



PROPERTIES OF THE OPTIMAL SINGULAR CONTROL OF FED-BATCH FERMENTATION PROCESSES

Jan F. VAN IMPE^{1,2,*} Bart DE MOOR^{2,†} Joos VANDEWALLE²

¹Laboratory for Industrial Microbiology and Biochemistry

²ESAT - Department of Electrical Engineering

Katholieke Universiteit Leuven

Kardinaal Mercierlaan 94, B-3001 Leuven (Belgium)

email: vanimpe@esat.kuleuven.ac.be

Keywords: optimal control, singular control, optimal adaptive control, fed-batch fermentation process, growth/production decoupling

1 Motivation

Optimization of fed-batch fermentations has been traditionally sought with respect to the volumetric substrate feed rate while keeping the substrate concentration in the feed fixed. Formulating the problem with the feed rate as the control variable yields a *singular* optimal control problem. A number of techniques have been proposed to convert the singular control problem into a nonsingular one. To avoid a singular control problem, variables other than the feed flow rate may be taken as the control variable.

As a matter of fact, these methods all suffer from problems with respect to practical implementation. Therefore, in this paper we adopt the traditional point of view, i.e., singular optimal control with the volumetric substrate feed rate as the manipulated variable. As a case study, we consider processes with a decoupling between growth and production, characterized by a monotonic specific growth rate and a non-monotonic specific production rate.

The results presented here are in this way general, that they are written in terms of the specific reaction rates. In other words, an exact analytical expression for these rates is not required a priori. In addition, no assumptions are made concerning the metabolism involved for biomass survival and product synthesis. The singular arc, which usually coincides with the production phase, is analyzed very carefully. The results obtained—summarized in Theorems 1 and 2—are at the basis of a *heuristic optimization methodology* described in detail in [1]. These heuristic controllers can also be motivated from the biochemical viewpoint. In [1],[2],[3] it is shown how these controllers then lead in a very natural way to the design of model-independent control strategies which combine nearly optimal performance with excellent robustness properties: *optimal adaptive control*.

*Senior research assistant with the N.F.W.O. (Belgian National Fund for Scientific Research) Corresponding author.

†Research associate with the N.F.W.O.

2 Problem statement

Consider the class of fed-batch fermentations described by a model of the form:

$$\begin{aligned} \frac{dS}{dt} &= -\sigma X + C_{s,in}u & \frac{dX}{dt} &= \mu X \\ \frac{dP}{dt} &= \pi X - k_h P & \frac{dV}{dt} &= u \end{aligned}$$

For an explanation of all symbols used, refer to the Nomenclature. S is considered the only limiting substrate for cell mass growth and production. Note that decay of product is explicitly taken into account using a first order model, where k_h denotes the specific product decay rate. At this point we allow the specific rates σ , μ and π to be arbitrary functions (which may depend on substrate, cell and product concentrations) interrelated by:

$$\sigma = \mu/Y_{x/s} + m + \pi/Y_{p/s} \quad (1)$$

This general model can represent *any* metabolism (maintenance, endogenous, or mixed) for biomass survival and product synthesis. For more details see [1]. The *shape* of the specific rates $\mu(C_s)$ and $\pi(C_s)$ is as depicted in Figure 1: the enzyme catalyzed production is *not associated* to the microbial growth. A practical example is the penicillin G fed-batch fermentation process [4].

By defining (T denotes the transpose):

$$\begin{aligned} \mathbf{x}^T &\triangleq [S \ X \ P \ V] \\ \mathbf{f}^T &\triangleq [-\sigma X \ \mu X \ (\pi X - k_h P) \ 0], \quad \mathbf{b}^T \triangleq [C_{s,in} \ 0 \ 0 \ 1] \end{aligned}$$

we obtain the following state space model linear in the control input u (i.e., the volumetric substrate feed rate):

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}) + \mathbf{b} u \quad (2)$$

The initial values for biomass X , $x_2(0) = X_0$, and product P , $x_3(0) = P_0$, are *fixed*. However, we assume that the initial value for substrate S , $x_1(0)$, is an *additional control parameter* that can be manipulated to minimize the performance index. The initial values for S and V are only constrained by:

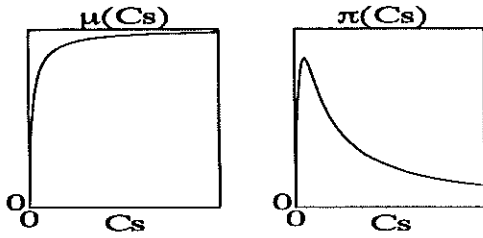


Figure 1: Specific rates μ and π

$$x_4(0) = V_* + x_1(0)/C_{s,in} \quad (3)$$

with V_* the given initial volume *without* substrate. Note that substrate is added as a solution with concentration $C_{s,in}$. The objective function considered here is:

$$J[u, x_1(0)] = g[x(t_f), t_f] \equiv -\gamma_x X(t_f) - \gamma_p P(t_f) + \gamma_t t_f \quad (4)$$

with γ_x, γ_p the unit 'prices' associated with cell mass and metabolite product respectively, and γ_t the unit 'operating cost'. The optimization problem is then to *determine for the set of differential equations (2) the optimal initial state x_0 and volumetric substrate feed rate profile $u^*(t)$ that minimize the performance index (4), subject to:*

- The final time t_f is free.
 - All variables are non-negative physical quantities:
- $$\forall t \in [0, t_f]: x_i(t) \geq 0, \text{ for } i = 1, \dots, 4 \wedge u(t) \geq 0$$
- The total amount of substrate available, α , is fixed:

$$x_1(0) + \int_0^{t_f} C_{s,in} u(t) dt = \alpha \quad (5)$$

$$\Downarrow$$

$$x_4(t_f) \equiv V(t_f) = V_f, V_f \text{ fixed} \quad (6)$$

In order to obtain a well-posed optimal control problem, we must fix either t_f or α . We always fix α , while letting t_f free. This can be motivated as follows:

- By fixing α , (6) can be easily taken into account.
- By letting t_f free, we can derive more general properties of the optimal control profile with a clear physical interpretation (see Section 4 and [1]).
- From an industrial point of view t_f is very often the most important factor. This can be taken into account in two ways. First, increase γ_t in (4). Second, use the additional degree of freedom $x_1(0)$ to calculate a *trade-off* between the value of the cost J and t_f .

If we neglect the unit operating cost γ_t and fix the total substrate amount α , then minimizing performance index (4) is equivalent to maximizing the *average yield* \mathcal{Y} .

3 Optimal control

The two point boundary value problem TPBVP. Pontryagin's Minimum Principle (see e.g., [5]) states that the following Hamiltonian \mathcal{H} must be minimized over all admissible control inputs $u(t)$:

$$\mathcal{H} = \lambda^T [f(x) + bu] \triangleq \phi + \psi u \quad (7)$$

$$\phi = \lambda_1 f_1 + \lambda_2 f_2 + \lambda_3 f_3 \quad \psi = C_{s,in} \lambda_1 + \lambda_4$$

The adjoint vector λ satisfies:

$$\frac{d\lambda}{dt} = -\frac{\partial \mathcal{H}}{\partial x} = -\frac{\partial f}{\partial x}^T \lambda$$

Together with (2), we obtain a system of 8 first order differential equations, with boundary conditions:

- $x_2(0), x_3(0)$, and $x_4(t_f)$ [see (6)] are given; $x_1(0)$ and $x_4(0)$ are interrelated by (3)
- $\lambda_i(t_f), i = 1, \dots, 3$ are given by (g is the terminal cost):

$$\lambda_i(t_f) = \frac{\partial g}{\partial x_i} [x(t_f), t_f]$$

- The boundary condition complementary to (3) is ([1]): $C_{s,in} \lambda_1(0) + \lambda_4(0) \equiv \psi(0) = 0$

Since \mathcal{H} does not depend explicitly on t , we have along an extremal trajectory (see e.g., [5]): $\mathcal{H} = \mathcal{H}^*$, with \mathcal{H}^* a constant. If in addition the cost index is independent of final time t_f [e.g., $\gamma_t = 0$ in (4)], we have: $\mathcal{H} = 0$.

