ADAPTIVE SLIDING MODE CONTROL OF FED-BATCH PROCESSES USING SPECIFIC GROWTH RATE ESTIMATION FEEDBACK

Hernán De Battista [*,1] **Jesús Picó** [**]
Enric Picó-Marco [**] **Virginia Mazzone** [***]

[*] *Faculty of Engineering, National University of La Plata, Argentina.*
[**] *Dept. of Systems Eng. & Control, Technical University of Valencia, Spain.*
[***] *Science and Technology Dept., National University of Quilmes, Argentina.*

Abstract: Regulation of the biomass specific growth rate is an important goal in many fermentation fed-batch processes. Inspired in an invariant control law, we propose in this paper a controller with the structure of a partial state feedback with gain dependent on the output error. Further, to make the desired state trajectory effectively invariant despite modeling errors and parameter variations, the feedback gain is continuously adapted by means of a sliding mode algorithm. The stability properties of the closed–loop process are investigated in detail.

Keywords: Fed-batch processes, nonlinear control, sliding mode, partial stability.

1. INTRODUCTION

Many biotechnological processes are characterized by pure cultures with one limiting substrate and with the metabolite of interest being formed in parallel to the microbial growth. These growth-linked reactions may be inhibited when a substrate or a certain product is in excess (Bastin and Dochain, 1990; Dunn *et al.*, 2003). From a biological and production standpoint, an important goal is the regulation of the specific growth rate in order to keep microorganisms into a given physiological state (Jobé *et al.*, 2003; Henson and Seborg, 1992).

The papers (Johnson, 1987; Lee *et al.*, 1999; Rani and Rao, 1999) describe the history and state of the art in the field of fermentation fed-batch process control. Many contributions deal with particular processes in which the substrate concentration is measurable. In other cases, the process is indirectly controlled by regulating some auxiliary variable such as dissolved oxygen. Another research line is dedicated to develop more generic controllers employing an estimation of the controlled variable obtained from on-line measurement of biomass concentration (Bastin and Dochain, 1986; Claes and van Impe, 1999). In this context, concepts of feedback linearization have been applied with the aim of canceling the process nonlinearities (Smets *et al.*, 2002). More recently, a globally stabilizing controller has been proposed inspired in passivation concepts, thus leading to more robust designs (De Battista *et al.*, 2006). This control law essentially differs from the previous one in the sense that the output error modulates the partial state feedback gain rather than appearing as a biomass-independent

[1] Member of CONICET

feedback term. Also, adaptive control techniques have been investigated with the aim of designing controllers having minimal knowledge of process parameters. In particular, a robust adaptive sliding mode algorithm was recently developed (Picó-Marco *et al.*, 2005). Essentially, the adaptation algorithm adjusts the partial state feedback gain in order to steer the state trajectory to a goal manifold. This control algorithm requires only on-line measurements of volume and biomass concentration [2], and an upper-bound for the specific growth rate. In the current paper, we further exploit the adaptive approach presented in (Picó-Marco *et al.*, 2005). More precisely, we introduce an estimation of the output error in the adaptive feedback law. This innovation allows improving the transient response. The proposed controller exhibits very interesting features. Most importantly, it is robust to process parameter uncertainties and bounded disturbances in environmental variables.

The paper is organized as follows. In section 2 the problem is formulated and the control strategy is posed in terms of a goal manifold. The proposed control law and its analysis is considered in section 3. Some examples highlighting the performance of the devised controllers are shown in section 4. Finally, section 5 outlines the conclusions of the work.

2. INVARIANT CONTROL APPROACH AND PROBLEM STATEMENT

A large portion of growth-linked fed-batch fermentation processes have the following description in state-space (Bastin and Dochain, 1990; Dunn *et al.*, 2003):

$$\Sigma : \begin{cases} \dot{x} = \mu(s)x - \dfrac{F}{v}x \\ \dot{s} = -y_s\mu(s)x - mx + \dfrac{F}{v}(s_i - s) \\ \dot{v} = F \end{cases} \tag{1}$$

where $x \in \mathcal{X} \subset \mathbb{R}^+$ and $s \in \mathcal{S} = (0, s_i)$ are the biomass and substrate concentrations respectively; $s_i > 0$ is the influent substrate concentration; $v \in \mathbb{R}^+$ is the volume; $F \in \mathbb{R}^+$ is the feeding flow; $y_s > 0$ is a yield coefficient; $m > 0$ is the maintenance constant. Finally, μ is the specific growth rate which is an either monotonic or non-monotonic function of substrate concentration taking values in the set $\mu \in (0, \mu_m)$. Typical examples are:

