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Optimal adaptive control of a bioprocess with yield–productivity conflict

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Abstract

This paper is concerned with the optimization of biological production processes. The process is characterized by a conflict between yield and productivity as revealed by the analysis of the model. The optimization problem is to find an operating mode that achieves the best trade off between yield and productivity. It is shown how this problem can be formulated as a parametric optimization involving parameters that have a clear engineering meaning. This parametric optimization leads to the definition of a control problem which requires a feedback implementation under the form of an adaptive regulator combined with a software sensor. A simple mechanistic model is considered as a benchmark example for this optimization study.

Keywords: Biotechnology; Multicriteria optimization; Feedback control; Adaptive algorithms

1. Introduction

We are concerned with the optimization of biological production processes. The process under consideration operates in the fed batch mode with possible withdrawals. The problem is to find the operating conditions that will guarantee the best trade off between yield and productivity. It is shown how this optimal control problem can be formulated as a parametric optimization involving two parameters that have a clear engineering meaning: (i) the amount of substrate devoted to the growth, (ii) the substrate set point during the production phase. This parametric optimization is analysed in detail with a special emphasis on the limits of performance aspects. During the production phase, the optimal control is implemented under the form of an adaptive regulation of the

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substrate concentration. The tuning of this regulator is discussed.

This process optimization follows a general methodology in three steps: characterization of the yield–productivity conflict, derivation of a parametric optimization algorithm and design of an adaptive feedback control. As a benchmark example for our presentation, we consider a simple mechanistic model which is described in the next section. This model should be viewed only as a vehicle to present our methodology in a more concrete way. Obviously other models could be used as well. They would lead to identical qualitative results provided the model exhibits clearly a yield–productivity conflict as observed in many practical applications.

2. Process and model description

The bioprocess is represented by the two following biological reactions:

$S \rightarrow X$ (R1)

$S \rightarrow P$ (R2)

with substrate S, biomass X and product P. The first reaction (R1) represents the growth of a single population of microorganisms X on a growth-limiting substrate S. The second reaction represents the biosynthesis of an extracellular secondary metabolite of interest P from the same substrate S. The process is assumed to take place in a stirred tank reactor. The substrate is fed to the reactor with a volumetric flow rate v. The process operates with withdrawals: all the species are withdrawn at the same volumetric flow rate w.

Using the species concentrations as state variables, the following standard mass balance model of the process can be written:

$$\dot{C}_s = -\sigma C_x - \frac{v}{V} C_s + \frac{v}{V} C_s^{in} \quad (1)$$

$$\dot{C}_x = \mu C_x - \frac{v}{V} C_x \quad (2)$$

$$\dot{C}_p = \pi C_x - \frac{v}{V} C_p \quad (3)$$

$$\dot{V} = v - w \quad (4)$$

where V denotes the volume, C_s, C_x, C_p denote the concentrations of the species S, X, P, respectively; v, w denote the substrate feed rate and the rate of withdrawals, respectively; C_{in}^{s} denotes the substrate influent concentration; μ, π denote the specific rates of growth and production, respectively; $\sigma = \mu / Y_{x/s} + \pi / Y_{p/s}$ denotes the substrate consumption rate with $Y_{x/s}$, $Y_{p/s}$ denoting the stoichiometric coefficients. The specific growth rate μ and the specific production rate π are described by Monod and Haldane kinetic functions, respectively:

$$\mu(C_s) = \mu_m \frac{C_s}{K_s + C_s}$$

(Monod)

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

(Haldane)

with μ_m, K_s, π_m, K_p, K_i denoting the kinetic coefficients.

The model (1)–(4) with the numerical values of Table 1 will be used as a benchmark example in this study. The functions $\mu(C_s)$ and $\pi(C_s)$ corresponding to these numerical values are shown in Fig. 1.

3. Yield–productivity conflict

3.1. Substrate feed rate profile

A standard substrate feed rate profile for the optimal control of the process (see Lim et al., 1986; Van Impe, 1993), consists of three successive phases as follows:

- 'lag phase' ($0 \leq t \leq t_o$): the process is operated in batch mode ($v = w = 0$) during a short initial period;

Table 1
Numerical values of the stoichiometric and kinetic coefficients

$Y_{x/s} = 0.99$ (g g^{-1})	$Y_{p/s} = 0.16$ (g g^{-1})	
$\mu_m = 0.13$ (h^{-1})	$K_s = 1$ (g l^{-1})	
$\pi_m = 0.005$ (h^{-1})	$K_p = 0.001$ (g l^{-1})	$K_i = 10$ (g l^{-1})

