LINEARIZING CONTROL OF YEAST AND BACTERIA FED-BATCH CULTURES

A Comparison of Adaptive and Robust Strategies

Laurent Dewasme, Alain Vande Wouwer
Service d'Automatique, Université de Mons, 31 Boulevard Dolez, 7000 Mons, Belgium

Daniel Coutinho
Group of Automation and Control Systems, PUCRS, Av. Ipiranga 6681, 90619-900, Porto Alegre, Brazil

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Abstract: Linearizing control is a popular approach to control bioprocesses, which has received considerable attention is the past several years. This control approach is however quite sensitive to modeling uncertainties, thus requiring some on-line parametric adaptation so as to ensure performance. In this study, this usual adaptive strategy is compared in terms of implementation and performance to a robust strategy, where the controller has a fixed parametrization which is determined using a LMI framework so as to ensure robust stability and performance. Fed-batch cultures of yeast and bacteria are considered as application examples.

1 INTRODUCTION

The culture of host recombinant micro-organisms is nowadays a very important way of producing biopharmaceuticals. Fed-batch operation is popular in industrial practice, since it is advantageous from an operational and control point of view. The off-line determination of the feeding profile is usually sub-optimal as some security margin has to be provided in order to avoid an excess of substrate leading to the accumulation of inhibitory by-products (inhibition of the cell respiratory capacity), namely ethanol for yeast cultures and acetate for bacteria cultures.

To optimize the culture conditions and to avoid high concentrations of inhibitory by-products, a closed-loop solution is required, and a wide diversity of approaches, e.g., (Pomerleau, 1990; Chen et al., 1995; Rocha, 2003; Renard and Wouwer, 2008; Dewasme et al., 2009a; Dewasme et al., 2009b) have been considered.

In particular, linearizing control (Bastin and Dochain, 1990) is a very popular approach, which has been applied successfully in a number of case studies. However, linearizing control requires the knowledge of an accurate model, and on-line parametric adaptation is usually implemented so as to ensure performance. Whereas parametric adaptation is a simple approach, it does not guarantee stability in the presence of unmodeled dynamics.

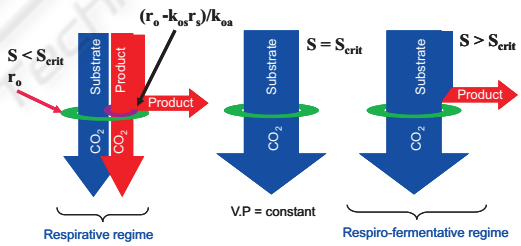

Figure 1: Illustration of Sonnleitner's bottleneck assumption for cells limited respiratory capacity.

In this study, another approach is also considered, which is based on nonlinear robust control and the used of Linear Matrix Inequalities (LMIs) to design the free linear dynamics so as to ensure robust stability and performance. A comparison of the adaptive and robust control approaches is provided in terms of implementation, and simulation tests shows the respective advantages and limitations of both strategies.

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2 MECHANISTIC MODEL

In this study, we consider a generic model that would, in principle, allow the representation of the culture of different strains presenting an overflow metabolism (yeasts, bacteria, animal cells, etc). This model describes therefore the cell catabolism through the following three main reactions:

Substrate oxidation :

$$k_{S1}\mathrm{S} + k_{O1}\mathrm{O} \xrightarrow{r_1 X} k_{X1}\mathrm{X} + k_{C1}\mathrm{C} \quad (1a)$$

Overflow reaction (typically fermentation) :

$$k_{S2}\mathrm{S} + k_{O2}\mathrm{O} \xrightarrow{r_2 X} k_{X2}\mathrm{X} + k_{P2}\mathrm{P} + k_{C2}\mathrm{C} \quad (1b)$$

Metabolite product oxidation :

$$k_{P3}\mathrm{P} + k_{O3}\mathrm{O} \xrightarrow{r_3 X} k_{X3}\mathrm{X} + k_{C3}\mathrm{C} \quad (1c)$$

where X, S, P, O and C are, respectively, the concentration in the culture medium of biomass, substrate (typically glucose or glycerol), product (i.e. ethanol or methanol in yeast cultures, acetate in bacteria cultures or lactate in animal cells cultures), dissolved oxygen and carbon dioxide. $k_{\xi i}$ (i=1,2,3) are the yield coefficients and r_1, r_2 and r_3 are the nonlinear specific growth rates given by:

$$r_1 = \frac{\min(r_S, r_{S_{crit}})}{k_{S1}} \quad (2)$$

$$r_2 = \frac{\max(0, r_S - r_{S_{crit}})}{k_{S2}} \quad (3)$$

$$r_3 = \frac{\max\left(0, \min\left(r_P, \frac{k_{os}(r_{S_{crit}} - r_S)}{k_{oa}}\right)\right)}{k_{P3}} \quad (4)$$