- Monod:

$$\mu(s) = \frac{\mu_m s}{k_s + s} \tag{2}$$

- Haldane:

$$\mu(s) = \frac{\mu_m(1 + 2\sqrt{\frac{k_s}{k_i}})s}{k_s + s + \frac{s^2}{k_i}}. \tag{3}$$

The control objective is the regulation of this specific growth rate at a given value $\mu = \mu_r < \mu_m$ using F as control input.

Note that the control specification does not imply stabilization around an operating point. On the contrary, the state follows an unbounded trajectory. In fact, only substrate concentration stabilizes around a value s_r satisfying $\mu(s_r) = \mu_r$, whereas biomass concentration follows a bounded trajectory and volume goes to infinity.

Let us define a reference model for Σ (Picó-Marco *et al.*, 2005):

$$\Sigma_r : \begin{cases} \dot{x} = \mu_r x - \lambda x^2, & x(t_0) = x_{r,0} \\ \dot{v} = \lambda x v, & v(t_0) = v_{r,0} \\ s = s_r. \end{cases} \tag{4}$$

This exosystem generates the following goal manifold for Σ:

$$Z_{r,0} : \begin{cases} z_1 = 1 - \dfrac{X_{r,0}}{X} - \dfrac{\mu_r}{\lambda X}(v - v_{r,0}) = 0 \\ z_2 = 1 - \dfrac{s}{s_r} = 0 \end{cases} \tag{5}$$

where $X(t) = x(t)v(t)$ is the total biomass population in the bioreactor and $X_{r,0} = x_{r,0}v_{r,0}$ is its initial value for the reference model.

It is clear that the control objective is satisfied on this manifold. That is, the biomass population grows exponentially with constant specific growth rate: $X(t) = X_{r,0}e^{\mu_r(t-t_0)}$. It is shown in (Picó-Marco *et al.*, 2005; Picó-Marco *et al.*, 2006) that the partial state feedback law

$$\begin{aligned} F(x, v) &= \lambda x v \\ \lambda = \lambda_r &= \frac{y_s\mu_r + m}{s_i - s_r} \end{aligned} \tag{6}$$

is an invariant control for Σ with respect to the reference manifold $Z_{r,0}$ generated by Σ_r. In other words, once the system Σ is on $Z_{r,0}$, it remains there.

Observation: Feedback laws similar to (6) have been widely investigated (see for instance (Lee *et al.*, 1999) and (Moya *et al.*, 2002)). However, this derivation based on invariance concepts is the key to the design of the adaptive control algorithm developed in the next section.

Our control objective is the design of a control law of the form $F = \lambda(t)xv$ that makes the reference manifold $Z_{r,0}$ an immersion for Σ. The control design is subject to the following constraints:

[2] A biomass sensor (Navarro *et al.*, 2001) that works accurately and reliably for a wide range of concentrations has been designed and patented by our research group.

- The only on-line measurable variables are volume and biomass concentration.
- The yield coefficient y_s, the maintenance constant m, and the influent substrate concentration s_i are uncertain parameters that, moreover, may vary during the process.
- The specific growth rate function $\mu(s)$ is imprecisely known.
- The control signal is nonnegative ($F \geq 0$).

We also make the following assumption:

- An estimation $\hat{\mu}$ of $\mu(s)$, obtained from the on-line measurement of x and v, is available for feedback.

3. PROPOSED CONTROL ALGORITHM

Let us consider the process Σ with partial state feedback $F = \lambda_f(t)xv$:

$$\Sigma_f : \begin{cases} \dot{x} = \mu(s)x - \lambda_f x^2 \\ \dot{s} = -y_s\mu(s)x - mx + \lambda_f x(s_i - s) \\ \dot{v} = \lambda_f xv. \end{cases} \quad (7)$$

The problem now is the following. For a given initial condition defined for the reference model Σ_r, define an adaptive law for λ_f so that Σ_f is immersed into Σ_r with minimal knowledge of the process parameters and possibly including an estimation of the specific growth rate error.

