OPTIMAL ADAPTIVE CONTROL OF FED-BATCH FERMENTATION PROCESSES WITH GROWTH/PRODUCTION DECOUPLING

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Abstract. We consider the design of a substrate feeding rate controller for a class of biotechnological processes in continuous stirred tank reactors, characterized by a decoupling between biomass growth and product formation. The main contribution is to illustrate how the insight, obtained by preliminary optimal control studies, leads to the design of an easy to implement adaptive controller. The controller derived this way combines a near optimal performance with good robustness properties against modeling uncertainties and process disturbances. As an example, simulation results are given for the penicillin G fed-batch fermentation process.

Keywords fed-batch fermentation process, growth/production decoupling, optimal control, adaptive (linearizing) control

PROBLEM STATEMENT

We consider the class of fed-batch fermentation processes described by an (unstructured) model of the form:

\[ \frac{dC_i}{dt} = -\sigma C_i + (C_i^{in} - C_i)u/V \]  
\[ \frac{dC_x}{dt} = -C_x + C_x u/V \]  
\[ \frac{dC_p}{dt} = \frac{\pi C_x - k_d C_p - C_p u/V}{V} \]  
\[ \frac{dV}{dt} = u \]

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

Dissolved oxygen is considered non-limiting, by maintaining a sufficiently high aeration level. The shape of the specific rates \( \mu(C_i) \) and \( \pi(C_x) \) is as depicted in Figure 1: the enzyme catalyzed production is not associated to the microbial growth. Due to balancing, the specific glucose uptake rate \( \sigma \) is given by:

\[ \sigma = \frac{\mu}{Y_f/\mu + m + \pi/Y_f/\mu} \]

The optimization problem we consider in this paper is to determine for the given set of differential equations (1-4) the optimal substrate feed rate profile \( u^*(t) \) which maximizes the final amount of product, \( C_p(t_f)V(t_f) \), subject to the following constraints:

- \( t_0 = 0, t_f = \text{free} \)
- \( C_p(t_0)V(t_0) \) and \( C_x(t_0)V(t_0) \) are given, \( C_i(t_0)V(t_0) \) is free. \( V(t_0) \) follows from \( V(t_0) = V_0C_i^{in}/[C_i^{in} - C_i(t_0)] \), with \( V_0 \) the initial volume without substrate.
- \( V(t) \) is subject to the physical constraint:
  \[ V(t_f) = V_f, \]
  \( V_f \) fixed.

OPTIMAL CONTROL

The solution to this problem using optimal control theory has been described elsewhere [Modak et al., 1986; Van Impe et al., 1991a,b]. Due to the decoupling between growth and production, the fermentation behaves as a biphasic process. The optimal profile can be summarized as follows:
The growth phase is a batch phase. All substrate consumed during growth is added all at once at time \( t_0 \), thus ensuring the highest possible specific growth rate for all \( t \). In case of an upper bound \( C_{i,\text{max}} \) on \( C_i \), the optimal feed rate keeps \( C_i = C_{i,\text{max}} \) as long as possible, whereafter a batch phase follows.

During the production phase, a singular control profile 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 maintenance, thus ensuring the lowest possible growth rate. When \( V(t) = V_f \), the fermentation continues in batch until the net penicillin formation rate (3) equals zero. As an example, consider the penicillin G fermentation process as modeled by Bajpai and Reuß [1980, 1981]. The specific rates are given by:

\[
\mu = \mu_{\text{max}} \frac{C_i}{K_x C_x + C_i} \quad \text{(Contois)}
\]

\[
\pi = \pi_{\text{max}} \frac{C_i}{K_p C_i + C_i(1 + C_i/K_i)} \quad \text{(Haldane)}
\]

The optimal control results are:

\[
\begin{align*}
C_{i,0} & = 528 \text{ g} \\
v_0 & = 28.271 \text{ g} \\
K_x & = 0.005 \text{ (g/g DW)} \\
Y_{zx} & = 0.1 \text{ (g/L)} \\
Y_{zp} & = 0.47 \text{ (g DW/g)} \\
V_f & = 63.846 \text{ g}
\end{align*}
\]

Note that the application of optimal control theory requires full knowledge of all analytic expressions and corresponding constants for the kinetics involved in the model (1-4). Further, in general the switching time \( t_s \) can not be obtained as a feedback law of state variables only. As a result, the optimal profile is very sensitive to modeling uncertainties and process disturbances. Finally, the singular control during the production phase requires on-line measurements of all state variables, a problem which has not been solved completely up to now. This motivates the search for near optimal, more robust and easy to implement feeding profiles.