where the kinetic terms associated with the substrate consumption r_S, the critical substrate consumption $r_{S_{crit}}$ (generally dependent on the cells oxidative or respiratory capacity r_O) and the product oxidative rate r_P are given by:

$$r_S = \mu_S \frac{\mathrm{S}}{\mathrm{S} + K_S} \quad (5a)$$

$$r_{S_{crit}} = \frac{r_O}{k_{os}} = \frac{\mu_O}{k_{os}} \frac{\mathrm{O}}{\mathrm{O} + K_O} \frac{Ki_P}{Ki_P + P} \quad (5b)$$

$$r_P = \mu_P \frac{\mathrm{P}}{\mathrm{P} + K_P} \quad (5c)$$

These expressions take the classical form of Monod laws where μ_S, μ_O and μ_P are the maximal values of specific growth rates, K_S, K_O and K_P are the saturation constants of the corresponding element, and Ki_P is the inhibition constant. k_{os} and k_{oa} represent the coefficients characterizing respectively the yield between the oxygen and substrate consumptions, and the yield between the acetate and oxygen consumptions.

This kinetic model is based on Sonnleitner's bottleneck assumption (Sonnleitner and Käppeli, 1986) which was developed for a yeast strain *Saccharomyces cerevisiae* (Figure 1). During a culture, the cells are likely to change their metabolism because of their limited respiratory capacity. When the substrate is in excess (concentration $S > S_{crit}$), the cells produce a metabolite product P through fermentation, and the culture is said in respiro-fermentative (RF) regime. On the other hand, when the substrate becomes limiting (concentration $S < S_{crit}$), the available substrate (typically glucose), and possibly the metabolite P (as a substitute carbon source), if present in the culture medium, are oxidized. The culture is then said in respirative (R) regime.

Component-wise mass balances give the following differential equations :

$$\frac{dX}{dt} = (k_{X1}r_1 + k_{X2}r_2 + k_{X3}r_3)X - DX \quad (6a)$$

$$\frac{dS}{dt} = -(k_{S1}r_1 + k_{S2}r_2)X + DS_{in} - DS \quad (6b)$$

$$\frac{dP}{dt} = (k_{P2}r_2 - k_{P3}r_3)X - DP \quad (6c)$$

$$\frac{dO}{dt} = -(k_{O1}r_1 + k_{O2}r_2 + k_{O3}r_3)X - DO + OTR \quad (6d)$$

$$\frac{dC}{dt} = (k_{C1}r_1 + k_{C2}r_2 + k_{C3}r_3)X - DC - CTR \quad (6e)$$

$$\frac{dV}{dt} = F_{in} \quad (6f)$$

where S_{in} is the substrate concentration in the feed, F_{in} is the inlet feed rate, V is the culture medium volume and D is the dilution rate ($D = F_{in}/V$). OTR and CTR represent respectively the oxygen transfer rate from the gas phase to the liquid phase and the carbon transfer rate from the liquid phase to the gas phase. Classical models of OTR and CTR are given by:

$$OTR = k_L a(O_{sat} - O) \quad (7a)$$

$$CTR = k_L a(P - P_{sat}) \quad (7b)$$

where $k_L a$ is the volumetric transfer coefficient and, O_{sat} and P_{sat} are respectively the dissolved oxygen and carbon dioxide concentrations at saturation.

3 A SUBOPTIMAL STRATEGY

The maximum of productivity is obtained at the edge between the respirative and respiro-fermentative

regimes, where the quantity of by-product is constant and equal to zero ($VP = 0$). Unfortunately, evaluating accurately the volume is a difficult task as it depends on the inlet and outlet flows including F_{in} but also the added base quantity for pH control and several gas flow rates. Moreover, maintaining the quantity of by-product constant in a fed-batch process means that the by-product concentration has to decrease while the volume increases. So, even if the volume is correctly measured, VP becomes unmeasurable once P reaches the sensitivity level of the by-product probe. For those practical limitations, a sub-optimal strategy is elaborated through the control of the by-product concentration around a low value P^* depending on the sensitivity of commercially available probes (for instance, a general order for ethanol probe is $0.1 g/l$), and requiring only an estimation of the volume by integration of the feed rate.

The basic principle of the controller is thus to regulate the by-product at a constant low setpoint, leading to a self-optimizing control in the sense of (Skogestad, 2004) and ensuring that the culture operates in the respiro-fermentative regime, close to the biological optimum, i.e., close to the edge with the respirative regime.

