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Control of overflow metabolism via sliding mode reference conditioning

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Abstract: In many biotechnological processes, the optimal productivity corresponds to operating at critical substrate concentration. The problem, then, consists of maximizing the feeding rate compatible with the critical constraint, so as to avoid overflow metabolism. This value may be unknown and may change from experiment to experiment and from strain to strain, and even in the same experiment due to changing environmental and/or process conditions. In previous works different strategies to cope with this problem have been applied to microorganisms of industrial interest, such as *E. coli* and *S. cerevisiae*. Thus, probing strategies have been used in fedbatch bioreactors to operate close to their maximum oxygen transfer rate while avoiding acetate accumulation in the first case. In the fed-batch fermentation of *S. cerevisiae* a small amount of ethanol is allowed to be present in the culture, and the control problem in one of regulating the ethanol concentration a a given low reference value.
Here an approach based on sliding mode reference conditioning is proposed to drive the system to a maximum specific growth rate compatible with a given constraint (e.g. ethanol concentration lower than a given threshold). It is shown how this approach is robust with respect to uncertainties in the process dynamics and with respect to unknown perturbations affecting the critical point.

Keywords: Biotechnology; fermentation processes; nonlinear control; sliding-mode control; reference adaptive control; constraint satisfaction problems; optimal search techniques; robust performance.

1. INTRODUCTION

Fed-batch processes are extensively used in the expanding biotechnological industry. The requirements for an efficient industrial production are encouraging the development of robust and reliable controllers. For this reason, fed-batch process control is receiving great attention by the research community. The control problem is characterized by modeling approximations, parameter uncertainties, nonlinear and non-minimum phase dynamics, scarce on-line measures, etc.

In many fermentation processes optimal productivity corresponds to operating at critical substrate concentration. But this value changes from experiment to experiment and from strain to strain, and even in the same experiment due to changing environmental and/or process conditions.

In some cases, the critical operating point might correspond to the maximum of some kinetic function. In such a case, when both uncertainty and non-monotonous kinetics are involved extremum seeking strategies are used in Titica et al. [2003]. Yet, if limitations are present – eg. due the production of additional toxic or inhibitory metabolites – the optimal point may not correspond to a maximum of the kinetic rates. Thus, for instance, the optimal production of biomass with *Saccharomyces cerevisiae* is attained for a feeding profile that avoids the production of ethanol, and is well below the maximum attainable specific growth rate (see Sonnleitner and Käpeli [1986]). In *E. coli* acetate accumulates under fully aerobic conditions by overflow metabolism (Xu et al. [1999]). The problem, then, consists of maximizing the feeding rate compatible with the critical constraint, so as to avoid overflow metabolism. In DeHaan and Guay [2005], an adaptive extremum-seeking controller with a reference update law is used to cope with state constraints.

Besides limitation due to the production of surplus metabolites, oxygen limitation may affect aerobic bioreactions. For small scale vessels oxygen can be easily supplied in excess by increasing the aeration rate and the stirrer velocity, provided sheer stress does not imperil the structural integrity of the cells. Yet, for large bioreactors there is a limit in the oxygen concentration that can be kept. To cope with shortage in the oxygen supply different strategies have been proposed, basically trying to attain a specific growth rate so as to operate close to the maximum oxygen transfer rate (Oliveira et al. [2004], Velut et al. [2007]). Thus, in Velut et al. [2007] a probing strategy is applied to *E. coli* fed-batch fermentation to dose the substrate feed avoiding acetate accumulation. The control goal is to maximize the feeding rate compatible with the mentioned constraint while coping with the saturation of the maximum oxygen transfer rate.

In Valentinotti et al. [2003] the maximization of biomass productivity in the fed-batch fermentation of *S. cerevisiae* is analyzed. They address the problem of keeping the substrate concentration at an *a priori* unknown critical value: that above which ethanol is produced (Sonnleitner and Käpeli [1986]). To this end, a small amount of ethanol is allowed to be present in the culture, and convert the control problem in one of regulating the ethanol concentration a a given low reference value. Previous attempts to regulate the ethanol concentration can be found in Chen et al. [1995] where an adaptive feedback linearizing control was used. In Valentinotti et al. [2003], it is assumed that the bioreactor is operated in such a way that a small production of ethanol always takes place. A two-degree-of-freedom adaptive controller is applied on simplified linear models. In Renard et al. [2006] and Dewasme et al. [2007] the approach is improved by means of a two-degrees-of-freedom controller with Youla parametrization. Both off-line and on-line estimation of parameters are required.