Extremal controls. In practice, the feeding pump capacity $u(t)$ is bounded:

$$0 \equiv U_{MIN} \leq u(t) \leq U_{MAX}, \quad U_{MAX} \text{ given}$$

Minimization of (7) then leads to:

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

Along a so-called *singular interval* $[t_i, t_{i+1}]$ the function ψ remains identically zero, so the Minimum Principle fails to provide $u(t)$ during this interval. The *singular control* $u_{sing}(t)$ is then obtained by repeatedly differentiating the function ψ until u appears explicitly ([1],[2],[3]):

$$d \triangleq \frac{\partial f}{\partial x} b$$

$$u_{sing}(t) = \frac{\lambda^T [(\partial f / \partial x) d - (\partial d / \partial x) f]}{\lambda^T [\partial d / \partial x] b} \quad (8)$$

REMARKS

1. As a generic result, the denominator of (8) is indeed different from zero. This is a *singular problem of order 2*.
2. In (8) both the numerator and the denominator are *linear* in the costates λ . On any singular interval, there exist three linear algebraic equations between them:

$$\psi \equiv \lambda^T b = 0, \quad \frac{d\psi}{dt} \equiv \lambda^T d = 0, \quad \dot{\phi} \equiv \lambda^T f = \mathcal{H}^* \quad (9)$$

with \mathcal{H}^* a constant. If the cost index is independent of final time t_f [e.g., $\gamma_t = 0$ in (4)] then $\mathcal{H}^* = 0$. The homogeneous system (9) specifies three costates as functions of the remaining fourth one. Then the singular control (8) is a *nonlinear feedback law of the state x only*. ■

Optimal control sequence for monotonic μ and non-monotonic π . The TPBVP has been reduced to the determination of the *optimal control sequence* $[U_{MAX}, U_{MIN}, u_{sing}]$ and the corresponding *switching times*. Initial work along the same lines has been reported in [6] and [7]. A more detailed analysis can be found in [1] and [3].

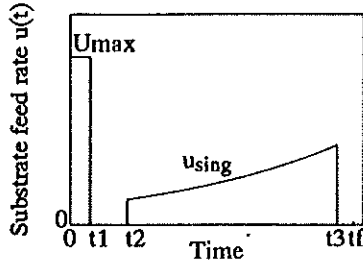


Figure 2: General feed rate profile for low $C_s(0)$

Obviously, the optimal sequence depends on the initial substrate concentration $C_s(0) = x_1(0)/x_4(0)$. Furthermore, we tacitly assume that the initial biomass amount $x_2(0)$ is low. If the initial substrate concentration is fixed at a low value, the optimal feed rate profile is as shown in Figure 2. If on the other hand the initial substrate concentration is high enough, the first interval $[0, t_1]$ of feeding at the maximum rate should be omitted. The growth phase $[0, t_2]$ is then a complete batch phase, until at time $t = t_2$ singular feeding starts the production phase. If the initial substrate concentration is free, the growth phase is again a batch phase, while all substrate consumed during growth, α_{growth} , is added at time $t = 0$. In other words, in all cases the TPBVP is reduced to a two-dimensional optimization of the switching time t_1 or the initial substrate concentration $C_s(0)$, and the switching time t_2 . An efficient computational algorithm, which has some marked advantages over the algorithm proposed in [7], can be found in [1], [3], and [8].

4 Physical interpretation

The generic case: maintenance coefficient $m > 0$

Consider first the following performance index:

$$J[u] = g[x(t_f)] = -P(t_f) \quad (10)$$

which is of the form (4) with $\gamma_x = 0$ and $\gamma_t = 0$, i.e., maximization of the final product amount. The total amount of substrate α (and thus the final volume) is fixed (5), while the initial substrate concentration $C_s(0)$ and the final time t_f are free. We prove the following Theorem, inspired by a result reported in [6]. Furthermore, the proof we present here is more rigorous.

Theorem 1 Consider the minimization of (10) subject to (2). Suppose that

1. σ , μ and π are functions of substrate concentration C_s only, with continuous derivatives up to 2nd order,
2. the maintenance coefficient m is strictly positive.

Then during singular control

1. the substrate concentration C_s remains constant if and only if the specific product decay rate $k_h = 0$,
2. this constant value maximizes the yield π/σ .

