark 2 (i) *Note that assumptions **(G1)**–**(G2)** are in some sense natural. In fact provided that $\Delta(t) \equiv 0$ and $f^-(s) \equiv f^+(s)$ (absence of uncertainty), assumption **(G2)** is equivalent to $g(0) = f(s^*)$ and combined with **(G1)** implies trivially that the closed–loop system satisfy:*

$$\lim_{t \to +\infty} s(t) = s^* \quad \text{and} \quad x(t) = \alpha^{-1}[s_{in} - s(t) + o(1)]$$

and the problem $(\mathcal{P})$ is solved.
(ii) *Assumption **(G3)** gives a lower bound for the function $\Delta(t)$ which guarantees positive outputs and gives bounded estimates for the substrate:*

$$\frac{y(t)}{1 + \Delta^+} \leq s(t) \leq \frac{y(t)}{1 + \Delta^-}.$$

(iii) *Because D is defined on a bounded interval, we will be able to fulfill the physical constraints: $0 < D_{\min} < D(y(t)) < D_{\max}$ for all t.*

Proof: Replacing D by $D(y(t))$, system (1) becomes:

$$\begin{aligned} \dot{s} &= g(s^* - s[1 + \Delta(t)])(s_{in} - s) - \alpha x f(s) = F(t, s, x), \\ \dot{x} &= x\big[f(s) - g(s^* - s[1 + \Delta(t)])\big] \qquad\qquad = G(t, s, x), \\ s_{in} &> s(0) > 0, \quad x(0) > 0. \end{aligned} \tag{3}$$

Note that, after **(H1)**–**(H2)**, system (3) satisfies Carathéodory conditions (see [5, Th 2.1.1]), guarantees existence and uniqueness of solutions. Let (s, x) be the solution of system (3). Using a standard argument, we build the function $v\colon \mathbb{R}^2_+ \mapsto \mathbb{R}$ defined by:

$$v = s + \alpha x - s_{in}. \tag{4}$$

Clearly, it follows that (s, v) is a solution of the system:

$$\begin{aligned} \dot{s} &= \big[g(s^* - s[1 + \Delta(t)]) - f(s)\big](s_{in} - s) - v f(s) = H(t, s, v), \\ \dot{v} &= -g(s^* - s[1 + \Delta(t)])v \qquad\qquad\qquad\qquad = J(t, s, v), \\ s(0) &> 0, \quad v(0) \in \mathbb{R}. \end{aligned} \tag{5}$$

The following properties of $v(t)$ are elementary:

(i) $\lim_{t\to+\infty} v(t) = 0$.

(ii) $v(t) = v(0)\exp\big(-\int_0^t g(s^* - s(r)[1+\Delta(r)])\,dr\big)$.

(iii) If $v(0) < 0$ (resp. $v(0) > 0$) then $v(t) < 0$ (resp. $v(t) > 0$) for all $t \geq 0$.

Let us introduce the following equations that will be useful for to study the asymptotic behavior of system (5):

$$g(s^* - s[1+\Delta^+]) - f^+(s) = 0, \tag{6}$$

$$g(s^* - s[1+\Delta^-]) - f^-(s) = 0. \tag{7}$$

Case (i) $v(0) < 0$**,** let us define the set:

$$\mathcal{D}_1 = \{(x_1, x_2) \in \mathbb{R}^2 : 0 < x_1 < s_{in}, x_2 < 0\}.$$

Notice that system (5) is competitive in $\mathcal{D}_1$, *i.e.* the off–diagonal entries of the Jacobian matrix are nonnegative or zero. Now we build the following comparison systems in $\mathcal{D}_1$:

$$\begin{array}{ll} \dot{\eta} = \big[g(s^* - \eta[1+\Delta^+(t)]) - f^+(\eta)\big](s_{in} - \eta) - zf^-(\eta) & = H^-(t,\eta,z), \\ \dot{z} = -g(s^* - \eta[1+\Delta^-(t)])z & = J^-(t,\eta,z), \\ \eta(0) \leq s(0) \quad \text{and} \quad 0 > \quad z(0) \geq v(0). & \end{array} \tag{8}$$

$$\begin{array}{ll} \dot{\phi} = \big[g(s^* - \phi[1+\Delta^-(t)]) - f^-(\phi)\big](s_{in} - \phi) - uf^+(\phi) & = H^+(t,\phi,u), \\ \dot{u} = -g(s^* - \phi[1+\Delta^+(t)])u & = J^+(t,\phi,u), \\ s_{in} \geq \phi(0) \geq s(0) \quad \text{and} \quad u(0) \leq v(0). & \end{array} \tag{9}$$

