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EVALUATION OF ON-LINE CONVENTIONAL AND ADAPTIVE CONTROLLERS FOR THE PENICILLIN G FED-BATCH FERMENTATION BASED ON SIMULATIONS USING A NEW MATHEMATICAL MODEL

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1 Abstract

Nowadays the optimization of product formation during penicillin G fed-batch fermentation as a part of total process control has gained a renewed attention (Spriet 1987). In the last two decades several attempts have been made towards modeling the fermentation process. Among others, the models proposed by Heijnen et al. (1979) and by Bajpai and Reuß (1980,1981) are well suited for advanced control purposes (Lim et al. 1986, Van Impe et al. 1990, Van Impe et al. 1991a). However, based on recent advances in the biochemistry of the penicillin synthesis, an updated model has been proposed in order to correct some physical and biochemical shortcomings in both models mentioned (Nicolaï et al. 1990).

Van Impe et al. (1991b) have applied optimal control theory to derive the substrate feeding strategy which optimizes the final amount of penicillin, for a given total amount of substrate. However, as the optimal profile is not obtained in complete closed-loop form and requires the on-line determination of the full bioreactor state, heuristic biphasic control strategies have been developed based on microbial insight (Van Impe et al. 1990, 1991a-b, Bonte et al. 1989). They represent a more realistic control objective, namely set-point control.

In this paper we shall indicate some drawbacks of these heuristic controllers, in particular with respect to their robustness. On the other hand, we shall illustrate that they can serve well as a basis for the development of more reliable control schemes : both conventional PID-based and adaptive model-independent controllers shall be investigated. In these schemes the time delay due to the on-line state determination shall be incorporated. We shall illustrate the performance of a discrete-time implementation with some typical simulation results.

2 The model of Nicolaï et al.

2.1 Mathematical description

The penicillin fermentation process can be modeled by the following set of mass balance equations :

$$\frac{dS}{dt} = -\sigma X + s_F u \quad (1)$$

$$\frac{dX}{dt} = \mu X \quad (2)$$

$$\frac{dP}{dt} = \pi X - k_h P \quad (3)$$

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

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

Based on recent advances in the biochemical knowledge of the penicillin biosynthesis, Nicolaï et al. (1990) have presented an updated unstructured mathematical model. The following specific rates have been incorporated in the model equations (1-4) :

$$\pi = \pi_m \frac{C_s}{K_p + C_s + C_s^2/K_i} \quad (5)$$

$$\mu = \mu_{substr} - Y_{x/s}(f_m(C_s)m_s + f_p(C_s)\pi/Y_{p/s}) \quad (6)$$

where μ_{substr} is the specific substrate to biomass conversion rate, either modeled by Contois- or Monod-kinetics :

$$\mu_{substr} = \mu_C \frac{C_s}{K_x C_x + C_s} \text{ or } \mu_{substr} = \mu_M \frac{C_s}{K_s + C_s} \quad (7)$$

The functions $f_m(C_s)$ and $f_p(C_s)$, a measure for the *endogenous fraction* of respectively maintenance requirements and production, are chosen as follows :

$$f_m(C_s) = \exp(-C_s/E_m) \quad f_p(C_s) = \exp(-C_s/E_p) \quad (8)$$

As a result of balancing, the specific glucose uptake rate is given by :

$$\sigma = \mu/Y_{x/s} + m_s + \pi/Y_{p/s} \quad (9)$$

A physical interpretation can be assigned to the parameters E_m and E_p as follows : they represent the *glucose concentration at which the respective endogenous fraction is equal to 36.8 percent.*

For intermediate values of E_m and E_p, there is a smooth transition between maintenance and endogenous metabolism as a function of C_s. The ability to choose different values for E_m and E_p makes it possible to simulate different endogenous fractions of respectively maintenance requirements and production.

