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A contribution to optimal control of fed-batch biochemical processes

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Abstract. The problem of looking for high efficient modern control strategies in fermentation technology is very urgent, nowdays. Particular attention should be paid to the processes in fed-batch mode. Both, optimal feedforward and feedback control approaches are suggested. A contribution is considered to have been made in the feedback control where continuous and discrete versions are treated as well. The control laws are carried out by a variation calculus problem and a polynomial pole placement synthesis solution, respectively. All the algorithms result in an optimal substrate feed rate profile. On the basis of recursive least squares identification of the model coefficients an adaptive discrete-time control strategy is proposed. Some satisfying simulation results are dealt with.

1 Introduction

In comparison with conventional chemical industries the fermentation industry still holds a backward position in respect of the application of modern control techniques. Some plausible reasons are the following:

- Shortage of adequate dynamic process models suitable for control purposes.
- Lack of on-line sensors for substrates, biomass and products.
- Major part of the processes in the biotechnical industries is carried out in batch for fed-batch reactors, causing operating points to vary.
- Some technical limiting factors, e.g. continuous feeding is not possible.

Many industrially important fermentation processes are carried out in a semibatch mode in which a feed stream containing substrate and/or nutrients is fed into the fermentor during the course of batch fermentation. At the end of fermentation the broth is withdrawn partially or completely, and the operation is repeated. These, so called fed-batch cultures have been used to produce antibiotics, amino acids, microbial cells, enzymes, and organic acids. Control of the substrate concentration is considered to be most effective in overcoming such effects as substrate inhibition, catabolite repression, product inhibition, glucose effect, and autotrophic mutation.

Numerous articles have been dealing with the determination of the optimal feed rate profiles for fed-batch fermentation, e.g. San and Stephanopoulos [1], Lim, Tayeb, Modak and Bonte [2], Modak and Lim [3], etc. This paper has not been designed to make a contribution in this field. Nevertheless, in order to complete the fed-batch process optimization problem, we shall list the basic mathematical formulas for optimal feed rate profile calculation. This is necessary for comparability with other methods.

Algorithms for optimal feed rate profile determination result in a feedforward control law. From the state of art in the off-line optimization of batch and fed-batch operations it may be concluded that a feedforward control of a biotechnological process is rather risky, not to say hazardous. Therefore, an additional feedback control seems to be an essential requirement. The implementation of such feedback control, however, is very often hampered by the absence of on-line sensors for the most important state variables. This is one of the reasons that development of various estimation schemes is of crucial importance for an effective control. Although progress in this area has led to improved on-line estimations of the bioreactor state, it is not likely that reliable identification in industrial processes with multiple substrates and products will be achieved by these methods. Special emphasis has been therefore given to new automatic sampling device, which may help to move the analysers from the laboratory to the process, Reuss [4]. As in many chemical processes these process analysers may then become key inputs to more reliable computerized process control systems.

In this paper a fed-batch process equipped with such an analyzer is considered. For this case an effective feedback control law is suggested. Both, a continuous and a digital control problem are treated. The first one is based on a linearized model of second order having been carried out under conditions of "quasi-steady state" [5]. The control law is given by a "classic" variation calculus method. For the second one a discrete-time model identified by a least squares method is used. The control law results from polynomial approach of discrete linear control [6]. This provides a basis for adaptive feedback control of biotechnological process when a recursive identification method is used. Herein a combination of the recursive least squares method with exponential forgetting with a polynomial pole-placement control strategy is proposed. For all cases as a control variable the feed flow rate is considered.

2 Optimization problem

The optimization problem is to determine, for a given fed-batch fermentation described by a set of mass balance equations, the optimal feed rate profile which will minimize a given profite function. The usual lumped mass balance equations under certain assumptions [5] are the following:

$$(xV)' = \mu x V, \qquad x(0) = x_0 \tag{1}$$

$$(sV)' = -\sigma x V + s_F F, \quad s(0) = s_0 \tag{2}$$

$$(pV)' = \pi x V - kpV, \qquad p(0) = p_0 \tag{3}$$

$$V' = F, \qquad V(0) = V_0 \tag{4}$$

where x, s and p are the concentrations of cell mass, substrate and product, respectively; s_F is the feed substrate concentration; V is the fermentor volume; F is the volumetric feed rate; k is the hydrolysis constant; and μ, σ and π are the specific rates of cell growth, substrate consumption, and product formation, respectively.