In the present work, we take advantage of the interesting features and the confined dynamics of a system operating on sliding mode to address the important issue of ethanol limitation in the fed-batch fermentation of *S. cerevisiae*. However, differing from conventional sliding mode control applications, sliding regimes are exploited here as a transitional mode of operation, in which the discontinuous signal is used for conditioning the rate of change of the reference signal instead of being the main control action. The proposed technique is inspired by recent proposals of the co-authors, where they have combined reference conditioning techniques (originally introduced by Hanus et al. [1987]) and SM ideas to overcome windup in SISO processes and control directionality problems in MIMO systems (Mantz et al. [2004], Garelli et al. [2007]).

A very interesting property of the proposal is that, due to the robustness properties of the SM to reject disturbances, the SM conditioning dynamics is not affected by the main (inner) control loop. Thus, the dynamics of the compensation (outer) loop may be designed independently of the main loop design. Because of the nature of the proposed scheme, the main drawbacks of variable structure control (i.e. chattering problems and reaching mode) do not affect the current application.

The outline of the paper is as follows. Section 2 introduces the the SM reference conditioning technique for constrained non-linear systems as a general variable structure control problem. The proposed methodology is applied in Section 3 to *S. cerevisiae* fed-batch fermentations, while the corresponding simulation results are presented in Section 4. Finally, some concluding remarks are given.

2. PROBLEM STATEMENT

Let the system

$$\Sigma : \begin{cases} \dot{x} = f(x) + g(x)\,u \\ y_1 = h_1(x) \\ y_2 = h_2(x) \end{cases} \tag{1}$$

where $x \in X \subset \mathbb{R}^n$ is the state vector, $u \in \mathbb{R}$ is the control input (possibly discontinuous), $f : \mathbb{R}^n \to \mathbb{R}^n$ and $g : \mathbb{R}^n \to \mathbb{R}^n$ two vector fields and $h(x) : \mathbb{R}^n \to \mathbb{R}$ a scalar field, all of them defined in X, with $g(x) \neq 0$, $\forall x \in X$.

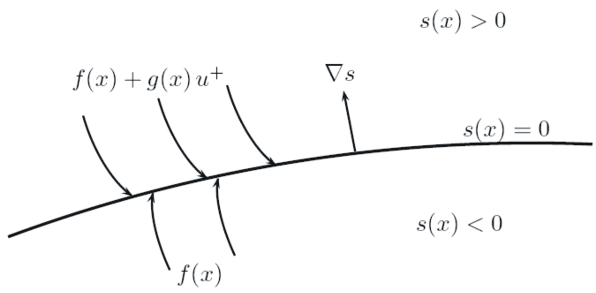

Fig. 1. SM establishment on $s(x) = 0$ to satisfy system constraints.

Variables y_1 and y_2 are both real valued system outputs, y_1 is the main controlled variable, while y_2 is a variable to be bounded because of unavoidable system constraints.

With the aim of satisfying the constraint

$$y_2 \leq \bar{y}_2 \tag{2}$$

the following variable structure control law is defined

$$u = \begin{cases} u^+(x) & \text{if} \quad s(x) > 0 \\ 0 & \text{if} \quad s(x) \leq 0 \end{cases} \qquad u^+(x) \neq 0. \tag{3}$$

where $u^+(x)$ is a smooth function of x and

$$s(x) = y_2 - \bar{y_2} + \sum_{i=1}^{l-1} \tau_i \, y_2^{(i)} \tag{4}$$

being l the relative degree between the output y_2 and the input u, $y_2^{(i)}$ the ith derivative of y_2, and τ_i constant gains.

Fact 1. Since $s : X \to \mathbb{R}$, the set:

$$S = \{x \in X \, : \, s(x) = 0\}, \tag{5}$$

defines a regular manifold in X of dimension $n - 1$, which is usually called sliding or switching surface.

