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SINGULAR OPTIMAL CONTROL OF FED-BATCH FERMENTATION PROCESSES WITH STATE INEQUALITY CONSTRAINTS

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Abstract. We consider the design of a substrate feed rate controller for a class of biotechnical processes in stirred tank reactors characterized by growth/production decoupling, for the most common case of monotonic specific growth rate and non-monotonic specific production rate. With the volumetric substrate feed rate as the manipulated variable, this yields a singular optimal control problem. Due to state inequality constraints complete solutions are especially hard to obtain and almost nonexistent in the literature. However, the techniques proposed in the literature to convert the problem into a non-singular one all suffer from problems with respect to practical implementation. Therefore, we adopt the traditional singular control viewpoint. The algorithm presented has some marked advantages over algorithms reported in the literature. In addition, we present a complete general solution in the realistic case of input and state inequality constraints. This approach leads in a natural way to the design of robust optimal adaptive control strategies (Van Impe 1993).

Key Words. singular optimal control, state inequality constraints, 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, by taking variables other than the feed flow rate as the control variable [for an overview see Van Impe (1993)]. As an example, San and Stephanopoulos (1989) proposed a procedure in two steps. First, the optimal control problem with the fermentor substrate concentration as the control variable is solved to yield an optimal substrate trajectory. State inequalities on both substrate and biomass concentration can be included with relative ease. In a second step the optimal reactor substrate profile must be realized by manipulating the substrate concentration in the feed while keeping the volumetric feed rate fixed. However, they do not solve this step.

These methods all suffer from problems with respect to practical implementation. Therefore, 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 biomass growth and product formation, characterized by a monotonic specific growth rate and a non-monotonic specific production rate.
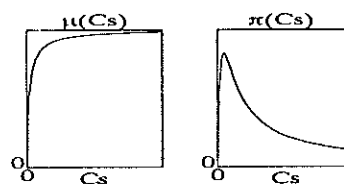

Figure 1: Specific rates μ and π

2. PROBLEM STATEMENT

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

$$\frac{dS}{dt} = -\sigma X + C_{S,in}u \qquad \frac{dX}{dt} = \mu X$$
$$\frac{dP}{dt} = \pi X - k_h P \qquad \frac{dV}{dt} = u \qquad (1)$$

For an explanation of all symbols used, refer to the Nomenclature. S is considered the only limiting substrate for cell mass growth and production. Decay of product is explicitly taken into account: k_h denotes the specific product decay rate. The *shape* of the specific rates μ and π as function of substrate concentration C_S is shown in Fig. 1: the enzyme catalyzed production is *not associated* to the microbial growth. The specific rates σ, μ and π are interrelated by:

$$\sigma = \mu/Y_{x/s} + m + \pi/Y_{p/s}$$

which can represent *any* metabolism for biomass survival and product synthesis.

The state vector is defined as $x^T = [S \ X \ P \ V]$. The initial values for biomass, X_0, and product, P_0, are *fixed*. The initial substrate value, S_0, is considered as an *additional control parameter* in minimizing some performance index.
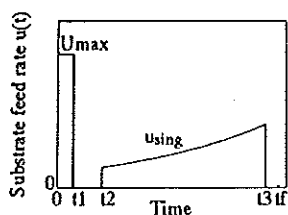
Figure 2: General feed rate profile for low $C_S(0)$

V_0 follows from $V_0 = V_* + S_0/C_{S,in}$, with V_* the (given) initial volume *without* substrate. Substrate is added as a solution with concentration $C_{S,in}$. Two general forms for the objective function are:

$$J_1[u, S_0] = -\gamma_x X(t_f) - \gamma_p P(t_f) + \gamma_t t_f \quad (2)$$
$$J_2[u, S_0] = -[\gamma_x X(t_f) + \gamma_p P(t_f)]/t_f \quad (3)$$

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* (1) *the optimal initial value S_0^* –or, equivalently, $C_S^*(0)$– and volumetric substrate feed rate profile $u^*(t)$ that minimize the performance index* (2) *or* (3), *subject to*:

■ the final time t_f is *free*
■ the total substrate amount available, α, is *fixed*:

$$x_1(0) + \int_0^{t_f} C_{s,in} u(t)\, dt = \alpha \quad (4)$$
$$\Downarrow$$
$$x_4(t_f) \equiv V(t_f) = V_f, \; V_f \text{ fixed} \quad (5)$$

If we neglect the unit operating cost γ_t, then minimizing (2) is equivalent to maximizing the *average yield $\mathcal{Y}$*. Minimizing (3) is equivalent to maximizing the *average productivity $\mathcal{P}$*.