Physical constraints must be imposed on the final fermentor volume and the feed rate:

$$V(t_f) = V_f \quad \text{and} \quad 0 = F_{\min} \le F(t) \le F_{\max},$$

where f is used to denote the final fermentation time.

Let $\boldsymbol{x}$ be a state vector which takes the form

$$\boldsymbol{x}^T = [xV, sV, pV, V, t] \tag{5}$$

Substitution of Eq. (5) into Eqs. (1)–(4) yields a state-space description:

$$\boldsymbol{x}' = \boldsymbol{a}(\boldsymbol{x}) + \boldsymbol{b}F; \quad \boldsymbol{x}(0) = \boldsymbol{x}_0 \tag{6}$$

Elements of vectors $\boldsymbol{a}(\boldsymbol{x})$ and $\boldsymbol{b}$ are obvious from Eqs. (1)–(4).

The profit function to be minimized is considered to be a function of the final outcome of fermentation:

$$g = -f[\boldsymbol{x}(t_f)] \tag{7}$$

Hence, the optimization problem is to determine the optimal feed rate profile, $F(t)$, which minimizes the performance index given by Eq. (7) for the fermentation processes described by Eqs. (1)–(4) with respect to the given physical constraints. According to the minimum principle of Pontryagin [8] the problem can be solved by minimizing of the Hamiltonian:

$$H = \boldsymbol{\lambda}^T [\boldsymbol{a}(\boldsymbol{x}) + \boldsymbol{b}F], \tag{8}$$

where $\boldsymbol{\lambda}^T$ is the adjoint vector defined by:

$$\boldsymbol{\lambda} = -\partial H/\partial \boldsymbol{x}; \quad \lambda_i(t_f) = -\partial f/\partial x_i(t_f); \quad i = 1, 2, 3, 5. \tag{9}$$

The optimal feed rate $F_\sigma(t)$ can be determined by examining the coefficient $\boldsymbol{\lambda}^T \boldsymbol{b} = \alpha$ the following equation:

$$F_\sigma(t) = \begin{cases} F_{\max} & \alpha < 0 \\ \boldsymbol{\lambda}^T(\boldsymbol{a}_x \boldsymbol{c} - \boldsymbol{c}_x \boldsymbol{a})\, \boldsymbol{\lambda}^T \boldsymbol{c}_x \boldsymbol{b} & \alpha = 0 \\ F_{\min} & \alpha > 0 \end{cases} \tag{10}$$

where $\boldsymbol{a}_x = \partial \boldsymbol{a}/\partial \boldsymbol{x}$, $\boldsymbol{c} = -\boldsymbol{a}_x \boldsymbol{b}$ and $\boldsymbol{c}_x = \partial \boldsymbol{c}/\partial \boldsymbol{x}$.

Thus, the procedure of optimal feed rate determination can be summarized as follows:

1. Choose an admissible profile of $F(t)$
2. Calculate elements of $\boldsymbol{x}$ by simulation of Eq. (6)
3. Calculate $\boldsymbol{\lambda}$ from Eq. (9) according to a backward time variable $\tau = t_f - t$
4. Examine coefficient α and choose the right formula for $F_\sigma(t)$ calculation using Eq. (10)
5. Calculate $F(t) \approx F_\sigma(t)$
6. Repeat the calculation procedure with the "new" $F(t)$ profile
7. Stop when $F(t) = F_\sigma(t)$

3 Continuous feedback control

Let us define the task of the optimal control as follows: Generate an optimal feed flow rate course such that the substrate concentration is maintained on a desired constant value for a certain phase of the fermentation.

For feedback control purposes the mathematical model can be transformed to:

$$x' = (\mu - u)x \tag{11}$$

$$s' = -\sigma x + u(s_F - s) \tag{12}$$

$$p' = \pi x - (k + u)p \tag{13}$$

where u denotes the control variable, $u = F/V$.