Assume that the initial condition of the system Σ lies within the set $\Phi = \{x | y_2 < \bar{y_2}\}$, i.e. $s(x) < 0$. Therefore, the surface S is reached provided the own trajectories of the system lead to the exterior of Φ. In order to avoid the system violating the constraint, the discontinuous action u must assure that the vector field of the continuous subsystem $f(x) + g(x)\,u^+$ points locally towards the manifold S. This situation is geometrically represented by Figure 1.

Mathematically, the following inequalities must be satisfied locally around S:

$$\dot{s}(x) = \begin{cases} L_f s + L_g s \, u^+ < 0 & \text{if} \quad s(x) > 0 \\ L_f s > 0 & \text{if} \quad s(x) < 0 \end{cases} \tag{6}$$

The second equation in (6) is satisfied when the system tries by itself to leave the set Φ. The first equation implies that for a sliding regime to be established on $s(x) = 0$,

$$L_g s = \frac{\partial s}{\partial x} \, g \neq 0, \tag{7}$$

must hold locally on S. The necessary condition (7)for SM imposes that the sliding surface must have unitary relative degree with respect to the discontinuous action, and this is the reason why $y_2^{(l-1)}$ is included in (11).

Assume $l < n$. In order to obtain the output dynamics which results from designing the switching function as in (11), consider the transformation:

$$z = \phi(x) = \begin{bmatrix} h_2(x) \\ L_f\, h_2(x) \\ \vdots \\ L_f^{(l-1)}\, h_2(x) \\ \phi_{l+1} \\ \vdots \\ \phi_n \end{bmatrix}, \tag{8}$$

where ϕ_k with $l+1 \leq k \leq n$ are arbitrarily chosen functions such that $\phi(x)$ remains a diffeomorphism. By applying $z = \phi(x)$ the system Σ can be led to its normal form [Isidori, 1995]

$$\begin{cases} \dot{z}_1 &= L_f\, h = z_2 \\ \dot{z}_2 &= L_f^2\, h = z_3 \\ &\vdots \\ \dot{z}_{l-1} &= L_f^{l-1} = z_l \\ \dot{z}_l &= L_f^l\, h + L_g L_f^{l-1}\, u \end{cases} \tag{9}$$

$$\begin{cases} \dot{z}_{l+1} &= q_{l+1}(z) \\ &\vdots \\ \dot{z}_n &= q_n(z). \end{cases} \tag{10}$$

The dynamics of the output y_2 can therefore be determined by means of the sliding surface design. Particularly, calling $\xi = [z_1\ z_2\ \ldots\ z_\rho]^T$ and $\eta = [z_{\rho+1}\ z_{\rho+2}\ \ldots\ z_n]^T$, the choice made in (11) can be rewritten as:

$$s(\xi) = \bar{y_2} - z_1 - \tau_1 z_2 - \ldots - \tau_{l-1} z_l. \tag{11}$$

During SM $s(\xi) = 0$, and thus $z_l = (1/\tau_{l-1})[\bar{y_2} - z_1 - \tau_1 z_2 - \ldots - \tau_{l-2} z_{l-1}]$. Replacing in (9)-(10) the reduced SM dynamics results:

$$\begin{cases} \dot{z}_1 &= z_2 \\ \dot{z}_2 &= z_3 \\ &\vdots \\ \dot{z}_{l-1} &= (1/\tau_{l-1})[\bar{y_2} - z_1 - \tau_1 z_2 - \ldots - \tau_{l-2} z_{l-1}] \end{cases} \tag{12}$$

$$\{\, \dot{\eta} = q(\xi, \eta). \tag{13}$$

With a proper choice of the gains τ_i, the output error and its derivatives will tend to zero with the desired dynamics. For the case considered, $\xi_0 = [\bar{y_2}\ 0 \ldots 0]^T \in \mathbb{R}^l$ in steady state. The hidden dynamics $\dot{\eta} = q(\xi_0, \eta) = \bar{q}(\eta)$ must be stable in order to implement the proposed strategy, which means that the transfer function between u and y_2 must be minimum phase.