4 LINEARIZING CONTROL STRATEGY

The component-wise mass balances of reaction scheme (1) lead to the following state-space representation

$$\dot{x} = Kr(x)X + Ax - ux + B(u) \tag{8}$$

where $x = [\ X \quad S \quad P \quad O \quad C \quad V\ ]'$ is the state vector, $r(x) = [\ r_1 \quad r_2 \quad r_3\ ]'$ is the vector of reaction rates, and $u = D = F_{in}/V$ is the control input (the dilution rate). The matrices K and A, and the vector function $B(\cdot)$ are given by:

$$K = \begin{bmatrix} k_{X1} & k_{X2} & k_{X3} \\ -k_{S1} & -k_{S2} & 0 \\ 0 & k_{P2} & -k_{P3} \\ -k_{O1} & -k_{O2} & -k_{O3} \\ k_{C1} & k_{C2} & k_{C3} \\ 0 & 0 & 0 \end{bmatrix}, \; B(u) = \begin{bmatrix} 0 \\ S_{in}\, u \\ 0 \\ k_L a\, O_{sat} \\ k_L a\, P_{sat} \\ 0 \end{bmatrix}, \tag{9}$$

$$A = \begin{bmatrix} 0_{3\times3} & 0_{3\times2} & 0_{3\times1} \\ 0_{2\times2} & -k_L a\, I_{2\times2} & 0_{2\times2} \\ 0_{1\times3} & 0_{1\times2} & 0 \end{bmatrix},$$

A feedback linearizing controller is illustrated in Figure 2. In a first step, this controller is derived assuming a perfect process knowledge. The basic idea

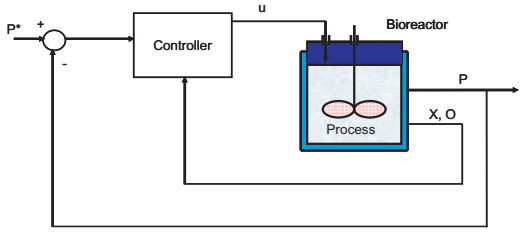

Figure 2: Linearizing control scheme.

is to derive a nonlinear controller, which allows a linearization of the process behavior ((Chen et al., 1995; Pomerleau, 1990)).

As the theoretical value of S_{crit} is very small (below $0.1\ g/l$) and assuming a quasi-steady state of S (i.e. considering that there is no accumulation of glucose when operating the bioreactor in the neighborhood of the optimal operating conditions), the small quantity of substrate VS is almost instantaneously consumed by the cells ($\frac{d(VS)}{dt} \approx 0$ and $S \approx 0$) and (6b) becomes:

$$k_{S2} r_2 X = -k_{S1} r_1 X + S_{in} u \tag{10}$$

where r_1 and r_2 are nonlinear functions of S, P and O as given by (2-3).

Replacing $r_2 X$ by (10) in the mass balance equation for P (6c), we obtain:

$$\dot{P} = -\frac{k_{P2} k_{S1}}{k_{S2}} r_1 X - k_{P3} r_3 X - u\left(P - \frac{k_{P2}}{k_{S2}} S_{in}\right) \tag{11}$$

A first-order linear reference model is imposed:

$$\frac{d(P^* - P)}{dt} = -\lambda(P^* - P)\ ,\ \lambda > 0 \tag{12}$$

and a constant setpoint is considered so that:

$$\frac{dP}{dt} = \lambda(P^* - P)\ ,\ \lambda > 0 \tag{13}$$

Equating (13) and (11), the following control law is obtained:

$$F_{in} = V \frac{\lambda(P^* - P) + (\frac{k_{P2} k_{S1}}{k_{S2}} r_1 + k_{P3} r_3) X}{\frac{k_{P2}}{k_{S2}} S_{in} - P} \tag{14}$$

where $\frac{k_{P2} k_{S1}}{k_{S2}} r_1$ and $k_{P3} r_3$, the kinetic expressions, contain several uncertain parameters.

4.1 A Classical Adaptive Strategy

In (Chen et al., 1995), the parameter uncertainties are handled using an on-line estimation of the kinetic term $\frac{k_{P2} k_{S1}}{k_{S2}} r_1 + k_{P3} r_3$ in the linearizing control law (14). In this study, the biomass concentration X is supposed to be measured using a probe (for instance

a optical density probe or a conductance probe, which are nowadays widely available), whereas in (Chen et al., 1995), an asymptotic observer is used to estimate this component concentration. The following adaptive scheme is therefore a simplified version of the original algorithm.

$$F_{in} = V\frac{\lambda(P^* - P) + \hat{\theta}X}{\frac{k_{P2}}{k_{S2}}S_{in} - P} \tag{15}$$

A direct adaptive scheme as described in (Bastin and Dochain, 1990) is used. Consider the following Lyapunov function candidate:

$$V(t) = \frac{1}{2}\left(\tilde{P}^2 + \frac{\tilde{\theta}^2}{\gamma}\right) \tag{16}$$

where $\tilde{P} = P^* - P$, $\tilde{\theta} = \theta - \hat{\theta}$ and γ is a strictly positive scalar. The specific growth rates r_1 and r_3 (and, of course, the pseudo-stoichiometric coefficient k_4) are assumed to be constant so that θ variations are negligible ($\frac{d\theta}{dt} = 0$).