The quasi-steady state of a constantly-fed-batch culture is characterized by $\mathrm{d}x/\mathrm{d}t \approx 0$, $\mathrm{d}s/\mathrm{d}t \approx 0$ and $\mu \approx D$ where D is the dilution rate. Assuming such a case, for the fed-batch process described by Eqs. (1)–(4) a linearized model of second order can be derived [9]:

$$a_2 s'' + a_1 s' + a_0 s = b_0 u + b_1 u'; \quad s(0) = s_0, \quad s'(0) = s_0^1. \tag{14}$$

For a time-invariant system, coefficients a_0, a_1, a_2, b_0 and b_1 are constant. The Laplace transform of the linearized system gives:

$$F_c(p) = \frac{b_1 p + b_0}{a_2 p^2 + a_1 p + a_0}, \tag{15}$$

where p is the Laplace argument. The performance criterion to be minimal is:

$$J = \int_0^\infty G_1\, \mathrm{d}t = \int_0^\infty [(s_w - s)^2 + A^2 (s')^2]\, \mathrm{d}t, \tag{16}$$

where s_w is the set-point value and A is a weight factor. The Hamiltonian, when a variation calculus method is applied,

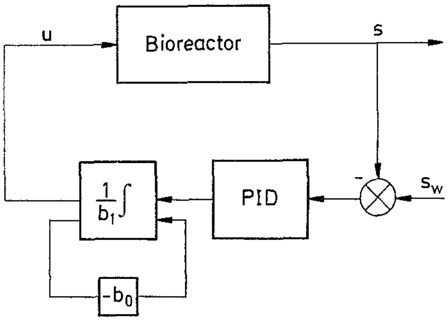

Fig. 1. Scheme of the continuous-time control strategy

takes the form:

$$H_J = G_1 + \lambda_J(t)\, G_2, \tag{17}$$

where λ_J is the Lagrange function and G_2 is the left side of the system description (14) transformed to an equation $G_2 = 0$. Using the Euler-Poisson equations [10] we can determine the optimal substrate concentration profile as:

$$s(t) = s_w[1 - \exp(-t/A)]. \tag{18}$$

Then, the optimal control law results from Eqs. (11)–(15) as:

$$b_1 u' + b_0 u = \frac{a_1}{A}(s_w - s) + \frac{a_0}{A}\int (s_w - s)\,\mathrm{d}t + \frac{a_2}{A}\frac{\mathrm{d}}{\mathrm{d}t}(s_w - s), \tag{19}$$

where the right side represents an optimal PID controller. The continuous feedback control scheme is proposed in Fig. 1.

4 Discrete feedback control

For a successful discrete control design the impulse transfer function of the controlled object

$$F_D = \frac{B(d)}{A(d)} \tag{20}$$

should be known. In Eq. (20) d is the shift operator, B and A are polynomials. The coefficients of Eq. (20) can be calculated directly from Eq. (15) using Z-transform, however, the utilization of the obtained transfer function is strongly limited. When a reliable input-output measurement system is at disposal coefficients B and A can be identified by means of a least squares identification method. Either a single or a recursive identification method can be applied. The latter, when combined with an effective discrete control algorithm, gives a good basis for adaptive control.

As a control strategy the algebraic polynomial approach with pole-placement design is proposed [6]. The adaptive control scheme is shown in Fig. 2, where R/P and Q/P represent a feedforward and a feedback controller, respectively. $R(d)$ is chosen as a zero-order polynomial. Polynomials $Q(d)$ and $P(d)$ fulfill the Diophantine equation:

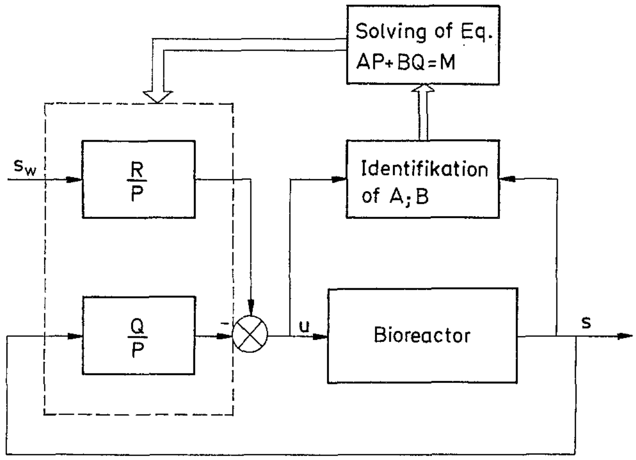

Fig. 2. Discrete-time adaptive control structure

$$AP + BQ = M, \tag{21}$$

where polynomial $M(d)$ includes all the designed poles of the feedback system.

