OPTIMAL ADAPTIVE CONTROL OF FED-BATCH FERMENTATION PROCESSES WITH GROWTH/PRODUCTION DECOUPLING

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Abstract *We consider the design of a substrate feeding rate controller for a class of biotechnological processes in continuous stirred tank reactors, characterized by a decoupling between biomass growth and product formation. The main contribution is to illustrate how the insight, obtained by preliminary optimal control studies, leads to the design of an easy to implement adaptive controller. The controller derived this way combines a near optimal performance with good robustness properties against modeling uncertainties and process disturbances. As an example, simulation results are given for the penicillin G fed-batch fermentation process.*

Keywords fed-batch fermentation process, growth/production decoupling, optimal control, adaptive (linearizing) control

PROBLEM STATEMENT

We consider the class of fed-batch fermentation processes described by an (unstructured) model of the form :

$$\frac{dC_s}{dt} = -\sigma C_x + (C_{s,in} - C_s)u/V \quad (1)$$

$$\frac{dC_x}{dt} = \mu C_x - C_x u/V \quad (2)$$

$$\frac{dC_p}{dt} = \pi C_x - k_h C_p - C_p u/V \quad (3)$$

$$\frac{dV}{dt} = u \quad (4)$$

For an explanation of all symbols used, we refer to the Nomenclature at the end of this paper.

Dissolved oxygen is considered non-limiting, by maintaining a sufficiently high aeration level. The *shape* of the specific rates $\mu(C_s)$ and $\pi(C_s)$ is as depicted in Figure 1 : the enzyme catalyzed production is *not associated* to the microbial growth. Due to balancing, the specific glucose uptake rate σ is given by :

$$\sigma = \mu/Y_{x/s} + m_s + \pi/Y_{p/s}$$

The *optimization problem* we consider in this paper is to determine for the given set of differential equations (1–4) the optimal substrate feed rate profile $u^*(t)$ which *maximizes the final amount of product*, $C_p(t_f)V(t_f)$, subject to the following constraints :

- $t_0 = 0$, t_f = free

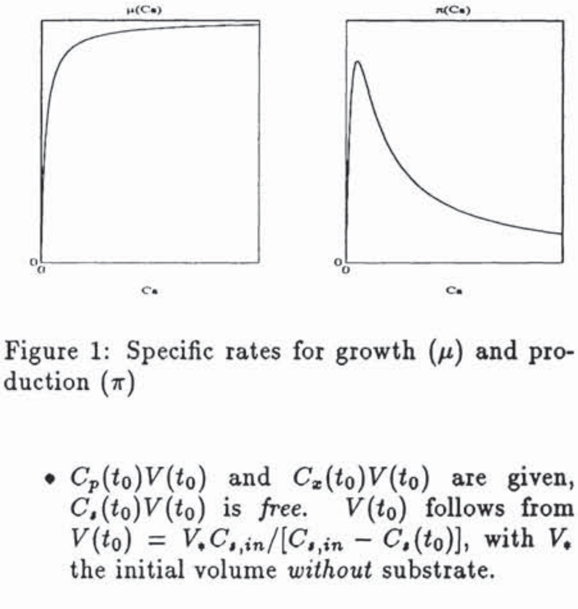

Figure 1: Specific rates for growth (μ) and production (π)

- $C_p(t_0)V(t_0)$ and $C_x(t_0)V(t_0)$ are given, $C_s(t_0)V(t_0)$ is *free*. $V(t_0)$ follows from $V(t_0) = V_s C_{s,in}/[C_{s,in} - C_s(t_0)]$, with V_s the initial volume *without* substrate.

- the total amount of feed is fixed, i.e. : $C_s(t_0)V(t_0) + \int_{t_0}^{t_f} C_{s,in}u(t)\,dt = \alpha$. This is equivalent to the *physical* constraint : $V(t_f) = V_f$, V_f fixed.

OPTIMAL CONTROL

The solution to this problem using optimal control theory has been described elsewhere [Modak *et al.*, 1986; Van Impe *et al.*, 1991a,b]. Due to the decoupling between growth and production, the fermentation behaves as a *biphasic* process. The optimal profile can be summarized as follows :

- The *growth phase* is a *batch* phase. All substrate consumed during growth is added all at once at time $t = t_0$, thus ensuring the highest possible specific growth rate for all t. In case of an upper bound $C_{s,max}$ on C_s, the optimal feed rate keeps $C_s = C_{s,max}$ as long as possible, whereafter a batch phase follows.
- During the *production phase*, a *singular control* profile forces the process to produce the product as fast as possible. At any time, there is a balance between glucose feeding and glucose demand for production and maintenance, thus ensuring the lowest possible growth rate. When $V(t) = V_f$, the fermentation continues in *batch* until the net penicillin formation rate (3) equals zero.

