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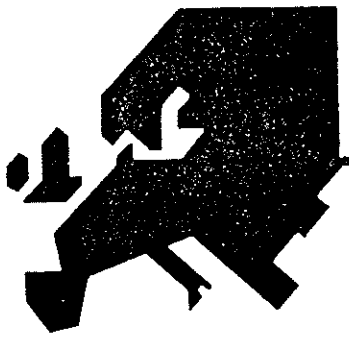


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OPTIMAL CONTROL OF THE PENICILLIN G FED-BATCH FERMENTATION : AN ANALYSIS OF THE MODEL OF BAJPAI AND REUß

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1 Abstract

Nowadays penicillin G is an almost common antibiotic; nevertheless the fermentation technology and the mathematical description of the production process are still a subject of interest. The optimization of product formation during fermentation as a part of total process control has gained a renewed attention (Spriet 1987).

This paper deals with the unstructured model proposed by Bajpai and Reuß (1980, 1981), that allows for the optimization of the final amount of product with respect to the substrate feeding rate.

In optimizing the glucose feeding rate for a given total amount of substrate, we shall consider different strategies with a varying number of degrees of freedom, going from a simple constant profile up to the solution obtained using Optimal Control theory. We shall verify—using simulations—the authors' statement that similar productivities can be obtained using any of these strategies, provided fermentations are carried out under optimal conditions corresponding to the strategy chosen.

The choice of a particular feeding strategy for this model can then be based on additional criteria, e.g. the need for on-line measurements and robustness properties.

2 Model of Bajpai and Reuß

2.1 Mathematical description

Bajpai and Reuß (1980, 1981) describe the penicillin-G fermentation by means of the following mechanistic model:

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

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

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

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

For an explanation of all symbols used we refer to the Nomenclature at the end of this paper. The specific growth rate is modeled by *Contois*-kinetics :

$$\mu = \mu_C \frac{C_s}{K_x C_x + C_s} \quad (5)$$

Hydrolysis of penicillin to penicilloic acid is modeled by a first-order decay reaction. For the specific production rate *substrate-inhibition* kinetics (Haldane) is used :

$$\pi = \pi_m \frac{C_s}{K_p + C_s + C_s^2/K_i} \quad (6)$$

As a consequence of balancing the specific substrate consumption rate is given by :

$$\sigma = \mu/Y_{x/s} + m_s + \pi/Y_{p/s} \quad (7)$$

which represents a *maintenance* metabolism.
Bajpai and Reuss have reported two *parameter sets*, according to different experimental results. They are shown in Table 1, together with the *initial* conditions we shall use in all simulations.

parameters					
	Set 1	*Set 2*		*Set 1*	*Set 2*
μ_C	0.092	0.11	K_x	0.15	0.006
π_m	0.005	0.004	k_h	0.04	0.01
K_p	0.0002	0.0001	K_i	0.1	0.1
$Y_{x/s}$	0.45	0.47	$Y_{p/s}$	0.9	1.2
m_s	0.014	0.029	s_F	500	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*

All simulations were done on a *VAX-VMS* system, using the *NAG*-routines *D02EBF* and *D02EHF* for stiff systems integration. The results of a simulation with a *constant* feed rate profile using parameter Set 2 are shown in Figure 1. With $S_0 = 0$ mol and $t_f = 120$ hr, $u(t) = 0.025$ L/hr corresponding to $\alpha = 1500$ g. The final amount of penicillin is $P_f = 59.65$ g.

2.2 A variant for the growth kinetics

Based on some experimental evidence, Bajpai and Reuß (1980, 1981) preferred Contois-kinetics over Monod-kinetics in modeling μ. However, *both* kinetics have been shown to be valid for fungal growth (Nihtilä and Virkkunen, 1977). From the *mathematical* point of view, it might be interesting to consider Monod-kinetics as well, as all specific rates become then functions of C_s only. Extensive simulations confirm that the transition from Contois- to Monod-kinetics does *not* cause fundamental changes in the dynamics of the variables.