Using the Lyapunov stability theory, the time derivative of the Lyapunov candidate function should be negative for the closed-loop system to be stable:

$$\frac{dV}{dt} = \frac{d\tilde{P}}{dt}\tilde{P} + \tilde{\theta}\frac{d\tilde{\theta}}{dt}\frac{1}{\gamma} \tag{17}$$

Considering (13) and a possible parameter mismatch ($\hat{\theta} \neq \theta$):

$$\frac{d\tilde{P}}{dt} = -\lambda\tilde{P} - \tilde{\theta}X \tag{18}$$

so that (17) becomes:

$$\frac{dV}{dt} = -\lambda\tilde{P}^2 - \tilde{P}\tilde{\theta}X - \tilde{\theta}\frac{d\hat{\theta}}{dt}\frac{1}{\gamma} \tag{19}$$

Choosing the following θ adaptive law cancels the second and the third terms:

$$\frac{d\hat{\theta}}{dt} = \gamma X\tilde{P} \tag{20}$$

4.2 A Robust Strategy

Structural and parametric uncertainties can be lumped into a global parametric error:

$$\delta = \bar{\theta} - \theta \tag{21}$$

where δ is a nonlinear function of (S,P,O) representing possible inexact cancellations of nonlinear terms due to model uncertainties and $\bar{\theta}$ represents the hypothetical exact unknown value. Rewriting the kinetic term in (15) using the new expression taken from (21), we obtain:

$$u = F_{in} = V\frac{\lambda(P^* - P) + \bar{\theta}X - \delta X}{\frac{k_{P2}}{k_{S2}}S_{in} - P} \tag{22}$$

which corresponds to the perturbed reference system:

$$\dot{P} = \lambda(P^* - P) - \delta X \tag{23}$$

Borrowing the ideas of the *Quasi-LPV* approach (Leith and Leithead, 2000), we bound the time-varying parameter δ which is supposed to belong to a known set $\Delta := \{\delta : \underline{\delta} \leq \delta \leq \overline{\delta}\}$ with $\underline{\delta}$ and $\overline{\delta}$ respectively representing the minimal and maximal admissible uncertainties.

The parameter λ is designed to ensure some robustness and tracking performance to the overall closed-loop system, which is modeled as follows:

$$\mathcal{M} : \left\{ \begin{array}{rcl} \dot{P} & = & -\lambda z - \delta X \\ z & = & P^* - P \end{array} \right. \tag{24}$$

where $z = P^* - P$ is the performance output.

Let $w = \left[\begin{array}{cc} P^* & X \end{array}\right]' \subset \mathcal{L}_{2,[0,T]}$ be the disturbance input to the system $\mathcal{M}$, $a(\lambda,\delta) = \left[\begin{array}{cc} \lambda & -\delta \end{array}\right]$ and $c = \left[\begin{array}{cc} 1 & 0 \end{array}\right]$. The closed-loop system (24) can be rewritten:

$$\mathcal{M} : \left\{ \begin{array}{rcl} \dot{P} & = & -\lambda P + a(\lambda,\delta)w \\ z & = & -P + c\,w\,,\ \delta \in \Delta \end{array} \right. \tag{25}$$

Consider the finite horizon (for instance, between the instant 0 and the time T) $\mathcal{L}_2$-gain of system $\mathcal{M}$ (M. Green and D.J.N. Limebeer, 1994), representing the worst-case of the ratio of $\|z\|_{2,[0,T]}$ (i.e., the finite horizon 2-norm of the tracking error) and $\|w\|_{2,[0,T]}$ (i.e., the finite horizon 2-norm of the disturbance input), which is defined as:

$$\|\mathcal{M}_{wz}\|_{\infty,[0,T]} = \sup_{\delta\in\Delta, 0\neq w\subset\mathcal{L}_{2,[0,T]}} \frac{\|z\|_{2,[0,T]}}{\|w\|_{2,[0,T]}} \tag{26}$$

Thus, the parameter λ is designed based on the $\mathcal{H}_\infty$ control theory (M. Green and D.J.N. Limebeer, 1994; Skogestad and Postlethwaite, 2001). Let $\alpha > 0$ be an upper limiting of $\|\mathcal{M}_{wz}\|_{\infty,[0,T]}$. Thus, the problem is to find α such that:

$$\min_{\lambda,\delta\in\Delta} \alpha : \|\mathcal{M}_{wz}\|_{\infty,[0,T]} \leq \alpha \tag{27}$$

while ensuring the robust stability of system (25).

This optimization problem can be written in terms of linear matrix inequalities (*LMIs*) and solved using readily available toolboxes, e.g., SeDuMi (Sturm et al., 2006) can be applied to solve the problem. These constraints can be easily obtained via a quadratic Lyapunov function (S.Boyd, L.El-Ghaoui, E.Feron and V.Balakrishnan, 1994)

$$V(P) = P'QP = QP^2 \tag{28}$$

where Q is a strictly positive symmetric matrix (i.e., $Q = Q' \succ 0$) and " $'$ " corresponds to the transposition matrix operation.