3. OPTIMAL CONTROL

3.1. Optimal Control Sequence

A detailed analysis of this problem can be found in Van Impe *et al.* (1992a), and Van Impe (1993). Initial work along the same lines has been reported by Modak *et al.* (1986). In practice, the feeding pump capacity $u(t)$ is bounded:

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

Fixed initial state x_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 Fig. 2. Due to the decoupling between growth and production, the fermentation behaves as a *biphasic* process. If 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. Finally, if the initial conditions are on the singular hyperplane, the growth phase can be omitted completely, while singular feeding starts from $t = 0$ on.

Free initial substrate concentration $C_S(0)$. The growth phase is again a batch phase, while all substrate consumed during growth, α_{growth}, is added at time $t = 0$.

3.2. Computational Algorithm

The optimal *switching times* can be obtained using the following straightforward algorithm. We consider the generic case shown in Fig. 2.

Step 1: Guess t_1, or equivalently, determine the amount of substrate α_{growth} consumed during growth. Integrate equations (1) from $t = 0$ to $t = t_1$ with $u(t) = U_{MAX}$.

Step 2: Guess t_2. Integrate (1) with $u(t) = 0$ until $t = t_2$. This completes the *growth* phase.

Step 3: Integrate (1) using a *singular control* until all substrate available α (4) is added, or equivalently, until the bioreactor is filled (5) at $t = t_3$.

Step 4: Complete the integration with $u(t) = 0$ until the stopping condition –depending on the cost index– is satisfied at time $t = t_f$. This completes the *production* phase.

Step 5: Repeat Steps 2 to 4, by iterating on t_2, until J (2) or (3) reaches its minimum.

Step 6: Repeat Steps 1 to 5 with a new guess of t_1 in order to minimize J.

3.3. Remarks

1. For the other cases considered in Section 3.1, some minor modifications are required. However, the problem is always reduced to a *2-dimensional optimization of t_1 (or equivalently $C_S(0)$), and t_2.*

2. An appropriate initial guess for t_1 and t_2 can be found in Van Impe (1993).

3. In Van Impe (1993), we prove that in all cases calculation of the singular control (Step 3) (and thus of the complete optimal control) can be done *without an explicit need for any costate variable*, which are introduced via Pontryagin's Minimum Principle [see, e.g., Bryson and Ho (1975)]. We can distinguish between the following cases.

(*i*) *The performance index is independent of final time t_f*, e.g., $\gamma_t = 0$ in (2). Then the singular control is a *nonlinear feedback law of the state* x.

(*ii*) *The performance index depends on final time t_f.* If J has the form (2), then the singular feed rate is a *nonlinear feedback law of the state* x *and the final time t_f*. If J has the form (3), the singular feed rate is a *nonlinear feedback law of the state* x *and the unknowns t_f, $X(t_f)$ and $P(t_f)$*. t_f, and possibly $X(t_f)$ and $P(t_f)$, must be determined iteratively.

4. The last phase $[t_3, t_f]$ (Step 4) is terminated if the following condition is met [Van Impe (1993)]. *Performance index of the form* (2):

$$\gamma_x \frac{dX}{dt}(t_f) + \gamma_p \frac{dP}{dt}(t_f) = \gamma_t$$

The fermentation is stopped when the average gain of producing an additional unit of biomass and product (i.e., weighted by their unit prices) has become equal to the unit operational cost.

Performance index of the form (3):

$$\gamma_x \frac{dX}{dt}(t_f) + \gamma_p \frac{dP}{dt}(t_f) = \frac{\gamma_x X(t_f) + \gamma_p P(t_f)}{t_f}$$

The fermentation is stopped when the average gain of producing an additional unit of biomass and product has become equal to the average productivity $\mathcal{P}$.

