

Characterization of Optimal Feed Rate Profiles for Fed-batch Fermentation Processes

Jan F. VAN IMPE** Johan E. CLAES* Vincent G. RYCKAERT*
 *Laboratory for Industrial Microbiology and Biochemistry °ESAT - Department of Electrical Engineering
 Katholieke Universiteit Leuven Kardinaal Mercierlaan 92, B-3001 Leuven (BELGIUM)

Georges BASTIN
 CESAME - Center for Systems Engineering and Applied Mechanics
 Université Catholique de Louvain Avenue Georges Lemaitre 4-6, B-1348 Louvain-la-Neuve (BELGIUM)

Abstract — We consider the optimization of fed-batch fermentation processes involving one limiting substrate for biomass growth and product synthesis, with respect to the volumetric feed rate of this substrate. Until now classification of these processes —and thus also the determination of the corresponding optimal feed rate strategy— has been based only on the qualitative behavior of the specific rates for growth and production as functions of substrate concentration. In this paper we illustrate that the optimal control sequence largely depends on other model characteristics as well, such as the value of the product degradation constant. A detailed optimization study for all possible combinations of the specific rates for growth and production reveals that the typical biphasic behavior of processes with growth/production decoupling disappears if product degradation is not modeled. In this sense numerical optimization can prove very useful in solving the model structure discrimination problem.

FED-BATCH FERMENTATION PROCESSES WITH PRODUCT FORMATION

Mathematical model

Consider a biotechnological process in a stirred tank reactor operated in fed-batch described by the following set of equations:

$$\begin{aligned} \frac{dS}{dt} &= -\sigma X + C_{S,in} u \\ \frac{dX}{dt} &= \mu X \\ \frac{dP}{dt} &= \pi X - k P \\ \frac{dV}{dt} &= u \end{aligned} \quad (1)$$

with S [g] the amount of substrate, X [g DW] the amount of biomass, P [g] the amount of product, V [L] the volume of the liquid phase, $C_{S,in}$ [g/L] the substrate concentration in the volumetric feed rate u [L/h], σ [g/g DW h] the specific substrate consumption rate, μ [1/h] the specific growth rate, π [g/g DW h] the specific production rate, and k [1/h] the product degradation constant. There is no dynamic equation for dissolved oxygen, as dissolved oxygen is considered

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non-limiting by maintaining a sufficiently high aeration level. The three specific rates σ , μ , and π are interrelated by the following linear law:

$$\sigma = \frac{1}{Y_{X/S}} \mu + m + \frac{1}{Y_{P/S}} \pi \quad (2)$$

with $Y_{X/S}$ [g DW/g] the biomass on substrate yield coefficient, $Y_{P/S}$ [g/g] the product on substrate yield coefficient, and m [g/g DW h] the specific maintenance demand. Notice that the mathematical model (1)-(2) can describe any metabolism for maintenance of living biomass.

Fed-batch fermentation processes have been found to be most effective in overcoming such effects as substrate inhibition, catabolite repression, and glucose effects. In other words, whenever the specific rates of growth (μ) and/or production (π) are non-monotonic functions of the limiting substrate concentration, a fed-batch operation may be superior and it is then necessary to determine the optimal feed rate of substrate.

Optimization of $P(t_f)$

The optimization problem we consider in this paper can be stated as follows. Determine the optimal volumetric feed rate $u^*(t)$ which minimizes the following performance index:

$$u(t), t \in [0, t_f] \quad J[u] \triangleq -P(t_f) \quad (3)$$

i.e., maximizes the final product amount $P(t_f)$, subject to:

1. $t_0 = 0$, t_f is free
2. $X(0) = X_0$, $P(0) = 0$
3. $S(0)$ is free; $V(0) = V_0 + S(0)/C_{S,in}$ with V_0 the initial volume without substrate. Note that substrate is added as a solution with concentration $C_{S,in}$.
4. $V(t_f) = V_{MAX}$, i.e., the final volume is fixed. Observe that this physical constraint is equivalent to fixing the total amount of substrate available α (see the differential equation for V):

$$S(0) + \int_0^{t_f} C_{S,in} u(t) dt = \alpha$$

5. $0 \leq u(t) \leq U_{MAX}$, i.e., the feeding pump capacity is limited.