The minimization in (27) is then equivalent to:

$$\min \alpha \ : \ V(P) \succ 0 \ , \ \dot{V}(P) + \frac{1}{\alpha} z'z - \alpha w'w \prec 0 \quad (29)$$

where, using (25) and (28), the time derivative of $V(P)$ is given by:

$$\begin{aligned} \dot{V}(P) &= \dot{P}'QP + P'Q\dot{P} \\ &= (-\lambda P + aw)'QP + P'Q(-\lambda P + aw) \\ &= -\lambda P'QP + (aw)'QP - \lambda P'QP + P'Qaw \\ &= -2\lambda P'QP + a'w'QP + P'Qaw \qquad (30) \end{aligned}$$

Using (30) in (29), the following expression is obtained:

$$\begin{bmatrix} P \\ w \end{bmatrix}' \begin{bmatrix} -2m & Qa \\ a'Q & -\alpha I_{n_w} \end{bmatrix} \begin{bmatrix} P \\ w \end{bmatrix} - \frac{1}{\alpha} zz' \prec 0 \quad (31)$$

where $m = \lambda Q$ and I_{n_w} is the unity matrix of dimension $n_w \times n_w$ and n_w is the dimension of w.

Now, consider the following lemma (*Schur Complement*):

Lemma 1. The following matrix inequalities are equivalent

$$\begin{aligned} &(i) \quad T > 0, R - ST^{-1}S' \succ 0 \\ &(ii) \quad R > 0, T - S'R^{-1}S \succ 0 \\ &(iii) \quad \begin{bmatrix} R & S \\ S' & T \end{bmatrix} \succ 0 \end{aligned}$$

Hence, using the expression of z, a and c in (25) and Lemma 1, the optimization problem in (27) can be written as follows:

$$\min_{Q,m} \alpha \ : \ \alpha > 0 \ , \ Q = Q' > 0 \ \text{ and } \begin{bmatrix} -2m & m & -\delta Q & -1 \\ m & -\alpha & 0 & 1 \\ -\delta Q & 0 & -\alpha & 0 \\ -1 & 1 & 0 & -\alpha \end{bmatrix} \prec 0 \quad (32)$$

If there exists a feasible solution to the above optimization problem for all δ evaluated at the vertices of Δ, then (27) is satisfied and $\lambda = mQ^{-1}$.

Remark 1. Quadratic Lyapunov functions may be conservative for assessing the stability of parameter-dependent systems (G. Chesi and Vicino, 2004). However, a parameter-independent Lyapunov function is considered in this study for two main reasons:

1. λ is parametrized with the Lyapunov matrix Q so as to obtain a convex design condition. A parameter-independent matrix Q therefore results in a parameter-independent control law;
2. the variation of δ is a priori unknown.

Remark 2. This method is likely to be conservative, as the parameter δ has to bound the nonlinearities of the inexactly cancelled terms. Less conservative results can be obtained by considering the approach of (D.F. Coutinho, M. Fu, A. Trofino and P. Danès, 2008) to deal with the nonlinearities at the cost of a larger computational effort.

5 NUMERICAL RESULTS

In this section, for comparing the adaptive and robust linearizing control strategies, several numerical simulations considering small-scale bacteria and yeast cultures (respectively in 5 and 20 $[l]$ bioreactors) are performed. The first simulation set is dedicated to yeast cultures with initial and operating conditions: $X_0 = 0.4g/l$, $S_0 = 0.5g/l$, $E_0 = 0.8g/l$, $O_0 = O_{sat} = 0.035g/l$, $C_0 = C_{sat} = 1.286g/l$, $V_0 = 6.8l$, $S_{in} = 350g/l$. The second simulation set is dedicated to bacteria cultures with initial and operating conditions: $X_0 = 0.4g/l$, $S_0 = 0.05g/l$, $A_0 = 0.8g/l$, $O_0 = O_{sat} = 0.035g/l$, $C_0 = C_{sat} = 1.286g/l$, $V_0 = 3.5l$, $S_{in} = 250g/l$

The values of all model parameters are listed in Tables 1, 2, 3 and 4. Note that, for yeast cultures, coefficients k_{os} and k_{oa} are simply replaced by k_{O1} and k_{03} while $k_{O2} = 0$, in accordance with the model of (Sonnleitner and Käppeli, 1986). For the bacteria model, parameters values are taken from (Rocha, 2003) and slightly modified to adapt the yield coefficient normalization to the proposed reaction scheme (1) and kinetic model (with a slight difference in the formulation of r_3).