2.2 Simulation results

All computations were done on a *VAX-VMS* system, using a Runge-Kutta-Gill solver and the *NAG*-routines *D02EHF* and *D02EBF* for stiff systems integration, and the *MATRIX$_X$*-routine *MAXLIKE* for parameter estimation. We have made the following assumptions. We always set E_m *equal to* E_p (further on simply denoted with E), as there is no *a priori* reason for not doing so. For μ_{substr} *Contois*-kinetics has been chosen. The *nominal parameter set* (due to Bajpai and Reuß 1981) and the *initial conditions* are summarised in Table 1. The total amount of substrate available for fermentation is equal to $\alpha = 1500$ g. A set of 120 *reference data* for S, X and P has been

generated, using the original Bajpai and Reuß model with a zero initial amount of substrate and a constant feed rate strategy during 120 hrs.

parameters			
μ_C	0.11	K_x	0.006
π_m	0.004	k_h	0.01
K_p	0.0001	K_i	0.1
$Y_{x/s}$	0.47	$Y_{p/s}$	1.2
m_s	0.029	s_F	500
initial conditions			
X_0	10.5	S_0	*to be specified*
P_0	0	V_0	$7 + S_0/s_F$
t_0	0	α	1500

Table 1 *Parameters and initial conditions*

We have tried to fit the model to these reference data in 2 limiting cases : (1) $E = 1.\ 10^{-9}$ g/L (simulating a maintenance metabolism) (2) $E = 1.\ 10^{+12}$ g/L (simulating an endogenous metabolism).

The value of π_m is adjusted—since its value seems not very reliable (Nicolaï et al. 1990)—so as to minimize the Euclidian distance to the *reference* data (Table 2). Of course, the results for the *maintenance* model coincide with the reference data, as C_s never becomes negative for this particular feeding strategy. For the *endogenous* model, the fit of X and P is still very good, although the S-profiles differ somewhat in the growth phase.

E	π_m	$S(t_f)$	$X(t_f)$	$P(t_f)$
$1.\ 10^{-9}$	$4.0000\ 10^{-3}$	$4.98\ 10^{-2}$	330.28	59.65
$1.\ 10^{+12}$	$5.2861\ 10^{-3}$	$3.82\ 10^{-1}$	330.97	60.82

Table 2 *Estimation of π_m and corresponding final state ($t_f = 120$ hrs), for some values of E*

We believe that this is a very important result, as it indicates that it is virtually *impossible to make a distinction between different kinds of metabolic behaviour*, using data from fermentations with this particular feeding strategy. However, it is indicated elsewhere that the metabolic assumptions might be very important for feeding strategy optimization (Van Impe et al. 1991b).

2.3 The optimization problem

Numerical values for the initial conditions are mentioned in Table 1. X_0 and P_0 are given, S_0 and V_0 are related by (V_s denotes the given initial volume *without* substrate) : $V_0 = V_s + S_0/s_F$. Glucose is added as a solution with concentration s_F.

The optimisation problem is to determine for the given set of equations (1-4) the optimal feed rate profile that minimizes the performance index : $J(u) = -P(t_f)$, i.e. maximizes the final amount of product, subject to the following constraints :

- $t_0 = 0$, t_f = free
- all variables have to be kept positive :
$S(t), X(t), P(t), V(t) \geq 0$, $u(t) \geq 0$, $\forall t \in [0, t_f]$
- the initial amount of substrate S_0 is *free*; the initial conditions S_0 and V_0 are only constrained by the given equation. In other words, some initial conditions can be manipulated to minimise the performance measure :

$$J \equiv J(u, S_0) = -P(t_f) \tag{10}$$

- the total amount of feed is fixed : $S_0 + s_F \int_{t_0}^{t_f} u(t)\, dt = \alpha$

The last *isoperimetric* constraint on the input is equivalent to the *physical* constraint $V(t_f) = V_f$, V_f fixed (4).

3 Heuristic control strategies

3.1 Optimal Control solution

The *optimal* feeding strategy which solves the above optimization problem has been described by Van Impe et al. (1991b) using Pontryagin's Minimum Principle. For $E = 10^{-9}$ g/L the results are : $S_{0,opt} = 528$ g, $t_f = 132.0$ hrs, $P_f = 63.846$ g; for $E = 10^{+12}$ g/L : $S_{0,opt} = 1411$ g, $t_f = 122.5$ hrs, $P_f = 89.709$ g.

The optimal control is obtained in a complete state feedback form, except for the switching time between batch (growth phase) and singular control (production phase), which has to be determined numerically in advance. Of course this makes a complete closed-loop implementation impossible. Further on, the singular control requires the on-line measurement—or at least a sufficiently accurate estimate—of all four variables S, X, P and V, which is hampered by a lot of practical difficulties.