We propose:

$$\begin{aligned} \lambda_f(\hat{\mu}) &= \lambda\left(1 - f(\hat{\mu})\right) \\ \dot{\lambda} &= \frac{-\lambda^2 X}{\mu_r\left(v - v_{r,0}\right)}\left(\frac{1}{T_z} - \mu_r\right) z_1, \quad \lambda(t_0) = \hat{\lambda}_r \end{aligned} \quad (8)$$

where we have included an increasing S-like function $f(\cdot)$ in the feedback gain λ_f to improve the convergence towards the goal manifold. This function satisfies the following conditions:

- f is lower and upper-bounded by $-\bar{f} \leq f \leq 1$,
- $f(\mu_r) = 0$
- f globally satisfies the Lipschitz condition with gain k/μ_r.

The first condition is necessary for the feeding flow to be nonnegative and bounded. The second condition guarantees that the control is effectively invariant on the goal manifold. The third condition is imposed to prove convergence towards the goal manifold. Finally, from the two last conditions, it follows that $|f(\mu)| \leq \frac{k}{\mu_r}|\mu - \mu_r|$.

With regards to the adaptation of λ, note that only the first off-the-manifold coordinate (z_1) is used since the second coordinate (z_2) is not available on-line. The initial value $\hat{\lambda}_r$ is obtained from (6) using estimated values of the parameters. For technical reasons, the starting point of the goal trajectory must satisfy the condition $v_{r,0} < v(t_0)$. Finally, the time constant T_z is given by

$$\begin{aligned} \frac{1}{T_z} &= \frac{N_0}{\max\{|z_1|, \delta\}} + N_1, \\ N_0 &= n_0(1+k)\Delta, \qquad n_0 > 1 \\ N_1 &= n_1\Delta, \qquad n_1 > 1 \\ \Delta &= \max\left\{\mu_r, \mu_m - \mu_r\right\} \end{aligned} \quad (9)$$

with $0 < \delta \ll 1$.

3.1 Convergence of the adaptation law

We prove here global convergence towards the sliding manifold $z_1 = 0$. We leave for the next subsection the proof of convergence on $z_1 = 0$ towards the goal manifold, which is the intersection of $z_1 = 0$ with $z_2 = 0$.

¿From (5) and (8), the time evolution of the sliding coordinate, i.e. the reaching dynamics, is

$$\dot{z}_1 = \left[\mu_r - \mu - \frac{1}{T_z}\right] z_1 + \left(\mu - \mu_r + \mu_r f(\hat{\mu})\right). \quad (10)$$

Now consider the Lyapunov-like function

$$W = \frac{1}{2}{z_1}^2. \quad (11)$$

Then:

$$\begin{aligned} \dot{W} &= \left(\mu - \mu_r\left(1 - f(\hat{\mu})\right)\right) z_1 - \\ &- \left(\frac{N_0}{\max\{|z_1|, \delta\}} + N_1 + \mu - \mu_r\right) {z_1}^2 \\ &< \Delta(1+k)|z_1| - \frac{N_0}{\max\{|z_1|, \delta\}}{z_1}^2 \\ &< 0 \text{ for } |z_1| > \frac{\delta}{n_0}. \end{aligned} \quad (12)$$

That is, the state can be driven arbitrarily close to the sliding manifold. In the limit, choosing $\delta \to 0$, an ideal sliding motion establishes on $z_1 \equiv 0$ (Utkin, 1977).

3.2 Stability analysis

This subsection is devoted to demonstrate that, at least locally, the system trajectories on the sliding surface $z_1 \equiv 0$ converge to its intersection with $z_2 \equiv 0$, i.e. to the goal manifold $Z_{r,0}$.

On the sliding manifold $z_1 \equiv 0$, the closed-loop system dynamics (7) is reduced to:

$$\Sigma_{z_1} : \begin{cases} \dot{s} = \left[-y_s\mu(s) - m + \lambda_f(\hat{\mu})(s_i - s)\right] x \\ \dot{\lambda} = \left[-\lambda^2 \frac{\mu(s) - \mu_r}{\mu_r} \frac{v}{v - v_{r,0}}\right] x \\ \dot{v} = \left[\lambda_f(\hat{\mu})v\right] x \end{cases} \quad (13)$$

where the equation for λ has been obtained from the sliding mode invariance condition ($z_1 = 0$,