**LINEARIZING CONTROL**

Assuming that \( \mu \) and \( \pi \) (and thus \( \sigma \)) are functions of \( C_i \) only, the optimal feeding rate during the production phase is given by:

\[
u_{\text{prod}} = \frac{\sigma C_i V}{C_{i,\text{in}} - C_i} + k_h F[C_i, C_x, C_p]
\]

which is linear in the hydrolysis constant \( k_h \), and a feedback law of state variables only. It can be easily seen that \( k_h = 0 \), i.e. neglecting product degradation, is a necessary and sufficient condition for \( C_i \) to be constant during the production phase. So a heuristic control law for the production phase is simply:

\[
u_{\text{prod}} = \frac{\sigma C_i V}{C_{i,\text{in}} - C_i}
\]

A reasonable choice for \( C_{i,\text{ini}} \) is the value \( C_i^* \) which maximizes \( \pi(C_i) \). By doing so, \( t_s \), is known as a function of the state: the control switches from batch to \( u_{\text{prod}} \) when \( C_i = C_i^* \). The initial substrate amount \( C_i(t_0)V(t_0) \) is the only degree of freedom left.

We obtain for the above example: \( C_{i,0}V_0 = 533 \text{ g} \), \( V_f = 63.597 \text{ g} \). Observe that this heuristic controller has an excellent performance, although \( \mu \) is function of \( C_i \) also. This can be explained as follows: the behaviour of the model with Contois kinetics (chosen by Bajpai and Reuß) is similar to a model with Monod kinetics \( \mu = \mu_{\text{max}} C_i/(K_x + C_i) \), which are function of \( C_i \) only.

This heuristic controller is a special case of the following nonlinear linearizing controller. If we want \( C_i = C_i^* \) (\( C_i^* \) constant) during the production phase, then a stable \( \lambda > 0 \) linear reference model of the tracking error is:

\[
\frac{d(C_i - C_i^*)}{dt} = -\lambda(C_i - C_i^*)
\]

Using model equation (1) and introducing boundaries on the control action, we obtain:

\[
u_0 = \frac{\sigma C_i^* - \lambda(C_i - C_i^*)V}{C_{i,\text{in}} - C_i}
\]

\[
u_0 = \begin{cases} u_0 & \text{if } 0 \leq u_0 \leq u_{\text{max}} \\ 0 & \text{if } u_0 < 0 \\ u_{\text{max}} & \text{if } u_0 > u_{\text{max}} \end{cases}
\]

Observe that this controller can be implemented from \( t = 0 \) on: during growth, \( C_i \gg C_i^* \) (provided \( C_{i,0} \) is sufficiently high), so \( u = 0 \). Further, the feed rate will switch automatically to positive values as soon as \( C_i \to C_i^* \), so the switch time \( t_s \) must not be specified a priori.
the right plot shows the optimization corresponding concentration profiles are shown in the of (3
w
533 g, we obtain
during 25 hrs, the rest is added at
500 g is fed in feed forward using a constant strategy during 25 hrs, the rest is added at
time adaptive implementation of controller (7) is
The corre-
cistion for C, can be replaced by specifying a profile for the specific growth rate (in the case of function of C, only this is even identical). So during growth, we want \( \mu \) as high as possible, while during production, we want \( \mu = \mu^*, \mu^* \) constant.
Estimating \( \mu \) can be done using the easily accessible measurement of CO2 in the effluent gas from the fermentor. At any time during the fermentation, carbon dioxide arises from (i) growth and associated energy production, (ii) maintenance energy and (iii) penicillin biosynthesis and other possible specialised metabolism [Calam and Ismail, 1980]:

\[
CER = Y_e/\mu C_a + m_o C_a + k_p
\]

where \( CER \) stands for the CO2 Evolution Rate.