5. The algorithm proposed by Lim *et al.* (1986) makes explicitly use of the costates. The advantages of the algorithm presented here are the following. First, an integration of costate equations forwards in time –which can cause (numerical) instabilities– is not required. Second, there is no need for an initial guess of some costates –which have no clear physical interpretation– at the beginning of the singular arc. If needed, an appropriate initial guess for t_f, $X(t_f)$, and $P(t_f)$ can be obtained, e.g., from knowledge about the process before optimization. ∎

4. STATE INEQUALITY CONSTRAINTS

4.1. Substrate concentration constraint

Too high values for substrate concentration C_S can lead to a lot of undesired effects, such as a *solubility* problem, an *inhibition* problem, *unproductive side-reactions*, ... This suggests the introduction of an upper limit on the substrate concentration during process optimization:

$$\forall t \in [0, t_f] \; : \; C_S(t) \le C_{S,MAX}$$

For the type of fermentations under study, this constraint can be violated only during the growth phase. As a general result, if C_S reaches its upper limit $C_{S,MAX}$, we use a control of the form

$$u_{C_S}(t) = \frac{\sigma X}{C_{S,in} - C_S} \qquad (6)$$

which keeps C_S constant at its upper bound $C_S = C_{S,MAX}$. As an example, consider the case of a free initial substrate concentration $C_S(0)$. If the optimization as described above results in an optimal initial concentration higher than the upper boundary $C_{S,MAX}$, the control sequence must be modified as follows. In order to ensure the highest possible growth rate without violating the constraint we start with $C_S(0) = C_{S,MAX}$ and apply controller (6). This control is shut off when all substrate for growth α_{growth} has been added at time $t = t_1$, whereafter the fermentation continues as described higher. If $u(t)$ is bounded and the control (6) should exceed the upper limit U_{MAX} before $t = t_1$, obviously $u(t)$ must be set equal to U_{MAX} until $t = t_1$, resulting in a substrate concentration decrease.

4.2. Biomass concentration constraint

Under certain conditions the optimal control sequence as described may result in high biomass concentrations in the bioreactor. The oxygen transfer capacity of the reactor will drop substantially as biomass builds up. Hence, very often these fermentations can be continued only to a limit dictated by the oxygen transfer capacity.

Since at present accurate oxygen limitation kinetics models are not available, we impose an upper limit $C_{x,MAX}$ on C_x:

$$\forall t \in [0, t_f] \; : \; C_x(t) \le C_{x,MAX}.$$

At first sight, we could adopt a similar line of reasoning as presented for bounded substrate concentration. By using (1) we deduce the control law which keeps C_x constant:

$$u_{C_x}(t) = \mu V \qquad (7)$$

However, we now show that *the optimal control sequence under biomass concentration limitation is characterized by a biomass concentration profile C_x which is tangent to the upper bound $C_{x,MAX}$ at at most one time instant.* In other words, $C_x = C_{x,MAX}$ for at most one value of time t.

As an example, consider again the case of a free initial substrate concentration $C_S(0)$. For another case a similar argumentation can be given. Suppose that, without taking the constraint into account, the optimal control sequence is characterized by the couple $(C_S^*(0), t_2^*)$. We can distinguish between the following 4 cases.

(i) *The constraint is not violated.* The optimal control sequence characterized by $(C_S^*(0), t_2^*)$ remains optimal under biomass limitation.

(ii) *The constraint is violated during the batch growth phase.* As a result, for some value of t within the interval $[0, t_2]$ the control must switch from zero to a positive value given by (7). Depending on the specific rates, C_S will decrease at a lower rate or may even start increasing. As a result, the singular conditions will either be reached only at some time $t_2 > t_2^*$, or will never be reached at all. More substrate will be added during the growth phase, in the first place to keep C_x constant due to dilution, which is then lost for the production phase, resulting in a higher value of the performance index to be minimized.

(iii) *The constraint is violated during the singular production phase.* During the production phase, a singular control keeps C_S within the region of optimal productivity. If C_x is decreasing, there is no problem. However, if C_x increases, the upper bound may be violated. At this time the feed rate should switch from the singular control to the control (7). As a generic result, the input (7) required to keep biomass concentration constant is larger than the singular control [Van Impe (1993)]. As a result, the substrate concentration will move away from the singular hyperplane, resulting in a decreasing performance.