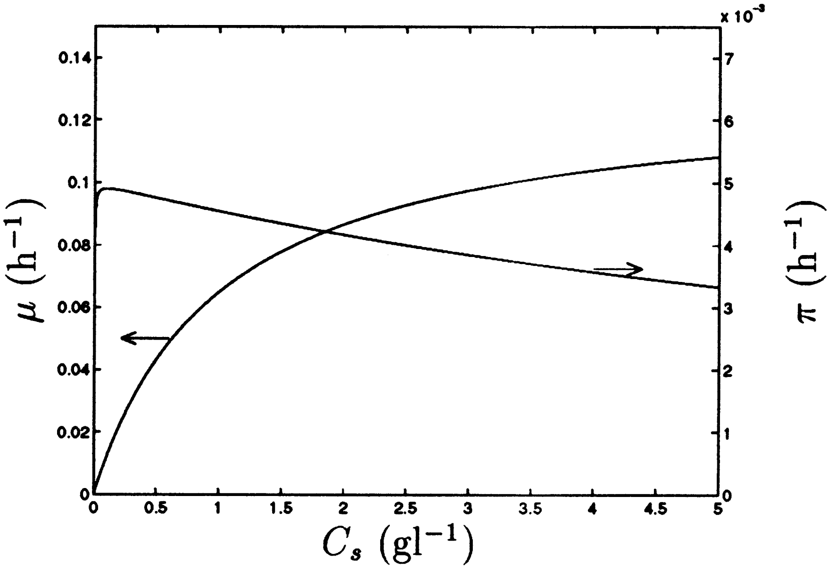

Fig. 1. Specific growth rate $\mu(C_s)$ and specific production rate $\pi(C_s)$.

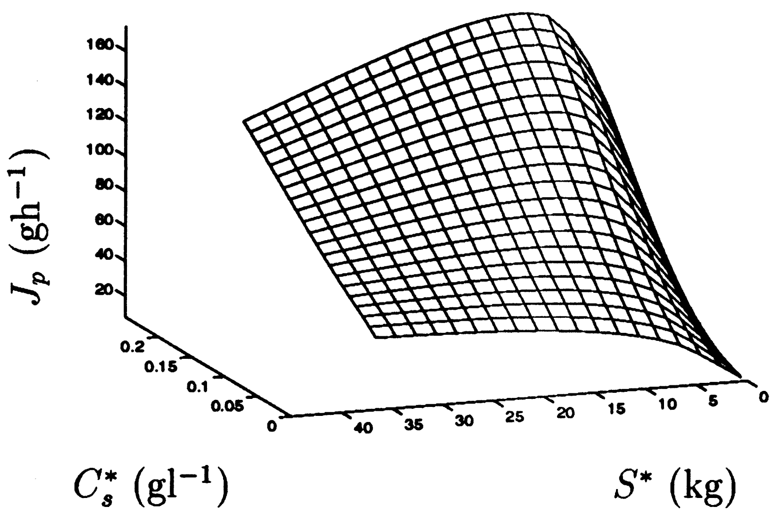

Fig. 2. Productivity J_p vs. parameters S^* and C_s^*.

- 'growth phase' ($t_o \leq t \leq t_s$): the process is operated in fed–batch mode with a constant substrate feed rate $v = v_{\mathrm{m}}$. The goal is to accumulate the biomass as fast as possible. The amount of substrate devoted to the growth phase is denoted $S^* = C_{in}^s v_m (t_s - t_0)$;
- 'production phase' ($t_s \leq t \leq t_f$): the process is operated in fed–batch mode with a substrate feed rate v controlled to maintain the substrate concentration C_s at a fixed set point C_s^*.

The optimization of this feed rate profile will be considered hereafter under the following constraints:

1. The overall duration of the process operation t_f is fixed a priori (on the basis of production planning considerations);
2. The rate w of withdrawals is set equal to the feeding rate v whenever the volume V reaches the reactor capacity $V_{\max}$, otherwise it is set to zero;

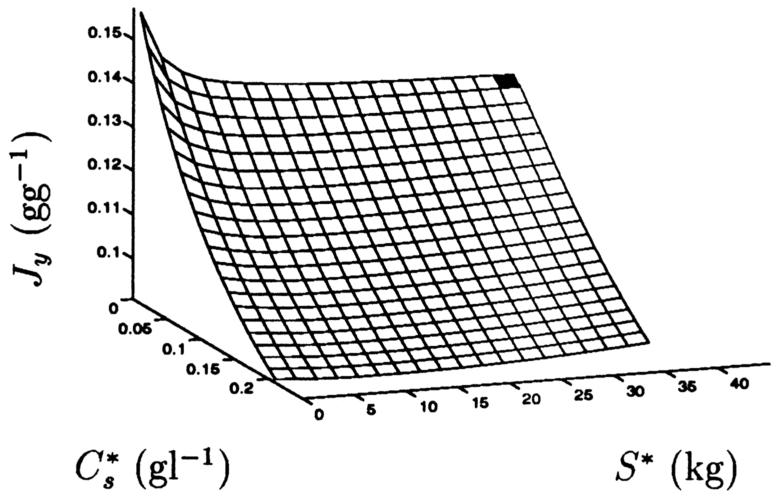

Fig. 3. Yield J_y vs. parameters S^* and C_s^*.

