Singular Optimal Control Strategy for a Fed-Batch Bioreactor: Numerical approach

The production of bakers' yeast in a fed-batch bioreactor can be maximized by controlling the substrate feed rate. This leads to a singular optimal control problem. An exact solution initially based on a heuristic argument and later quantified by the generalized Legendre-Clebsch convexity condition is obtained. A numerical technique, obtained by embedding the singular problem in a sequence of nonsingular problems that converge to the singular one in a limit as $\epsilon \rightarrow \infty$ is demonstrated.

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Introduction

The production of many biochemicals requires the growth of microorganisms. In general the fermentor productivity depends strongly upon the concentration of the cells present. Thus, an impetus exists for developing fermentor operating strategies that maximize the cell concentration. The growth rate of a cell culture depends on its environment, subject to metabolic constraints inherent to the organism. Some of the important environmental variables include nutrient concentration, temperature, and pH. Such complexity of the biological processes requires simple though realistic mathematical descriptions of growth in order to develop operating strategies to maximize the cell concentration.

Several fermentation processes in practice are neither continuous nor batch but are semicontinuous. In these processes, the feed rate may not equal the harvest rate (exit stream). Such an operation with noncontinuous harvesting is known as fed-batch, and is used in the production of bakers' yeast. Yeast produces undesirable ethanol if excess sugar accumulates in the medium, even in the presence of sufficient oxygen for its complete oxidation; for example see Fiechter, et al. (1981). Although yeast can utilize ethanol as a carbon source, the growth rate is considerably lower than that obtained on sugar. Therefore, in principle, the sugar should be fed to the bioreactor such that it minimizes ethanol formation, yet prevents glucose starvation.

The optimization of a fed-batch bioreactor for maximum cells results in a nonlinear singular control problem. The singularity arises because of the linear dependence of sugar concentration on the feed rate. A numerical technique based on the epsilon method of Jacobson et al. (1970), is developed for determining the solution of the singular control problem. A reduced form of the growth model is used for technique development. The validity of this technique is demonstrated by comparing the solution with an exact solution derived first by a heuristic argument and later substantiated by invoking the Legendre-Clebsch convexity condition.

Several investigators have explored optimal control of fermentation processes, and reviews of this area have been reported by Weigand (1978) and Zabriskie (1979). Pontryagin's principle was used to obtain the optimal temperature and pH control in batch penicillin fermentation (Constantinides et al., 1970a,b; Rai and Constantinides, 1973), the optimal feed policy for the maximum metabolite yield in a fed-batch culture modeled by the Monod equation (Weigand, 1978), and the asymptotic case of repeated fed-batch culture of bakers' yeast where the cell concentration becomes time-invariant (Weigand et al., 1979; Weigand, 1981). A simple controller for an open-loop suboptimal temperature profile in a fixed-time batch fermentation was devised using Fletcher-Powell minimization with a nonlinear parameter-space transformation (King et al., 1974). Green's theorem has been applied to circumvent the singularity of the problems for maximizing the bacterial growth modeled by the Haldane-Monod function in a continuous culture (D'Ans et al., 1972). A combination of Pontryagin's principle with Kelly's transformation (Ohno et al., 1978) and with Green's theorem (Takamatsu et al., 1975, and Ohno et al. 1976) has also been used for optimal production of amino acids.

Singular optimal control problems are encountered in other fields as well and present a formidable task in obtaining the optimal control law (Bell and Jacobson, 1975). The various algorithms for solving the nonsingular problems are not usable in the singular case. The algorithms that are able to handle the singularity are of the first order or the gradient type, and have been shown to behave particularly poorly (Johansen, 1966) when applied to singular optimal control problems. Very few techniques have been reported in the literature for calculating the

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singular optical control trajectory. A judicious combination of control and state variables as independent variables (Mehra and Davis, 1972) can result in the control problem being nonsingular in these variables. This approach is problem-dependent and is not systematized yet. The Davidon and Broyden parameter optimization methods were extended to the function space (Edge and Powers, 1976) to compute the optimal control. The approximate solutions have also been obtained by spanning the finite-dimensional subspaces by suitable basis functions. Different variations of the Ritz method, where splines (piecewise polynomials) are used as basis functions, have been used for nonsingular problems (Sirisena and Chou, 1979). Balakrishanan's epsilon method (Balakrishanan, 1968) was extended in a Raleigh-Ritz expansion (Taylor and Constantinides, 1972a,b) and was demonstrated on a partially singular control problem (Shmueli and Steinberg, 1981).