PROOF

In the following, a prime denotes derivation with respect to substrate concentration C_s . The Hamiltonian \mathcal{H} is given by (7), with $\phi = (-\lambda_1\sigma + \lambda_2\mu + \lambda_3\pi)x_2 - \lambda_3k_hx_3$, and $\psi = C_{s,in}\lambda_1 + \lambda_4$. The adjoint equations are:

$$\begin{aligned} \dot{\lambda}_1 &= (\lambda_1\sigma' - \lambda_2\mu' - \lambda_3\pi')x_2/x_4 \\ \dot{\lambda}_2 &= \lambda_1\sigma - \lambda_2\mu - \lambda_3\pi = -(\phi + \lambda_3k_hx_3)/x_2 \\ \dot{\lambda}_3 &= \lambda_3k_h \\ \dot{\lambda}_4 &= -(\lambda_1\sigma' - \lambda_2\mu' - \lambda_3\pi')x_1x_2/x_4^2 \end{aligned}$$

with boundary conditions

$$\lambda^T(t_f) \equiv \frac{\partial g^T}{\partial x} [x(t_f)] = [0 \quad 0 \quad -1 \quad -] \quad (11)$$

On the singular interval, we have $\phi = 0$, $\psi = 0$, $\dot{\psi} = 0$:

$$\begin{aligned} -\lambda_1\sigma + \lambda_2\mu + \lambda_3\pi &= \lambda_3k_hx_3/x_2 \quad (12) \\ C_{s,in}\lambda_1 + \lambda_4 &= 0 \\ (\lambda_1\sigma' - \lambda_2\mu' - \lambda_3\pi')(C_{s,in} - \frac{x_1}{x_4}) &= 0 \end{aligned}$$

The case $x_1/x_4 \equiv C_s = C_{s,in}$ can be excluded as C_s is then unrealistic high during production. So the last equation is equivalent to:

$$\lambda_1\sigma' - \lambda_2\mu' - \lambda_3\pi' = 0 \quad (13)$$

The adjoint equations reduce to (C_i is a constant):

$$\begin{aligned} \lambda_1 &= C_1 \\ \dot{\lambda}_2 &= -\lambda_3k_hx_3/x_2 = -\dot{\lambda}_3x_3/x_2 \quad (14) \\ \lambda_3 &= -e^{k_h(t-t_f)} \\ \lambda_4 &= C_4 \end{aligned}$$

The equation for λ_3 has been solved using boundary condition $\lambda_3(t_f) = -1$ (11). As we know from the optimal control sequence that the product $\psi(t)u(t) = 0$ for all t , it follows from (7) that $\phi = 0$ for all t , so (14) holds for all t , with boundary condition $\lambda_2(t_f) = 0$ due to (11).

For the complete costate to be constant on the singular interval, obviously it is necessary and sufficient that the specific product decay rate $k_h = 0$.

Evaluating $d^2\psi/dt^2 = 0$ on the singular interval yields:

$$\dot{C}_s = k_h \frac{\lambda_3(\pi'x_2 - \mu'x_3)}{x_2(\lambda_1\sigma'' - \lambda_2\mu'' - \lambda_3\pi'')} \quad (15)$$

$$= -\sigma \frac{X}{V} + \frac{u_{sing}}{V} (C_{s,in} - C_s) \quad (16)$$

the second equality due to (2). We first verify that the denominator in (15) is different from zero. We give a demonstration by contradiction. So suppose that:

$$\lambda_1\sigma'' - \lambda_2\mu'' - \lambda_3\pi'' = 0 \quad (17)$$

Together with (12) and (13) we obtain the linear system:

$$\begin{pmatrix} -\sigma & \mu & \pi - k_h x_3/x_2 \\ -\sigma' & \mu' & \pi' \\ -\sigma'' & \mu'' & \pi'' \end{pmatrix} \begin{pmatrix} \lambda_1 \\ \lambda_2 \\ \lambda_3 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix} \quad (18)$$

We know there exists a nontrivial solution $\lambda(t)$ since at least $\lambda_3(t) \neq 0$. So for assumption (17) to be true, a necessary and sufficient condition is that the system matrix has its determinant equal to zero. We have using (1):

$$A \triangleq \begin{pmatrix} -\mu/Y_{s/s} - m - \pi/Y_{p/s} & \mu & \pi - k_h x_3/x_2 \\ -\mu'/Y_{s/s} - \pi'/Y_{p/s} & \mu' & \pi' \\ -\mu''/Y_{s/s} - \pi''/Y_{p/s} & \mu'' & \pi'' \end{pmatrix}$$

Obviously, A has no zero rows or columns, nor any identical rows or columns. The only possibility for $\det(A)$ to be zero is that both k_h and m are zero, which is in contradiction with $m > 0$.