The yield \mathcal{Y} is defined as the ratio of the final product amount $P(t_f)$ to the total substrate amount α added. If we fix α , then minimizing performance index (3) is equivalent to maximizing the yield \mathcal{Y} .

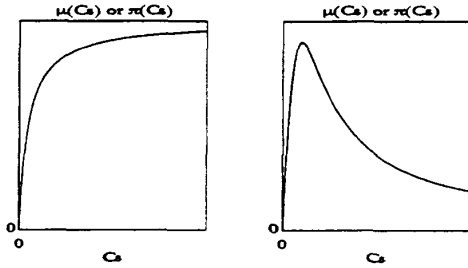


Figure 1: Monotonic and non-monotonic specific rates

Optimal control solution

A detailed analysis of this problem, by using Pontryagin's Minimum Principle, can be found in [1]. Initial work along the same lines has been reported in [2]. The optimal control profile $u^*(t)$ consists of intervals of feeding at the maximum rate $u(t) = U_{MAX}$ and at the minimum rate $u(t) = 0$, and so-called *singular* intervals during which the manipulated variable follows a very specific, time-varying pattern $u(t) = u_{sing}(t)$. The determination of the *optimal control sequence* $[U_{MAX}, 0, u_{sing}]$ and the corresponding *switching times* basically depends on the *qualitative behavior* of the specific rates μ and π as functions of substrate concentration $C_S \equiv S/V$ [1],[2]. We can distinguish between the following cases.

- **Case I: monotonic μ and non-monotonic π**
This type is most common, in which cell growth follows a monotonic kinetics (left plot of Figure 1) while product formation is inhibited or repressed (right plot of Figure 1). Typical examples are production of amino-acids and pharmaceuticals.
- **Case II: non-monotonic μ and monotonic π**
In this case, μ behaves as shown in the right plot of Figure 1, while π behaves as in the left plot. Examples include glutamic acid fermentation on ethanol and vitamin B_{12} fermentation.
- **Case III: non-monotonic μ and non-monotonic π**
In this least common case, both μ and π behave as shown in the right plot of Figure 1. An example is ethanol fermentation from fructose.
- **Case IV: monotonic μ and monotonic π**
To complete the analysis this case must be considered as well. Both μ and π behave as shown in the left plot of Figure 1.

If the synthesis of the product of interest P is directly associated to biomass growth, i.e., if

$$\pi \triangleq Y_{P/X} \mu$$

with $Y_{P/X}$ [g/g DW] the product on biomass yield coefficient, then P is a so-called primary metabolite and product formation is of the *growth associated* type. Observe that this special case can occur within Case III and Case IV.

On the other hand, secondary metabolites are compounds produced through special enzymatic reactions that apparently have no direct relation to growth of biomass: the enzyme catalyzed production is *not associated* to the microbial growth. These processes are characterized by a *decoupling* between growth and product formation. The first phase is characterized by rapid cell growth with almost no product

parameters			
$Y_{X/S}$	0.47	$Y_{P/S}$	1.2
m	0.029	$C_{S,in}$	500
initial conditions			
X_0	10.5	S_0	to be optimized
P_0	0	V_0	$7 + S_0/C_{S,in}$
t_0	0	α	1500

Table 1: Model parameters and initial conditions

synthesis, while during the production phase the product of interest is formed with only limited growth.

Until now classification of these processes –and thus also the determination of the corresponding optimal feed rate strategy– has been based on the qualitative behavior of the specific rates μ and π only (see, e.g., [1] and [2]). In this paper we illustrate that the *optimal control sequence largely depends on other model characteristics as well*, such as

1. the value of the product degradation constant k [eqs. (1)]
2. the value of the specific maintenance demand m [see the linear law (2)] and the type of metabolism (exogenous, endogenous, or mixed exogenous/endogenous).