This solution is similar to the one reported by San and Stephanopoulos [1989] who used C_s as control input. The problem reduces to the *optimization of the initial substrate amount* $C_s(t_0)V(t_0)$ *and the time* t_s at which the switch from batch to singular control occurs.

As an example, consider the penicillin G fermentation process as modeled by Bajpai and Reuß [1980,1981]. The specific rates are given by :

$$\mu = \mu_{max}\frac{C_s}{K_x C_x + C_s} \quad \text{(Contois)}$$

$$\pi = \pi_m \frac{C_s}{K_p + C_s(1 + C_s/K_i)} \quad \text{(Haldane)}$$

parameters	
μ_{max}	0.11 (1/h)
K_x	0.006 (g/g DW)
π_m	0.004 (g/g DW h)
k_h	0.01 (1/h)
K_p	0.0001 (g/L)
K_i	0.1 (g/L)
$Y_{x/s}$	0.47 (g DW/g)
$Y_{p/s}$	1.2 (g/g)
m_s	0.029 (g/g DW h)
$C_{s,in}$	500 (g/L)
initial conditions	
$C_{x,0}V_0$	10.5 (g DW)
$C_{p,0}V_0$	0 (g)
$C_{s,0}V_0$	*to be optimized* (g)
V_*	7 (L)
α	1500 (g)

The optimal control results are : $C_{s,0}V_0 = 528$ g, $t_s = 28.271$ g, $\boxed{C_{p,f}V_f = 63.846 \text{ g}}$.

Note that the application of optimal control theory requires full knowledge of all analytic expressions and corresponding constants for the kinetics involved in the model (1–4). Further, in general the switching time t_s can not be obtained as a feedback law of state variables only. As a result, the optimal profile is very sensitive to modeling uncertainties and process disturbances. Finally, the singular control during the production phase requires on–line measurements of all state variables, a problem which has not been solved completely up to now. This motivates the search for *near optimal, more robust* and *easy to implement* feeding profiles.

LINEARIZING CONTROL

Assuming that μ and π (and thus σ) are functions of C_s only, the *optimal* feeding rate during the production phase is given by :

$$u_{prod} = \frac{\sigma C_x V}{C_{s,in} - C_s} + k_h F[C_s, C_x, C_p] \qquad (5)$$

which is linear in the hydrolysis constant k_h, and a feedback law of state variables only. It can be easily seen that $k_h = 0$, i.e. *neglecting product degradation*, is a necessary and sufficient condition for C_s to be constant during the production phase. So a *heuristic* control law for the production phase is simply :

$$u_{prod} = \frac{\sigma C_x V}{C_{s,in} - C_s} \qquad (6)$$

A reasonable choice for C_s is the value $C_s^* = (K_p K_i)^{1/2}$ which maximizes $\pi(C_s)$. By doing so, t_s is known as a function of the state : the control switches from batch to u_{prod} when $C_s = C_s^*$. The *initial substrate amount* $C_s(t_0)V(t_0)$ *is the only degree of freedom* left.

We obtain for the above example : $C_{s,0}V_0 = 533$ g, $\boxed{C_{p,f}V_f = 63.597 \text{ g}}$. Observe that this heuristic controller has an excellent performance, although μ is function of C_x also. This can be explained as follows : the behaviour of the model with Contois kinetics (chosen by Bajpai and Reuß) is similar to a model with Monod kinetics [$\mu = \mu_{max}C_s/(K_s + C_s)$], which are function of C_s only.

This heuristic controller is a special case of the following *nonlinear linearizing controller.* If we want $C_s = C_s^*$ (C_s^* constant) during the production phase, then a stable ($\lambda > 0$) linear reference model of the tracking error is :

$$\frac{d(C_s - C_s^*)}{dt} = -\lambda(C_s - C_s^*)$$

Using model equation (1) and introducing boundaries on the control action, we obtain :

$$\begin{aligned} u_0 &= \frac{\sigma C_x - \lambda(C_s - C_s^*)}{C_{s,in} - C_s} V \\ u &= \begin{cases} u_0 & \text{if } 0 \le u_0 \le u_{max} \\ 0 & \text{if } u_0 \le 0 \\ u_{max} & \text{if } u_0 \ge u_{max} \end{cases} \end{aligned} \qquad (7)$$

Observe that this controller can be implemented from $t = 0$ on : during growth, $C_s >> C_s^*$ (provided $C_{s,0}$ is sufficiently high), so $u = 0$. Further, the feed rate will switch automatically to positive values as soon as $C_s \rightarrow C_s^*$, so the switch time t_s must not be specified a priori.