So a useful alternative for (5) is :

$$\mu = \mu_M \frac{C_s}{K_s + C_s} \tag{8}$$

The equivalent kinetic constants μ_M and K_s can be calculated from (Van Impe et al. 1991a) :

$$\mu_M = \mu_C \frac{1}{1 - Y_{s/s} K_x} \tag{9}$$

$$K_s = K_x \frac{Y_{s/s}}{1 - Y_{s/s} K_x} (C_{s,0} + C_{x,0}/Y_{s/s}) \tag{10}$$

Observe that K_s depends on the initial state ! With e.g. $S_0 = 560$ g and $X_0 = 10.5$ g, we obtain :

$$\mu_M = 0.110 \tag{11}$$

$$K_s = 0.203 \tag{12}$$

For simplicity, we have used the above values in *all* simulations involving Monod-kinetics, thus neglecting the dependence on the initial state.

As an example, a simulation with the same operational conditions as mentioned above results in a final amount of product $P_f = 58.77$ g.

3 The optimization problem

An obvious choice for a state space vector is (the superscript "T" denotes the transpose of a vector) :

$$\mathbf{x} \triangleq (\ S \quad X \quad P \quad V\ )^{\mathrm{T}} \tag{13}$$

and with the definition of :

$$\mathbf{f} \triangleq (\ -\sigma X \quad \mu X \quad \pi X - k_h P \quad 0\ )^{\mathrm{T}} \tag{14}$$

$$\mathbf{b} \triangleq (\ s_F \quad 0 \quad 0 \quad 1\ )^{\mathrm{T}} \tag{15}$$

we obtain a state space model linear in the control u :

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}) + \mathbf{b}u \tag{16}$$

$x_{2,0}$ and $x_{3,0}$ are given, $x_{1,0}$ and $x_{4,0}$ are related by (V_s denotes the given initial volume *without* substrate) :

$$x_{4,0} = V_s + x_{1,0}/s_F \tag{17}$$

Glucose is added as a solution with concentration s_F.

The optimisation problem is to determine for the given set of state equations (16) the optimal feed rate profile that minimises the performance index :

$$J(u) = g(\mathbf{x}(t_f)) \triangleq -P(t_f) \tag{18}$$

i.e. maximises the final amount of product, subject to the following constraints :
- $t_0 = 0$, t_f = free
- all variables have to be kept positive :

$$x_i(t) \geq 0,\ i = 1, \ldots, 4\ \wedge\ u(t) \geq 0,\ \forall t \in [0, t_f] \tag{19}$$

- the initial amount of substrate is *free*; the initial conditions $x_{1,0}$ and $x_{4,0}$ are only constrained by equation (17).

In other words, some initial conditions can be manipulated to minimize the performance measure, so (18) should be replaced by:

$$J \equiv J(u, \mathbf{x}_0) = -x_3(t_f) \tag{20}$$

- the total amount of feed is fixed, i. e. :

$$x_{1,0} + s_F \int_{t_0}^{t_3} u(t)\, dt = \alpha \tag{21}$$

where t_3 is the last time for which $u(t) > 0$. This *isoperimetric* constraint on the input is equivalent to a *physical* constraint of the form—due to (4)—:

$$x_{4,f} \equiv V(t_f) = V_f,\ V_f \text{ fixed} \tag{22}$$

4 Polynomial Control

If we propose a feeding strategy of the form :

$$s_F u(t) = \sum_{i=0}^{N} a_i t^i \tag{23}$$

then the above optimisation problem is equivalent to finding optimal values for the polynomial coefficients a_i, $i = 1 \ldots N$: *parametric* optimisation of a controller with *predetermined structure*. Initial work in this field has been reported by Van Gompel and Spriet (1988).