As a consequence, it is useful to construct *suboptimal* strategies that do not suffer from the above difficulties, at the expense of an as small as possible loss in performance.

3.2 Heuristic C_s- and μ-control

The construction of a suboptimal profile is based principally on the concept of a *biphasic* fermentation. Some of the ideas concerning heuristic C_s-control are reported elsewhere (e.g. Bonte et al. 1989, Van Impe et al. 1990, 1991a-b).

For the control during *growth*, we refer to the *optimal* solution : the substrate consumed for growth is added all at once at $t = 0$ in order to obtain the highest possible value of μ for all t during growth (equation (6)). This results in a fast biomass accumulation and—depending on the metabolic assumptions and some parameter values—almost no penicillin production.

During *production*, we focus on the specific rate π. Equation (5) indicates that π reaches its maximum at $C_s = C_{s,crit} = \sqrt{K_p K_i}$. The maximum value is $\pi_{max} = \pi_m/(1 + 2\sqrt{K_p/K_i})$. So during production, we shall keep C_s at $C_{s,crit}$. The control needed can be obtained from the differential equations (1) and (4) :

$$u_{prod} = \frac{\sigma X}{s_F - C_s} \tag{11}$$

As a consequence, the *conjunction* point t_7 of growth and production is simply dictated by the condition $C_s = C_{s,crit}$. The control is stopped when all substrate α is used. As in the optimal case, the concluding batch-phase is stopped when $dP/dt = 0$. Note that the complete suboptimal control (called *heuristic C_s-control*) is obtained in *closed-loop* for a given initial amount S_0. As a result, the optimization problem is reduced to the *one-dimensional optimization of S_0* ($E = 10^{-9}$ g/L : $S_{0,opt} = 533$ g, $P_f = 63.597$ g; $E = 10^{+12}$ g/L : $S_{0,opt} = 1404$ g, $P_f = 89.430$ g).

Remark that for μ_{substr} modeled with *Monod*-kinetics, (11) also keeps μ constant. An equivalent *heuristic μ-control* for *Contois*-kinetics follows from $d\mu/dt = 0$:

$$u_{prod} = \frac{\mu_C K_x C_x (C_s \mu + C_x \sigma)/N^2 + F(E_m, E_p)\sigma X/V}{\mu_C K_x C_x s_F/VN^2 + F(E_m, E_p)(s_F - C_s)/V} \tag{12}$$

$$N \triangleq K_x C_x + C_s \quad (13)$$

$$F(E_m, E_p) \triangleq \exp(-C_s/E_m) m_s Y_{x/s}/E_m + \exp(-C_s/E_p)\frac{Y_{x/s}}{Y_{p/s}}\left(\frac{\pi}{E_p} - \frac{d\pi}{dC_s}\right) \quad (14)$$

As for the conjunction of both phases in the case of Contois-kinetics, it is straightforward to keep switching on $C_s = C_{s,crit}$ which maximizes π. Observe that this value does not follow from the equations themselves, but is rather a natural extension of the case of Monod-kinetics.

A further refinement of these strategies exists in *optimizing* the switching time. In other words, during production C_s (or μ) is kept constant, but not necessarily at $C_s = C_{s,crit}$ (or ...). As in the case of Optimal Control, a *two-dimensional optimization of S_0 and t_2* is obtained.

As for the measurement problem mentioned, remark that the number of variables to be determined has been reduced by one : there is no need for P in (11) or (12).

However, inspection of (11) and (12) indicates that these controllers can result in an unstable closed-loop performance : e.g. a positive step disturbance on the substrate feed rate u results in an increase of C_s (1), and thus in X (2). Both effects amplify the feed-back control (11) or (12), resulting in an unstable closed-loop behaviour. This is illustrated in Figure 1, where the influence of a step disturbance on u (11) with amplitude 10^{-3} L/hr at time $t = 90$ hr is shown : $S_0 = 533$ g, $t_f = 98.60$ hrs, $P_f = 43.27$ g. Obviously, even a small disturbance causes a large decrease in P_f ! So *a straightforward implementation of the controller (11) or (12) is not robust at all.*

However, as these heuristic controllers are the translation of a realistic control objective—namely set-point control—, we shall show in the following that they can serve as a basis for the development of more reliable *conventional* and even model-independent *adaptive control* schemes. In this paper we shall restrict the simulation results to the heuristic C_s-controller.