To this end, it is interesting to notice that (1) may represent the joint dynamics of a system consisting of two control loops as depicted in figure 2.

The internal loop in figure 2 represents a system

$$\dot{x}_p = f_p(x_p, p) + g_p(x_p) v \tag{14}$$

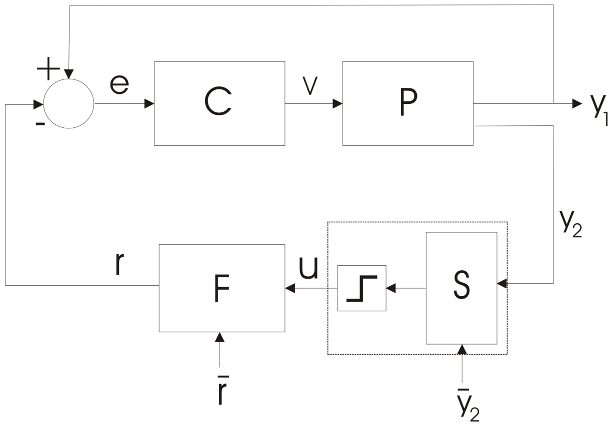

Fig. 2. Reference conditioning scheme.

where $p \in \mathbb{R}^p$ is a time-varying unmeasurable perturbation signal, the outputs are defined as in (1), and $v \in \mathbb{R}^u$ the control input.

Fact 2. Assume that there is an output feedback controller

$$\begin{aligned} \dot{x}_c &= g(x_p, x_c) \\ v &= k(x_p, x_c, e) \\ e &= r - y_1 \end{aligned} \tag{15}$$

such that the output y_1 can be driven to a feasible reference value r, and leaves the internal loop stable.

Now, consider the constraint 2.

Fact 3. There exists a maximum reference value $r_{\max} = \xi(x, p)$ for the output y_1, such that the constraint (2) is violated whenever a reference greater that $r_{\max}$ is sought.

The control goal is to drive the reference r to the unknown $r_{\max}$ in such a way that the constraint (2) is satisfied, robustly with respect to the process dynamics and the unknown perturbation p. The problem can be seen as that of maximizing the output reference r while achieving the set $\Phi(x, p) = \{(x, p) \mid y_2 \leq \bar{y_2}\}$ to be robustly invariant.

The outer reference conditioning loop depicted in figure 2, with S defined as in (11) and F being the filter

$$\dot{r} = -\alpha\,(r - \bar{r}) + \alpha u \tag{16}$$

with u defined in (3), acts as the reference seeking element.

Notice that by defining $x = (x_p, x_c, r)$ the scheme just described can be cast within the initial general framework.

3. APPLICATION TO *S. CEREVISIAE*

3.1 Process model

The model of *S. cerevisiae* metabolism based on the bottleneck hypothesis of Sonnleitner and Käpeli [1986] has been extensively used in recent works (e.g. see Valentinotti et al. [2003], Renard et al. [2006], Dewasme et al. [2007]). Its main traits are briefly summarized in the following. The mass balance macroscopic model is given by (17):

$$
\begin{aligned}
\dot{x} &= (\gamma_1 r_1 + \gamma_2 r_2 + \gamma_3 r_3)x - x\frac{F}{v} \\
\dot{s} &= -(r_1 + r_2)x + (s_i - s)\frac{F}{v} \\
\dot{e} &= (\gamma_4 r_2 - r_3)x - e\frac{F}{v} \\
\dot{v} &= F
\end{aligned}
\tag{17}
$$

with reaction rates and kinetic terms given by (18) and (19) respectively.

$$
\begin{aligned}
r_1 &= \min(r_g, \frac{r_o}{\gamma_5}) \\
r_2 &= \max(0.0, r_g - \frac{r_o}{\gamma_5}) \\
r_3 &= \max(0, \min(r_e, \frac{r_o - \gamma_5 r_g}{\gamma_6}))
\end{aligned}
\tag{18}
$$

$$
\begin{aligned}
r_g &= \mu_{m,g}\frac{s}{k_{s,g} + s} \\
r_e &= \mu_{m,e}\frac{e}{k_{s,e} + e} \\
r_o &= \mu_{m,o}\frac{o}{k_{s,o} + o}
\end{aligned}
\tag{19}
$$

Table 3.1 shows typical values of the models parameters.