From (21) we know that, once α has been fixed, t_3 can be considered as an additional degree of freedom. Optimising t_3 implies that not all coefficients a_i are independent, as (21) must be satisfied. We can write e.g. :

$$a_0 = \frac{\alpha - x_{1,0}}{t_3} - \sum_{i=1}^{N} \frac{a_i}{i+1} t_3^i \tag{24}$$

After $t = t_3$, the fermentation continues in *batch*-mode ($u(t) = 0$), until the net penicillin formation rate dP/dt becomes zero at $t = t_f$. Obviously, the optimisation of $x_{1,0}$ (and thus of $x_{4,0}$ too) can be easily included in the algorithm.

The combined optimisation of a_i, $i = 1 \ldots N$, $x_{1,0}$ and t_3 has been done—after an appropriate rescaling—with a minimisation algorithm proposed by Brent (1973).

5 Optimal Control

5.1 Statement of the TPBVP

The Hamiltonian H for this problem is given by (λ is the vector of *adjoint* variables) :

$$H = \lambda^{\mathrm{T}}(\mathbf{f}(\mathbf{x}) + \mathbf{b}u) \triangleq \phi + \psi u \tag{25}$$

$$\phi = \lambda_1 f_1 + \lambda_2 f_2 + \lambda_3 f_3 \qquad \psi = s_F \lambda_1 + \lambda_4 \tag{26}$$

The adjoint vector λ satisfies the following system of differential equations :

$$\frac{d\lambda}{dt} = -\frac{\partial H}{\partial \mathbf{x}} = -\frac{\partial \mathbf{f}}{\partial \mathbf{x}}^{\mathrm{T}} \lambda \tag{27}$$

Together with the state equations (16), we obtain a system of $2 \times n$ first order differential equations—where n denotes

the dimension of the state vector $\mathbf{x}$, here $n = 4$—which needs of course $2 \times n$ boundary conditions. These can be specified as follows :
- $x_{2,0}$ and $x_{3,0}$ are given
- $x_{1,0}$ and $x_{4,0}$ are interrelated by equation (17)
- $x_{4,f}$ is given due to equation (22)
- $\lambda_{i,f}$, $i = 1, \ldots, 3$ are given by $\lambda_{i,f} = \frac{\partial g}{\partial x_i}(t_f)$:

$$\begin{pmatrix} \lambda_{1,f} & \lambda_{2,f} & \lambda_{3,f} \end{pmatrix}^{\mathrm{T}} = \begin{pmatrix} 0 & 0 & -1 \end{pmatrix}^{\mathrm{T}} \qquad (28)$$

It should be clear that we need still another boundary condition, as $x_{1,0}$ and $x_{4,0}$ are not given explicitly. The missing condition is given by (Van Impe et al. 1990) :

$$\psi(0) \equiv s_F \lambda_{1,0} + \lambda_{4,0} = 0 \qquad (29)$$

An *extremal* control $u^*(t)$ follows from the minimization of the Hamiltonian H over all *admissible* control functions (Pontryagin's Minimum Principle) :

$$\min_{\text{all admiss } u} H(\mathbf{x}^*, \lambda^*, u) = H(\mathbf{x}^*, \lambda^*, u^*) \qquad (30)$$

Since the state equations (16) and the cost index (20) are time-invariant, H remains constant along an optimal trajectory. As the final time t_f is free, we know that $H = 0$.

5.2 Computational algorithm

Optimal Control with bounded input and fixed initial state

As a first step in the solution, we shall solve the given problem subject to an *additional* constraint on the input ($0 \leq u(t) \leq U_{max}$, U_{max} given), and with the *complete* initial state being given (say $x_{1,0} = 0$, so $x_{4,0} = V_*$, and condition (29) is superfluous).