Note that systems (8)–(9) are positively invariants in $\mathcal{D}_1$; moreover **(H1)**–**(H2)** give the following inequality for any $(t,s,v) \in \mathbb{R}_+ \times \mathcal{D}_1$:

$$H^-(t,s,v) \leq H(t,s,v) \leq H^+(t,s,v) \quad \text{and} \quad J^+(t,s,v) \leq J(t,s,v) \leq J^-(t,s,v).$$

Let (η, z) and (ϕ, u) be the solutions of systems (8) and (9) respectively. Moreover, by Proposition 1 (see Appendix) it follows that:

$$s^-(t) \leq s(t) \leq s^+(t) \quad \text{and} \quad u(t) \leq v(t) \leq z(t) \quad \text{for all } t \geq 0,$$

where $s^-(t)$ and $s^+(t)$ are defined by:

$$s^-(t) = \max\Big\{\eta(t), \frac{y(t)}{1+\Delta^+(t)}\Big\} \quad \text{and} \quad s^+(t) = \min\Big\{\phi(t), \frac{y(t)}{1+\Delta^-(t)}\Big\}. \tag{10}$$

Notice that we have improved the estimations for $s(t)$ stated in Remark 2

Finally, Eq.(4) implies that for any $t \geq 0$:

$$x^-(t) = \alpha^{-1}[s_{in} - s^+(t) + u(t)] \leq x(t) \leq \alpha^{-1}[s_{in} - s^-(t) + z(t)] = x^+(t) \tag{11}$$

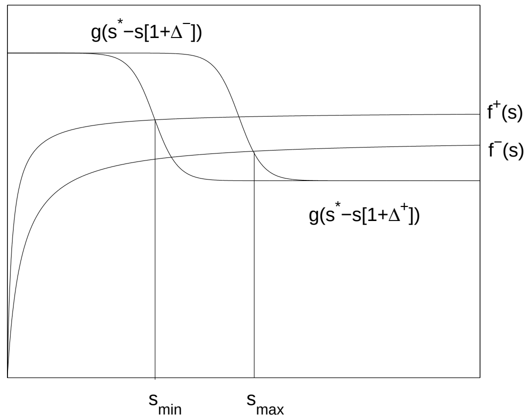

Figure 1: Geometrical interpretation of Eqs.(6)–(7)

and property (a) is verified.

In order to verify property (b), let us define by $s_{\min}$ and $s_{\max}$ the solutions of equations (6) and (7) respectively. Notice that **(G2)**–**(G3)** implies that $s^* \in (s_{\min}, s_{\max})$ and $s_{\max} < s_{in}$.

Let us denote by (8') and (9') the competitive systems (8) and (9) with $\Delta^-(t)$ and $\Delta^+(t)$ replaced by Δ^- and Δ^+ respectively. Moreover, let $(\bar{\eta}, \bar{z})$ and $(\bar{\phi}, \bar{u})$ be the solutions of systems (8') and (9'); applying again Proposition 1 it follows that:

$$\bar{\eta}(t) \leq s(t) \leq \bar{\phi}(t) \quad \text{and} \quad \bar{u}(t) \leq v(t) \leq \bar{z}(t) \quad \text{for any } t \geq 0.$$

Letting $t \to +\infty$, we use Proposition 2 (see Appendix) and obtain:

$$s_{\min} \leq \liminf_{t\to+\infty} s(t) \leq \limsup_{t\to+\infty} s(t) \leq s_{\max} \quad \text{and} \quad \lim_{t\to+\infty} \bar{u}(t) = \bar{z}(t) = 0. \tag{12}$$