The technique of the present study is based upon the method of Jacobson et al., (1970) in which the performance index is augmented by addition of a quadratic term in the control vector, $\boldsymbol{u}$

$$\epsilon \int_{t_0}^{t_1} \langle \boldsymbol{u}, \boldsymbol{u} \rangle \, dt$$

where ϵ is a parameter tending to zero in the limit. This augmentation transforms the original singular control problem into a sequence of nonsingular problems for which solutions can be obtained.

The Optimization Problem

A semicontinuous fermentor with biomass as the primary product can be modeled as follows. If perfect mixing with no metabolite formation is assumed and density variations are negligible, the material balance on cells X, the substrate S, and the overall system yields

$$\frac{d(VX)}{dt} = \mu VX - F_o X \tag{1}$$

$$\frac{d(VS)}{dt} = F_i S_i - F_o S - \frac{\mu VX}{Y_{x/s}} - m_s VX \tag{2}$$

$$\frac{d(V)}{dt} = F_i - F_o \tag{3}$$

where μ is the specific growth rate given by the Haldane-Monod function

$$\mu = \frac{\mu_m S}{K_1 + S} \cdot \frac{K_2}{K_2 + S} \tag{4}$$

The above expresses the catabolic repression at high substrate concentrations. Although this is a simple model of catabolic repression, it is useful in numerical technique development. A more comprehensive growth model and its optimization is currently under study. The term m_s is the rate of substrate consumption by the cells for their maintenance. The glucose concentration in the feed is constant at S_i. Additional constraints in a physical system are

$$0 \le F_i \le F_{i,\max}$$
$$0 \le F_o \le F_{o,\max}$$
$$0 < V \le V_{\max} \tag{5}$$

The general problem is that of finding $F_i(t)$ and $F_o(t)$ such that the amount of cells harvested over a period of time is maximized subject to the above constraints. Here we shall consider the optimum fed-batch fermentor, whose operating characteristics are given by fixed batch time ($t_0 \le t \le t_1$) and no continuous harvesting ($F_o(t) = 0$).

The model can be put into a nondimensional form by defining the following variables

$$x = \frac{X}{K_2 Y_{x/s}} \quad s = \frac{S}{K_2} \quad v = \frac{V}{V_0}$$
$$\tau = \mu_m t \quad u = \frac{F_i}{\mu_m V_0}$$
$$\beta_1 = \frac{K_1}{K_2} \quad \beta_2 = \frac{m_s Y_{x/s}}{\mu_m} \quad s_i = \frac{S_i}{K_2}$$

The values of the model parameters are:

$$K_1 = 0.5 \quad K_2 = 500 \quad Y_{x/s} = 0.5$$
$$V_0 = 1.0 \quad \mu_m = 0.5 \quad m_s = 0.0, 0.05, 0.5$$

The nondimensional model is as follows:

$$x' = \frac{sx}{(\beta_1 + s)(1 + s)} - \frac{xu}{v} \tag{6a}$$

$$s' = \frac{u}{v}(s_i - s) - \frac{sx}{(\beta_1 + s)(1 + s)} - \beta_2 x \tag{6b}$$

$$v' = u \tag{6c}$$

The objective function may include minimization of the operating costs (energy, residual substrates, feed), the fixed costs (maximum volume), and the maximization of the products. In this study the objective is to maximize the amount of biomass produced at the end of one fed-batch cycle with nutrient feed rate as the control or the manipulated variable. It is an important criterion because the majority of the primary metabolites are growth-related, that is their production is directly linked with the cell production. Furthermore, many microorganisms, for example yeasts, are commodity products, thus maximization of the biomass is a desirable criterion. The performance index may be written as

$$J[u(\cdot)] = \inf_{u(\cdot)} \{x(\tau_0)v(\tau_0) - x(\tau_1)v(\tau_1)\} \tag{7}$$

A Heuristic Solution

The optimization problem described above can be solved by physical insight into the dynamic process. For example, the growth of the cells expressed by Eq. 4 is a concave function;

therefore, a unique maximum exists at $s^* = \sqrt{\beta_1}$; thus

$$\mu^* = \frac{1}{2\sqrt{\beta_1} + (1 + \beta_1)} \tag{8}$$

If the instantaneous growth rate of the cells were maintained at the rate expressed by Eq. 8, the fermentor would produce cells at the maximum possible rate at all times, resulting in maximum cell production over one batch period. In the present formulation, maintaining the specific growth rate at the maximum implies the manipulation of feed substrate, such that the substrate concentration in the fermentor is maintained at $s^* = \sqrt{\beta_1}$. This heuristic approach is similar to the quasi steady state assumption of Dunn and Mor (1975) and the extended culture model presented by Lim et. al. (1977).

