ADAPTIVE CONTROL OF FED-BATCH FERMENTATION PROCESSES

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Abstract. In this paper, it is shown how a simple adaptive control algorithm can contribute to optimize the yield of fermentation processes operated in fed-batch. The proposed algorithm does not require any prior analytical expression for the fermentation parameters (like the specific growth rate or the specific production rate). Its performances are compared in simulation to other control solutions (optimal control, PI regulator).

Keywords : Adaptive control, fermentation processes, fed-batch reactors

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1. Introduction

The fed-batch operation is very commonly used for a large class of industrial fermentation processes since it allows to avoid undesirable effects which may appear with other operation modes (e.g. substrate inhibition in batch reactors, or secondary metabolite production in continuously-fed reactors).

Optimal control theory appears to be a priori well suited for solving optimization problems of fed-batch reactors, such as "what is the distribution of nutrient in the influent over the fermentation duration which will optimize the yield of the process?". From the early 70's, a number of theoretical works have concentrated on the optimal control of fed-batch reactors (e.g. Fishman & Biryukov, 1974; Ohno et al, 1976; Yamane et al, 1977; Ohno et al, 1978; Peringer & Blachere, 1979; Kishimoto et al, 1981; Wu et al, 1984; Parulekar et al, 1985; Parulekar & Lim, 1985; Duvivier & Sevely, 1987). However, the practical implementation of optimal control strategies is subject to great difficulties. Besides the complexity of the controller itself, it also requires the (precise) knowledge of the process kinetics and particularly of the analytical structure of the fermentation parameters (like the specific growth rate or the specific production rate).

Our contribution in this paper is to show that adaptive control algorithms can constitute a valuable alternative to optimal control of fed-batch processes. The main advantages are :

- their implementation is much more simple
- they do not require any prior analytical model of the specific growth rate and the specific production rate
- their behaviour can be nearly optimal (and even completely optimal in some instances, see section 3).

We describe two applications : optimization of the biomass production (section 3) and optimization ot the production of a synthesis product in liquid phase (section 4). In each case, the effectiveness of the adaptive controller is illustrated by realistic simulation results. And in section 3, its performances are compared to those of an optimal control strategy and of a PI regulator.

2. Dynamical Model

The kinetics of the microbial growth and the metabolites production in a stirred tank bioreactor operating in the fed-batch mode is described by the following (commonly used) dynamical state-space model :

$$\dot{X}(t) = \mu(t)X(t) - \frac{F(t)}{V(t)} X(t) \tag{1}$$

$$\dot{S}(t) = k_1\mu(t)X(t) + \frac{F(t)}{V(t)} [S_{in}(t) - S(t)] \tag{2}$$

$$\dot{P}(t) = \nu(t)X(t) - \frac{F(t)}{V(t)} X(t) \tag{3}$$

$$\dot{V}(t) = F(t) \tag{4}$$

with $X(t)$: the biomass concentration
$S(t)$: the substrate concentration
$S_{in}(t)$: the influent substrate concentration
$P(t)$: the synthesis product concentration
$V(t)$: the volume of the culture
$F(t)$: the influent flow rate
$\mu(t)$: the specific growth rate
$\nu(t)$: the specific production rate
k_1 : the yield coefficient

3. Control Objective : Maximization of the Biomass Production X(t)

Statement of the algorithm

We assume that the specific growth rate $\mu(t)$ is a non linear function of the substrate concentration S(t) inhibited at high concentrations as shown in Fig.1.

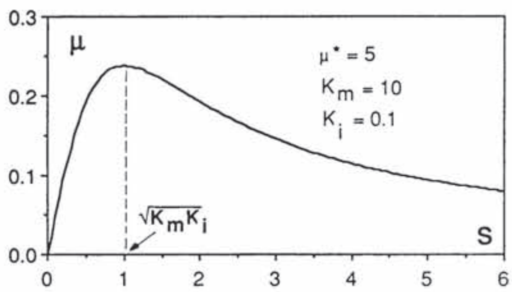

Fig.1 The Haldane growth rate model

Our modelling assumption about $\mu(t)$ is that it can be written as follows :