From (15) we conclude now that a necessary and sufficient condition for C_s to be constant on the singular interval is $k_h = 0$. Let us determine that constant value. Solving the first two equations of (18) for λ_2/λ_3 yields:

$$\frac{\lambda_2}{\lambda_3} = -\frac{\pi'\sigma - (\pi - k_h x_3/x_2)\sigma'}{\mu'\sigma - \mu\sigma'} \quad (19)$$

From $k_h = 0$ it follows that $\lambda_2(t)$ and $\lambda_3(t)$ are constant for all t , so from boundary conditions (11) we obtain:

$$\begin{aligned} \lambda_2(t) = \lambda_2(t_f) &= 0 \\ \lambda_3(t) = \lambda_3(t_f) &= -1 \end{aligned}$$

As a consequence, equation (19) reduces to: $\pi'\sigma - \pi\sigma' = 0$, or in other words, the singular control extremizes the product yield:

$$\frac{d}{dC_s} \left(\frac{\pi}{\sigma} \right) = 0 \quad (20)$$

which completes the proof. ■

REMARKS

1. The specific rates σ , μ and π are required to be smooth functions of C_s , in order to ensure the existence and continuity of at least the first two derivatives with respect to C_s , thus enabling the calculation of $u_{sing}(t)$ from equations (15) and (16). Note that the singular control is linear in the specific product decay rate k_h :

$$u_{sing} = \frac{\sigma X}{C_{s,in} - C_s} + \frac{k_h V \lambda_3 (\pi' x_2 - \mu' x_3)}{x_2 (C_{s,in} - C_s) (\lambda_1 \sigma'' - \lambda_2 \mu'' - \lambda_3 \pi'')}$$

2. It follows from the above Theorem that the condition $k_h = 0$ is also necessary and sufficient to obtain the complete optimal control for a given S_0 -or equivalently $C_s(0)$ - as a closed loop solution: clearly the switch from batch to singular control is then dictated by the condition $C_s = C_s^*$, C_s^* denoting the value of C_s for which π/σ has its optimum.

3. It has been shown in [1] under which conditions the above results can be extended to the case of continuous

but non-smooth kinetics, i.e., kinetics which exhibit so-called corner points at certain values of C_s . ■

At this point we can generalize the above results to performance indices of the form:

$$J[u] = g[x(t_f)] \quad (21)$$

Following a similar way of reasoning, we obtain that the singular control keeps the substrate concentration at a constant level if and only if $k_h = 0$, where that constant level satisfies

$$\lambda_2(t_f)(\mu'\sigma - \mu\sigma') + \lambda_3(t_f)(\pi'\sigma - \pi\sigma') = 0 \quad (22)$$

which generalizes (20).

REMARKS

1. As an example, if the performance index is taken to be a profit function of the form (4) with $\gamma_i = 0$:

$$J[u] = -\gamma_x X(t_f) - \gamma_p P(t_f)$$

the final conditions on λ_2 and λ_3 are, using (11):

$$\lambda_2(t_f) = -\gamma_x \quad \lambda_3(t_f) = -\gamma_p$$

Substitution in condition (22) yields:

$$\frac{d}{dC_s} \left(\gamma_x \frac{\mu}{\sigma} + \gamma_p \frac{\pi}{\sigma} \right) = 0$$

which can be interpreted as that the singular control maximizes the average yield, weighted by the unit prices of cell mass and product.