The above discussion of substrate concentration being constant at s^* enables us to set the derivative $(ds/dt) = 0$ in Eq. 6b. Solving for the control variable u yields the feedback control law:

$$u^* = \frac{\mu^* + \beta_2}{s_i - s^*} xv \tag{9}$$

The trajectories of the states x and v and of the control u are analytically evaluated as:

$$x^* = \frac{\mu^* \exp[\mu^*(\tau - \tau_0)]}{\left(\frac{\mu^* + \beta_2}{s_i - s^*}\right)\left\{\exp[\mu^*(\tau - \tau_0)] - 1\right\} + \frac{\mu^*}{x_0}} \tag{10}$$

$$v^* = \frac{x_0}{\mu^*}\left(\frac{\mu^* + \beta_2}{s_i - s^*}\right)\left\{\exp[\mu^*(\tau - \tau_0)] - 1\right\} + 1 \tag{11}$$

$$u^* = x_0\left(\frac{\mu^* + \beta_2}{s_i - s^*}\right)\exp[\mu^*(\tau - \tau_0)] \tag{12}$$

The above equations describe the cell concentration, the fermentor volume, and the feed rate that maximize the instantaneous cell growth rate.

The expontential feeding profile presented above will be called the heuristic solution. It is illustrated in Figure 1 in terms of the cell mass ($\xi_1 = x \cdot v$), the substrate ($\xi_2 = s \cdot v$), and the volume ($\xi_3 = v$) in the fermentor. It is interesting to note from Eq. 10 that as τ approaches infinity, the cell concentration approaches the limit

$$\lim_{\tau \to \infty} x^* \longrightarrow \frac{s_i - s^*}{1 + \{\beta_2/\mu^*\}} \tag{13}$$

This condition corresponds to the continuous fermentor or chemostat dilution rate $D = \mu^*$ (holdup time $\theta = 1/\mu^*$). The control policy given in Eq. 12 can also be interpreted as the optimal start-up policy for a chemostat expected to operate at optimum dilution rate equal to μ^*. Equation 13 gives the maximum cell concentration attainable in the fed-batch fermentor and is proportional to the difference between feed substrate concentration and optimum concentration for growth. Additionally, when $(\beta_2/\mu^*) \longrightarrow 0$, the maximum cell concentration is $(s_i - s^*)$,

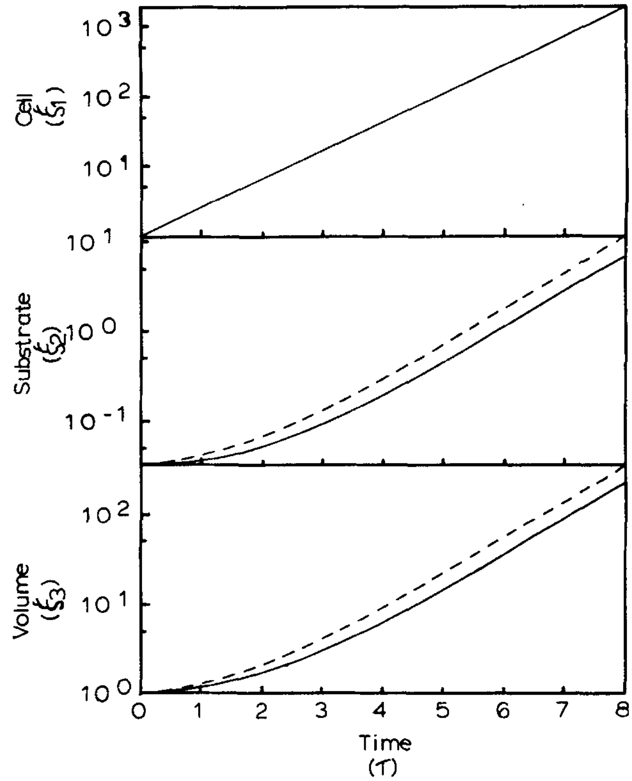

Figure 1. State trajectories of the optimal fed-batch fermentor obtained by the heuristic argument.
--- $\beta_2 = 0.5$; — $\beta = 0.0$

which conforms with the stoichiometric conversion model of a chemostat.