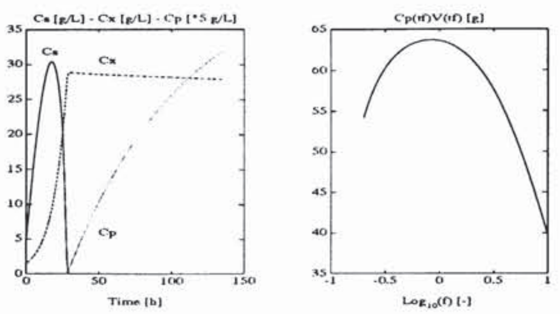

Figure 2: Adaptive control using on-line C_s measurements

ADAPTIVE CONTROL USING ON-LINE MEASUREMENTS OF C_s

An *adaptive* implementation of controller (7) can be obtained as follows. We assume that both C_s and V are measured on-line. $C_{s,in}$ and λ are known constants. The rate β is defined as follows :

$$\sigma C_x \triangleq \beta C_s$$

In agreement with the minimal modeling concept [Bastin and Dochain, 1990], we consider β as a time varying parameter, estimated using a state-observer based parameter estimator :

$$\begin{aligned}\frac{d\hat{C}_s}{dt} &= -\hat{\beta}C_s + (C_{s,in} - C_s)\frac{u}{V} + \omega(C_s - \hat{C}_s)\\ \frac{d\hat{\beta}}{dt} &= -\gamma C_s(C_s - \hat{C}_s)\end{aligned}$$

Tuning of this estimator reduces to the calibration of the (positive) constants ω and γ. A continuous time adaptive implementation of controller (7) is then :

$$\begin{aligned}u_0 &= \frac{\hat{\beta}C_s - \lambda(C_s - C_s^*)}{C_{s,in} - C_s}V\\ u &= \begin{cases} u_0 & \text{if } 0 \le u_0 \le u_{max}\\ 0 & \text{if } u_0 \le 0\\ u_{max} & \text{if } u_0 \ge u_{max}\end{cases}\end{aligned} \quad (8)$$

This controller does not need any a priori information, such as yield coefficients, ... Moreover, treating β (and thus σ) as a time varying parameter makes it robust against modeling uncertainties.

Some simulation results for the penicillin G model are shown in Figure 2. In order to sufficiently excite the system to guarantee estimator convergence, the amount of substrate consumed during growth (α_{growth}) is added as follows : 500 g is fed in feed forward using a constant strategy during 25 hrs, the rest is added at $t = 0$. Using $\omega = 10^5$, $\gamma = 10^9$, $\lambda = 3000$, an initial estimate of $\beta = 0.075$ (true value 0.084) and $\alpha_{growth} =$ 533 g, we obtain $\boxed{C_{p,f}V_f = 63.592 \text{ g}}$. The corresponding concentration profiles are shown in the left plot. The right plot shows the optimization of $C_{p,f}V_f$ with respect to the value of C_s^*. With $C_{s,nom}^* = (K_pK_i)^{1/2}$, f is defined as $C_s^* = fC_{s,nom}^*$. The optimum value is $\boxed{C_{p,f}V_f = 63.680 \text{ g}}$ for $f = 0.85$. Due to the shape of this plot, it is clear that three experiments should suffice to optimize the process.

ADAPTIVE CONTROL USING ON-LINE MEASUREMENTS OF *CER*

In the above scheme, the only bottle-neck is the accuracy of the on-line substrate concentration measurements. Kleman *et al.* [1991] reported a control algorithm maintaining C_s as tight as 0.49 ± 0.04 g/L during growth of *E. coli*. Using the parameter values reported by Bajpai and Reuß (see table), $C_s^* = (K_pK_i)^{1/2} = 3.16\ 10^{-3}$ g/L, which is two orders of magnitude smaller.

Observe however that prespecifying a reference profile for C_s can be replaced by *specifying a profile for the specific growth rate* (in the case of μ function of C_s only this is even identical). So during growth, we want μ as high as possible, while during production, we want $\mu = \mu^*$, μ^* constant.