2. Let us check whether the results of Theorem 1 can be extended to a performance index which depends explicitly on final time t_f :

$$J[u] = g[x(t_f), t_f]$$

Combining the transversality condition:

$$\mathcal{H}[x(t_f), \lambda(t_f), u(t_f)] + \frac{\partial g}{\partial t}[x(t_f), t_f] = 0$$

with $\forall t: \mathcal{H} = \mathcal{H}^*$ (\mathcal{H}^* is a constant), leads to:

$$\forall t \in [0, t_f]: \mathcal{H}[x(t), \lambda(t), u(t)] \equiv \phi + \psi u = -\frac{\partial g}{\partial t}[x(t_f), t_f]$$

On a singular arc the following conditions hold:

$$\begin{aligned} \psi = 0 &: C_{s,in} \lambda_1 + \lambda_4 = 0 \\ \dot{\psi} = 0 &: \lambda_1 \sigma' - \lambda_2 \mu' - \lambda_3 \pi' = 0 \\ \phi + \frac{\partial g}{\partial t_f} = 0 &: (-\lambda_1 \sigma + \lambda_2 \mu + \lambda_3 \pi) x_2 - \lambda_3 k_h x_3 + \frac{\partial g}{\partial t_f} = 0 \end{aligned}$$

The adjoint differential equations then become:

$$\begin{aligned} \dot{\lambda}_1 &= 0 & \dot{\lambda}_2 &= -\lambda_3 k_h x_3/x_2 + \frac{\partial g}{\partial t_f}/x_2 \\ \dot{\lambda}_3 &= \lambda_3 k_h & \dot{\lambda}_4 &= 0 \end{aligned}$$

Evaluating $d^2\psi/dt^2 = 0$ on the singular interval yields:

$$C_s^* = \frac{k_h \lambda_3 (\pi' x_2 - \mu' x_3) + \frac{\partial g}{\partial t}[x(t_f), t_f] \mu'}{x_2 (\lambda_1 \sigma'' - \lambda_2 \mu'' - \lambda_3 \pi'')}$$

which generalizes (15).

We conclude that for the results of Theorem 1 to hold an additional necessary and sufficient condition is that the performance index is independent of the final time t_f :

$$\frac{\partial g}{\partial t}[\mathbf{x}(t_f), t_f] = 0 \quad \blacksquare$$

Special case: maintenance coefficient $m = 0$

The results of Theorem 1 have been obtained under the somewhat artificial condition $m > 0$. We now consider the limiting case of negligible energy demands for maintenance ($m = 0$). From the proof of Theorem 1 we know that only the case where both m and k_h equal zero needs additional justification. Equation (1) reduces to:

$$\sigma(C_s) = \mu(C_s)/Y_{x/s} + \pi(C_s)/Y_{p/s} \quad (23)$$

In this case the dimension of the state \mathbf{x} can be reduced by one. Using state equations (2), (23) can be written as:

$$C_{s,in} u dt = dS + dX/Y_{x/s} + dP/Y_{p/s}$$

Integrating from $t = t_0$ and using (3) we obtain:

$$P(t) - P_0 = Y_{p/s} [C_{s,in}(V(t) - V_*) - S(t) - \frac{1}{Y_{x/s}}(X(t) - X_0)]$$

As $P(t)$ does not appear explicitly in the differential equations for S and X , we can omit the differential equation for P , $P(t)$ being determined for all t by the above algebraic equation. Furthermore, as the total amount of substrate α is limited (5), we have using the last state equation:

$$C_{s,in}(V_f - V_*) = \alpha$$

So we obtain at $t = t_f$:

$$P(t_f) = P_0 + Y_{p/s} [\alpha + X_0/Y_{x/s}] - Y_{p/s} [S(t_f) + X(t_f)/Y_{x/s}] \quad (24)$$

As a result, maximizing the final amount of product $P(t_f)$ is equivalent to minimizing the performance measure:

$$J[u] = S(t_f) + X(t_f)/Y_{x/s}$$

For reasons of compatibility with the above notations, we denote the costate vector as:

$$\lambda^T(t) \triangleq (\lambda_1(t) \quad \lambda_2(t) \quad \lambda_4(t))$$

with boundary conditions:

$$\lambda^T(t_f) = \frac{\partial g}{\partial \mathbf{x}}[\mathbf{x}(t_f)] = (1 \quad 1/Y_{x/s} \quad -) \quad (25)$$