An Analytical Solution

The control function $\omega(\cdot)$ for a Bolza problem (Fleming and Rishel, 1975) that minimizes the performance functional

$$J[\omega(\cdot)] = \inf_{\omega(\cdot)} \left\{L[\alpha(\theta_1), \theta_1] + \int_{\theta_0}^{\theta_1} G[\alpha, \omega, \theta]\, d\theta\right\} \tag{14}$$

with system equations given by

$$\alpha' = h[\alpha, \omega, \theta] \quad \alpha(\theta_0) = \alpha_0 \quad \theta \epsilon [\theta_0, \theta_1] \tag{15}$$

can be obtained using Pontryagin's principle. The associated Hamiltonian is

$$H[\alpha, \omega, \lambda, \theta] = G[\alpha, \omega, \theta] + \lambda^t \cdot h[\alpha, \omega, \theta] \tag{16}$$

and the necessary conditions that hold along the optimal trajectory are

$$-\lambda' = H_\alpha[\alpha^\#, \omega^\#, \lambda, \theta] \tag{17}$$

$$\lambda(\theta_1) = L_\alpha[\alpha^\#(\theta_1), \theta_1] \tag{18}$$

$$H(\theta_1) = -L_\theta[\alpha^\#(\theta_1), \theta_1] \tag{19}$$

where

$$\omega^{\#} = \{\omega : \inf H[\alpha^{\#}, \omega, \lambda, \theta]\} \tag{20}$$

The $\lambda(\cdot)$ denotes an n-dimensional vector of the adjoint states that are functions of time, and $\alpha^{\#}(\cdot)$ and $\omega^{\#}(\cdot)$ are the candidate state and control functions, respectively.

An extremal arc of the control problem, with unbounded controls, is singular if the determinant $H_{\omega\omega}$ vanishes at any point along the optimal trajectory. In other words, if the Hamiltonian H is linear in one or more elements of the control function then, $\det(H_{\omega\omega})$ vanishes, resulting in a singular problem. If all of the elements of the control vector ω are singular simultaneously then it is called a totally singular control function. For the minimum of Hamiltonian consider the Euler condition

$$H_{\omega}[\alpha^{\#}, \omega, \lambda, \theta] = 0 \quad \forall \theta \epsilon [\theta_0, \theta_1] \tag{21}$$

In addition to H_{ω} being zero over a finite interval of time, its time derivative must also vanish over the same interval of time. Successive differentiation with respect to time will eventually yield an explicit relationship between the optimal control vector ω and the state and adjoint state vectors. It has been shown that an even number of derivatives with respect to time is needed for an explicit solution (Bell and Jacobson, 1975). Such a relationship, called the generalized Legendre-Clebsch convexity condition, can be expressed by

$$\frac{\partial}{\partial \omega} \cdot \frac{d^p}{d\theta^p} H_{\omega} = 0 \quad \forall \theta \epsilon (\theta_0, \theta_1) \text{ and } p - \text{odd} \tag{22}$$

and

$$(-1)^q \frac{\partial}{\partial \omega} \cdot \frac{d^{2q}}{d\theta^{2q}} H_{\omega} \geq 0 \quad \forall \theta \epsilon (\theta_0, \theta_1) \tag{23}$$

where q is called the order of the singular arc.

When the control function is scalar and appears linearly in the state equation, Eq. 15 can be written as

$$\alpha' = f(\alpha) + g(\alpha) \cdot \omega \tag{24}$$

When the performance functional is not an explicit function of the control variable ω one may show that the optimal control law is a singular arc of order unity and is given by (Bryson and Ho, 1975; Brockett, 1978)

$$\omega = -\frac{\lambda'[f, l]}{\lambda'[g, l]} \tag{25}$$

with $l = [f, g]$ and $[\cdot, \cdot]$ the Lie bracket defined by $[b, a] = (a_{\alpha} b - b_{\alpha} a)$.

The fed-batch fermentor problem given by Eq. 6 can be restructured in the form of Eq. 24 by defining the state vector $\alpha' = [x, s, v]$, the control function $\omega = u$ and the vector functional $f(\alpha)$ and $g(\alpha)$ of Eq. 24 as

$$f(\alpha) = \begin{bmatrix} \dfrac{sx}{[\beta_1 + s][1 + s]} \\ -\left(\dfrac{sx}{[\beta_1 + s][1 + s]} + \beta_2 x\right) \\ 0 \end{bmatrix}; \quad g(\alpha) = \begin{bmatrix} -\dfrac{x}{v} \\ \dfrac{s_i - s}{v} \\ 1 \end{bmatrix}$$

with $\alpha_0' = [x_0, s_0, v_0]$. The Hamiltonian is written as

$$H = \left[\frac{\lambda_s(s_i - s)}{v} - \frac{\lambda_x x}{v} + \lambda_v\right] u + \left[\frac{(\lambda_x - \lambda_s) x s}{[\beta_1 + s][1 + s]} - \beta_2 x \lambda_s\right] \tag{26}$$

where the adjoint state vector, $\lambda' = [\lambda_x, \lambda_s, \lambda_v]$, is given by

$$\lambda_x' = -\frac{(\lambda_x - \lambda_s)s}{(\beta_1 + s)(1 + s)} + \frac{\lambda_x u}{v} + \beta_2 \lambda_s \tag{27a}$$

$$\lambda_s' = \frac{(\lambda_x - \lambda_s)(\beta_1 - s^2)x}{[(\beta_1 + s)(1 + s)]^2} + \frac{\lambda_s u}{v} \tag{27b}$$

$$\lambda_v' = \left[\frac{\lambda_s(s_i - s) - \lambda_x x}{v^2}\right] u \tag{27c}$$

with $\lambda(\tau_1)' = [-v(\tau_1), 0, -x(\tau_1)]$.