Yield coefficients					
γ_1	γ_2	γ_3	γ_4	γ_5	γ_6
0.49	0.05–0.12	0.5–1.2	0.48	0.396	1.104
Kinetic parameters					
$\mu_{m,g}$	$k_{s,g}$	$\mu_{m,e}$	$k_{s,e}$	$\mu_{m,o}$	$k_{s,o}$
3.5	0.01	0.17	0.1–0.5	0.256	0.1

From $F = \lambda x v$ and using standard notation, the model (17) can be written as

$$
\Sigma : \begin{cases} \dot{x} = (\mu_x - \lambda x)x \\ \dot{s} = -\mu_g + \lambda(s_i - s)x \\ \dot{e} = (\mu_e - \lambda e)x \end{cases}
\tag{20}
$$

where the volume dynamics have not been included for the sake of notation simplicity. Indeed, as the fed-batch case is considered, this dynamics must be taken into account in the inner-loop controller design. The model given by equation (20) will be used in the following for constrained control purposes.

3.2 Problem statement

Differently from the approach used in Valentinotti et al. [2003], Renard et al. [2006] and Dewasme et al. [2007] where the goal is to regulate ethanol at a given low set-point, the goal here is to control the biomass specific growth rate $\gamma_1 r_1 + \gamma_2 r_2 + \gamma_3 r_3$ in (17) to its maximum value such that the ethanol concentration e lies below a given threshold (i.e $y_2 = h_2(x) = e$). Notice that the desired reference for the biomass specific growth rate is unknown and possibly time-varying (due, for example, to variations in the available oxygen). Assuming the desired reference is obtained by some outer loop to be designed later, it can be robustly reached by means of the dynamic controller proposed in Picó-Marco et al. [2005], Battista et al. [2006], and Battista et al. [2007]. This inner loop controller takes the general form:

$$
\begin{aligned}
F(x,v) &= \lambda\epsilon(\hat{\mu}, \mu_r)xv \triangleq k(\lambda, x, \hat{\mu}, \mu_r)\, v \\
\dot{\lambda} &= g(\lambda, x, v, \mu_r)
\end{aligned}
\tag{21}
$$

where $\hat{\mu}$ is an estimation of the biomass specific growth rate $\gamma_1 r_1 + \gamma_2 r_2 + \gamma_3 r_3$ and μ_r its desired reference value. The first can be obtained using high gain observers from measurements of biomass, as explained in Battista et al. [2007]. On-line biomass measurements are required for this inner-loop controller. They can be obtained using several commercially available devices (see for instance Navarro et al. [2004], Kivijarju et al. [2007]).

In order to simplify the proposed algorithm description, the following controller –also considered in Battista et al. [2006]–will be implemented in the inner loop

$$
C(s) : \left\{ \lambda = \lambda_r(1 - k\frac{\mu_r - \mu_x}{\mu_d}) \right.
\tag{22}
$$

3.3 Reference seeking

A sliding-mode reference conditioning outer loop is used to seek the biomass specific growth rate reference value μ_r.

The first-order filter F is intended to smooth out the conditioned reference signal, and it should be designed much faster than the closed loop dynamics in order to avoid degrading the original (inner) control loop performance when ethanol constraints are not reached. Its state space representation is given by

$$
F : \begin{cases} \dot{x_f} = -\alpha x_f + \alpha(\mu_d + w) \\ \mu_r = x_f \end{cases}
\tag{23}
$$

According to the sign of the switching function $s(e)$, the discontinuous signal w takes the following values

$$
\omega = \begin{cases} -\bar{\mu}_r & s(e) > 0 \\ 0 & s(e) \leq 0, \end{cases}
\tag{24}
$$

where $\bar{\mu}_r$ is an upper threshold on the biomass specific growth rate. The output of the filter, μ_r, is then used as reference by the inner loop controller.