For now we only focus on the first item, i.e., on the *possible influence of the product degradation constant k on the optimal control sequence*, while the metabolism mechanism is always assumed to be of the exogenous type (often called *maintenance metabolism*). This means that maintenance requirements are completely fulfilled by consumption of the substrate source S .

A more detailed analysis, together with a description of the influence of the specific maintenance demand m (and the corresponding *endogenous fraction*) upon optimization results, can be found in Reference [3].

During all simulations the model parameters and initial conditions summarized in Table 1 have been used.

We assume that the specific rates μ and π are functions of substrate concentration C_S only. When modeling a *monotonic* specific growth rate, a *Monod* type model has been used:

$$\mu \triangleq \mu_m \frac{C_S}{K_{M,\mu} + C_S} \quad (4)$$

or, equivalently, for the specific production rate:

$$\pi \triangleq \pi_m \frac{C_S}{K_{M,\pi} + C_S} \quad (5)$$

with μ_m [1/h] and π_m [g/g DW h] the maximum specific rate for growth and production respectively, and $K_{M,\mu}$ [g/L] and $K_{M,\pi}$ [g/L] the Monod saturation constant for substrate limitation of growth and production respectively. This Monod type kinetics reaches its maximum value for substrate concentration C_S going to ∞ . When modeling a *non-monotonic* specific rate, the following *Haldane* type expressions have been used:

$$\mu \triangleq \mu_m \frac{C_S}{K_{M,\mu} + C_S + C_S^2/K_{I,\mu}} \quad (6)$$

$$\pi \triangleq \pi_m \frac{C_S}{K_{M,\pi} + C_S + C_S^2/K_{I,\pi}} \quad (7)$$

with $K_{I,\mu}$ [g/L] and $K_{I,\pi}$ [g/L] the substrate inhibition constant for growth and production respectively. Observe that

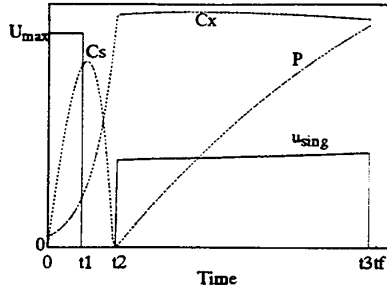


Figure 2: Case I - optimal control profiles

for Haldane type kinetics, μ_m does *not* represent the maximum value. Instead, the maximum value is given by

$$\max(\mu) = \mu_m \frac{1}{1 + 2\sqrt{K_{M,\mu}/K_{I,\mu}}}$$

and occurs at the substrate concentration $C_{S,\mu}$

$$C_{S,\mu} \triangleq \sqrt{K_{M,\mu} K_{I,\mu}}$$

and analogous expressions for $\max(\pi)$ and $C_{S,\pi}$.

CASE I: MONOTONIC μ AND NON-MONOTONIC π

Optimal control strategy

Application of the Minimum Principle leads to the following optimal control sequence (see also Figure 2):

1. The first phase $[0, t_2]$ is the *growth phase*. Since μ is monotonically increasing, the substrate available for biomass growth, denoted with S_{growth} , must be added as fast as possible in order to ensure rapid biomass accumulation. Therefore, during the interval $[0, t_1]$ the feed rate is at its maximum value, i.e., $[u^*(t) = U_{MAX}]$, whereafter a batch phase follows $[u^*(t) = 0, t_1 < t < t_2]$. As a limiting case, all substrate for growth S_{growth} can be added all at once at time $t = 0$, thus ensuring the highest possible specific growth rate μ for all $t \in [0, t_2]$, with a low production rate.
2. During the second phase, the *production phase*, a *singular control* $[u_{sing}(t), t_2 < t < t_3]$ 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 possibly maintenance, thus ensuring the lowest possible growth rate. When $V(t_3) = V_f$, the fermentation continues in *batch* $[u^*(t) = 0, t_3 < t < t_f]$ until the net product formation rate dP/dt equals zero at $t = t_f$.