3. The substrate feed rate v_m is selected in order to avoid side limitations effects (such as oxygen limitation in aerobic processes, for instance).

3.2. Performance criteria

The amount of product which may be harvested at the end of operation is given by the following expression:

$$J = V(t_f)C_p(t_f) + \int_0^t w(t)C_p(t)\,dt$$

The first term of the right-hand side is the amount of product which remains in the tank. The second term is the amount of product which has been withdrawn. Then for the optimization of the process, two performance criteria are considered:

- the productivity J_p which is the production per unit of time, expressed as the ratio between the harvested amount of product and the duration of the process operation t_f;
- the yield J_y which is the production per unit of substrate fed to the reactor, expressed as the ratio between the harvested amount of product and the added amount of substrate $\int_0^t v(t)C_s^{in}\,dt$.

$$J_p = \frac{J}{t_f} \qquad J_y = \frac{J}{\int_0^t v(t)C_s^{in}\,dt}$$

The sensitivity of these criteria J_p and J_y with respect to the parameters S^* and C_s^* is illustrated in Figs. 2 and 3 under the operating conditions given in Table 2.

The following conclusions can be drawn from these figures:

1. A conflict between yield and productivity is clearly apparent: for a given S^*, the productivity J_p is an increasing function of C_s^* while the yield J_y is a decreasing function of C_s^* as best illustrated in Fig. 4 for $S^* = 18$ (kg);
2. The dependence of J_p and J_y on S^* is more intricate: in particular, it appears that there is an optimal value of S^* that maximizes the productivity J_p while the yield J_y is rather insensitive to variations of S^*.

Table 2
Operating conditions

$t_0 = 12$ (h)	$t_f = 260$ (h)
$t_s = \text{to} + S^*/(v_m C_s^{in})$ (h)	$v_m = 1$ (l h^{-1})
$C_s^{in} = 400$ (g l^{-1})	C_s (0) = 5 (g l^{-1})
C_s (0) = 2 (g l^{-1})	C_p (0) = 0 (g l^{-1})
V (0) = 250 (l)	$V_{max} = 400$ (l)

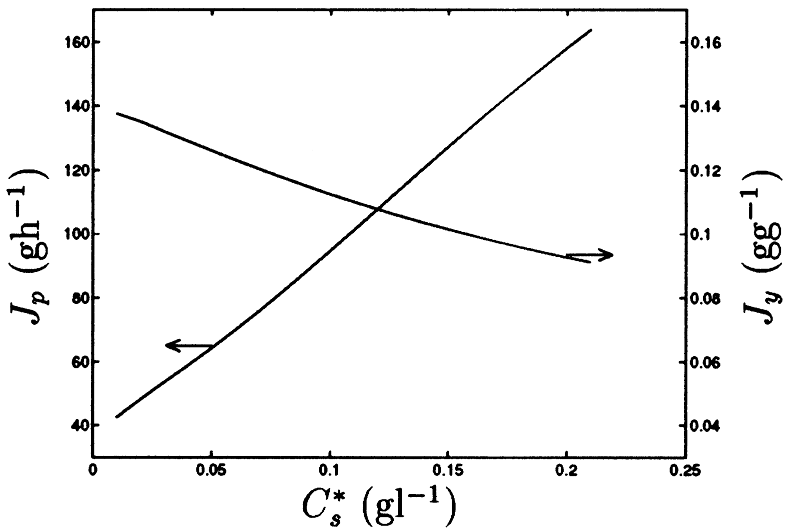

Fig. 4. Illustration of the yield–productivity conflict.