4 *PID*-controllers

4.1 Mathematical description

We assume that the substrate concentration C_s can be measured on-line, although with some time delay ΔT. Recently some promising results concerning glucose concentration monitoring have been reported : e.g. Rishpon et al. 1990. However, there are still some difficulties with "in situ" sterilization, recalibration, ... Flow Injection Analysers have been proposed also, but these suffer from very large time delays (e.g. Nielsen et al. 1989).
So a measurement at time t becomes available to the controller at time $t + \Delta T$. We suppose that ΔT is known in advance. As the measurement device can only take a new sample *after* completely processing the previous one, the sampling time of the discrete-time P-, PI- and PID-controllers is set equal to this time delay ΔT.

Besides the measurement device and the associated A/D and D/A convertors, a practical realisation of such a controller should consist of a *timing logic* circuit and a *controller* circuit. When the (initially very high) substrate concentration has fallen to an a priori specified (low) set-point value C_s^*, the timing logic circuit triggers the controller circuit. The controller then tries to keep this set-point during the production phase, in spite of disturbances and model uncertainties. Let us consider first of all the influence of ΔT. Suppose that $C_{s,k} \triangleq C_s(t = k\Delta T) > C_s^*$ and $C_{s,k+1} < C_s^*$. Due to the time delay, the controller only starts at time $t = (k+2)\Delta T$. In other words, the process remains uncontrolled for a time interval $\Delta t \leq 2\Delta T$!

The controller output (the substrate feeding rate) is a continuous-time signal with two components.
The *first* component is the feed-forward implementation of control law (11), calculated and stored in advance at some discrete-time instants, using the model equations (1-4) with the nominal parameters and the optimal value of S_0 : the *nominal heuristic C_s-controller*. The value of this feed-forward control is adjusted continuously by linear interpolation between subsequent values. The *second* component is due to the P-, PI- or PID-controller. Between two samples, the second component remains constant.

A standard "textbook" discrete-time PID-controller has been implemented (Åström and Wittenmark 1984) :

$$u_k = K_D\left(1 + \frac{\Delta T}{T_{i,D}}\frac{1}{q-1} + \frac{T_{d,D}}{\Delta T}\frac{q-1}{q+\gamma}\right)e_k \quad (15)$$

where $e_k = C_s^* - C_{s,k-1}$ (C_s-control) or $e_k = \mu^* - \mu_{k-1}$ (μ-control), $\gamma = -T_{d,D}/(10\Delta T)$, and e_{k-1} is initialized on 0. The controller parameters K_D, $T_{i,D}$ and $T_{d,D}$ have been *tuned* by minimising :

$$J = \sum_{i=1}^{30} e(t + i\Delta T)^2 \triangleq \sum_{i=1}^{30}(C_s^* - C_{s,i})^2 \quad (16)$$

after a step disturbance of amplitude 10^{-3} L/hr at time $t = 30.0$ hr ($E = 10^{-9}$ maintenance model) or at time $t = 45.0$ hr ($E = 10^{+12}$ endogenous model). The numerical minimization has been done using an algorithm proposed by Brent (1973) (conjugated directions method).

4.2 Simulation results

E	ΔT	K_D	$T_{i,D}$	$T_{d,D}$	P_f
10^{-9}	0.01	1.73	-	-	63.591
		1.41	$3.94\ 10^{-2}$	-	63.592
		1.27	$2.18\ 10^{-2}$	$5.61\ 10^{-3}$	63.592
	0.10	.517	-	-	63.543
		.427	.169	-	63.550
		.382	.127	$2.97\ 10^{-2}$	63.550
	1.00	.494	-	-	62.998
		.416	1.65	-	63.070
		.372	1.26	.284	63.070
10^{+12}	0.01	2.10	-	-	89.428
		1.71	$3.90\ 10^{-2}$	-	89.428
		1.54	$2.17\ 10^{-2}$	$5.59\ 10^{-3}$	89.428
	0.10	.648	-	-	89.357
		.531	.169	-	89.368
		.476	.127	$2.96\ 10^{-2}$	89.368
	1.00	.632	-	-	87.111
		.519	1.65	-	87.278
		.467	1.26	.285	87.279

Table 3 *Optimal controller parameters, for some values of E and ΔT*

The optimal controller parameters are shown in Table 3.