The singular control is given by:

$$u_{sing} = \frac{\sigma C_X V}{C_{S,in} - C_S} + k \mathcal{F}(S, X, P, V) \quad (8)$$

where \mathcal{F} is a complicated function of S , X , P , and V . An excellent approximation results when neglecting product degradation in calculating u [1]:

$$u_{heur} = \frac{\sigma C_X V}{C_{S,in} - C_S} \quad (9)$$

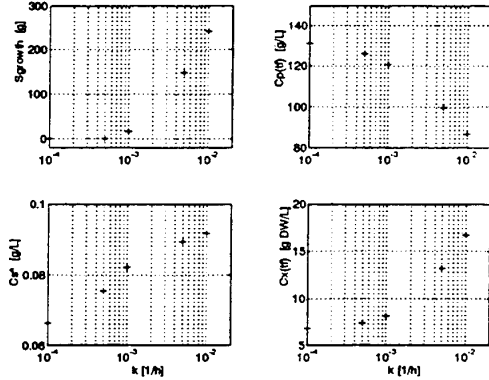


Figure 3: Case I - optimal values for $k \rightarrow 0$

This *heuristic* controller keeps substrate concentration C_S constant at some value C_S^* , which plays the role of a *set-point*. From a mathematical point of view, this can be justified by the following Theorem for the performance measure under consideration (3) [1]:

Theorem 1 *Physical interpretation of singular control*

If σ , μ , and π are functions of C_S only, with continuous second derivatives

Then during singular control:

1. C_S remains constant $\Leftrightarrow k = 0$,
2. C_S satisfies:

$$\frac{d}{dC_S} \left(\frac{\pi}{\sigma} \right) = 0$$

Observe that in the case where product degradation k equals zero, the *heuristic* controller coincides exactly with the *optimal control sequence*.

In summary, the optimal control problem reduces to the *two dimensional optimization* of (i) the switching time t_1 , or more generally, the fraction S_{growth} of the total substrate amount available α , and (ii) the switching time t_2 , or in the case of heuristic control, the set-point C_S^* for substrate concentration during production.

Optimal control for $k \rightarrow 0$

The optimal values of S_{growth} and C_S^* , and the corresponding values for $C_X(t_f)$ and $C_P(t_f)$ are shown in Figure 3 for decreasing values of the product degradation constant k . The following observations can be made.

1. When k decreases, the amount of substrate consumed during growth S_{growth} decreases too. In the limit, when $k = 0$, we have $S_{growth} = 0$. This means that there is no growth phase at all, i.e., the *characteristic biphasic behavior has disappeared completely*. In other words, it is then better to start production right from the beginning by singular feeding than to consume part of the substrate available for biomass build-up.
2. When $k \rightarrow 0$, the set-point for substrate concentration during production C_S^* reaches the value $C_{S,\pi/\sigma}$, i.e., the value which maximizes the ratio π/σ (Theorem 1). This also illustrates that the heuristic control coincides with the optimal control if $k = 0$.

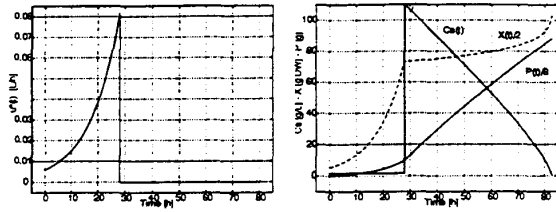


Figure 4: Case II - optimal control profiles

CASE II: NON-MONOTONIC μ AND MONOTONIC π

Optimal control strategy

The following optimal control sequence is obtained:

1. The first phase is the *growth* phase. Since μ is non-monotonic, a singular control [$u^*(t) = u_{sing}(t)$] is required to ensure rapid biomass accumulation. If the initial substrate amount S_0 is free, the optimal choice is such that $C_S(0) \equiv S_0/V_0$ satisfies the singular arc conditions.
2. In order to start the *production* phase, substrate concentration must be as high as possible since π is monotonically increasing. Therefore, the feed rate must be set to its maximum level [$u^*(t) = U_{MAX}$] until the remaining substrate available for production ($\alpha - S_{growth}$) has been added ($V = V_f$), whereafter a batch phase [$u^*(t) = 0$] follows until the net product formation rate dP/dt equals zero at $t = t_f$. As a limiting case, all remaining substrate for production ($\alpha - S_{growth}$) is added all at once at the beginning of the production phase (*Dirac impulse*) (Figure 4), thus ensuring the highest possible specific production rate π .

As in Case I, the singular control (8) –which now occurs during the growth phase– can be replaced by an easier to implement heuristic controller (9) which keeps substrate concentration constant at some prespecified set-point C_S^* . Since

$$S(0) \leq S_{growth}$$

the following boundaries on the admissible values of C_S^* can be easily deduced

$$0 \leq C_S^* \leq C_{S,in} \frac{S_{growth}}{C_{S,in} V_0 + S_{growth}}$$

In summary, the optimal control problem reduces to a *two dimensional optimization problem*, in this case of (i) the fraction S_{growth} of the total substrate amount available α , and (ii) the set-point C_S^* for substrate concentration during growth.

Optimal control for $k \rightarrow 0$

The optimal values of S_{growth} and C_S^* , and the corresponding values for $C_X(t_f)$ and $C_P(t_f)$ are shown in Figure 5 for decreasing values of the product degradation constant k . Similar observations as in Case I can be made.

1. When k decreases, S_{growth} decreases too. In the limit, when $k = 0$, we have $S_{growth} = 0$. This means that there is no growth phase at all, i.e., the *characteristic biphasic behavior has disappeared completely*. It is then better to start production right from the beginning by feeding all substrate available α as fast as possible.

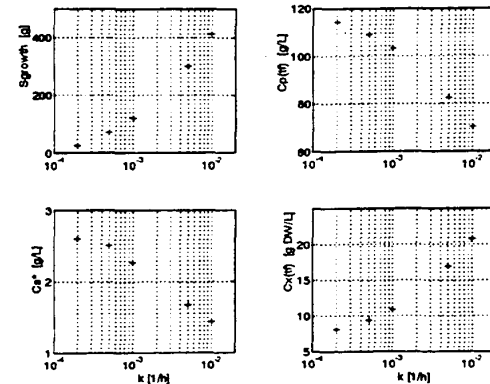


Figure 5: Case II - optimal values for $k \rightarrow 0$

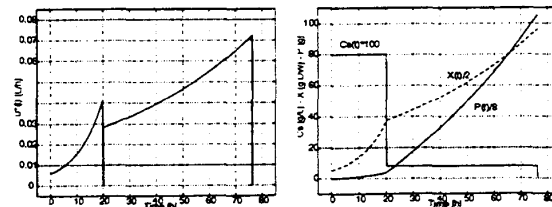


Figure 6: Case III - optimal control profiles

2. As a result, when $k \rightarrow 0$, there is no need for a set-point for substrate concentration during growth C_S^* . This corresponds to the fact that there are no real positive roots which satisfy $d(\pi/\sigma)/dC_S = 0$ [3].

CASE III: NON-MONOTONIC μ AND NON-MONOTONIC π

Optimal control strategy

Since both μ and π are non-monotonic functions of substrate concentration, the optimal control sequence basically consists of two singular phases (Figure 6). They are linked together by a (short) interval of feeding at the maximum or the minimum rate, depending on whether or not substrate concentration during production is higher than during growth. Again, both singular controls can be replaced by heuristic controllers of the form (9), which keep substrate at the desired set-points $C_{S,\mu}^*$ and $C_{S,\pi}^*$ for growth and production respectively. Similar boundaries on these set-points as in Case II can be deduced.