As H is *linear* in the control u, we know by Pontryagin's Minimum Principle that our problem has become a *Bang-Singular-Bang* problem :

$$u(t) = \begin{cases} U_{max} & \text{if } \psi < 0 \\ u_{sing} & \text{if } \psi = 0 \\ 0 & \text{if } \psi > 0 \end{cases} \quad t_i \leq t \leq t_{i+1} \qquad (31)$$

On any *singular* interval $[t_i, t_{i+1}]$, the *singular* control is obtained by repeatedly differentiating the function ψ until u appears explicitly :

$$\frac{d\psi}{dt} = \dot{\lambda}^{\mathrm{T}}\mathbf{b} = -\lambda^{\mathrm{T}}\frac{\partial \mathbf{f}}{\partial \mathbf{x}}\mathbf{b} \triangleq \lambda^{\mathrm{T}}\mathbf{d} = 0 \qquad (32)$$

$$\frac{d^2\psi}{dt^2} = -\lambda^{\mathrm{T}}\frac{\partial \mathbf{f}}{\partial \mathbf{x}}\mathbf{d} + \lambda^{\mathrm{T}}\frac{\partial \mathbf{d}}{\partial \mathbf{x}}(\mathbf{f} + \mathbf{b}u) = 0 \qquad (33)$$

The last equation can be solved for u_{sing}:

$$u_{sing}(t) = \frac{\lambda^{\mathrm{T}}((\partial \mathbf{f}/\partial \mathbf{x})\mathbf{d} - (\partial \mathbf{d}/\partial \mathbf{x})\mathbf{f})}{\lambda^{\mathrm{T}}(\partial \mathbf{d}/\partial \mathbf{x})\mathbf{b}} \qquad (34)$$

Remark that in this case the denominator of the above expression is indeed different from zero. Obviously, this problem is a *singular problem of order 2*.

Note that both the numerator and the denominator are *linear* in the costate λ. On any singular interval, the optimal control is a *nonlinear feedback law of the state-variables only*, as there are three linear homogeneous equations in the *costate*-variables :

$$\psi \equiv \lambda^T \mathbf{b} = 0 \quad \frac{d\psi}{dt} \equiv \lambda^T \mathbf{d} = 0 \quad \phi \equiv \lambda^T \mathbf{f} = 0 \qquad (35)$$

We conclude that the *Two Point Boundary Value Problem (TPBVP)* has been reduced to the determination of the *optimal sequence* and the corresponding *switching times*. The solution to this problem starts from the following *model-independent* conjecture (based on reported fermentation data) :

Conjecture 1 *The feed rate profile must be determined so that during the growth phase the cells grow as fast as possible, while during the production phase the cells are forced to produce the desired product as much as possible.*

The resulting straightforward algorithm can be seen as a modification of the one proposed by Lim et al. (1986). However, simulations have indicated that our scheme is numerically more reliable, as it does not use any costate variable at all. In the case of small initial values S_0 and X_0, we have the following algorithm :

Algorithm

Step 1 : Make a guess of t_1, or equivalently, determine the amount of substrate reserved to the growth-phase. Integrate the state equations (16) from $t = 0$ to $t = t_1$ with $u(t) = U_{max}$.
Step 2 : Make a guess of t_2. Integrate the state equations from $t = t_1$ to $t = t_2$ with $u(t) = 0$. This completes the *growth*-phase.
Step 3 : Integrate the state equations using the above determined singular control (34) until condition (22) is met at $t = t_3$.
Step 4 : Complete the integration with $u(t) = 0$ until dP/dt becomes 0 at $t = t_f$ (as $H(t_f) \equiv \phi(t_f) \equiv -f_3(t_f) = 0$), and store the value of the cost index $J(u, \mathbf{x}_0)$ (20). This completes the *production*-phase.
Step 5 : Repeat Step 2 to 4, considering $t_{2,new} = t_{2,old} \pm \delta t$, with δt as small as required. Save the time t_2 for which $J(u, \mathbf{x}_0)$ reaches its minimum.
Step 6 : Repeat Step 1 to 5 with a new guess of t_1 in order to minimise $J(u, \mathbf{x}_0)$. For the problem at hand, a linear search method for t_1 has been chosen.
A detailed mathematical justification for this algorithm has been given in an other paper (Van Impe et al. 1990).