In Figures 2 and 3, the step responses for the optimal P-, PI- and PID-controllers have been shown ($\Delta T = 0.1$ hr). For the P-controller, the gain K_D must be high enough in order to achieve an acceptable steady state error, which results in a very long settling time. As could be expected, the PI-controller is somewhat more sluggish than the PID-controller.

Table 3 also shows the *nominal* performance of these controllers. Figures 4 and 5 ($\Delta T = 0.1$ hr) show the simulation results for the following *disturbances* : $\mu_C = 0.088$ (-20 %), $K_x = 0.0072$ ($+20$ %), a step $\Delta u = 10^{-3}$ on u at $t = 90$ hrs. The final production is for $E = 10^{-9}$ g/L: $P_f = 58.277$ g (P), $P_f = 63.144$ g (PI), $P_f = 63.146$ g (PID); for $E = 10^{+12}$ g/L: $P_f = 58.471$ g (P), $P_f = 79.377$ g (PI), $P_f = 79.385$ g (PID). Observe that in the figures shown the set-point C_s^* has been reached quite fast !

5 Adaptive control

5.1 Mathematical description

Since industrial high producing strains can undergo mutations during the fermentation process—reflected in time-varying model parameters—, the use of an adaptive controller can be investigated. In an adaptive controller the controller parameters are updated on-line in response to changes in the dynamics of the process and to disturbances.

Parameter identification of stirred tank bioreactors essentially concerns the determination of both the *yield coefficients* and the parameters involved in the (usually nonlinear) *specific rates*, in a nonlinear state space model. Recent advances in both topics have been reported by e.g. Chen et al. 1990, Chen and Bastin 1991.

An application of *STR* (Self-Tuning Regulator) has been discussed by Montague et al. (1986) : a *linear* transfer function model is estimated on-line, and based on this model a *linear* controller is designed according to some criterion.

However, as the fermentation process is known to be inherently non-linear, it is reasonable to expect that better control would result by exploiting from the outset the non-linearities in the model in the design of a *nonlinear* adaptive control algorithm. Several authors have recently adopted this philosophy (e.g. Goodwin and Sin 1984). A detailed survey of the use of adaptive controllers in bioreactor control is given by Bastin and Dochain (1990).

In this paper, we shall incorporate the measurement time delay ΔT into an adaptive control algorithm proposed in Bastin and Dochain (1990). No assumption has been made concerning the exact analytical structure of the specific rates σ and μ, thus circumventing the parameter identification problem. They are treated as time-varying parameters and estimated on-line, using a recursive least squares estimation scheme with a forgetting factor λ. Further, we assume that both C_s and C_x can be measured on-line with a time delay ΔT. C_s and C_x satisfy :

$$\frac{dC_s}{dt} = -\sigma C_x + (s_F - C_s)\frac{u}{V} \quad (17)$$

$$\frac{dC_x}{dt} = \mu C_x - C_x\frac{u}{V} \quad (18)$$

A first-order Euler discretisation of the above equations and equation (4), with sampling time ΔT, results in the following discrete-time system :

$$C_{s,k+1} - C_{s,k} = -\sigma_k C_{x,k}\Delta T + (s_F - C_{s,k})\frac{u_k}{V_k}\Delta T \quad (19)$$

$$C_{x,k+1} - C_{x,k} = \mu_k C_{x,k}\Delta T - C_{x,k}\frac{u_k}{V_k}\Delta T \quad (20)$$

$$V_{k+1} - V_k = u_k\Delta T \quad (21)$$

A discrete-time adaptive weighted one-step-ahead controller design has been chosen, minimising the following quadratic performance index :

$$J_{k+1} = \frac{1}{2}((C_{s,k+1} - C_s^*)^2 + \rho u_k^2) \quad (22)$$

where the weighting factor ρ makes limitation of the control effort possible, in contrast with an ordinary one-step-ahead controller where the output can become very large. After substituting (19) in (22) and minimising the resulting expression with respect to u_k, we obtain the following *non-linear* control law :

$$u_k = \frac{\Delta T}{V_k}(s_F - C_{s,k})\frac{\sigma_k C_{x,k}\Delta T - (C_{s,k} - C_s^*)}{(s_F - C_{s,k})^2(\frac{\Delta T}{V_k})^2 + \rho} \quad (23)$$