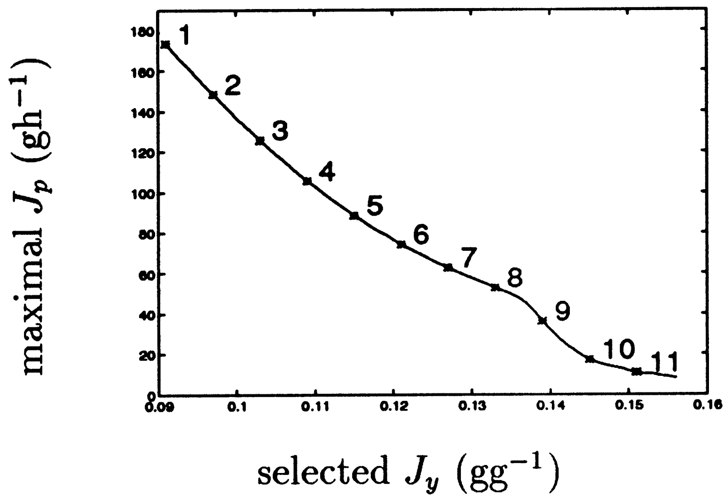

Fig. 5. Maximal achievable productivity J_p vs. selected yield J_y.

4. Process optimization

The problem is to find the optimization parameters S^* and C_s^* which correspond to the best trade off between yield and productivity. This is a typical 'multicriteria optimization' problem since the two criteria are clearly antagonistic. Motivated by the shape of the criteria J_p and J_y in Figs. 2 and 3, we propose the following algorithm:

1. Select a value of the yield J_y between 0 and $Y_{p/s}$;
2. Determine the set of the couples (S^*, C_s^*) which give this value of J_y;
3. Determine the optimization parameters S^* and C_s^* within this set that achieve the maximal productivity J_p.

The application of this algorithm to the nominal model of the process under the conditions of Table 2 gives the results that are shown in Fig. 5 where the maximal achievable values of the productivity J_p are represented for selected values of the yield J_y lying between 0.09 and 0.16 and in

Fig. 6 where the optimization parameters S^* and C_s^* which achieve the maximal productivity under the yield constraint are represented.

The following conclusions can be drawn from these figures:

1. The problem is well posed: the maximal productivity J_p is a monotonic function of the selected yield J_y, that is to say to each selected value of J_y corresponds to one and only one maximal value of J_p;
2. A yield J_y close to the theoretical yield upper bound $Y_{p/s}$, can result in a dramatic decrease of the productivity J_p (and vice-versa): it does not really make sense to optimize one of the criteria disregarding the other one;
3. The locus of the optimal couples (S^*, C_s^*) is a priori unexpected: both criteria J_p and J_y are nonmonotonic functions of the optimal S^*;
4. The insight obtained from this analysis is essentially qualitative but it can be of great help when trying to determine S^* and C_s^* by trial and error on a real-life process.

5. Adaptive feedback control

During the production phase, the substrate feed rate $v(t)$ must be such that the substrate concentration C_s, is equal to the set point C_s^*. In order to achieve this objective, a 'feedback' controller is required because a feedforward controller would be unstable, see (Van Impe and Bastin, 1995). The equations of an adaptive feedback controller are as follows:

$$v = \frac{\hat{\sigma}\hat{C}_x + \frac{u}{V}C_s^m + \lambda(C_s^* - C_s^m)}{V^{-1}(C_s^{in} - C_s^m)} \tag{5}$$

$$\dot{\hat{\sigma}} = \frac{\kappa(C_s^* - C_s^m)}{\hat{C}_x} \tag{6}$$

where $\hat{C}_x$ and $\hat{\sigma}$ denote on-line estimates of the biomass C_x and the substrate consumption rate σ and λ, κ are positive design parameters. The on-line estimate $\hat{C}_x$ is provided by a model based adaptive observer (software sensor). This is a particular case of a general adaptive control scheme described in Bastin and Dochain (1990). Eq. (6) is the adaptation law obtained from a Lyapunov design while Eq. (5) is the control law derived from the principle of feedback linearizing control. Let us briefly discuss the tuning of the controller. We assume that the adaptive controller (5)–(6) is applied to the model (1)–(4) during the production phase for a set point $C_s^* = 0.1$ (g l^{-1}) under the conditions of Table 2 with $S^* = 14$ (kg).

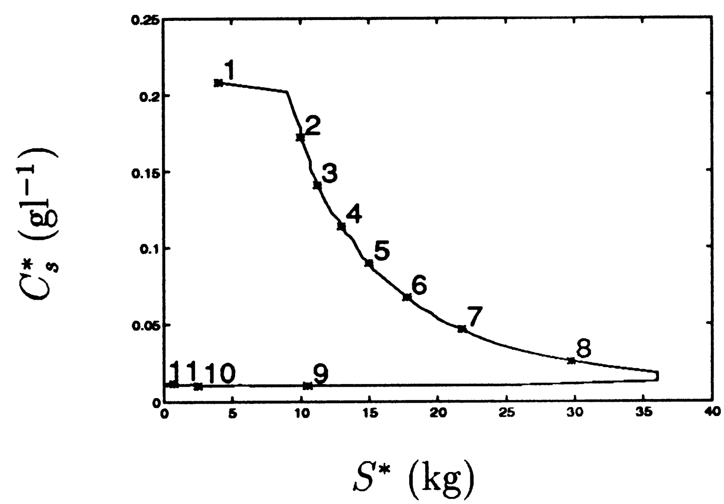

Fig. 6. Optimal set point of the substrate concentration during the production phase C_s^* vs. the optimal value of the substrate for growth S^*.