O. C. with unbounded input and some initial states free

In (Van Impe et al. 1990), it is shown how to solve the *original* problem considering the limits $U_{max} \to \infty$ and $t_1 \to 0$. The growth-phase becomes a *batch*-phase ($u(t) = 0$). In the above computational algorithm, the only modification is to replace the time t_1 by the *equivalent* initial condition $x_{1,0}$. In other words, the *TPBVP* has been reduced to the *two-dimensional optimization of S_0 and t_2*.

Additional properties of the O. C.

If μ is modeled by *Monod*-kinetics, we have :

$$k_h = 0 \Leftrightarrow \begin{cases} (1)\ C_s(t_2) \text{ maximizes } \pi(C_s)/\sigma(C_s) \\ (2)\ C_s \text{ constant during singular control} \end{cases}$$

(Staniskis and Levisauskas, 1984; Van Impe et al. 1991b) If μ is modeled by *Contois*-kinetics, we have :

$$k_h = 0 \Leftrightarrow C_s(t_2) \text{ maximizes } \pi(C_s)$$

(Modak et al. 1986; Van Impe et al. 1991b)
Note that in both cases, the *complete* optimal control is in closed-loop for a given value of $x_{1,0}$.

6 Heuristic control strategies

The construction of a suboptimal profile is based principally on the concept of a *biphasic* fermentation (see Conjecture 1). Some of the ideas concerning *heuristic C_s-control* are reported elsewhere (Bonte et al. 1989; Van Impe et al. 1990, 1991c).
For the control during *growth*, we refer to the previous section : 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 (5) or (8)).

During *production*, we focus on the specific rate π. Equation (6) 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) :

$$u_{prod} = \frac{\sigma X}{s_F - C_s} \tag{36}$$

As a consequence, the *conjunction* point t_2 of growth and production is simply dictated by the condition $C_s = C_{s,crit}$. The control is stopped at $t = t_3$ when all substrate 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 S_0. As a result, the optimization problem is reduced to the *one-dimensional optimization of S_0*.
A further refinement of this strategy exists in *optimizing* the switching time t_2. In other words, during production C_s is kept constant, but not necessarily at $C_s = C_{s,crit}$. As in the case of Optimal Control, a *two-dimensional optimization of S_0 and t_2* is obtained.

Remark that for μ modeled with *Monod*-kinetics, the control (36) also keeps μ constant during production. An equivalent *heuristic μ-control* for *Contois*-kinetics follows from the condition $d\mu/dt = 0$:

$$u_{prod} = \frac{\sigma X + \mu S}{s_F} \tag{37}$$

As a result of the previous section we have : if μ is modeled with *Monod*-kinetics and if we switch on $C_s(t_2)$ which maximizes $\pi(C_s)/\sigma(C_s)$, then—for S_0 fixed—the *heuristic* controller (36) *coincides* with the *optimal* one, if and only if $k_h = 0$.

7 Simulation results

The simulation results for both parameter sets of Table 1 are summarized in Table 2. As for the *polynomial* strategies, we have considered the following cases : (1) $N = 0$ (constant strategy) : $x_{1,0}$ and t_3 are free; a_0 follows then from (24). (2) $N = 1$ (linear strategy) : $x_{1,0}$, t_3 and a_1 are free.

Observe that, for parameter Set 1, there is almost no difference between the *heuristic C_s-control* with switching on $C_s = \sqrt{K_p K_i}$, and the *optimal control*. For this reason we do not mention the results for the other heuristic strategies.

Figure 2 shows the *optimal* feeding strategy and the corresponding time profiles, for parameter Set 2. In Figure 3, the different control strategies for the same parameter set are shown.