A partially adaptive observer for \( C_a \) and \( \mu \) is (based on [Di Massimo et al., 1989]):

\[
\frac{d\hat{C}_a}{dt} = \frac{\hat{C}_a - \hat{C}_a u}{V + \omega(CER - \hat{CER})}
\]

\[
\hat{C}_a = \frac{\hat{C}_a - \hat{C}_a u}{V + \omega(CER - \hat{CER})}
\]

\[
\hat{C}_a = \frac{Y_e/\mu + m_o C_a + k_p}{\mu}
\]

\[
\hat{\mu} = \frac{\hat{C}_a}{C_a}
\]

\[
\hat{\sigma} = \hat{\mu}/Y_e/\mu + m_v.
\]

In the estimation of \( \sigma \) we neglected the contribution of \( \pi \). Note that this scheme requires the knowledge of the parameters \( Y_e/\mu, m_o \) and \( k_p \) (which may be all time varying), \( Y_e/\mu \) and \( m_v \), which is clearly the price to pay for estimating state variables using measurements of easily accessible auxiliary variables.

An alternative adaptive implementation of controller (7) is then (\( C_i \) is considered negligible as compared with \( C_{i,in} \)):
During simulations, we used \( Y_{e/p} = 0.4 \), \( m_p = 0.01 \) and \( k_p = 0.3 \) [Nelligan and Calam, 1983]. In the discrete time version of this controller, we added integral action to compensate for the approximations made above. The results are shown in Figure 3. A similar optimization study as mentioned higher yields \( C_pUf \frac{V_f}{U_f} = 63.630 \text{ g} \) for \( \mu^* = 1.5 \times 10^{-3} \text{ L CO}_2 /\text{g DW} \). Note that a trade-off can be made between \( C_pUf \frac{V_f}{U_f} \) and \( t_f \).

CONCLUSIONS
In this paper we presented the design of substrate feed rate controllers for a class of biotechnological processes, characterized by a decoupling between the biomass growth and the product formation. The major contribution was to show how the information obtained during optimal control studies leads to the design of suboptimal, but robust and easy to implement adaptive controllers. As an example, we considered the penicillin G fed-batch fermentation process. The trade-off between on-line measurement requirements (e.g. accessibility and accuracy) and a priori information needs (e.g. yield and maintenance coefficients) was clearly illustrated.

NOMENCLATURE
- \( t \) : time (h)
- \( C_e \) : cell mass concentration in broth (g/L)
- \( C_p \) : product concentration in broth (g/L)
- \( C_s \) : substrate concentration in broth (g/L)
- \( C_{s,in} \) : substr. conc. in feed stream (g/L)
- \( V \) : fermentor volume (L)
- \( u \) : input substrate feed rate (L/h)
- \( \alpha \) : total amount of substrate available (g)
- \( \mu \) : specific growth rate (1/h)
- \( \pi \) : specific production rate (g/g DW h)
- \( \sigma \) : sp. substr. consumption rate (g/g DW h)
- \( m_v \) : maintenance constant (g/g DW h)
- \( Y_{e/s} \) : cell mass on substrate yield (g DW/g)
- \( Y_{p/s} \) : product on substrate yield (g/g)
- \( CER \) : CO\(_2\) Evolution Rate (L CO\(_2\)/L medium/h)
- \( Y_{e/p} \) : CO\(_2\) due to growth (L CO\(_2\)/g DW)

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### REFERENCES

b \( U_r \) : relative performance index
k \( p \) : CO\(_2\) due to prod. (L CO\(_2\)/L medium/h)
m \( s \) : CO\(_2\) due to maint. (L CO\(_2\)/g DW/h)