However, at time $t = k\Delta T$, only $C_{s,k-1}$ and $C_{x,k-1}$ are known ! We propose the following algorithm :

Step 1 : *Estimation of σ_{k-1} and μ_{k-1} with RLS.*

$$\epsilon_{C_s,k-1} = C_{s,k-1} + \hat{\sigma}_{k-2}C_{x,k-2}\Delta T - (s_F - C_{s,k-2})\frac{u_{k-2}}{V_{k-2}}\Delta T - C_{s,k-2} \quad (24)$$

$$\epsilon_{C_x,k-1} = C_{x,k-1} - \hat{\mu}_{k-2}C_{x,k-2}\Delta T + C_{x,k-2}\frac{u_{k-2}}{V_{k-2}}\Delta T - C_{x,k-2} \quad (25)$$

$$P_{k-1} = P_{k-2}/(\lambda + C_{x,k-2}^2\Delta T^2 P_{k-2}) \quad (26)$$

$$K_{k-1} = -C_{x,k-2}\Delta T P_{k-1} \quad (27)$$

$$\hat{\sigma}_{k-1} = \hat{\sigma}_{k-2} + K_{k-1}\epsilon_{C_s,k-1} \quad (28)$$

$$\hat{\mu}_{k-1} = \hat{\mu}_{k-2} - K_{k-1}\epsilon_{C_x,k-1} \quad (29)$$

Step 2 : *Prediction of $C_{s,k}$, $C_{x,k}$ and V_k, using* (19-21) *and the results of Step 1.*

Step 3 : *Calculation of the controller action.*

u_k is calculated by substituting the results of the previous steps in (23). As σ varies slowly as compared with the dynamics of the system, we take $\sigma_k \approx \hat{\sigma}_{k-1}$. Finally the controller action is limited by :

$$u_k = \begin{cases} 0 & \text{if } u_k < 0 \\ U_{max} & \text{if } u_k > U_{max} \end{cases} \quad (30)$$

Observe that this controller can be implemented from $k = 0$ on. For $C_s = C_s^*$ and $\rho = 0$, the control law reduces to the heuristic C_s-controller (11) !

5.2 Simulation results

For $E = 10^{-9}$ g/L, $S_0 = 533$ g, $\Delta T = 0.1$ hr, $\rho = 0$, $P_0 = 10^9$, $\lambda = 0.6$ and $U_{max} = \infty$, we obtain a *nominal* performance $P_f = 62.848$ g at $t_f = 115.02$ hrs. The convergence of the estimated and predicted values and of the control action is illustrated in Figures 6 and 7. With the following *disturbances*: $\mu_C = 0.088$ (-20 %), $K_x = 0.0072$ ($+20$ %), the final amount is $P_f = 63.183$ g at $t_f = 137.46$

hrs. An additional step $\Delta u = 10^{-3}$ on u at $t = 90$ hrs results in $P_f = 60.911$ g at $t_f = 131.01$ hrs. In this case, there is an *off-set* on C_s, as the control (23) has no integrating action.
For $E = 10^{+12}$ g/L, $S_0 = 1404$ g, $\lambda = 0.7$ and $U_{max} = 10^{-2}$, the other values as given, we obtain a *nominal* performance $P_f = 87.978$ g at $t_f = 108.99$ hrs. With the same *disturbances* on μ_C and K_x, the final amount is $P_f = 83.778$ g at $t_f = 156.91$ hrs. An additional step $\Delta u = 10^{-3}$ on u at $t = 90$ hrs results in $P_f = 82.503$ g at $t_f = 117.39$ hrs. For $\Delta T = 1$, the controller did *not* converge.

6 Conclusions

In this paper, we have compared the performance of two controllers for the penicillin G fed-batch fermentation : a *PID*-controller superposed on a *heuristic* controller, and an *adaptive* controller. The influence of a measurement delay has been built in. Although the adaptive scheme needs no *a priori* information on the specific rates, simulation results indicate that it has excellent robustness properties for limited time delays. A detailed convergence analysis, incorporating the influence of the time delay, is the subject of an ongoing study.