Then, the control law in accordance with Fig. 2 is

$$u = \frac{R}{P}s_w - \frac{Q}{P}s. \tag{22}$$

4 An example

The object of feedback control is a fed-batch biochemical reactor described by equations (11)–(13) while $s_F = 500$ g/l and $k = 0.01$ 1/h. The initial conditions are $x_0 = 1.3$ g/l, $s_0 = 69$ g/l, $p_0 = 0$ g/l and $V_0 = 8.121$ l.

The bioprocess kinetics is governed by the equations

$$\mu = 0.11\, s\,x/(0.006\, x + s) \tag{23}$$

$$\pi = 0.004\, s/(0.0061\, x + s + 10\, s^2) \tag{24}$$

$$\sigma = \mu/0.47 + \pi/1.2 + 0.029 \tag{25}$$

The system has been modelled and simulated on a digital computer. In Fig. 3 and Fig. 4 we offer a comparison when the process is operated in a batch and a fed-batch mode, respectively. The advantages of the fed-batch fermentation are obvious. Applying the Taylor's expansion to Eqs. (23) and (24) in the neighbourhood of $x = x_s$, $s = s_s$ and $p = p_s$ the coefficients of linearized model (14) can be calculated. For $x_s = 30.535$ g/l, $s_s = 1.57 \cdot 10^{-2}$ g/l and $p_s = 0.188$ g/l we have obtained: $s_2 = 1.489$, $a_1 = 47.732$, $a_0 = 0.738$, $b_0 = 1$ and $b_1 = 744.313$.

Some optimal feedback control simulation results for the continuous case using the control law in accordance with Eq. (19) are demonstrated in Fig. 5 and Fig. 6. While in Fig. 5 the influence of the weight-factor A upon the control