(iv) *The constraint is violated during the terminating batch phase.* Obviously, this situation must be avoided also since there is no substrate available anymore to dilute the liquid phase.

The procedure to obtain the optimal sequence under biomass limitation can be summarized as follows. First, we determine the optimal couple $(C_S^*(0), t_2^*)$ without taking the constraint into account. Second, we verify if the constraint is violated for some value of t. If so, the optimal substrate concentration $C_S^*(0)$ must be decreased to

such a level that the resulting biomass concentration profile and the constraint are tangent to each other for at most one value of t. Then the control (7) will never become active. Of course, the corresponding optimal switching time t_2^* will decrease accordingly.

5. EXAMPLE

Consider the penicillin G fermentation process as modeled by Bajpai and Reuß (1981):

$$\mu = \mu_{max} \frac{C_s}{K_x C_x + C_s}, \pi = \pi_m \frac{C_s}{K_p + C_s + C_s^2/K_i}$$

The model parameters are: $\mu_{max} = 0.11$ [1/h], $K_x = 0.006$ [g/g DW], $\pi_m = 0.004$ [g/g DW h], $K_p = 0.0001$ [g/L], $K_i = 0.1$ [g/L], $k_h = 0.01$ [1/h], $Y_{x/s} = 0.47$ [g DW/g], $Y_{p/s} = 1.2$ [g/g], and $m = 0.029$ [g/g DW h]. We used the following initial and operational conditions: $X_0 = 10.5$ [g DW], $P_0 = 0$ [g], $V_* = 7$ [L], $C_{s,in} = 500$ [g/L], and $\alpha = 1500$ [g].

In the case of an unbounded input u and state x with free initial substrate concentration $C_s(0)$, optimization of $P(t_f)$ [which is a performance index of type (2)] yields: $S_0 = 528$ g, $t_2 = 28.271$ h, $t_f = 132.033$ h, $\mathcal{Y} \equiv P(t_f) = 63.846$ g. Lim et al. (1986) obtain with their algorithm: $S_0 = 561.2$ g, $t_f = 124.9$ h and $P(t_f) = 86.99$ g; which also contradicts the findings of Reuß (1992).

If $U_{MAX} = 0.05$ L/h, $C_{s,MAX} = 4$ g/L, and $C_{x,MAX} = 23$ g/L, then the optimal results are: $\alpha_{growth} = 339$ g, $t_2 = 24.668$ h, $t_f = 181.407$ h and $P(t_f) = 61.015$ g; the yield $\mathcal{Y}$ decreases with 4.43 %, while the productivity $\mathcal{P} \equiv P(t_f)/t_f$ decreases from $\mathcal{P} = 0.484$ g/h to $\mathcal{P} = 0.336$ g/h, i.e., −30.445 %.

Optimization of $P(t_f)/t_f$ [which is of type (3)] without constraints yields: $S_0 = 950$ g, $t_2 = 33.430$ h, $t_f = 71.414$ h and $P(t_f) = 49.721$ g. The corresponding optimal productivity is $\mathcal{P} = 0.696$. Clearly, the optimal values of yield and productivity do not occur at the same value of S_0. This is an illustration of the *yield-productivity conflict* in fed-batch reactors. A realistic process optimization strategy should consist of searching for the optimal initial substrate amount S_0, which results in the best *trade off* between *yield* and *productivity*. This represents also a trade off between *yield* and *total fermentation time*.

6. CONCLUSION

We have analyzed the optimization of fed-batch bioreactors with respect to the volumetric substrate feeding rate, for processes with monotonic growth rate and non-monotonic production rate. Performance indices of both the yield type and the productivity type, as well as the optimization of the initial substrate concentration have been considered. The resulting straightforward computational algorithm has some advantages over the algorithms proposed in the literature.

In addition, we have presented for the first time a *complete solution in the realistic case of both substrate and biomass inequality constraints*.

The optimal solution can be computed using basically the same algorithm.

In [Van Impe et al. (1992b), Van Impe (1993)] it is shown how a detailed analysis of this singular control solution leads in a natural way to the design of model-independent control strategies which combine nearly optimal performance with excellent robustness properties: *optimal adaptive control.*

NOMENCLATURE

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

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