$$\mu(t) = \rho(t)S(t) \tag{5}$$

with $\rho(t)$ a positive bounded function : $0 \le \rho(t) \le \rho_{max}$

The function $\rho(t)$ is considered as a completely unknown time-varying parameter, regardless of the (known and unknown) biological or physico-chemical factors that can influence the growth. This is in line with a number of recent works on estimation and control of fermentation processes (e.g. Holmberg & Ranta, 1982; Dochain & Bastin, 1984; Stephanopoulos & San, 1984; Bastin & Dochain, 1986). This assumption (5) does not introduce any restriction on the structure of $\mu(t)$: it simply implies that $\mu(t) = 0$ when $S(t) = 0$ in accordance with the physical reality.

Our conjecture is then that adaptive regulation of S(t) at values corresponding to a maximum specific growth rate should contribute to a maximization of the yield of biomass production, without any modelling of $\rho(t)$ being necessary, unlike in optimal control methods.

Defining the time-varying parameter :

$$\phi(t) = k_1\rho(t)X(t)$$

equation (2) is rewritten as follows :

$$\dot{S}(t) = -\phi(t)S(t) + \frac{F(t)}{V(t)}[S_{in}(t) - S(t)] \tag{6}$$

This equation is the basis for the derivation of the control algorithm.

We assume that :

- the flow rate F(t) is constant : $F(t) = F_0$ (until the tank is full, of course)
- the substrate concentration S(t) is measured on-line
- the influent substrate concentration $S_{in}(t)$ is the control input.

The control input $S_{in}(t)$ is calculated as follows :

$$S_{in}(t) = \frac{V(t)}{F_0}\{C_1[S^* - S(t)] + [\frac{F_0}{V(t)} + \hat{\phi}(t)]S(t)\} \tag{7}$$

except if $\frac{V(t)}{F_0}\{C_1[S^* - S(t)] + [\frac{F_0}{V(t)} + \hat{\phi}(t)]S(t)\} < 0$,
then $S_{in}(t) = 0$

with $C_1 > 0$ and $\hat{\phi}(t)$ an adaptive estimate of $\phi(t)$, which is calculated as follows :

$$\dot{\hat{\phi}}(t) = C_2S(t)[S^* - S(t)] \quad , \quad C_2 > 0 \tag{8}$$

except if $\hat{\phi}(t) = 0$ and $S(t) > S^*$, then $\dot{\hat{\phi}}(t) = 0$

The theoretical motivation for the above control algorithm (7)(8) can be found in Dochain and Bastin (1988).

Simulation Results : Comparison with Open Loop Operation

The simulation of the "true" process is carried out by using equations (1)(2)(4) with an Haldane growth rate structure (Fig.1) :

$$\mu(t) = \frac{\mu^* S}{(K_m + S + S^2/K_i)}$$

and the following set of parameters :

$$k_1 = 1,\ K_m = 10,\ K_i = 0.1,\ \mu^* = 5.$$

Obviously, the above analytical expression for $\mu(t)$ is completely ignored by the control algorithm. The desired set point S^* is the value of the substrate concentration S which maximizes the specific growth rate $\mu(t)$:

$$S^* = \sqrt{K_m K_i} = 1$$

In Fig.2, the initial and operating conditions and the design parameters C_1 and C_2 have been set to the following values :

$$S(0) = 1,\ X(0) = 0.1,\ V(0) = 10,\ S_{in}(0) = 3.5$$
$$F_0 = 0.1,\ V_f = 12,\ C_1 = 20,\ C_2 = 99,\ \hat{\phi}(0) = 0.1$$

(with V_f : final volume of the culture).

Fig.2 compares closed loop and open loop operations of the fedbatch process. In both cases, the reactor is fed with the same amount of substrate (Fig.2c). In open loop, a constant input concentration $S_{in}(t)$ is used, while in closed loop, $S_{in}(t)$ is computed by the control algorithm (7)(8). One hour after the end of the feeding period, X(t) has already reached its maximum value, while in open loop, it remains below 10% of the closed loop value of X(t).