Nomenclature

t	: time (hr)
ΔT	: time delay, sampling time (hr)
S	: amount of substrate in broth (g) (glucose)
X	: amount of cell mass in broth (g DM) (biomass)
P	: amount of product in broth (g) (penicillin)
V	: fermentor volume (L)
u	: input substrate feed rate (L/hr)
C_s	: substrate concentration in broth (g/L)
C_x	: cell mass concentration in broth (g/L)
s_F	: substrate concentration in feed stream (g/L)
E_m	: parameter related to the endogenous fraction of maintenance (g/L)
E_p	: parameter related to the endogenous fraction of production (g/L)
K_x	: Contois saturation constant for substrate limitation of biomass production (g/g DM)
K_s	: Monod saturation constant for substrate limitation of biomass production (g/L)
K_p	: saturation constant for substrate limitation of product formation (g/L)
K_i	: substrate inhibition constant for product formation (g/L)
m_s	: maintenance constant (g/g DM hr)
k_h	: penicillin hydrolysis constant (hr^{-1})
$Y_{x/s}$	: cell mass on substrate yield (g DM/g)
$Y_{p/s}$	: product on substrate yield (g/g)
σ	: specific substrate consumption rate (g/g DM hr)
μ	: specific growth rate (hr^{-1})
μ_{substr}	: sp. substrate to biomass conversion rate (hr^{-1})
μ_C	: max. sp. growth rate for Contois kinetics (hr^{-1})
μ_M	: max. sp. growth rate for Monod kinetics (hr^{-1})
π	: specific production rate (g/g DM hr)
π_m	: specific production constant (g/g DM hr)
γ	: filter parameter in discrete PID-controller
q	: forward shift operator
K_D	: proportional gain (L^2/g hr)
$T_{i,D}$	: reset time (hr)
$T_{d,D}$	: derivative time (hr)

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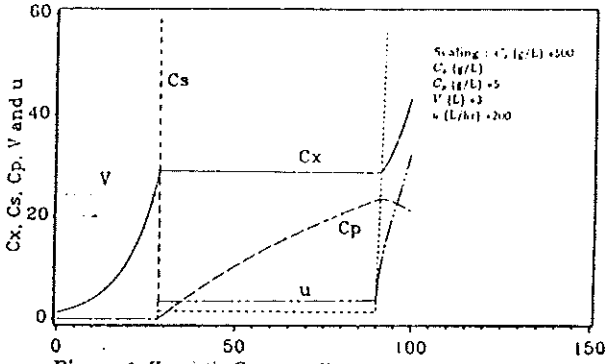

Figure 1 *Heuristic C_s-controller in closed-loop* $E = 10^{-9}$ *g/L,* $S_0 = 533$ *g,* $\Delta u = 10^{-3}$ *L/hr on* $t = 90$ *hr*