The Euler necessary condition, $H_{\omega} = 0$, for the above problem is

$$\frac{\lambda_s(s_i - s)}{v} - \frac{\lambda_x x}{v} + \lambda_v = 0 \tag{28}$$

Since the control function u does not occur explicitly in the above equation, the first time derivative, $H_{\omega}' = 0$, is evaluated

$$\frac{(\lambda_x - \lambda_s)(\beta_1 - s^2)(s_i - s)x}{[(\beta_1 + s)(1 + s)]^2 v} = 0 \tag{29}$$

Three nontrivial solutions to the above equation exist:

Solution I: $(\beta_1 - s^2) = 0$. This results in the optimal control law requiring the substrate concentration in the fermentor to remain constant at $\sqrt{\beta_1}$. It is identical to the condition derived by the heuristic approach. Hence, the heuristic solution is a possible candidate for the optimal solution.

Solution II: $(\lambda_x - \lambda_s) = 0$. If $(\lambda_x - \lambda_s)$ vanishes along the entire length of the singular arc $[\tau \epsilon (\tau_0, \tau_1)]$, then its time derivative must also vanish, i.e., $\lambda_x' = \lambda_s'$. It is evident from Eqs. 27a and 27b that $\beta_2 \lambda_s = 0$; since β_2 is a nonzero (positive) system parameter, λ_s must vanish and thus λ_x also. Since the control variable is unconstrained, the trajectory at the terminal time τ_1 also lies on the singular arc. In other words, the singular trajectory must also satisfy the boundary conditions. Although the condition $\lambda_x = \lambda_s = 0$ satisfies the boundary condition on λ_s, it does not meet the required conditions on λ_x, since $\lambda_x(\tau_1) = -v(\tau_1)$ and $v(\tau_1)$ is nonzero. Hence, it may be concluded that this is not a feasible solution.

Solution III: $(s_i - s) = 0$. This solution requires s to be a constant at s_i along the optimal trajectory, implying $s' = 0$. It can be seen from Eq. 6b that x must vanish along the singular arc for this condition to be satisfied. It is thus a trivial solution.

From the foregoing discussion it is apparent that the heuristic solution qualifies as a candidate for the extremal. However, an important constraint is realized from solution III, that is $(\beta_1 - s_i^2) \neq 0$, for obtaining an optimal trajectory.

The control law for the first-order singular arc, given by Eq.

25, for the fed-batch bioreactor problem yields:

$$u^* = \left(\frac{xv}{s_i - s}\right)\left[\frac{s}{(\beta_1 + s)(1 + s)} + \beta_2\right] - \left[\frac{\lambda_s}{\lambda_x - \lambda_s}\right]\left\{\frac{\beta_2(\beta_1 - s^2)x}{\Upsilon[(\beta_1 + s)(1 + s)]^2}\right\} \quad (30)$$

where Υ is given by

$$\Upsilon = \frac{-s^4 + [2s_i + (1 + \beta_1)]s^3 + 6\beta_1 s^2 + [\beta_1(1 + \beta_1) - 6\beta_1 s_i]s - [\beta_1^2 + 2(1 + \beta_1)\beta_1 s_i]}{[(\beta_1 + s)(1 + s)]^3 v}$$

The first term in Eq. 30 is identical to the feedback control law of Eq. 9 obtained by the heuristic approach with $s = s^*$. The second term in the above equation vanishes over the entire domain of the singular arc since the time derivative of the Euler condition ($H_\omega = 0$) vanishes only when $s^2 = \beta_1$.