Parameters	*Set 1*		*Set 2*	
Polynomial Control				
	$N = 0$	$N = 1$	$N = 0$	$N = 1$
S_0 (g)	639	672	235	279
a_1 (g/hr^2)	–	$4.29\ 10^{-3}$	–	$8.25\ 10^{-3}$
t_3 (hr)	106.093	99.281	131.941	132.042
t_f (hr)	106.094	99.288	131.942	132.044
P_f (g)	42.435	43.730	63.738	63.843
Heuristic C_s-Control	$C_s(t_2) = \sqrt{K_p K_i}$			
S_0 (g)	1053		533	
t_2 (hr)	44.457		28.355	
t_f (hr)	96.636		131.323	
P_f (g)	44.926		63.597	
Heuristic C_s-Control	$C_s(t_2)$ *optimized*			
S_0 (g)	–		551	
t_2 (hr)	–		28.644	
t_f (hr)	–		131.372	
P_f (g)	–		63.724	
Heuristic μ-Control	$\mu(t_2)$ *optimized*			
S_0 (g)	–		551	
t_2 (hr)	–		28.644	
t_f (hr)	–		131.321	
P_f (g)	–		63.736	
Optimal Control				
S_0 (g)	1053		528	
t_2 (hr)	44.457		28.271	
t_f (hr)	96.636		132.033	
P_f (g)	44.926		63.846	

Table 2 *Numerical results*

8 Discussion & Conclusions

In this paper we have investigated the substrate feeding rate optimization problem for the penicillin G fermentation, using the model of Bajpai and Reuß. We have compared different *suboptimal strategies* with the *optimal control* solution. The above simulation results illustrate that, *using any of these strategies, we can obtain productivities similar to the optimal ones, provided the associated degrees of freedom are at their optimal values.*

As this conclusion holds true for the two widely different parameter sets of Table 1, we might expect the same result for any parameter set "between" them. In other words, this property is rather related to the model *structure* than to the model *parameters*.

As a consequence, the choice for a particular feeding strategy can be based on other criteria.

It is well-known that putting an *optimal control* into practice may be hampered by a lot of problems. If the control law is not obtained in complete closed-loop form—as is the case here—, it cannot compensate for unmodeled disturbances, parameter variations, ... Further on, as Optimal Control is a very model-sensitive technique, a *feed-forward* shall not generate the predicted results. As long as a sufficiently accurate model for the penicillin fermentation is not available, the determined profiles can be used only to obtain a greater qualitative insight in the process.

On the other hand, the *suboptimal heuristic* profiles we present here are the translation of a more realistic control objective, namely *setpoint* control. The simulation results indicate that these strategies have an excellent performance. Further on, there is no a need for a complete measurement of the state, a problem which has not been solved completely up to now.

As for the *robustness* of the strategies considered in this paper, we have made the following simulation experiment. Asssume that—for parameter Set 1—the "real" value of μ_C is 0.0736 (−20 %), and K_x = 0.18 (+20 %). Feed-forward of the polynomial controllers results in P_f = 32.665 g for N = 0, and P_f = 32.788 g for N = 1. The closed-loop implementation of the heuristic C_s-controller results in P_f = 44.250 g. For parameter Set 2, the results for μ_C = 0.088 (−20 %) and K_x = 0.0072 (+20 %) are respectively P_f = 63.151 g, P_f = 63.287 g and P_f = 63.205 g. Although the results seem to be dependent on the parameter set used, it is well known that the feed-forward polynomial controllers *in general* have poor robustness properties. On the other hand, the heuristic C_s-controller in closed-loop is very sensitive to disturbances on the control itself : e.g. using parameter Set 2, a positive step disturbance on u with amplitude 10^{-3} L/hr at time t = 90 hr results in 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 !

However, we have shown in an other paper that the heuristic controllers can serve well as a basis for the development of more reliable *conventional* (*PID*-based) and even *adaptive* model-independent controllers, with excellent robustness properties (Van Impe et al. 1991d).