$\dot{z}_1 = 0$) (Utkin, 1977; Sira-Ramírez, 1988), and the equation for biomass concentration has been omitted to avoid redundancy. In fact, on $z_1 \equiv 0$, x is algebraically dependent on the other state variables: $x = \frac{X_{r,0}}{v} + \frac{\mu_r}{\lambda v}(v - v_{r,0})$. See that x follows a bounded trajectory on $\mathbb{R}^+$. Besides, replacing x in the last equation of (13) yields $\dot{v} = \mu_r(1 - f(\hat{\mu}))(v - v_{r,0}) + \lambda_f(\hat{\mu})X_{r,0}$, which confirms that the volume diverges exponentially on $z_1 \equiv 0$ (Recall that $v_0 > v_{r,0}$). By this reason, we have to use concepts of partial stability in order to show convergence towards the goal manifold.

Definition: Let $\Psi : \mathcal{V} \triangleq [v_0, \infty) \mapsto (1, \psi_0]$ be the function $\psi(v) = \frac{v}{v - v_{r,0}}$.

Definition: Let us call ζ the partial state $\zeta = \mathrm{col}(s, \lambda)$ and $\zeta_r = \mathrm{col}(s_r, \lambda_r)$. Let $\mathcal{M} = \mathcal{S} \times \Re^+$.

Consider now the continuously differentiable function

$$V(\zeta, \psi) = \psi \int_{s_r}^{s} \frac{\mu(\varsigma) - \mu_r}{\mu_r} \mathrm{d}\varsigma + +(s_i - s_r)\left(\ln\frac{\lambda}{\lambda_r} + \frac{(\lambda_r - \lambda)}{\lambda}\right) \quad (14)$$

with time derivative

$$\begin{aligned}\dot{V}(\zeta, \psi, \hat{\mu}) = -\psi x(\lambda, \psi) \cdot \Bigg[&\frac{y_s}{\mu_r}(\mu(s) - \mu_r)^2 + \\ &+ \frac{\lambda}{\mu_r}(\mu(s) - \mu_r)(s - s_r) + \\ &(\psi - 1)\lambda_f(\hat{\mu}) \int_{s_r}^{s} \frac{\mu(\varsigma) - \mu_r}{\mu_r} \mathrm{d}\varsigma + \\ &+ \frac{\lambda(s_i - s)}{\mu_r}(\mu(s) - \mu_r) f(\hat{\mu})\Bigg]. \quad (15)\end{aligned}$$

Let us assume for the moment that we have a perfect estimation of μ, that is $\tilde{\mu} \triangleq \hat{\mu} - \mu = 0$. This assumption allows us to study the inherent stability properties of the feedback law. In a following paragraph we analyze the effect of the estimation error on the convergence of the control algorithm. Thus, replacing $\hat{\mu}$ in (15) with μ renders

$$\begin{aligned}\dot{V}(\zeta, \psi) = -\psi x(\lambda, \psi) \cdot \Bigg[&\frac{y_s}{\mu_r}(\mu(s) - \mu_r)^2 + \\ &+ \frac{\lambda}{\mu_r}(\mu(s) - \mu_r)(s - s_r) + \\ &+(\psi - 1)\lambda_f(\mu(s)) \int_{s_r}^{s} \frac{\mu(\varsigma) - \mu_r}{\mu_r} \mathrm{d}\varsigma + \\ &+ \frac{\lambda(s_i - s)}{\mu_r}(\mu(s) - \mu_r) f(\mu(s))\Bigg]. \quad (16)\end{aligned}$$

At least locally around ζ_r, $V(\zeta, \psi)$ is upper and lower bounded by the positive definite functions $\overline{V}(\zeta) \triangleq V(\zeta, \psi_0)$ and $\underline{V}(\zeta) \triangleq V(\zeta, 1)$:

$$\underline{V}(\zeta) \leq V(\zeta, \psi) \leq \overline{V}(\zeta). \quad (17)$$

Additionally,

$$\dot{V}(\zeta, \psi) \leq -Q(\zeta) \quad (18)$$

where $Q(\zeta) \triangleq -\dot{V}(\zeta, 1)$ is nonnegative definite.