Combining these estimates with (11) gives that property (b) is verified with:

$$K = [s_{\min}, s_{\max}] \times [\alpha^{-1}(s_{in} - s_{\max}), \alpha^{-1}(s_{in} - s_{\min})].$$

Case (ii) $v(0) > 0$**,** let us define the set:

$$\mathcal{D}_2 = \{(x_1, x_2) \in \mathbb{R}^2 : 0 < x_1 < s_{in}, x_2 > -\ln(\alpha)\}.$$

Note that in this case it is clear that $x(t)[s_{in} - s(t)]^{-1} > \alpha^{-1}$ for any $t \geq 0$. Let us build the function $w : \mathbb{R}^2_+ \mapsto \mathbb{R}$ defined by:

$$w = \ln\left(\frac{x}{s_{in} - s}\right). \tag{13}$$

It is easy to show that (s, w) is a solution of the system:

$$\begin{array}{ll} \dot{s} \ = \big[g(s^* - s[1+\Delta(t)]) - \alpha e^w f(s)\big](s_{in} - s) & = H(t,s,v), \\ \dot{w} = f(s)[1-\alpha e^w] & = J(t,s,v), \\ s(0) > 0, \quad w(0) \in \mathbb{R}. & \end{array} \tag{14}$$

In the same spirit as before, we build the following systems of differential equations:

$$\begin{array}{ll} \dot{\xi} = \big[g(s^* - \xi[1+\Delta^+(t)]) - \alpha e^z f^+(\xi)\big](s_{in} - \xi) & = H^-(t,\xi,z), \\ \dot{z} = f^-(\xi)[1-\alpha e^z] & = J^-(t,\xi,z), \\ 0 < \xi(0) \leq s(0), \quad z(0) \geq w(0). & \end{array} \tag{15}$$

$$\begin{array}{ll} \dot{\psi} = \big[g(s^* - \psi[1+\Delta^-(t)]) - \alpha e^u f^-(\psi)\big](s_{in} - \psi) & = H^+(t,\psi,u), \\ \dot{u} = f^+(\psi)[1-\alpha e^u] & = J^+(t,\psi,u), \\ s(0) \leq \psi(0) < s_{in}, \quad w(0) \leq u(0). & \end{array} \tag{16}$$

Note that systems (14)–(16) are positively invariants in $\mathcal{D}_2$. Moreover, systems (15) and (16) are competitive in $\mathcal{D}_2$ and **(H1)**–**(H2)** give the following inequalities for any $(t, s, w) \in \mathbb{R}_+ \times \mathcal{D}_2$:

$$H^-(t,s,w) \leq H(t,s,w) \leq H^+(t,s,w) \quad \text{and} \quad J^+(t,s,w) \leq J(t,s,w) \leq J^-(t,s,w).$$

Let (ξ, z) and (ψ, u) be the solutions of systems (15) and (16) respectively. Moreover, by Proposition 1, it follows that:

$$s^-(t) \leq s(t) \leq s^+(t) \quad \text{and} \quad u(t) \leq w(t) \leq z(t) \quad \text{for any } t \geq 0,$$

where the functions $s^-(t)$ and $s^+(t)$ are defined by:

$$s^-(t) = \max\left\{\xi(t), \frac{y(t)}{1+\Delta^+(t)}\right\} \quad \text{and} \quad s^+(t) = \min\left\{\psi(t), \frac{y(t)}{1+\Delta^-(t)}\right\}.$$

Finally, Eq.(13) implies that for any $t \geq 0$:

$$x^-(t) = e^{u(t)}[s_{in} - s^+(t)] \leq x(t) \leq e^{z(t)}[s_{in} - s^-(t)] = x^+(t). \tag{17}$$

and property (a) is verified.