Nomenclature

t	: 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)
C_p	: product concentration in broth (g/L)
s_F	: substrate concentration in feed stream (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)
α	: amount of glucose available for fermentation (g)
σ	: specific substrate consumption rate (g/g DM hr)
μ	: specific growth 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)

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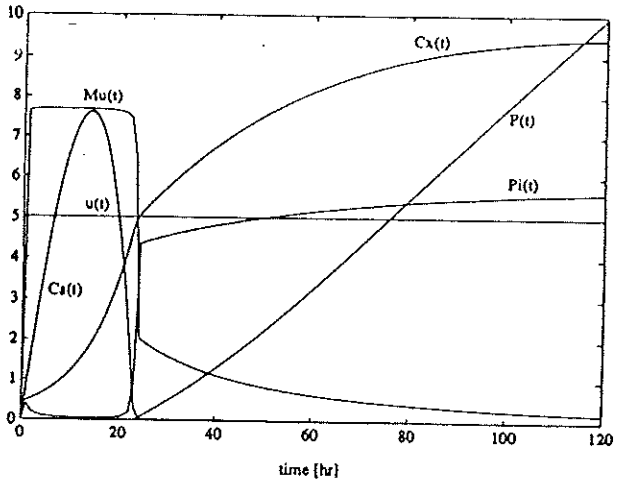
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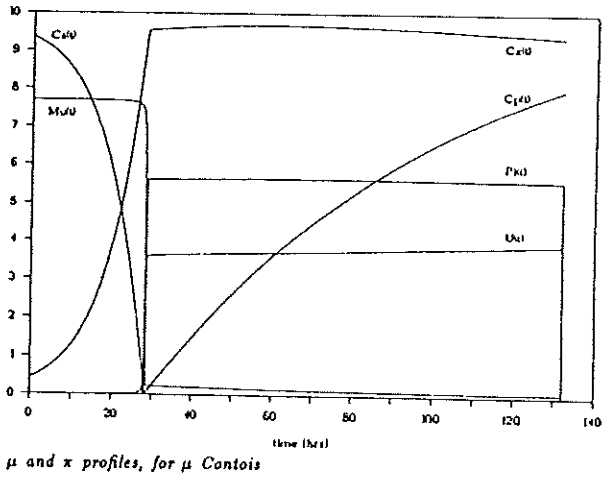
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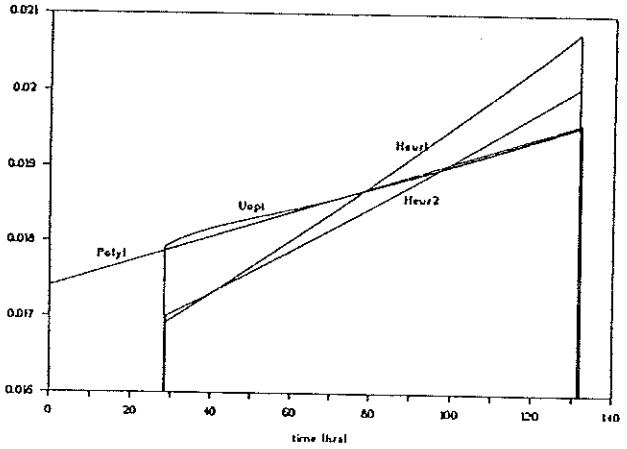
Scaling :
P (g) /6
C_s (g/L) /1.5
C_x (g/L) /3.5
μ (hr^{-1}) *70
π (g/g DM hr) *1500
u (L/hr) *200

Figure 1 *Constant glucose feed rate and corresponding cell, glucose, product, μ and π profiles*



Scaling :
C_p (g) *1.25
C_s (g/L) /7
C_x (g/L) /3
μ (hr^{-1}) *70
π (g/g DM hr) *1500
u (L/hr) *200

Figure 2 *Optimal glucose feed rate and corresponding cell, glucose, product, μ and π profiles, for μ Contois and parameter Set 2*



Legend :
Poly1 : *Polynomial Controller with $N = 1$*
Heur1 : *Heuristic C_s-controller - $C_s(t_2) = \sqrt{K_p K_i}$*
Heur2 : *Heuristic C_s-controller - $C_s(t_2)$ optimized*
Uopt : *Optimal Controller*

Figure 3 *Suboptimal and Optimal glucose feed rate profiles, for μ Contois and parameter Set 2*