The state variables are assumed available (i.e., measured) online for feedback. The adaptive and robust linearizing feedback controllers proposed in section 4 aim at tracking the byproduct set-point (E^* and $A^* = 1\ g/l$) which is chosen sufficiently low so as to stay in the neighborhood of the optimal trajectory but also sufficiently high to avoid probe sensitivity limitations. In this setup, a noisy byproduct measurement is considered.

To design the parameter λ in (23) via the optimization problem (27), the parameters K_S, K_P, K_O, K_{iP} and μ_S, μ_O are assumed to be respectively varying of $\pm 100\%$ and $\pm 15\%$ from their nominal values. Simulating the operating conditions of the control strategy in (22), we may infer that $\overline{\delta} = -\underline{\delta} = 0.5/3600\ s^{-1}$ for yeast cultures and $\overline{\delta} = -\underline{\delta} = 0.1/3600\ s^{-1}$ for bacteria cultures. In light of (25) and (27), these constraints yield for yeasts and bacteria, respectively to $\lambda = 0.0056$ and $\lambda = 0.0046$.

Concerning the adaptive control law, $\lambda = 1$ and

Table 1: Yield coefficients values of Sonnleitner and Käppeli for *S. cerevisiae* model (Sonnleitner and Käppeli, 1986)

Yield coefficients	Values	Units
k_{X1}	0,49	$g\,of\,X/g\,of\,S$
k_{X2}	0,05	$g\,of\,X/g\,of\,S$
k_{X3}	0,72	$g\,of\,X/g\,of\,E$
k_{S1}	1	
k_{S2}	1	
k_{P2}	0,48	$g\,of\,E/g\,of\,S$
k_{P3}	1	
k_{O1}	0,3968	$g\,of\,O_2/g\,of\,S$
k_{O2}	0	$g\,of\,O_2/g\,of\,S$
k_{O3}	1,104	$g\,of\,O_2/g\,of\,E$
k_{C1}	0,5897	$g\,of\,CO_2/g\,of\,S$
k_{C2}	0,4621	$g\,of\,CO_2/g\,of\,S$
k_{C3}	0,6249	$g\,of\,CO_2/g\,of\,E$

Table 2: Kinetic coefficients values of Sonnleitner and Käppeli for the *S. cerevisiae* model (Sonnleitner and Käppeli, 1986)

Kinetic coefficients	Values	Units
μ_O	0,256	$g\,of\,O_2/g\,of\,X\ /h$
μ_S	3,5	$g\,of\,S/g\,of\,X\ /h$
K_O	0,0001	$g\,of\,O_2/l$
K_S	0,1	$g\,of\,S/l$
K_E	0,1	$g\,of\,E/l$
Ki_E	10	$g\,of\,E/l$

$\gamma = 0.05$ for yeast cultures while $\lambda = 2$ and $\gamma = 0.25$ for bacteria cultures. Note also that the sampling period is chosen equal to 0.1 h.

Before discussing the results of the proposed methods, it is interesting to observe the performance of a plain linearizing controller, i.e. without adaptation or robustification, applied to the yeast process in the presence of modeling errors. For instance, consider the situation where the user selects a relatively high gain $\lambda = 1$, and $\hat{\theta}$ is fixed to $k_{P2}/2$. Figure 3 illustrates the consequences of such choices. Even if the controller behaves correctly during the first hours, the divergence of the ethanol signal during the last hours will impact the quality of the culture.

Figure 4 shows now the closed-loop response of biomass X, ethanol E concentrations, and the inlet feed rate F_{in}, for five different values of the kinetic parameters (which were randomly chosen) in yeast cultures under a robust control strategy. In all simulation runs, a white noise is added to the ethanol concentration measurement with a standard deviation of ± 0.1 $[g/l]$ and the culture is considered as always evolving in the optimal operating conditions in which $r_1 = \frac{r_O}{k_{O1}}$ and $r_3 = 0$ so that the hypothetical parameter

Table 3: Yield coefficients values of Rocha's *E.coli* model (Rocha, 2003)

Yield coefficients	Values	Units
k_{X1}	1	
k_{X2}	1	
k_{X3}	1	
k_{S1}	0,316	$g\,of\,S/g\,of\,X$
k_{S2}	0,04	$g\,of\,S/g\,of\,X$
k_{P2}	0,157	$g\,of\,A/g\,of\,X$
k_{P3}	0,432	$g\,of\,A/g\,of\,X$
k_{O1}	0,339	$g\,of\,O_2/g\,of\,X$
k_{O2}	0,471	$g\,of\,O_2/g\,of\,X$
k_{O3}	0,955	$g\,of\,O_2/g\,of\,X$
k_{C1}	0,405	$g\,of\,CO_2/g\,of\,X$
k_{C2}	0,754	$g\,of\,CO_2/g\,of\,X$
k_{C3}	1,03	$g\,of\,CO_2/g\,of\,X$
k_{os}	2,02	$g\,of\,O_2/g\,of\,X$
k_{oa}	1,996	$g\,of\,O_2/g\,of\,X$