Let us define by (15') and (16') the competitive systems (15) and (16) with $\Delta^-(t)$ and $\Delta^+(t)$ replaced by Δ^- and Δ^+ respectively. Moreover, let $(\bar{\xi}, \bar{z})$ and $(\bar{\psi}, \bar{u})$ the solutions of systems (15') and (16') respectively. Applying Proposition 1 it follows that:

$$\bar{\xi}(t) \leq s(t) \leq \bar{\psi}(t) \quad \text{and} \quad \bar{z}(t) \leq w(t) \leq \bar{u}(t) \quad \text{for any } t \geq 0.$$

Letting $t \to +\infty$, Proposition 2 implies that:

$$s_{\min} \leq \liminf_{t\to+\infty} s(t) \leq \limsup_{t\to+\infty} s(t) \leq s_{\max} \tag{18}$$

$$\lim_{t \to +\infty} \bar{z}(t) = \lim_{t \to +\infty} \bar{u}(t) = -\ln(\alpha). \tag{19}$$

Finally, property (b) is verified with the set K defined above $\square$.

Notice that the area of K is $\alpha^{-1}(s_{\max} - s_{\min})^2$ and it can be reduced by choosing a control g such that the difference between $s_{\min}$ and $s_{\max}$ is minimal. The following result gives an estimation depending of Δ^- and Δ^+.

Corollary 1 *Given $\varepsilon > 0$, there exists an appropriate control g such that:*

$$\left| \frac{s_{\max}}{s_{\min}} - \frac{1 + \Delta^+}{1 + \Delta^-} \right| < \varepsilon.$$

Proof: We can choose a neighborhood V of s^* such that $(s_{\min}, s_{\max}) \subset V$. Hence, Eqs.(6)–(7) and mean value Theorem give:

$$\left| \frac{s_{\max}}{s_{\min}} - \frac{1 + \Delta^+}{1 + \Delta^-} \right| = \frac{C(\Delta^-, \Delta^+)}{g'(\xi)}$$

for some $\xi \in (s_{\min}, s_{\max})$ and $C > 0$ is a constant depending of Δ^- and Δ^+. Now, choosing a control such that $g'(u) > C\varepsilon^{-1}$ for any $u \in V$ completes the proof. $\square$

Remark 3 (i) *The corollary above means that, if $\Delta^+ \equiv \Delta^- \equiv 0$ (small noise in the output), the we are able to stabilize s nearly exactly around s^*.* (ii) *The most realistic choice for g is to choose the slope positive enough between $s_{\min}$ and $s_{\max}$ and then to build a smooth increasing function with two lower and upper bounds, interpreted as the extreme dilution rates $D_{\min}$ and $D_{\max}$. As it is clear on Figure 1, the minimal difference between these two values will be of the order of $|f^+(s_{\min}) - f^-(s_{\max})|$.*

5 Application: Modeling marine ecosystems in a chemostat avoiding washout of biomass

A potential application of problem $(\mathcal{P})$ is the improvement of simulation of marine ecosystems using chemostat (see [3] and the references given there). In fact, several features of the homogeneous liquid medium (*e.g.* temperature and light intensity) can be reproduced externally. Moreover, controlling chemostat allows reproduction of several fixed levels s^* of limiting substrate, and consequently, makes possible study the growth of unicellular phytoplanktonic algae in a wide range of substrate levels, temperature and/or brightness.

Nevertheless, to run a chemostat with a level of limiting substrate close to s_{in} is a difficult task. Indeed, notice that $E_0 = (s_{in}, 0)$ is an equilibrium of system (1); hence if we choose a reference value s^* close to s_{in}, uncertainties stated in **(H1)**–**(H2)** can destabilize the chemostat, and the point E_0 could become stable, forcing washout of biomass from the chemostat.

The washout of biomass must be avoided in any experiment concerning unicellular phytoplanktonic algae because it will be necessary to start the experiment again with a loss of time and material. However, solving problem ($\mathcal{P}$) we avoid the washout; in fact, property (b) gives a lower bound for the biomass, guaranteeing the *uniform persistence* of the biomass, that means that for any positive initial condition it follows that:

$$\liminf_{t\to+\infty} x(t) \geq x^- > 0.$$

6 Numerical example

We consider *Dunaniella Tertiolecta* growth (a chlorophilian phytoplanktonic microalgae) in a chemostat with nitrate as limiting substrate (see [3] for more details), and realistic values (from experiments [4]) for uncertainties and parameters.