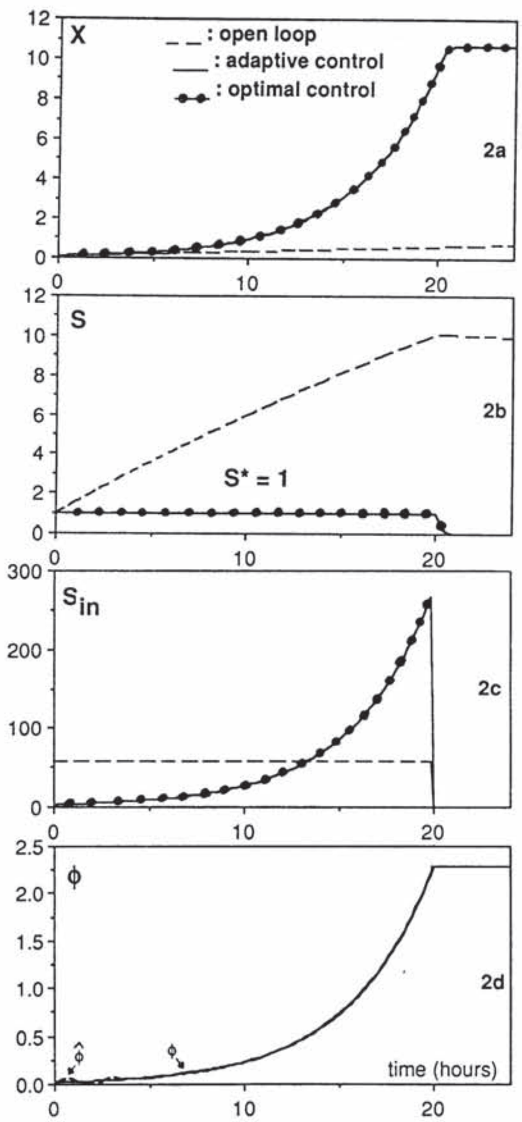

Fig.2 Maximization of the biomass production

Comparison with Optimal Control

We have also calculated the solution of the optimal control which consists of maximizing

$$J = X(T)V(T)$$

i.e. the biomass production over the feeding duration T.

This solution is written :

$$S(0) = \sqrt{K_m K_i} \tag{9}$$

$$S_{in}(t) = \sqrt{K_m K_i} + k_1 \frac{V(t)}{F_0} \frac{\mu^* \sqrt{K_m K_i}}{2K_m + \sqrt{K_m K_i}} X(t) \tag{10}$$

with V(t) and X(t) computed from :

$$\dot{V}(t) = F_0 \tag{11}$$

$$\dot{X}(t) = \frac{\mu^* \sqrt{K_m K_i}}{2K_m + \sqrt{K_m K_i}} X(t) - \frac{F_0}{V(t)} X(t) \tag{12}$$

The choice of the initial value of the substrate concentration, S(0) (equal to the optimum S^*) induces a relatively simple optimal control solution (the general solution when S(0) is arbitrary, is much more complex). However, the optimal control still requires the knowledge of the growth structure and of the coefficients μ^*, K_m, K_i and k_1 in this case, while our controller (7)(8) is much simpler and only needs an appropriate choice for the "optimal" set point S^*.

The closed loop behaviour of X(t) with the control algorithm (7)(8) is very close to the optimal trajectory given by (9)(10)(11)(12) : actually, no significant discrimination between both curves can be made in Fig.2, and this despite an initial error of 75% in the value of $\hat{\phi}(t)$.