In order to design the switching function $s(e)$, it is illustrative to express the whole system composed of the bioreactor (20), the controller (22) and the conditioned filter (23) in the form as system (1) is described. To this end, a new state vector is defined as $\chi \triangleq [x\ s\ e\ \lambda]^T$. The whole system description results

$$
\begin{aligned}
\dot{\chi} &= \begin{bmatrix} (\mu_x - \lambda x)x \\ -\mu_g + \lambda(s_i - s)x \\ (\mu_e - \lambda e)x \\ \lambda_r k\alpha\mu_r/\mu_d \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 0 \\ -\lambda_r k\alpha/\mu_d \end{bmatrix} w + \\
&+ \begin{bmatrix} 0 \\ 0 \\ 0 \\ -\lambda_r k\alpha\bar{r}/\mu_d + \lambda_r k/\mu_d \dot{\mu}_x \end{bmatrix} \\
e &= [0\ \ 0\ \ 1\ \ 0]\,\chi
\end{aligned}
\tag{25}
$$

Notice the from the ethanol concentration e to the new input signal ω the relative degree is $l = 2$. Moreover, there is strong invariance with respect to the derivative of the biomass specific growth rate $\dot{\mu}_x$, as this term, seen as a perturbation, is collinear with the control signal w.

Hence, assuming the ethanol concentration can be measured, the sliding surface is designed as:

$$S = e - E + \tau \dot{e} \tag{26}$$

where $e \leq E$ is the desired constraint, and the derivative of the ethanol concentration has to be added so as to achieve the unitary relative degree condition already mentioned in the previous section.

As the kinetic term μ_e is not assumed to be known, the derivative $\dot{e}$ must be estimated. This can be done using different approaches. Exact differentiation can be used from measurements of e (see Levant [2003]). On the other hand, μ_e can be estimated using a high gain observer in the same way as $\hat{\mu}$. The other terms in (26) are known.

Recall, the goal is not to reach sliding regime. This is only established if the constraint is to be violated. In such a case, it can be easily deduced from (25) and (26) that the sliding dynamics are given by

$$\dot{e} = -\frac{1}{\tau} e + \frac{\bar{y}_2}{\tau} \tag{27}$$

Thus, the ethanol concentration is smoothly driven to the constraint $\bar{y}_2$ with dynamics imposed by the user defined coefficient τ. The sliding regime is abandoned as soon as the system trajectories point inside the allowed region.

Concerning the internal dynamics, if biomass x and substrate s are chosen as the two last coordinates in (8), the internal dynamics coincide with the dynamics of the inner-loop, which can be seen to be stable in Battista et al. [2006].

4. SIMULATIONS

The model (17) with parameters chosen from table 3.1 is used to show the performance of the scheme proposed. Ethanol is assumed to be measured. In turn, the inner-loop control uses biomass and volume as the only measured variables. Both, the inner-loop control with and without the sliding-mode based reference conditioning are run. In both cases, limitations in oxygen have been simulated by considering it varies following a sinusoidal. Thus, no real situation has been looked after concerning this, but a simple effective way to show robustness with respect to unmeasured disturbances. Noise was added to all the measurements. Figures 3,4,5 and 6 show some of the results obtained. As it can be seen in figure 4, the conditioning loop achieves the goal. The sliding regime is reached when oxygen limitation activates the fermentative path (see figure 5). As soon as the process conditions allow it, the sliding regime is left (bottom subplot). Notice how the reference to be tracked by the inner-loop control varies accordingly. In the top subplot, where no reference conditioning is used, activation of the fermentative path leads to a temporal decrease in growth rate, followed by a growth rate overshoot as ethanol in excess is oxidized. If reference conditioning is used, no ethanol in excess is produced (middle subplot). Thus the specific growth rate is the maximum compatible with the constraint on ethanol. In figure 6 the ethanol and its derivative trajectories highlight the constraint satisfaction ($e \leq 0.1$) achieved with the reference conditioning.