In summary, the optimal control problem reduces to the *three dimensional optimization* of (i) the fraction S_{growth} of the total substrate amount available α , (ii) the set-point $C_{S,\mu}^*$ for substrate concentration during growth, and (iii) the set-point $C_{S,\pi}^*$ for substrate concentration during production.

Optimal control for $k \rightarrow 0$

During simulations μ and π have been modeled by *Haldane* type kinetics (6) and (7). Depending on the relative position of μ and π as functions of C_S , 10 different cases can be considered. The optimal values of S_{growth} , $C_{S,\mu}^*$, and $C_{S,\pi}^*$, and the corresponding value for $C_P(t_f)$ are shown in Table 2 for


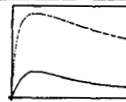



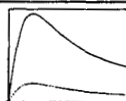

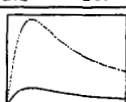
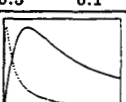
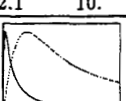
$C_{S,\mu}$	$C_{S,\pi}$	μ_m	$K_{M,\mu}$	$K_{I,\mu}$	π_m	$K_{M,\pi}$	$K_{I,\pi}$	$C_{S,\mu}$	$C_{S,\pi}$	μ_m	$K_{M,\mu}$	$K_{I,\mu}$	π_m	$K_{M,\pi}$	$K_{I,\pi}$				
Case 1: $K_{I,\mu} = K_{I,\pi}$								Case 7: $C_{S,\mu} = C_{S,\pi}$											
1.	0.1	2.1	10.	0.1	0.45	0.1	0.1	1.	1.	2.1	10.	0.1	0.45	0.2	5.				
S_{growth}		-				S_{growth}		-				S_{growth}		-					
$C_{S,\mu}^* = C_{S,\pi}^*$		0.04997				$C_{S,\mu}^* = C_{S,\pi}^*$		0.11805				$C_{S,\mu}^* = C_{S,\pi}^*$		1.00000		$C_{S,\mu}^* = C_{S,\pi}^*$		1.00000	
$C_P(t_f)$		121.81103		$C_P(t_f)$		113.70693		$C_P(t_f)$		18.81301		$C_P(t_f)$		12.37242		$C_P(t_f)$		94.89737	
Case 2: $K_{I,\mu} = K_{I,\pi}$								Case 8: $C_{S,\mu} = C_{S,\pi}$											
0.1	1.	0.45	0.1	0.1	2.1	10.	0.1	1.	1.	0.45	0.2	5.	2.1	10.	0.1				
S_{growth}		-				S_{growth}		-				S_{growth}		-					
$C_{S,\mu}^* = C_{S,\pi}^*$		2.00450				$C_{S,\mu}^* = C_{S,\pi}^*$		1.00000				$C_{S,\mu}^* = C_{S,\pi}^*$		1.00000		$C_{S,\mu}^* = C_{S,\pi}^*$		1.00000	
$C_P(t_f)$		85.15067		$C_P(t_f)$		18.81301		$C_P(t_f)$		12.37242		$C_P(t_f)$		94.89737		$C_P(t_f)$		94.89737	
Case 3: $K_{M,\mu} = K_{M,\pi}$								Case 9: $\pi = Y_{P/X} \mu$											
1.	0.1	2.1	0.1	10.	0.45	0.1	0.1	1.	1.	2.1	10.	0.1	0.45	10.	0.1				
S_{growth}		-				S_{growth}		-				S_{growth}		-					
$C_{S,\mu}^* = C_{S,\pi}^*$		0.01584				$C_{S,\mu}^* = C_{S,\pi}^*$		1.00000				$C_{S,\mu}^* = C_{S,\pi}^*$		1.00000		$C_{S,\mu}^* = C_{S,\pi}^*$		1.00000	
$C_P(t_f)$		13.09258		$C_P(t_f)$		12.37242		$C_P(t_f)$		94.89737		$C_P(t_f)$		94.89737		$C_P(t_f)$		94.89737	
Case 4: $K_{M,\mu} = K_{M,\pi}$								Case 10: $\pi = Y_{P/X} \mu$											
0.1	1.	0.45	0.1	0.1	2.1	0.1	10.	1.	1.	0.45	10.	0.1	2.1	10.	0.1				
S_{growth}		-				S_{growth}		-				S_{growth}		-					
$C_{S,\mu}^* = C_{S,\pi}^*$		5.80166				$C_{S,\mu}^* = C_{S,\pi}^*$		1.00000				$C_{S,\mu}^* = C_{S,\pi}^*$		1.00000		$C_{S,\mu}^* = C_{S,\pi}^*$		1.00000	
$C_P(t_f)$		172.69611		$C_P(t_f)$		12.37242		$C_P(t_f)$		94.89737		$C_P(t_f)$		94.89737		$C_P(t_f)$		94.89737	
Case 5: $\max(\mu) = \max(\pi)$								Case 6: $\max(\mu) = \max(\pi)$											
1.	0.1	2.1	10.	0.1	0.3	0.1	0.1	0.1	1.	0.3	0.1	0.1	0.1	10.	0.1				
S_{growth}		-				S_{growth}		-				S_{growth}		-					
$C_{S,\mu}^* = C_{S,\pi}^*$		0.04997				$C_{S,\mu}^* = C_{S,\pi}^*$		1.79584				$C_{S,\mu}^* = C_{S,\pi}^*$		1.79584		$C_{S,\mu}^* = C_{S,\pi}^*$		1.79584	
$C_P(t_f)$		104.86236		$C_P(t_f)$		95.61239		$C_P(t_f)$		95.61239		$C_P(t_f)$		95.61239		$C_P(t_f)$		95.61239	