The Hamiltonian \mathcal{H} is given by (7), with:

$$\phi = (-\lambda_1\sigma + \lambda_2\mu)x_2 \quad \psi = C_{s,in}\lambda_1 + \lambda_4$$

The adjoint equations become:

$$\begin{aligned} \dot{\lambda}_1 &= (\lambda_1\sigma' - \lambda_2\mu')x_2/x_4 \\ \dot{\lambda}_2 &= \lambda_1\sigma - \lambda_2\mu \\ \dot{\lambda}_4 &= -(\lambda_1\sigma' - \lambda_2\mu')x_1x_2/x_4^2 \end{aligned}$$

On the singular interval, we obtain:

$$\begin{aligned} C_{s,in}\lambda_1 + \lambda_4 &= 0 \\ \lambda_1\sigma - \lambda_2\mu &= 0 \\ \lambda_1\sigma' - \lambda_2\mu' &= 0 \end{aligned}$$

which again results in a constant costate vector on the singular interval. We also have from the start of the singular arc on: $\lambda_2(t) = \lambda_2(t_f) = 1/Y_{x/s}$. For the above system to have a non-trivial solution λ , it is necessary and sufficient that $\sigma'\mu - \sigma\mu' = 0$, or in other words:

$$\frac{d}{dC_s}\left(\frac{\sigma}{\mu}\right) = 0 \quad \text{or} \quad \frac{d}{dC_s}\left(\frac{\pi}{\sigma}\right) = 0$$

by using relation (23). This determines the constant value of C_s during singular control. Note that $d^2\psi/dt^2 = 0$ leads to:

$$(\lambda_1\sigma'' - \lambda_2\mu'')\dot{C}_s = 0$$

Clearly, $\lambda_1\sigma'' - \lambda_2\mu''$ cannot be zero, so we obtain indeed:

$$\dot{C}_s = 0$$

resulting in

$$u_{sing}(t) = \frac{\sigma X}{C_{s,in} - C_s}$$

The final time t_f for this case is obtained as follows. During the last batch phase, we have $u = 0$, so from (7) we obtain:

$$\phi(t_f) = 0 \quad (26)$$

Using boundary conditions (25) this results in:

$$-\sigma(t_f) + \mu(t_f)/Y_{x/s} = 0$$

or using equation (23):

$$\pi(t_f) = 0$$

This is equivalent with:

$$\frac{dP}{dt}(t_f) = 0$$

as we might expect on physical grounds. Note that for most analytical expressions for the specific production rate this means that:

$$C_s(t_f) = 0$$

Again, we can generalize these results to a more general performance measure (21), wherein $P(t_f)$ has to be replaced by expression (24). Note that the analytical expression for $g[\mathbf{x}(t_f)]$ does not influence the (constant) level of C_s during singular control. It only determines the final time t_f through condition (26). \blacksquare

The above results can be summarized in a more general Theorem.

Theorem 2 Consider the minimization of performance index $J[u] = g[x(t_f)]$, subject to the dynamic constraint (2). Suppose that σ , μ and π are functions of substrate concentration C_s only, with continuous derivatives up to 2nd order. Then during singular control

1. the substrate concentration C_s remains constant if and only if the specific product decay rate $k_h = 0$,
2. this constant value satisfies

$$\text{if } m > 0 : \frac{\partial g}{\partial x_2}(\mu'\sigma - \mu\sigma') + \frac{\partial g}{\partial x_3}(\pi'\sigma - \pi\sigma') = 0$$

$$\text{if } m = 0 : \pi'\sigma - \pi\sigma' = 0$$

Furthermore, the optimal feed rate $u^*(t)$ is obtained in closed loop for a given value of S_0 .

5 Concluding remarks

In this paper we have analyzed the optimization of fed-batch bioreactors with respect to the volumetric substrate feeding rate. As a case study, we considered the optimal control sequence for processes characterized by growth/production decoupling, with monotonic specific growth rate and non-monotonic specific production rate.

The singular arc occurring during the production phase has been analyzed very carefully. Besides the results summarized in Theorems 1 and 2, which are important on their own, the main contribution is the following.