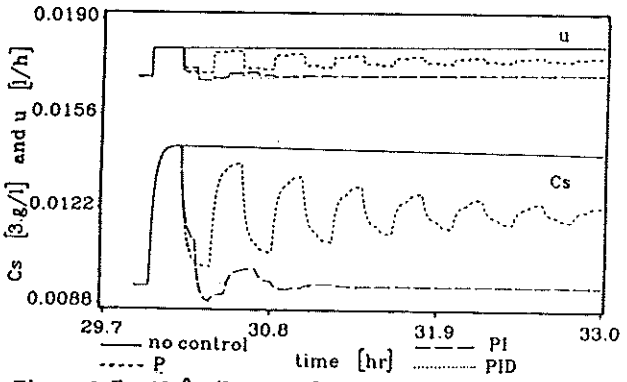

Figure 2 $E = 10^{-9}$ *g/L*

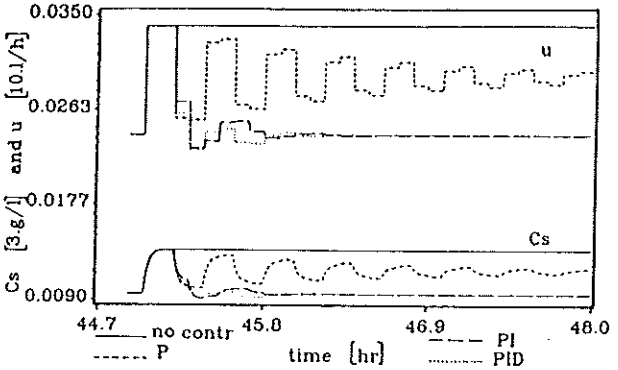

Figure 3 $E = 10^{12}$ *g/L*

Step response of the optimal P-, PI- and PID-controller - $\Delta T = 0.1$ *hr*

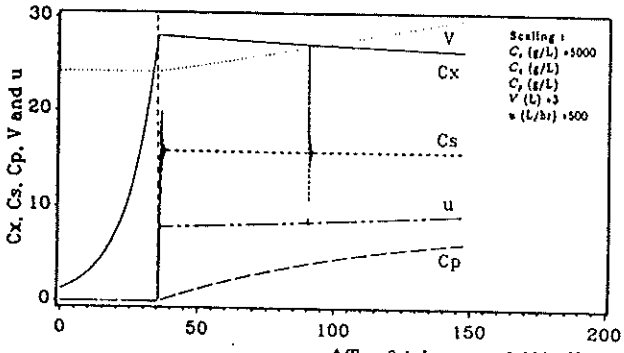

Figure 4 $E = 10^{-9}$ *g/L*

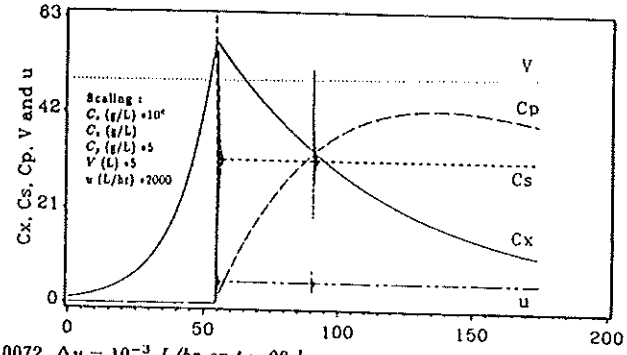

Figure 5 $E = 10^{12}$ *g/L*

$\Delta T = 0.1$ *hr,* $\mu_C = 0.088$, $K_s = 0.0072$, $\Delta u = 10^{-3}$ *L/hr on* $t = 90$ *hr*
PID-controlled fed-batch fermentation

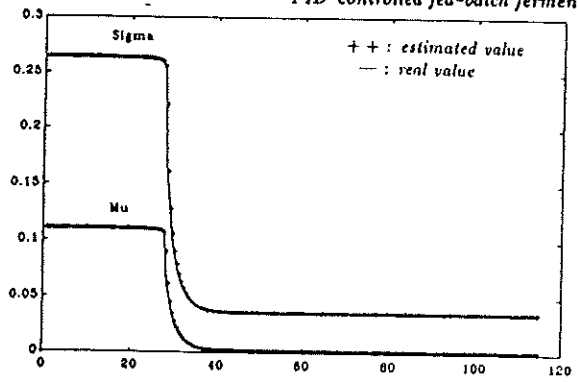

Figure 6 $E = 10^{-9}$, $\Delta T = 0.1$ *hr*
estimation of σ *and* μ

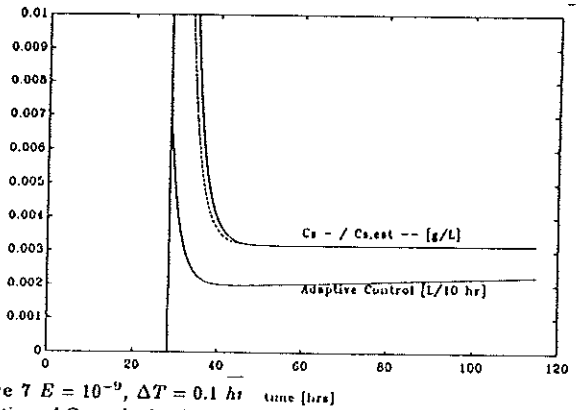

Figure 7 $E = 10^{-9}$, $\Delta T = 0.1$ *hr*
prediction of C_s *and adaptive controller*