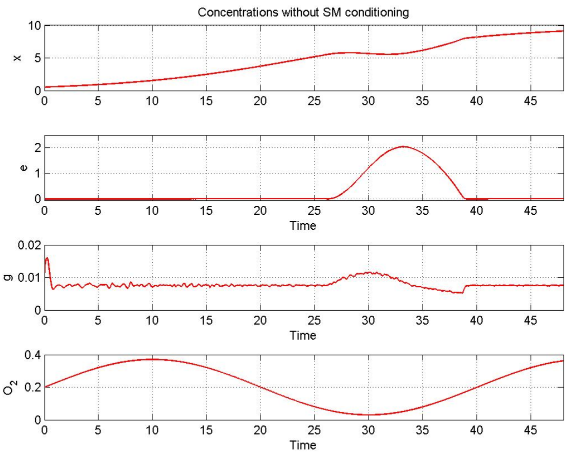

Fig. 3. Evolution of the biomass, ethanol, glucose and oxygen concentrations for the system with the original controller.

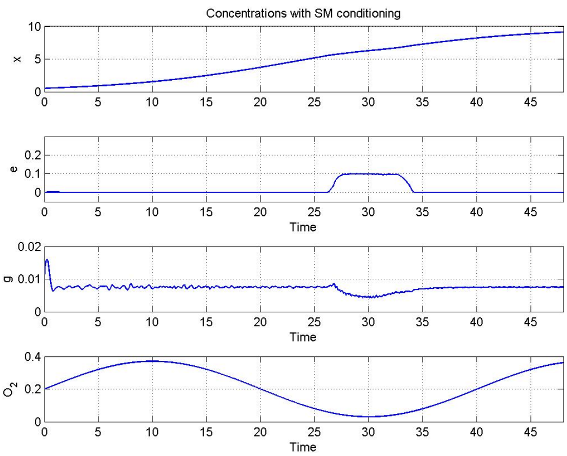

Fig. 4. Evolution of the biomass, ethanol, glucose and oxygen concentrations for the system with SM reference conditioning.

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5. CONCLUSION

An approach based on sliding mode reference conditioning has been proposed to drive the system to a maximum specific growth rate compatible with a given constraint. It has been shown how this approach is robust with respect to uncertainties in the process dynamics and with respect to unknown perturbations affecting the critical point. Although it has been showed applied to limit ethanol production in *S. cerevisiae* fed-bath fermentations, the scheme can be applied to seek the maximum reference (tantamount flow rate) compatible with a given constraint in the state in any system with the general characteristics described in section 2.

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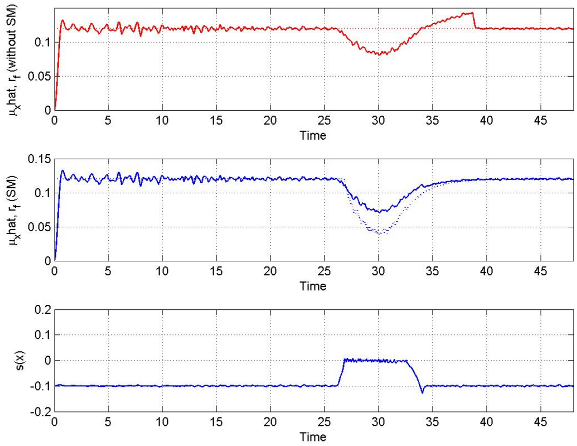

Fig. 5. Biomass rate with and without SM reference conditioning, and sliding surface.

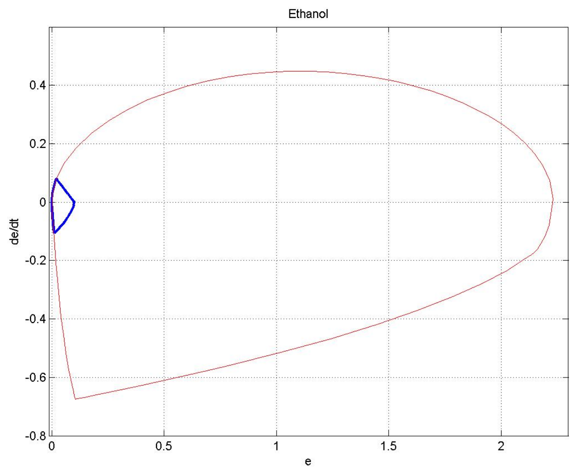

Fig. 6. Evolution of ethanol and its derivative with (small loop) and without SM reference conditioning.

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