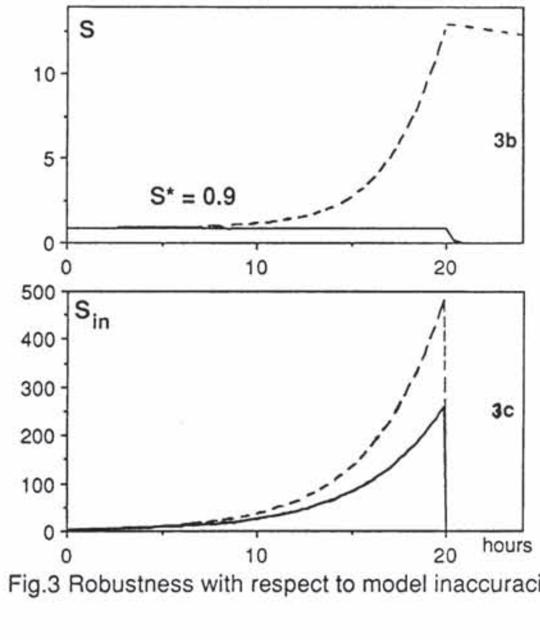

Fig.3 Robustness with respect to model inaccuracies

Robustness of the Control Algorithms : Sensitivity to Model Inaccuracies

A critical problem with the above control algorithms is the precise knowledge of the value of the substrate concentration S^* which maximizes the specific growth rate $\mu(t)$. It may appear very difficult in practice to evaluate S^* with accuracy (e.g. due to the lack of reproductible experiments).

We have studied the sensitivity of both control algorithms to such inaccuracies. In Fig.3, we have considered that the "optimal" value of S^* was known with a 10% error. This means that in our simulations, the adaptive controller (7)(8) has been implemented with a desired set point $S^* = 0.9$ (while the "true" S^* is equal to 1). A similar 10% error on S^* has been introduced in the optimal control law (9)-(12) by setting K_m equal to 8.1 (instead of 10). Our adaptive controller appears more robust to this model inaccuracy : with respect to the ideal case of Fig.2, only a slight diminution of the final biomass concentration X has been noticed, while with the optimal control, the production of biomass has fallen under 50% of the optimal value.

Comparison with a PI Regulator

One of the basic feature of our controller (7)(8) is its adaptive structure which allows for the tracking of the time-varying parameter $\phi(t)$. It is worth noting that in our application, the variations of $\phi(t)$ are quite substantial (about two orders of magnitude (fig.2d)). It would therefore be interesting to compare our controller with a non-adaptive control scheme, e.g. a PI regulator.

The PI regulator equation can be written in Laplace transform (with p as Laplace variable) :

$$S_{in}(p) = (K_P + \frac{K_I}{p})\,(S^* - S(p))$$

where K_P and K_I are the proportional and integral gains of the PI regulator.

Let us choose K_P and K_I as follows. If ϕ and F/V are constant, then equation (6) is a first order stationary linear equation, with a pole equal to $-(\phi + F/V)$ and a static gain $F/(\phi V + F)$, i.e. in Laplace transform :

$$S(p) = \frac{F/V}{p + \phi + F/V}\, S_{in}(p)$$

Consider mean values for $\phi(t)$ and F/V in our application (e.g. $\phi_{mean} = 1.25$ and $(F/V)_{mean} = 0.01$), and take K_P and K_I so as to compensate the pole $-(\phi + F/V)_{mean}$ and have a closed loop dynamics close to the open loop dynamics which corresponds to these mean values, e.g. :

$$K_P = 100,\; K_I = 125$$

Fig.4 compares the adaptive controller and the PI regulator when S(0) is equal to 0.02. Note the oscillating behaviour of the PI regulator. Due to the non stationarity of the parameter $\phi(t)$, the PI is not able to maintain the substrate concentration S(t) at the set point S^* at the end of the feeding period. Moreover the final biomass production with the PI is only about 85% of the value obtained with the adaptive scheme.