The Legendre-Clebsch condition for the first-order singular arc becomes

$$\lambda^t[g, l] \leq 0 \quad (31)$$

which for the present problem with $\beta_1 = s^2$ is

$$\frac{(\lambda_x - \lambda_s)\Upsilon(s_i - \sqrt{\beta_1})}{v} \geq 0 \quad (32)$$

This condition can be weakly satisfied by $s_i^2 = \beta_1$ resulting in $\Upsilon = 0$. However at this point the control functional becomes nonanalytic. At the terminal point where $\lambda_x(\tau_1) = -v(\tau_1)$ and $\lambda_s(\tau_1) = 0$, the strengthened form of Eq. 32 reduces to

$$\frac{2\mu^{*2}}{v\beta_1\sqrt{\beta_1}}(s_i - \sqrt{\beta_1})^2 > 0 \quad (33)$$

This would always be satisfied as long as $s_i^2 \neq \beta_1$, which agrees with the earlier observation.

Numerical Solution

The basic numerical approach taken here is to convert the singular control problem into a sequence of nonsingular control problems by augmenting a nonlinear function in the control variable. Although this approach was proposed by Jacobson et al. (1970), very few singular problems have been solved using this technique. The performance index given by Eq. 14 is modified to

$$J[\omega(\cdot), \epsilon] = \inf_{\omega(\cdot)}\left\{L[\alpha(\theta_1), \theta_1] + \int_{\theta_1}^{\theta_2}\{G[\alpha, \omega, \theta] + \frac{1}{2\epsilon}\omega^t\omega\}\,d\theta\right\} \quad (34)$$

where $\epsilon \neq 0$. (This is a modification of Jacobson's algorithm. The embedding parameter ϵ is present in the denominator instead of the numerator as originally proposed. Such a modification has significantly better numerical stability for the present problem. Further, Jacobson et al. used a differential dynamic programming algorithm instead of direct integration.)

The performance index for the fed-batch bioreactor given by Eq. 7 is written as

$$J[u(\cdot), \epsilon] = \inf_{u(\cdot)}\left[x(\tau_0)v(\tau_0) - x(\tau_1)v(\tau_1) + \frac{1}{2\epsilon}\int_{\tau_0}^{\tau_1} u^2 d\tau\right] \quad (35)$$

The Euler necessary condition, $H_\omega = 0$, for this new functional becomes

$$\frac{\lambda_s(s_i - s)}{v} - \frac{\lambda_x x}{v} + \lambda_v + \frac{1}{\epsilon}u = 0 \quad (36)$$

This provides an expression for u in terms of the state vector, the adjoint state vector, and the parameter ϵ. A series of solutions can now be obtained by varying the value of ϵ. As $\epsilon \to \infty$, the augmented term in Eq. 35 approaches zero and the righthand side of Eq. 35 converges to the original optimal control problem.

The system of Eq. 6 for the state variables, Eq. 27 for the adjoint state variables, along with Eq. 36 for the control variable u, constitutes a six-dimensional system that is ill-conditioned. The conditioning of this system is improved by defining the instantaneous cell and substrate masses as the state variables instead of their concentrations. The new state variables are: $\xi_1 = x \cdot v$; $\xi_2 = s \cdot v$; $\xi_3 = v$. The new state equations become

$$\xi_1' = \frac{\xi_1\xi_2\xi_3}{(\beta_1\xi_3 + \xi_2)(\xi_3 + \xi_2)} \quad (37a)$$

$$\xi_2' = s_i u - \frac{\xi_1\xi_2\xi_3}{(\beta_1\xi_3 + \xi_2)(\xi_3 + \xi_2)} - \beta_2\xi_1 \quad (37b)$$

$$\xi_3' = u \quad (37c)$$

with the associated adjoint state (η) equations as

$$\eta_1' = \frac{(\eta_2 - \eta_1)\xi_2\xi_3}{(\beta_1\xi_3 + \xi_2)(\xi_3 + \xi_2)} + \eta_2\beta_2 \quad (38a)$$

$$\eta_2' = \frac{(\eta_2 - \eta_1)\xi_1\xi_3(\beta_1\xi_3^2 - \xi_2^2)}{[(\beta_1\xi_3 + \xi_2)(\xi_3 + \xi_2)]^2} \quad (38b)$$

$$\eta_3' = \frac{-(\eta_2 - \eta_1)\xi_1\xi_2(\beta_1\xi_3^2 - \xi_2^2)}{(\beta_1\xi_3 + \xi_2)(\xi_3 + \xi_2)} \quad (38c)$$

The performance index of Eq. 35 is rewritten in the new variables as

$$J[u(\cdot), \epsilon] = \inf_{u(\cdot)}\left[\xi_1(\tau_0) - \xi_1(\tau_1) + \frac{1}{2\epsilon}\int_{\tau_0}^{\tau_1} u^2 d\tau\right] \quad (39)$$

The control variable u along the optimal trajectory using the Euler condition is given by

$$u = -\epsilon[s_i\eta_2 + \eta_3] \quad (40)$$

The backward integration of Eqs. 37 and 38 along with Eq. 40 was performed by a third-order semiimplicit Runge-Kutta method with Richardson extrapolation to attain fourth-order accuracy. The step size was automatically adjusted to meet the allowed maximum relative error of 10^{-6} in each step. The results are presented in Figures 2 to 4 for $\beta_2 = 0.0$ and 0.5. The solution for $\beta_2 = 0.05$ was also computed but not shown here since the profiles are similar to those for $\beta_2 = 0.0$. Details of calculation schemes and other numerical results may be found in Menawat (1986).