Table 4: Kinetic coefficients values of Rocha's *E.coli* model (Rocha, 2003)

Kinetic coefficients	Values	Units
μ_O	0,7218	$g\,of\,O_2/g\,of\,X\ /h$
μ_S	1,832	$g\,of\,S/g\,of\,X\ /h$
K_O	0,0001	$g\,of\,O_2/l$
K_S	0,1428	$g\,of\,S/l$
K_A	0,5236	$g\,of\,A/l$
Ki_A	6,952	$g\,of\,A/l$

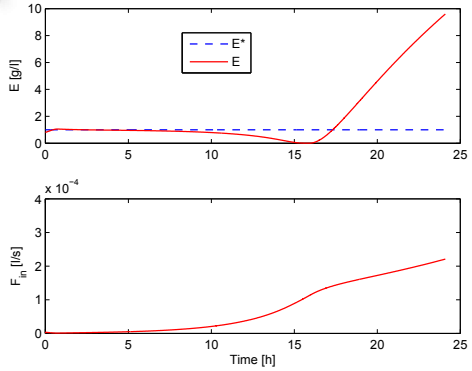

Figure 3: Yeast cultures – ethanol concentration and feed rate when the controller is designed using a plain linearizing control approach (no adaptation and no robustification) in the presence of modeling errors.

$\bar{\theta}$ in (22) is taken as

$$\bar{\theta} = \frac{k_{P2}\tilde{k}_{S1}}{k_{S2}} r_1 + k_{P3}\tilde{r}_3 \approx \frac{\frac{k_{P2}k_{S1}}{k_{S2}} r_O}{k_{O1}} \qquad (33)$$

Figure 4 shows that during the start-up phase, F_{in} saturates to 0, leading to an ethanol overshoot (see

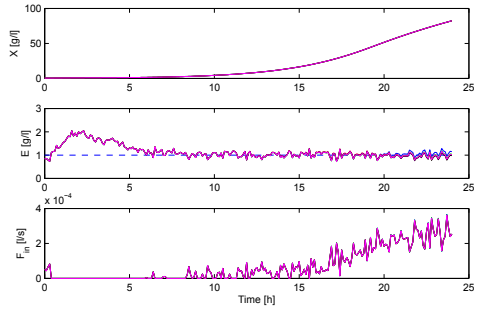

Figure 4: Yeast cultures – biomass and ethanol concentrations, and feed rate – robust control strategy – results of 5 runs with random parameter variations and a noise standard deviation of ± 0.1 $[g/l]$.

Figure 4). The different curves are more or less indistinguishable (the same noise signal is applied during the 5 runs) except in the last hours where the consequences of model errors appear. Nevertheless, these results are very satisfactory as model errors have a negligible influence.

Figures 5 and 6 show the results of a simulation performed with the same initial and operating conditions with the adaptive strategy, in the ideal case where there is no measurement noise, whereas Figures 7 and 8 correspond to a noise standard deviation of ± 0.05 $[g/l]$ added to the ethanol concentration measurements. Due to sensitivity problems of the adaptive law, higher noise levels usually lead to computational failures. When the parameter adaptation performs well, the productivity of the adaptive and robust strategies is more or less the same, i.e., a biomass concentration of approximately 80 g/l is obtained within 24 hours.

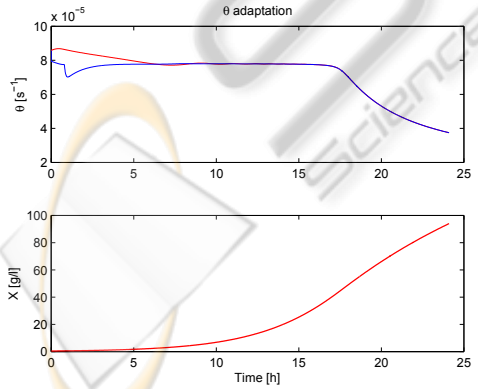

Figure 5: Yeast cultures – θ adaptation and biomass concentration – adaptive control strategy – no measurement noise.

Figure 9 shows the closed-loop response of biomass X, acetate A concentrations, and inlet feed rate F_{in}, for five different values of the kinetic parameters which are randomly chosen, in the bacteria

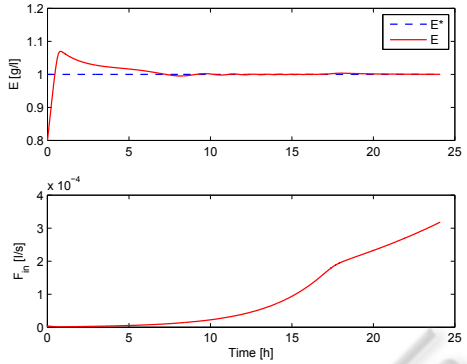

Figure 6: Yeast cultures – ethanol concentration and feed flow rate – adaptive control strategy – no measurement noise.