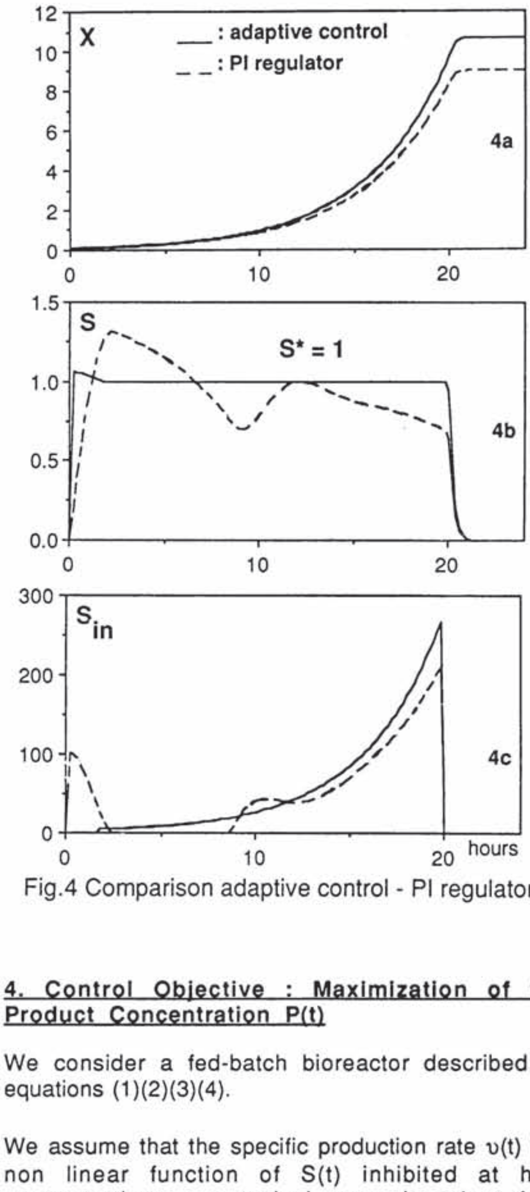

Fig.4 Comparison adaptive control - PI regulator

4. Control Objective : Maximization of the Product Concentration P(t)

We consider a fed-batch bioreactor described by equations (1)(2)(3)(4).

We assume that the specific production rate $\upsilon(t)$ is a non linear function of S(t) inhibited at high concentrations : a typical example taken from Takamatsu et al (1975) is shown in Fig.5.

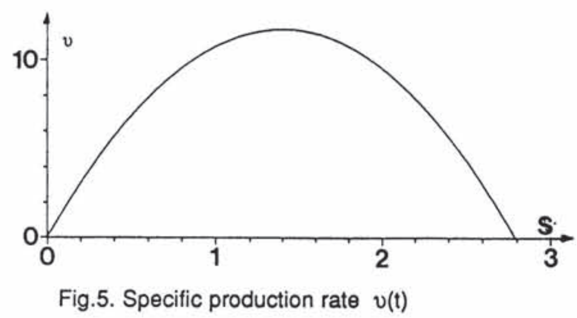

Fig.5. Specific production rate $\upsilon(t)$

Our conjecture is now that regulating the substrate concentration S(t) at values corresponding to a maximum υ(t) would contribute to the maximization of the yield of the product formation.

The same control algorithm (7)(8) can be used which do not need a model for υ(t) but only requires a good a priori knowledge of the value of S(t) which maximizes υ(t).

Simulation Results

The "true" fed-batch process is simulated by using equations (1) (2) (3) (4) with a Monod specific growth rate :

$$\mu = \frac{\mu^* S}{K_m + S}$$

and the following specific production rate υ(t) suggested by Ohno et al (1976) (see fig.5) :