The parameter ϵ can be viewed as a weighting factor for the two terms in the performance index (cf. Eq. 35). When ϵ is small, i.e., approaches zero, the first term becomes negligible in magnitude compared to the second. Hence, the functional being minimized is the instantaneous quadratic feed rate. The minimum value for this would be attained, by inspection, when there is no feed to the system, i.e., when u is identically equal to zero along the entire length of the trajectory. This results in batch mode operation of the bioreactor. This is shown in Figure 2 for $\epsilon = 10^{-15}$ for two different values of β_2 (the nondimensional maintenance coefficient). The trajectories obtained are identical, to five significant digits, to the batch growth trajectories.

A shift from the domination of the second term in Eq. 35 to the first term occurs as ϵ gets larger. For the present problem the total shift is observed when ϵ attains the value of 10^8, shown in Figure 3. The trajectories for different values of ϵ are identical, again up to five significant digits, with the exact solution trajectories. As expected, the substrate mass curve is equal to the volume curve multiplied by $\sqrt{\beta_1}$, which is the substrate concentration for the maximum growth rate. It is interesting to note that the value of ϵ required for the convergence is not very large numerically and is within reasonable computational capabilities. The ϵ was further increased to 10^{10}, 10^{12}, and 10^{15}, resulting in identical trajectories; hence the convergence was confirmed (Menawat, 1986). A reduction in integration time is a favorable consequence of further increasing the value of ϵ. Table 1 compares the number of steps required for integration for the maximum allowable relative error of 10^{-6} at each step. A ten-millionfold increase in the value of ϵ ($10^8 \rightarrow 10^{15}$) resulted in a sixteen- to fortyfold decrease in the number of steps needed.

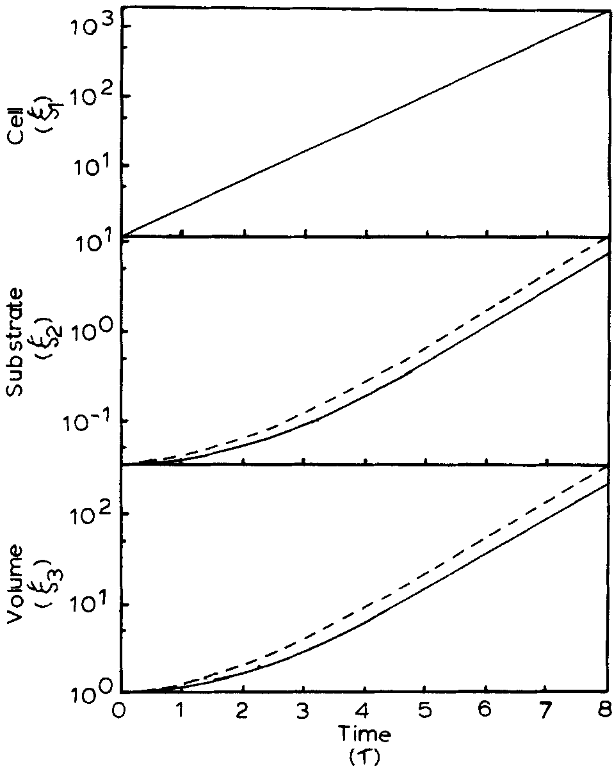

Figure 3. State trajectories obtained using epsilon method with $\epsilon = 10^8$.
--- $\beta_2 = 0.5$; — $\beta = 0.0$