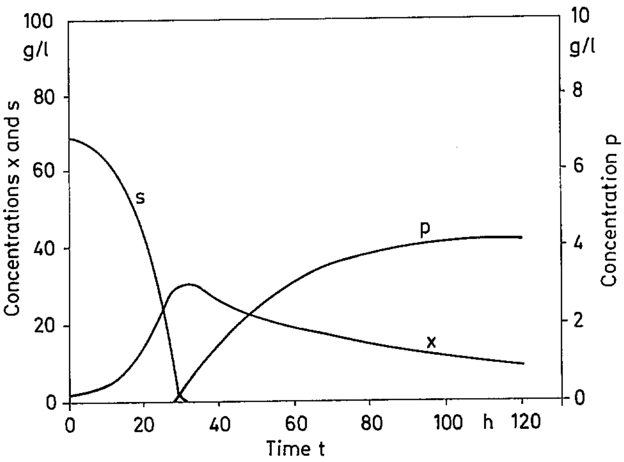

Fig. 3. Batch process concentration profiles

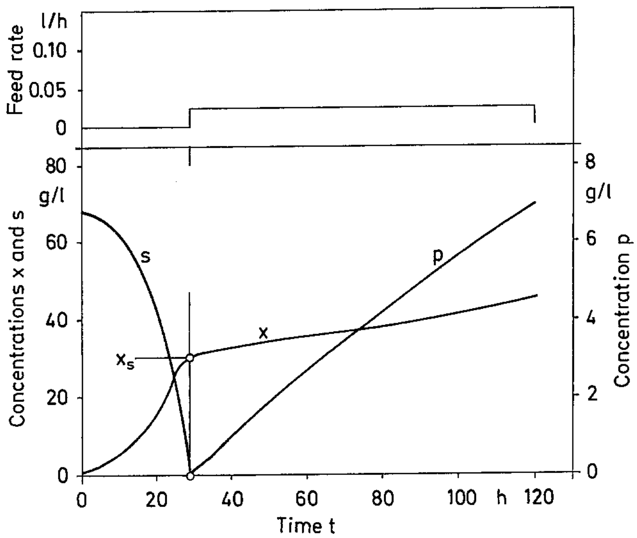

Fig. 4. Fed-batch process concentration profiles

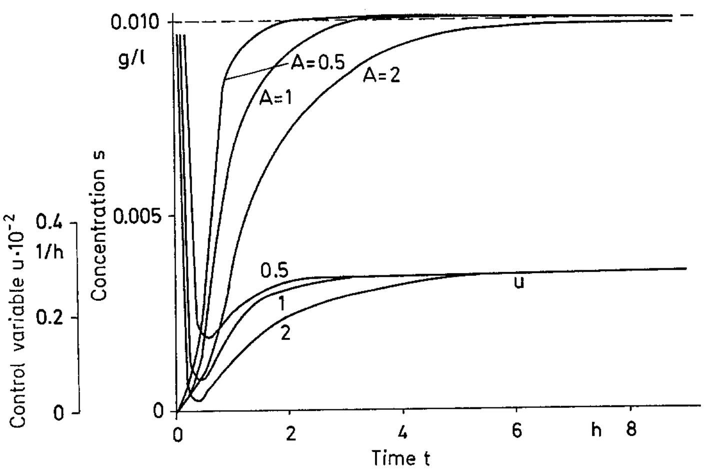

Fig. 5. Input and output variable courses for various A

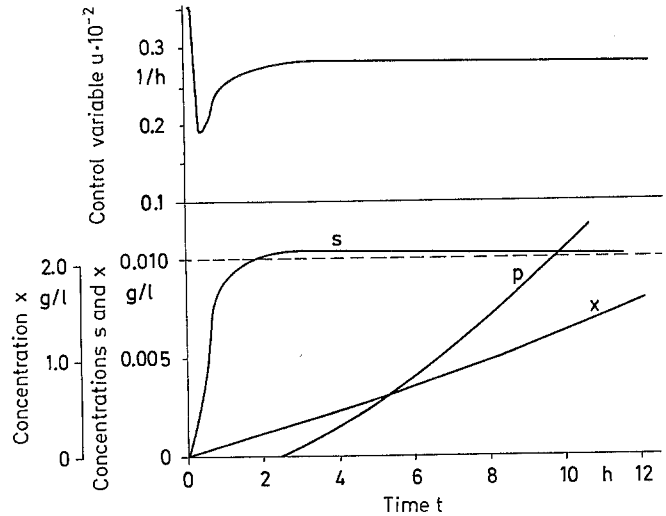

Fig. 6. Input and output variable courses by substrate continuous-time control

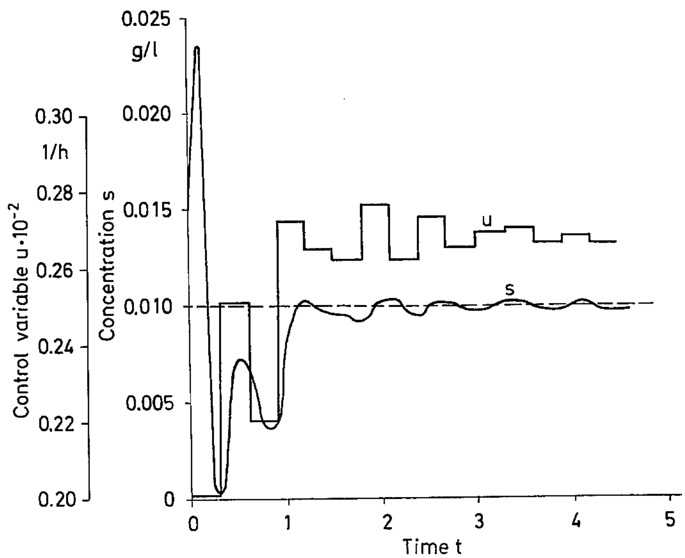

Fig. 7. Simulation results of adaptive discrete-time control

action is underlined, Fig. 6 shows the behaviour of the concentration profiles in the reactor. The substrate set-point value $s_w = 0.01$ g/l was strictly maintained.

In Fig. 7 we introduce a result of the adaptive version of discrete-time optimal feedback control on the basis of the control scheme in Fig. 2 for the discussed fed-batch process. For evaluation of Eq. (20) the recursive least squares identification method has been used.

5 Conclusion

Plenty of simulation events have been carried out. However, it would exceed the normal extent of this paper to present all results. The complex analysis of fed-batch process control shows, that the control design is strongly influence by both, mathematical model availabilities and measurement possibilities. When an exact mathematical model is at disposal an open-loop process control can be proposed, however, experience shows that an only feedforward control action is rarely entirely sufficient. On the other hand, the feedback control needs a highly reliable measurement system.

The present results confirm a good ability of the proposed algorithms in set-points value tracking. It is better, of course, for continuous control but, unfortunately, very few of industrial processes are equipped with continuous substrate feeding facilities so far. Taking into account the relatively large time constants of these processes and with respect to the rapid development in computer control strategies recently, the adaptive discrete-time control should be preferred. A reasonable choice of the sampling period for the control variable calculation and the system parameter identification is of significant importance. Obviously, this should be made in accordance with system dynamics.

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