For numerical simulations we take Monod's function defined in Remark 1 with the kinetic parameters μ_m and k_s with uncertainties given in [20] summarized in the following table (Liters are denoted by L, micro atom grams by μatg and number of cells by Cell):

Parameter	Uncertainty	Units
μ_m	$\mu_m \in [1.2, 1.6]$	Day^{-1}
k_s	$k_s \in [0.01, 0.2]$	μatg/L
s_{in}	$s_{in} \in [80, 120]$	μatg/L
α^{-1}	$\alpha^{-1} \in [0.15, 0.6]$	μatg/Cell

Hence, for any growth function $f(s)$ it follows that:

$$f^-(s) = \frac{1.2s}{0.2+s} \leq f(s) \leq \frac{1.6s}{0.01+s} = f^+(s).$$

We will work with the following function:

$$f(s) = \frac{[1.4+\omega_1(t)]s}{0.105+\omega_2(t)+s}$$

where $\mu_m = 1.42, k_s = 0.105$ and the functions ω_1 and ω_2 has been constructed interpolating two sets of random data bounded by $[-0.19, 0.19]$ and $[-0.07, 0.07]$ respectively. In the same way we build a function $\Delta(t)$ bounded by $[-0.03, 0.03]$.

We will work with the following realistic values for parameters s_{in} and α:

$$s_{in} = 85\mu\text{gat/L} \quad \alpha = 2\text{Cell}/\mu\text{atg}.$$

The feedback control law considered is:

$$g(u) = a + bh(s^* - u), \quad a \geq b > 0;$$

where $h\colon \mathbb{R} \mapsto \mathbb{R}_+$ is a piecewise linear function defined by:

$$h(s) = \begin{cases} \delta^{-1}s & \text{if } -\delta \leq s \leq \delta, \\ sign(s) & \text{otherwise.} \end{cases}$$

Figure 2 shows the numerical results (Using MATLAB ODE23) for a reference value $s^* = 82$, $a = 1.3$,$b = 1.2$ and $\delta = 0.5$. Conditions **(G1)**–**(G3)** can be verified easily. The concentration of *Dunaniella Tertiolecta* is graduated in 10^6 Cell L^{-1}, nutrient axis is graduated in μgat L^{-1} and time axis in days. Notice that washout is avoided.

Notice that these estimations have been obtained mixing the output $y(t)$ with the solutions of systems (8)–(9); we can compare these ones with the numerical results given in Fig.3 with the same values for parameters neglecting Eq.(10) but considering only the estimations given for the comparison systems (8)–(9). We see that we are able to improve the estimates of s and x by combining the bound of the outputs with the solutions of comparison systems (8)–(9).

7 Discussion

In this article, we have proposed sufficient conditions for solve a problem of feedback stabilization and estimation of unmeasured variables in a chemostat model with deterministic uncertainties in its outputs and internal structure. Our approach is based on the theory of competitive dynamical systems.

Many extensions are available in the spirit of **(H1)** and/or **(H2)**: for example to suppose that the parameter s_{in} is unknown and:

$$s_{in}^-(t) \leq s_{in} \leq s_{in}^+(t)$$

where s_{in}^- and s_{in}^+ are bounded and measurable functions.

Another natural extension of the present work would be to treat outputs of type $y(t) = s(t) + \Delta(t)$ (*additive disturbance*). These two extensions can be certainly be solved by the methods presented in the proof of Th.1 combined with alternative/additional hypothesis.

Finally, several extensions and generalizations of this initial study can be envisaged. For example, the study of chemostat model with a more general uptake function (*e.g.* non monotone function); we could also consider models with competition and different removal rates with uncertainties in the growth functions and the outputs. Another way consists in adding delay (discrete or distributed) in the measured output, representing the time necessary to this measure: the resulting closed loop system is now a delayed system, the behavior of which is the subject of ongoing work.

Appendix: Planar competitive systems

In this appendix we present some definitions and results from the theory of planar competitive systems [18],[19].