Then, Σ_{z_1} is Lyapunov stable with respect to ζ uniformly in v, and there exists $\mathcal{D} \subseteq \mathcal{M}$ ($\mathcal{D} \ni \zeta_r$) such that for all $(\zeta, v) \in \mathcal{D} \times \mathcal{V}$, $\zeta(t) \to \mathcal{E}(\mathcal{D}) \triangleq \{\zeta \in \mathcal{D} : Q(\zeta) = 0\}$ as $t \to \infty$ (Chellaboina and Haddad, 2002). Although it is not generally true for partially stable systems, an invariance principle can be derived for asymptotically autonomous partial systems (Chellaboina and Haddad, 2002),(Rouche *et al.*, 1977)(Ch. 8). Fortunately, this is our case. In fact, $\psi \to 1$ and $x \to \mu_r/\lambda$ as v diverges. So, the partial system defined by the first two equations of (13) asymptotically converges to the autonomous system

$$\Sigma_{z_1}^{\infty} : \begin{cases} \dot{s} = (-y_s\mu(s) - m + \lambda_f(\mu(s))(s_i - s))\dfrac{\mu_r}{\lambda} \\ \dot{\lambda} = -\lambda(\mu(s) - \mu_r) \end{cases} \quad (19)$$

It is easy to see that ζ_r is the largest invariant set for (19) in $\mathcal{E}(\mathcal{D})$. Consequently, Σ_{z_1} is asymptotically stable with respect to ζ uniformly in v.

Remark: The inclusion of the increasing function f in the feedback gain λ_f improves convergence to the goal manifold. This is observed in (16) where the last term in brackets is always positive.

Monotonic kinetic functions. For monotonic kinetic functions, e.g. Monod,

* $V(\zeta, \psi)$ verifies (17) for all $\zeta \in \mathcal{M}$ and $\underline{V}(\zeta)$ is radially unbounded.
* $\dot{V}(\zeta, \psi)$ verifies (18) for all $\zeta \in \mathcal{M}$ and ζ_r is the largest invariant set for (19) in $\mathcal{E}(\mathcal{M})$.

Consequently, Σ_{z_1} is globally asymptotically stable with respect to ζ_r uniformly in v (Chellaboina and Haddad, 2002). Then, the system Σ_f on $z_1 \equiv 0$ globally asymptotically converges to the goal manifold $Z_{r,0}$ defined by the reference model Σ_r.

Non-monotonic kinetic functions. For processes with Haldane-like kinetic functions the previous results about stability are only local. In fact, it is well known that such processes may exhibit multiplicity. Let us denote s_m the substrate concentration at which the growth rate is maximum, $s_l < s_m$ and $s_h > s_m$ the substrate concentrations satisfying $\mu(s_l) = \mu(s_h) = \mu_r$. Locally around $s_r = s_l$, the kinetic function is increasing. Then, Σ_{z_1} locally asymptotically stabilizes (partially) around ζ_r uniformly in v. Furthermore, if the kinetic function $\mu(s)$ were known, an estimate of the domain of attraction could be derived from (16). In particular, the second term becomes negative for $s > s_h$. Therefore, a way of avoiding unstable responses consists in upper-bounding the value of λ in such a way that substrate concentration cannot exceed s_h. This method was proposed in (Picó-Marco *et al.*, 2005) and can directly be applied to the current problem.

Effects of estimation errors. Biomass-based observers proposed so far, under the assumption that the model parameters are unknown, do not exhibit uniform exponential convergence. So, the separation principle cannot be applied to show stability of the whole control system. Stability analysis of the controller plus observer is beyond our scope since it would be a particular result valid for a given observer. In general, biomass-based observers achieve a finite-time bounded error provided the rate of change of the specific growth rate is also bounded. So, let us suppose that, after a finite time, the estimation error satisfies $\tilde{\mu} < \rho$. Then,

$$\begin{aligned}(\mu - \mu_r)f(\hat{\mu}) &= (\hat{\mu} - \mu_r)f(\hat{\mu}) - \tilde{\mu}f(\hat{\mu}) \\ &\geq |f(\hat{\mu})|(|\hat{\mu} - \mu_r| - \rho).\end{aligned} \quad (20)$$

Therefore, it can be seen that the last term in brackets in (15) is always positive for $|\hat{\mu} - \mu_r| > \rho$ and thereby for $|\mu - \mu_r| > 2\rho$. Consequently, as a first approach, we can say that after a finite time, the output error enters the vicinity $|\mu - \mu_r| \leq 2\rho$. It should be observed that, though a general result, this is a conservative bound since the contribution of the remaining terms in (15) to the sign of $\dot{V}$, which are all nonnegative, has been ignored. If the function $\mu(s)$ were known an the observer dynamics were included in the model, then a less conservative bound could be obtained. Moreover, asymptotic stability conditions for the complete control system (i.e. including the observer) could potentially be derived.