During the last two decades, two trends for the design of monitoring and control algorithms for biotechnological processes have emerged [9]. In a *first approach*, the difficulties in obtaining an accurate mathematical process model are ignored. In numerous papers classical methods (e.g., Kalman filtering, optimal control theory, ...) are applied under the assumption that the model is perfectly known. Due to this oversimplification, it is very unlikely that a real life implementation of such controllers—very often this implementation is already hampered by, e.g., monitoring problems—would result in the predicted simulation results. In a *second approach*, the aim is to design specific monitoring and control algorithms without the need for a complete knowledge of the process model, using concepts from, e.g., adaptive control and nonlinear linearizing control. However, there is no guarantee for at least suboptimality of the results obtained. A comprehensive treatment of these ideas can be found in [10] and the references therein.

We adopt a rather pragmatic viewpoint: we try to combine the best of both trends into one unifying methodology for optimization of biotechnological processes, *optimal adaptive control*. The gap between both approaches is bridged by the development of *heuristic control strategies* with nearly optimal performance under all conditions. These suboptimal controllers are based on biochemical knowledge concerning the process and on a careful mathematical analysis of the optimal control solution. As an example, in [1],[2],[3] it is shown how to design,

based on the analysis of the singular arc reported in this contribution, model-independent control strategies which combine nearly optimal performance with excellent robustness properties: *optimal adaptive control*.

Nomenclature

t	time	[h]
V	fermentor volume	[L]
X	amount of cell mass	[g DW]
P	amount of product	[g]
S	amount of substrate	[g]
C_s	substrate concentration	[g/L]
$C_{s,in}$	substrate concentration in feed	[g/L]
u	input substrate feed rate	[L/h]
m	maintenance constant	[g/g DW h]
$Y_{x/s}$	cell mass on substrate yield	[g DW/g]
$Y_{p/s}$	product on substrate yield	[g/g]
k_h	product degradation constant	[1/h]
α	total amount of substrate available	[g]
μ	specific growth rate	[1/h]
π	specific production rate	[g/g DW h]
σ	specific substrate consumption rate	[g/g DW h]

References

- [1] Van Impe J.F., *Modeling and optimal adaptive control of biotechnological processes*. PhD thesis, Katholieke Universiteit Leuven, Leuven (Belgium) (1993)
- [2] Van Impe J.F., G. Bastin, B. De Moor, V. Van Breusegem, and J. Vandewalle. Optimal adaptive control of fed-batch fermentation processes with growth/production decoupling. In: M.N. Karim and G. Stephanopoulos (Eds.), *Modelling and Control of Biotechnological Processes 1992*, 351-354, Pergamon Press, Oxford (1992)
- [3] Van Impe J.F., B. Nicolai, P. Vanrolleghem, J. Spriet, B. De Moor, and J. Vandewalle. Optimal control of the penicillin G fed-batch fermentation: an analysis of a modified unstructured model. *Chemical Engineering Communications*, **117**, 337-353 (1992)
- [4] Bajpai R.K., and M. Reuß. A mechanistic model for penicillin production. *J. Chem. Tech. Biotechnol.*, **30**, 332-344 (1980)
- [5] Bryson, A.E.Jr., and Y.-C. Ho. *Applied optimal control*. Hemisphere, Washington (1975)
- [6] Modak J.M., H.C. Lim and Y.J. Tayeb. General characteristics of optimal feed rate profiles for various fed-batch fermentation processes. *Biotechnol. Bioeng.*, **28**, 1396-1407 (1986)
- [7] Lim, H.C., Y.J. Tayeb, J.M. Modak, and P. Bonte. Computational algorithms for optimal feed rates for a class of fed-batch fermentation: numerical results for penicillin and cell mass production. *Biotechnol. Bioeng.*, **28**, 1408-1420 (1986)
- [8] Van Impe J.F., B. De Moor, and J. Vandewalle. Singular optimal control of fed-batch fermentation processes with growth/production decoupling and state inequality constraints. Accepted for presentation at the *12th IFAC World Congress, July 19-23, 1993, Sydney (Australia)* (1993)
- [9] Bastin G., Nonlinear and adaptive control in biotechnology: a tutorial. *Proceedings of the 1991 European Control Conference*, Grenoble (France), 2001-2012 (1991)
- [10] Bastin G., and D. Dochain. *On-line estimation and adaptive control of bioreactors*. Elsevier (1990)