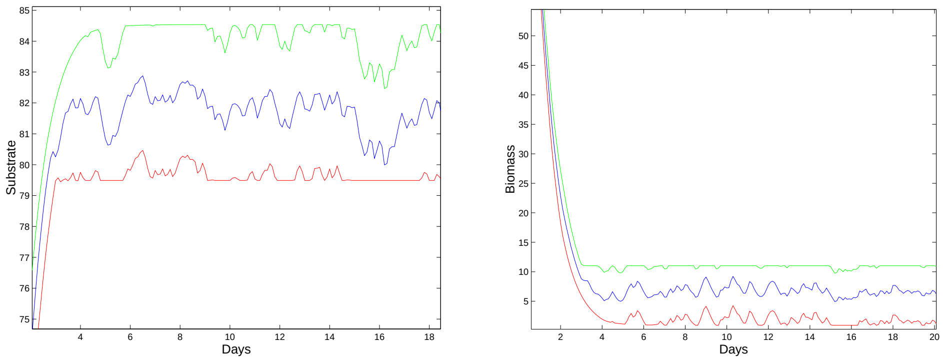

Figure 2: Simulation of system (3), $s_{in} = 85$, $s^* = 82$ and $(a, b, \delta) = (1.3, 1.2, 0.5)$. **Left**, the real substrate (blue) has an upper bound $s^+(t)$ (green) and a lower bound $s^-(t)$ (red). **Right**, the biomass (blue) has an upper bound $x^+(t)$ (green) and a lower bound $x^-(t)$ (red).

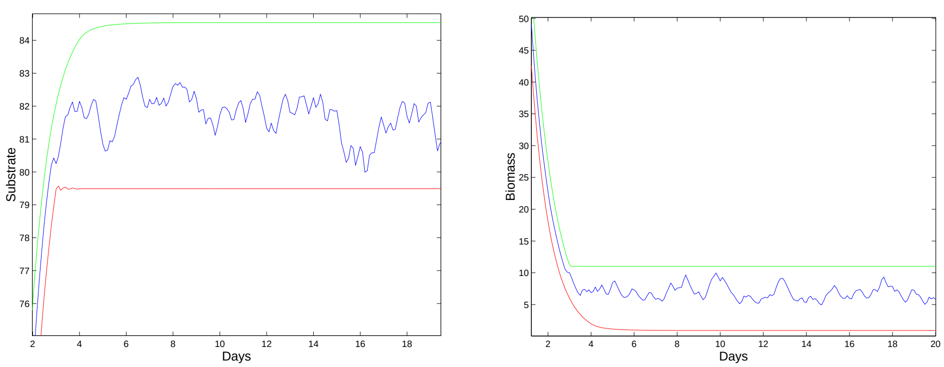

Figure 3: Same simulation as Fig.2, without Eq.(10).

Definition 1 *A vector field in the Euclidean space determines a* competitive system *of differential equations provided that all the off–diagonal terms of its Jacobian matrix are nonnegative on a convex domain.*

Let the convex cone $K_{(0,1)}$ defined as:

$$K_{(0,1)} = \{(u_1, u_2) \in \mathbb{R}^2 : u_1 \geq 0 \quad \text{and} \quad u_2 \leq 0\}$$

and define an order in $\mathbb{R}^2$ by $\vec{y} \leq_{K_{(0,1)}} \vec{x}$ if $\vec{x} - \vec{y} \in K_{(0,1)}$, that means that $y_1 \leq x_1$ and $y_2 \geq x_2$.

The goal is to study the asymptotic behavior of the competitive system:

$$\dot{x} = F(x) \tag{20}$$

and to compare its solutions with these ones of the following systems of differential equations:

$$\dot{z} = G(z), \tag{21}$$

$$\dot{y} = H(y) \tag{22}$$

provided that the continuous functions $G,H\colon \Omega \mapsto \mathbb{R}^2$ verify $H \leq_{K_{(0,1)}} F \leq_{K_{(0,1)}} G$.

Proposition 1 (Comparison Theorem) *Assume that system* (20) *is competitive. Moreover, let $x(t)$ be a solution of* (20) *defined on $[a,b]$, hence*:

(i) *If $z(t)$ is a continuous function on $[a,b]$ satisfying* (21) *on (a,b) with $z(a) \leq_{K_{(0,1)}} x(a)$, then $z(t) \leq_{K_{(0,1)}} x(t)$ for all t in $[a,b]$.*

(ii) *If $y(t)$ is a continuous function on $[a,b]$ satisfying* (22) *on (a,b) with $y(a) \geq_{K_{(0,1)}} x(a)$, then $y(t) \geq_{K_{(0,1)}} x(t)$ for all t in $[a,b]$.*

Proof: See Theorem 3.5.1 from [18] or lemma 2 from [19]. □.