4. SIMULATION RESULTS

Simulation results are presented in this section to show the main features of the proposed control law. The parameters of the adaptive control algorithm are $\delta = 10^{-3}$ and $n_0 = n_1 = 1.5$, whereas the function f has been selected as

$$f = \begin{cases} -1 \text{ if } f_L \leq -1 \\ 1 \text{ if } f_L \geq 1 \\ f_L \text{ otherwise} \end{cases}, f_L = \frac{k}{\mu_r}(\hat{\mu} - \mu_r) \ . \quad (21)$$

The estimation $\hat{\mu}$ was obtained using the Bastin & Dochain observer with a time constant of 10 minutes.

In the first example (Fig. 1) we considered a process with Monod kinetics. We assumed a 50% error in the parameter y_s that led to a 34% error in the estimation $\hat{\lambda}_r$ of λ_r. In dashed line, it is shown the response of the conventional control law $F = \hat{\lambda}_r xv$, which exhibits large steady state error. In dot-dashed line it is shown the effect of output error feedback. This simulation run corresponds to a control law $F = \hat{\lambda}_r(1 - f(\hat{\mu}))xv$ with $k = 3$. A steady state error still appears though it is lower than in the previous case. It can be corroborated that the error decreases as gain k increases. However, k is limited by the noise of the estimation and the speed of response of the observer. Finally, the solid lines depict the response of the proposed control law with adaptation of λ_r and error feedback. See in the middle part of the figure how the parameter λ is adapted during the process. This adaptation allows eliminating the steady state error.

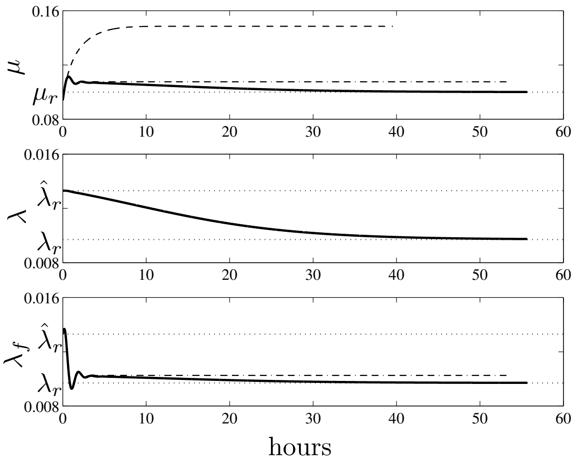

Fig. 1. Example 1: Response of different control laws in the presence of model uncertainty. $F = \lambda_r xv$ (dashed), $F = \lambda_r(1-f(\hat{\mu}))xv$ (dot-dashed), $F = \lambda(1 - f(\hat{\mu}))xv$ with adaptation of λ (solid).

The second example (Fig. 2) provides simulation results for a process with Haldane kinetics. This example is aimed at showing the evolution from a large initial substrate concentration towards the desired one. In particular, the response of the adaptive control law is evaluated for different values of the gain k. Besides, we selected an initial condition far from the surface in order to corroborate the convergence of the algorithm. It is observed in the figure that the convergence towards the sliding surface and then towards the set-point speed up as gain k increases.

5. CONCLUSIONS

In this work we proposed a control law for fed-batch processes which consists of two factors. The first one is continuously adapted using sliding mode techniques in order to guarantee zero steady state error in the regulation of the specific

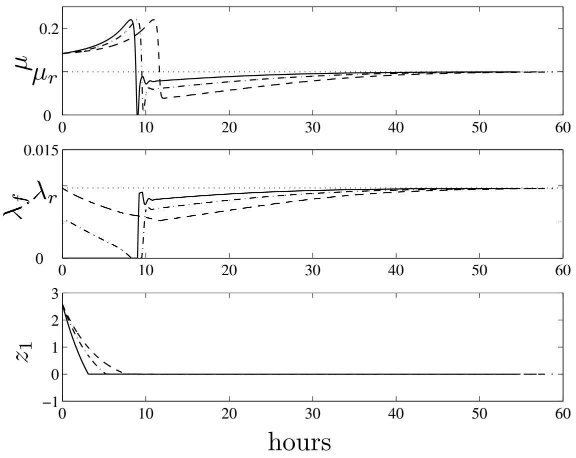

Fig. 2. Example 2: Response of the adaptive control law with different feedback gains from large initial substrate concentration. $k = 0$ (dashed), $k = 1$ (dot-dashed), $k = 3$ (solid).