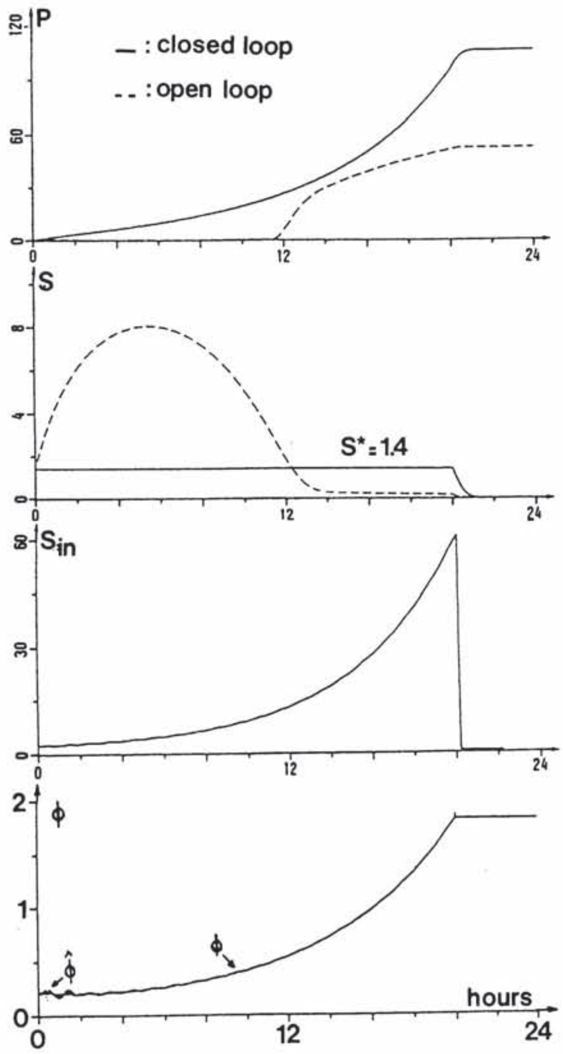

Fig.6. Adaptive control of fedbatch bioreactors : maximization of P(t)

$$\upsilon(t) = -6\ S(t)^2 + 16.75\ S(t)$$

with the following values for the model parameters :

$$\mu^* = 0.35,\ K_m = 1,\ k_1 = 1/0.135$$

Fig.6 compares closed loop and open loop operations of the fed-batch bioreactor : the closed loop operation doubles the final product concentration P(t). The following parameters and initial conditions have been considered :

$$C_1 = 0.33,\ C_2 = 20,\ \hat{\phi}(0) = 0.2,\ S^* = 1.4$$
$$S(0) = 1.4,\ P(0) = 0,\ X(0) = 0.2,\ S_{in}(0) = 1.6$$
$$F_0 = 0.3,\ V(0) = 1,\ V_f = 7$$

Quasi-Optimization of the Process

It is straightforward that the control problem here looks very similar to the preceding one (maximization of the biomass production, section 3). In fact, it would be completely similar if the production rate in equation (3) was proportional to the product concentration P(t), i.e. of the form υ(t)P(t) (instead of υ(t)X(t)).

A first consequence is that the optimal control problem which consists of maximizing the final product quantity V(T)P(T) is much more complex. And no analytical solution (such as in equations (9)-(12) in section 3) can be emphasized here.

As a second consequence, our adaptive controller (7)(8) can no more be shown to be optimal (as in section 3, Fig.2). However, quasi-optimization of the process could be carried out as follows. Let us use the adaptive algorithm (7)(8) and search (e.g. by some trial and error method over a few fed-batch experiments) for the "best" value of the set point S*. By the "best" value of S*, we mean the value of S* which, with algorithm (7)(8), maximizes the final product quantity V(T)P(T), or alternatively, the value of S* which gives the highest yield

$$\eta = \frac{V(T)P(T)}{\int_0^T F(t)S_{in}(t)dt + V(0)S(0) - V(T)S(T)}$$

i.e. the ratio of the final product quantity over the quantity of nutrient which has been consumed. This is illustrated in Fig.7. Note that the simulation of fig.6 (with

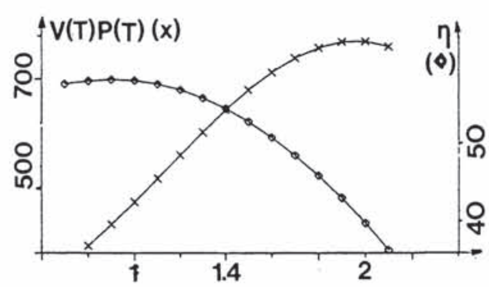

Fig.7. Final product quantity V(T)P(T) (x) and yield η (◆) vs set point S*

a desired set point $S^* = S(\upsilon_{max})$, i.e. the substrate concentration which maximizes the production rate $\upsilon(t)$ (see fig.5)) gives a very good compromise between both criterions.

5. Conclusions

In this paper, we have shown that simple adaptive control algorithms can contribute to optimize fed-batch fermentation processes. The proposed algorithm does not require any analytical expression for the fermentation parameters (like the specific growth rate and the specific production rate). In particular, its performances has been compared to other control strategies (optimal control, PI regulator).

It is worth noting that similar ideas can be used in other control problems or for on-line estimation purposes (see Dochain & Bastin, 1984; Bastin & Dochain, 1986; Dochain & Bastin, 1988).

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