Table 2: Case III - optimal values for $k \rightarrow 0$
 ——— : μ - - - - : π

$$C_{S,\mu}^* (\equiv C_{S,\pi}^*) = C_{S,\pi/\sigma} = C_{S,\mu} (\equiv C_{S,\pi})$$

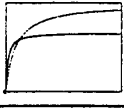
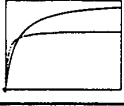


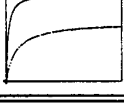

independent of the value of k (see also [3]). The same result holds true for Case 8, but only for $k = 0$. For Case 7, the set-point $C_{S,\mu}^* (\equiv C_{S,\pi}^*) = C_{S,\mu} (\equiv C_{S,\pi})$ corresponds to a local minimum of π/σ .

CASE IV: MONOTONIC μ AND MONOTONIC π
 Since both μ and π are monotonically increasing functions and therefore have similar behavior around their maximum values, this can be considered as a degenerate case of growth associated production. Therefore, the optimal control sequence would be to feed all substrate available as fast as possible—in the limit this corresponds to a batch process—, while growth and production occur at the same time (one phase).

We have investigated all possible relative positions of μ and π , modeled by Monod type models (4) and (5) respectively. The results for product degradation $k \rightarrow 0$ are shown in Table 3. The following observations can be made.

1. For all cases of Table 2 there is no growth phase. This is rather obvious for Case 9 and Case 10—growth associated production—, independent of the value of k . In all other cases the characteristic biphasic behavior disappears completely when $k \rightarrow 0$.
2. When $k \rightarrow 0$, both set-points $C_{S,\mu}^*$ and $C_{S,\pi}^*$ converge to $C_{S,\pi/\sigma}$ which maximizes π/σ (Theorem 1). In Case 9 and Case 10 (growth associated production), we have

1. In most cases, the above line of reasoning is correct, i.e., the optimal mode of operation is batch, all substrate available being added at time $t = 0$. In addition, this result is independent of the value of k [3].