Proposition 2 (Asymptotic behavior) *Assume that system* (20) *is competitive. Moreover, if, for any initial condition x_0, $\omega(x_0)$ has a compact closure, then the solutions of system* (20) *are convergent to a critical point.*

Proof: See Theorem 3.2.2 from [18]. □

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References

[1] Bailey J. and Ollis D., *Biochemical Engineering Fundamentals*, McGraw–Hill, 1986.

[2] Bastin G. and Dochain D., *On–line estimation and adaptive control of bioreactors*, Elsevier, 1990.

[3] Bernard O. *Étude expérimentale et théorique de la croissance de Dunaniella Tertiolecta (clorophyceae) soumise à une limitation variable de nitrate, utilisation de la dynamique transitoire pour la conception et la validation de modèles*; PhD Thesis, Unversité Paris VI, 1995.

[4] Bernard O., Malara G. and Sciandra A. *The effects of a controlled fluctuating nutrient environment on continuous cultures of phytoplankton monitored by computers*; J.Exp.Mar.Biol.Ecol., **197**:263–278,1996.

[5] Coddington E. and Levinson N., *Theory of ordinary differential equations*. McGraw–Hill, 1955.

[6] P. De Leenheer and H. Smith., *Feedback control for chemostat models*, J.Math.Biol., **46**:48–70,2003.

[7] Dochain D. (Ed.), *Automatique des bioprocédés*. Hermes, Paris, 2001.

[8] Estaben M., Polit M. and Steyer J–Ph., *Fuzzy control of an anaerobic digestor*, Control Engineering Practice, Vol.5,**9**:1303–1310, 1997.

[9] Gouzé J.L., Rapaport A. and Hadj–Sadok M.Z., *Interval observers for uncertain biological systems*, Ecological Modelling, **133**:45–56, 2000.

[10] Hadj–Sadok M.Z. and Gouzé J.L., *Estimation of uncertain models of activated sludge processes with interval observers*, J.Proc.Contr., **11**:299–310, 2001.

[11] Henson M.A. and Seborg D.E. (Eds.), *Nonlinear process control*. Prentice Hall, 1997.

[12] Keesman K.J. and Stigter J.D., *Optimal parametric sensitivity control for the estimation of kinetic parameters in bioreactors*, Mathematical Biosciences, **179**:95–111, 2002.

[13] Perrier M. and Dochain D., *Evaluation of control strategies for anaerobic digestion processes*, Int.Journ. for adaptive control, **7**:309–321, 1993.

[14] Raisch J. and Bruce F., Modeling deterministic uncertainty. In Levine W. (Ed.), *The control handbook*, CRC Press, IEEE Press, 1996.

[15] Rapaport A. and Dochain D., *Interval observers for biochemical processes with uncertain kinetics and inputs*. To appear in Mathematical Biosciences.

[16] Rapaport A. and Harmand J., *Robust regulation of a class of partially observed nonlinear continuous bioreactors.* J.Proc.Contr., **12**:291–302, 2002.

[17] Smith H. and Waltman P., *The theory of the chemostat. Dynamics of microbial competition* Cambridge Studies in Mathematical Biology, **13**, Cambridge Univ. Press, 1995.

[18] Smith H., *Monotone dynamical systems: an introduction to the theory of competitive and cooperative systems*, Mathematical surveys and monographs, **41**, Providence, RI,AMS, 1995.

[19] Smith H., Dynamics of competition, in *Mathematics inspired by biology*, Springer Lecture Notes in Math, **1714**:191-240, 1999.

[20] Vatcheva I., Bernard O., De Jong H. and Mars N., *Experiment Selection for the Discrimination of Semi–Quantitative Models of Dynamical Systems.* To appear in Artificial Intelligence.

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