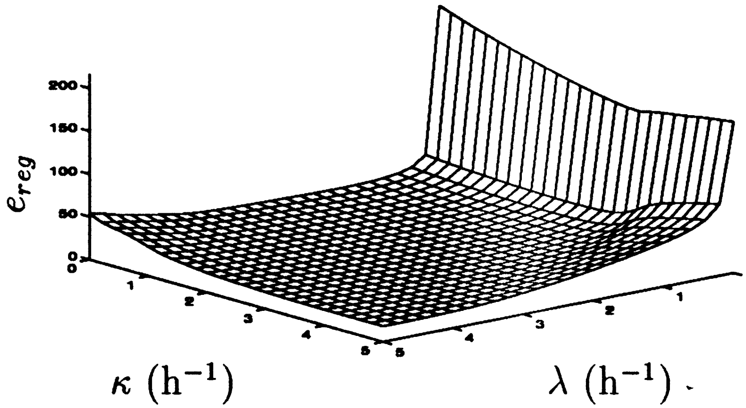

Fig. 7. Performance of the adaptive controller.

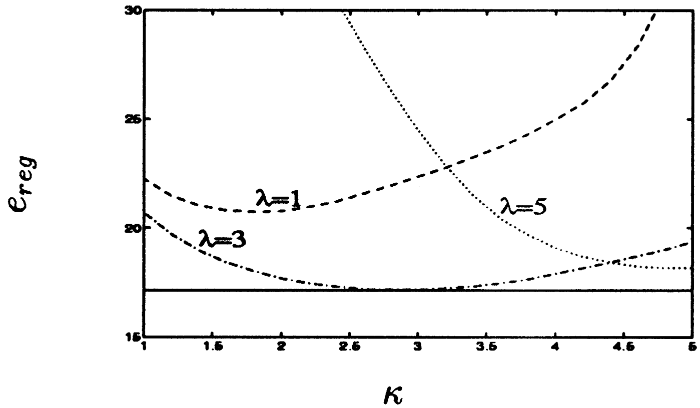

Fig. 8. Tuning of the design parameters.

Moreover, some measurement noise is introduced in order to obtain realistic measurements from simulations of the nominal model of the process. The relative mean square regulation error is defined as:

$$e_{reg} = \frac{100}{C_s^*}\sqrt{\int_{ts}^{tf}\frac{(C_s(t) - C_s^*)^2}{t_f - t_s}}$$

It is represented in function of the design parameters λ and κ in Fig. 7.

As expected, a dramatic increase of the relative mean square regulation error e_{reg} occurs as the couple (λ, κ) tends to zero, the increase being more important with $\lambda \rightarrow 0$ than with $\kappa \rightarrow 0$. Moreover, there exists an optimal choice of the design parameters which corresponds to $\lambda = 3$ and $\kappa = 3$ as best illustrated in Fig. 8.

6. Conclusion

We have presented an approach for the optimization of a bioprocess for the production of a secondary metabolise with a yield–productivity conflict. This process of optimization follows a general methodology in several steps: characterization of the yield–productivity conflict, derivation of a parametric optimization algorithm and design of an adaptive feedback control. The yield–productivity conflict is characteristic of many practical applications. The problem of finding the best trade off between yield and productivity is solved through a parametric optimization. The involved optimization parameters have a clear engineering meaning. The optimization algorithm leads to the implementation of an adaptive controller coupled with an adaptive observer.

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References

Bastin, G., Dochain, D., 1990. On-line estimation and adaptive control of bioreactors. Elsevier, Amsterdam.

Lim, H.C., Tayeb, Y.J., Modak, J.M., Bonte, P., 1986. 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.

Van Impe, J.F., 1993. Modelling and Optimal Adaptive Control of Biotechnological Processes. PhD thesis, ESAT, Katholieke Universiteit Leuven, Belgium.

Van Impe, J.F., Bastin, G., 1995. Optimal adaptive control of fed-batch fermentation processes. Control Eng. Pract. 3, 939–954.