Case	μ_m	$K_{M,\mu}$	π_m	$K_{M,\pi}$
$\mu_m < \pi_m$ $K_{M,\mu} < K_{M,\pi}$				
1	0.1	1.	0.15	5.
S_{growth}	-			
$C_{S,\mu}^*, C_{S,\pi}^*$	-			
$C_P(t_f)$	57.14030			
$\mu_m > \pi_m$ $K_{M,\mu} > K_{M,\pi}$				
2	0.15	5.	0.1	1.
S_{growth}	-			
$C_{S,\mu}^*, C_{S,\pi}^*$	0.88734			
$C_P(t_f)$	60.59035			
$\pi = Y_{P/X}\mu$				
3	0.15	1.	0.1	1.
S_{growth}	-			
$C_{S,\mu}^*, C_{S,\pi}^*$	-			
$C_P(t_f)$	34.64377			
$\pi = Y_{P/X}\mu$				
4	0.1	1.	0.15	1.
S_{growth}	-			
$C_{S,\mu}^*, C_{S,\pi}^*$	-			
$C_P(t_f)$	61.10292			
$\mu_m > \pi_m$ $K_{M,\mu} < K_{M,\pi}$				
5	0.15	1.	0.1	5.
S_{growth}	-			
$C_{S,\mu}^*, C_{S,\pi}^*$	-			
$C_P(t_f)$	53.94851			
$\mu_m < \pi_m$ $K_{M,\mu} > K_{M,\pi}$				
6	0.1	5.	0.15	1.
S_{growth}	-			
$C_{S,\mu}^*, C_{S,\pi}^*$	1.13192			
$C_P(t_f)$	88.63113			

2. However, Case 2, Case 6, and Case 8, are exceptions on this rule. As in the other cases, growth and production occur at the same time, i.e., there is only one phase whatever the value of k . However, all substrate must be added following a *singular control* of the form (8). Again, this singular control law can be successfully replaced by a *heuristic control law* (9) which keeps substrate concentration constant at some pre-specified set-point C_S^* . For product degradation k going to zero, this set-point converges to the value $C_{S,\pi}/\sigma$ which maximizes π/σ (Theorem 1). Analysis of the roots of $d(\pi/\sigma)/dC_S = 0$ leads to the following criterion for optimal *singular control*:



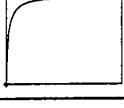
Case	μ_m	$K_{M,\mu}$	π_m	$K_{M,\pi}$
$\mu_m = \pi_m$				
7	0.1	1.	0.1	5.
S_{growth}	-			
$C_{S,\mu}^*, C_{S,\pi}^*$	-			
$C_P(t_f)$	42.65956			
$\mu_m = \pi_m$				
8	0.1	5.	0.1	1.
S_{growth}	-			
$C_{S,\mu}^*, C_{S,\pi}^*$	0.13192			
$C_P(t_f)$	70.69693			
$\mu = \pi$				
9	0.1	5.	0.1	1.
S_{growth}	-			
$C_{S,\mu}^*, C_{S,\pi}^*$	-			
$C_P(t_f)$	45.93593			

Table 3: Case IV - optimal values for $k \rightarrow 0$

$$K_{M,\mu} > K_{M,\pi} \left(m \frac{Y_{X/S}}{\mu_m} + 1 \right)$$

CONCLUSION

We have investigated the optimization of fed-batch fermentation processes involving one limiting substrate for biomass growth and product synthesis, with respect to the volumetric feed rate of this substrate.

Until now classification of these processes –and thus also the determination of the corresponding optimal feed rate strategy– has been based only on the qualitative behavior of the specific rates for growth and production as functions of substrate concentration. In this paper we have illustrated that the *optimal control sequence largely depends on other model characteristics as well*, such as the value of the product degradation constant.

A detailed optimization study for all possible combinations of the specific rates for growth and production reveals that the typical *biphasic behavior of processes with growth/production decoupling disappears if product degradation is not modeled*. In this sense numerical optimization can prove very useful in solving the *model structure discrimination problem*.

A more detailed analysis of the results mentioned, together with a description of the influence of the specific maintenance demand m (and the corresponding *endogenous fraction*) upon optimization results, can be found in [3].

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