growth rate. The second one is aimed at speeding up the transient response. The proposed control law only requires on-line measurement of biomass concentration and volume, and exhibits excellent robustness properties against model uncertainties.

ACKNOWLEDGMENTS

This work was partially supported by ANPCyT PICT2003 11-14111 and CONICET PIP 5532/05 of Argentina and by grant DPI2005-01180 of Spain (CICYT) and European Union (FEDER).

REFERENCES

Bastin, G. and D. Dochain (1986). On-line estimation of microbial specific growth rates. *Automatica* **22**, 705–709.

Bastin, G. and D. Dochain (1990). *On-line Estimation and Adaptive Control of Bioreactors.* Elsevier. Amsterdam, The Nederlands.

Chellaboina, V. and W. Haddad (2002). A unification between partial stability and stability theory for time-varying systems. *IEEE Control Systems Magazine* **22**, 66–75.

Claes, J. and J. van Impe (1999). On-line estimation of the specific growth rate based on viable biomass measurements: experimental validation. *Bioprocess Engineering* **21**, 389–395.

De Battista, H., J. Picó and E. Picó-Marco (2006). Globally stabilizing control of fed-batch processes with haldane kinetics using growth rate estimation feedback. *Journal of Process Control* **16**(8), 865–876.

Dunn, I., E. Heinzle, J. Ingham and J. Přenosil (2003). *Biological Reaction Engineering. Dynamic Modelling Fundamentals with Simulation Examples.* Wiley-VCH Verlag.

Henson, M. and D. Seborg (1992). Nonlinear control strategies for continuous fermenters. *Chemical Engineering Science* **47**, 821–835.

Jobé, A., C. Herwig, M. Surzyn, B. Walker, I. Marison and U. von Stockar (2003). Generally applicable fed-batch culture concept based on the detection of metabolic state by on-line balancing. *Biotechnology and Bioengineering* **82**, 627–639.

Johnson, A. (1987). The control of fed-batch fermentation processes - a survey. *Automatica* **23**, 691–705.

Lee, J., S. Lee, S. Park and A. Middelberg (1999). Control of fed-batch fermentations. *Biotechnology Advances* **17**, 29–48.

Moya, P., R. Ortega, M. Netto, L. Praly and J. Picó (2002). Application of nonlinear time-scaling for robust controller design of reaction systems. *International Journal of Robust and Nonlinear Control* **12**, 57–69.

Navarro, J., J. Picó, J. Bruno, E. Picó-Marco and S. Vallés (2001). On-line method and equipment for detecting, determining the evolution and quantifying a microbial biomass and other substances that absorb light along the spectrum during the development of biotechnological processes. Papent ES20010001757, EP20020751179.

Picó-Marco, E., J. Picó and H. De Battista (2005). Sliding mode scheme for adaptive specific growth rate control in biotechnological fed-batch processes. *International Journal of Control* **78**(2), 128–141.

Picó-Marco, E., J.L. Navarro and J.M. Bruno (2006). A closed loop exponential feeding law: invariance and global stability analysis. *Journal of Process Control* **16**(4), 395–402.

Rani, K. and V. Rao (1999). Control of fermenters - a review. *Bioprocess Engineering* **21**, 77–88.

Rouche, N., P. Habets and M. Laloy (1977). *Stability Theory by Lyapunov's Direct Method.* Springer-Verlag. New York.

Sira-Ramírez, H. (1988). Differential geometric methods in variable structure systems. *International Journal of Control* **48**(4), 1359–1390.

Smets, I., G. Bastin and J. van Impe (2002). Feedback stabilization of fed-batch bioreactors: non-monotonic growth kinetics. *Biotechnology Progress* **18**, 1116–1125.

Utkin, V.Y. (1977). Variable structure systems with sliding modes. *IEEE Transactions on Automatic Control* **22**(2), 212–222.