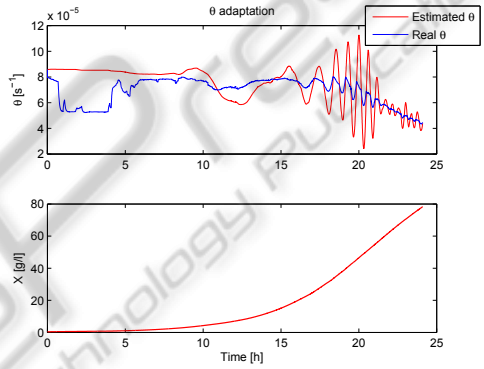

Figure 7: Yeast cultures – θ adaptation and biomass concentration – adaptive control strategy – noise standard deviation of ± 0.05 $[g/l]$.

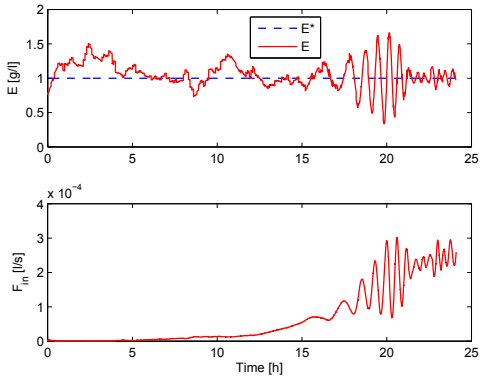

Figure 8: Yeast cultures – ethanol concentration and feed flow rate – adaptive control strategy – noise standard deviation of ± 0.05 $[g/l]$.

cultures under a robust control strategy. Figures 10 and 11 show similar simulation runs with the adaptive strategy. The same comments concerning the noise sensitivity apply.

Note that the productivity is lower in the bacteria

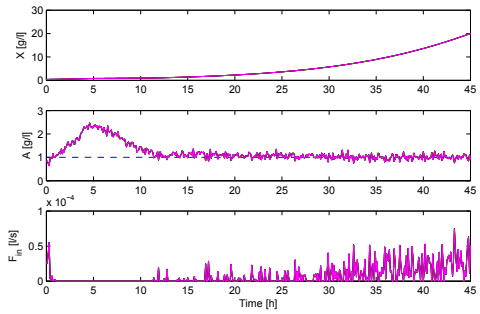

Figure 9: Bacteria cultures – biomass and acetate concentrations, and feed rate – robust control strategy – results of 5 runs with random parameter variations and a noise standard deviation of ± 0.1 $[g/l]$.

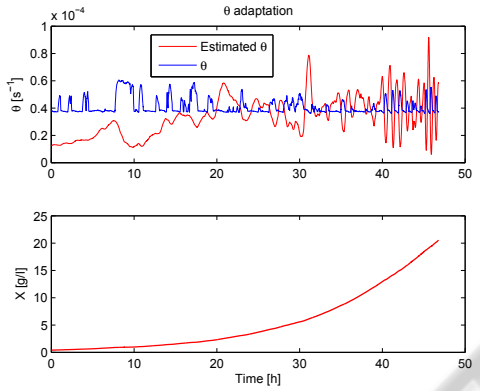

Figure 10: Bacteria cultures – θ adaptation and biomass concentration – adaptive control strategy – noise standard deviation of ± 0.05 $[g/l]$.

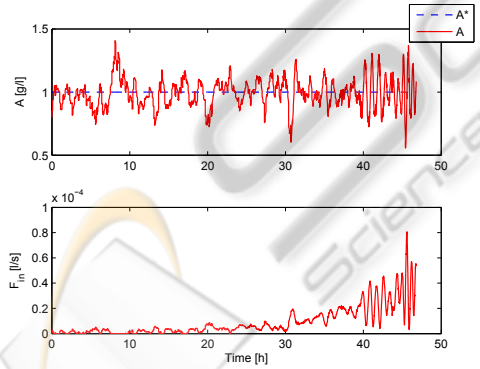

Figure 11: Bacteria cultures – acetate concentration and feed flow rate – adaptive control strategy – noise standard deviation of ± 0.05 $[g/l]$.

cultures (for biological and operating reasons, bacteria strains lead to reaction rates and, therefore, growth rates that are smaller than yeast reaction rates). However, from a control point of view, results are satisfactory in both cases.

6 CONCLUSIONS

Linearizing control is a powerful approach to the control of fed-batch bioprocesses. In most applications reported in the literature, on-line parameter adaptation is proposed in order to ensure the control performance despite modeling uncertainties. On-line parameter adaptation is however sensitive to measurement noise, and requires some kind of tuning. On the other hand, robust control provides an easy design procedure, based on well established computational procedures using the LMI formalism. Large parametric and structural uncertainties, as well as measurement noise levels can be dealt with.

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