Estimating μ can be done using the easily accessible measurement of CO_2 in the effluent gas from the fermentor. At any time during the fermentation, carbon dioxide arises from (i) growth and associated energy production, (ii) maintenance energy and (iii) penicillin biosynthesis and other possible specialised metabolism [Calam and Ismail, 1980] :

$$CER = Y_{c/x}\mu C_x + m_c C_x + k_p$$

where *CER* stands for the CO_2 Evolution Rate.

A partially adaptive observer for C_x and μ is (based on [Di Massimo *et al.*, 1989]) :

$$\begin{aligned}\frac{d\hat{C}_x}{dt} &= \hat{\delta} - \hat{C}_x u/V + \omega(CER - \hat{CER})\\ \frac{d\hat{\delta}}{dt} &= \gamma(CER - \hat{CER})\\ \hat{CER} &= Y_{c/x}\hat{\delta} + m_c\hat{C}_x + k_p\\ \hat{\mu} &= \frac{\hat{\delta}}{\hat{C}_x}\\ \hat{\sigma} &= \hat{\mu}/Y_{x/s} + m_s\end{aligned}$$

In the estimation of σ we neglected the contribution of π. Note that this scheme requires the knowledge of the parameters $Y_{c/x}$, m_c and k_p (which may be all time varying), $Y_{x/s}$ and m_s, which is clearly the price to pay for estimating state variables using measurements of easily accessible auxiliary variables.

An alternative adaptive implementation of controller (7) is then (C_s is considered negligible as compared with $C_{s,in}$) :

$$u_0 = \frac{\hat{\sigma}\hat{C}_x - \lambda(\hat{\mu} - \mu^*)}{C_{s,in}}V$$

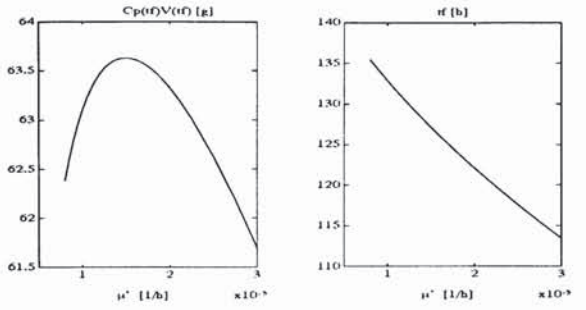

Figure 3: Adaptive control using on-line *CER* measurements

$$u = \begin{cases} u_0 & \text{if } 0 \leq u_0 \leq u_{max} \\ 0 & \text{if } u_0 \leq 0 \\ u_{max} & \text{if } u_0 \geq u_{max} \end{cases} \quad (9)$$

During simulations, we used $Y_{c/x} = 0.4$, $m_c = 0.01$ and $k_p = 0.3$ [Nelligan and Calam, 1983]. In the discrete time version of this controller, we added integral action to compensate for the approximations made above. The results are shown in Figure 3. A similar optimization study as mentioned higher yields $\boxed{C_{p,f}V_f = 63.630 \text{ g}}$ for $\mu^* = 1.5\ 10^{-3}$ 1/h ($C_{s,0}V_0 = 533$ g). Note that a *trade-off* can be made between $C_{p,f}V_f$ and t_f.

CONCLUSIONS

In this paper we presented the design of substrate feed rate controllers for a class of biotechnological processes, characterized by a decoupling between the biomass growth and the product formation. The major contribution was to show how the information obtained during optimal control studies leads to the design of suboptimal, but robust and easy to implement adaptive controllers. As an example, we considered the penicillin G fed-batch fermentation process. The trade-off between *on-line measurement requirements* (e.g. accessibility and accuracy) and *a priori information needs* (e.g yield and maintenance coefficients) was clearly illustrated.

NOMENCLATURE

t	time (h)
C_x	cell mass concentration in broth (g/L)
C_p	product concentration in broth (g/L)
C_s	substrate concentration in broth (g/L)
$C_{s,in}$	substr. conc. in feed stream (g/L)
V	fermentor volume (L)
u	input substrate feed rate (L/h)
α	total amount of substrate available (g)
μ	specific growth rate (1/h)
π	specific production rate (g/g DW h)
σ	sp. substr. consumption rate (g/g DW h)
m_s	maintenance constant (g/g DW h)
$Y_{x/s}$	cell mass on substrate yield (g DW/g)
$Y_{p/s}$	product on substrate yield (g/g)
CER	CO_2 Evolution Rate (L CO_2/L medium/h)
$Y_{c/x}$	CO_2 due to growth (L CO_2/g DW)
k_p	CO_2 due to prod. (L CO_2/L medium/h)
m_c	CO_2 due to maint. (L CO_2/g DW/h)

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