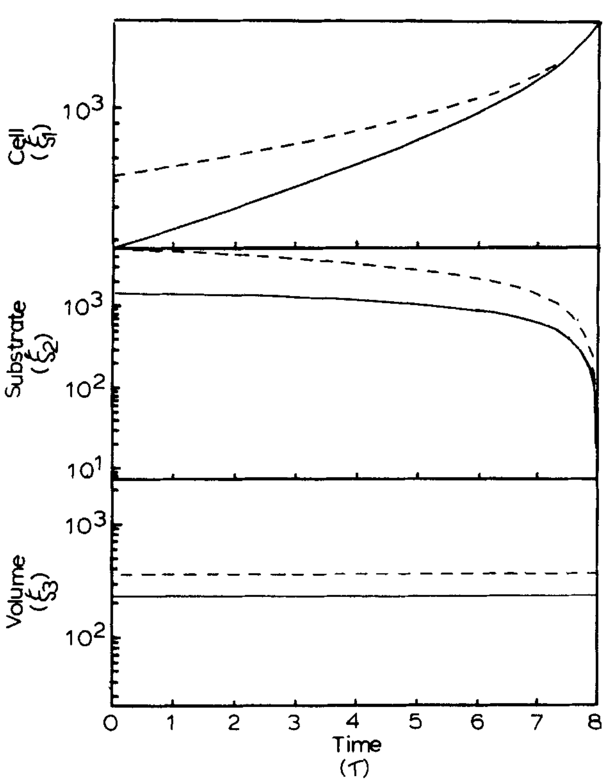

Figure 2. State trajectories obtained using epsilon method with $\epsilon = 10^{-15}$.
--- $\beta_2 = 0.5$; — $\beta = 0.0$

The difficulties encountered in this method occur when the two terms of the performance index are of comparable value, i.e., the system tries to produce maximum cell mass but has to pay a severe penalty to feed the substrate to the system. The weighting factor ϵ is a reciprocal indicator of this penalty. Therefore, for each value of ϵ a different optimal control problem is solved. For an unconstrained optimal control problem, the system behaves chaotically. This was observed at values of ϵ between 10^0 to 10^6 in this study. An example of this behavior is presented in Figure 4 for $\epsilon = 10^2$. The oscillations observed are not caused by instability in the numerical integration, but are

Table 1. Number of Steps for Numerical Integration*

ϵ	β_2 0.0	0.05	0.5
10^{-15}	1,517	1,522	1,492
10^2	61,422	55,416	10,732
10^8	924,302	969,459	2,583,524
10^{15}	55,256	556,437	65,266

*Maximum allowable relative error, 10^{-6}

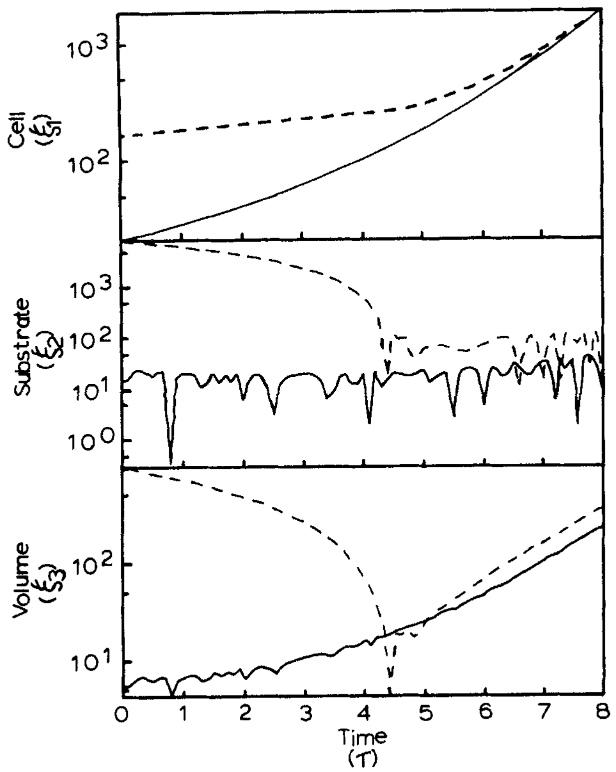

Figure 4. State trajectories obtained using epsilon method with $\epsilon = 10^2$.
--- $\beta_2 = 0.5$; — $\beta = 0.0$

caused by the two competing forces of minimizing the feed and maximizing the cell production. Since the control variable u is unconstrained, it is allowed to have a negative feed to the bioreactor, thus reducing the volume. However, this negative feed is not an exit stream but corresponds to the selective removal of substrate only, hence the cell mass does not decrease in the bioreactor.

Another interesting fact about this case of competing effects is that the substrate concentration is no longer constant at $\sqrt{\beta_1}$ as required for the maximum growth rate; rather, it oscillates in the vicinity of $\sqrt{\beta_1}$. The parameter ϵ is related to the cost associated with feeding the system. When ϵ is not very large in magnitude, we can no longer assume a cheap control. Although the maximum growth rate requires the substrate concentration to be constant at $\sqrt{\beta_1}$, it is not optimal because of the penalty associated with the feed. That is, in a practical situation where the feeding material is not cost-free (or essentially cost-free in comparison to the product), the exponentially fed-batch mode is not a true optimum from an economic standpoint.

Inclusion of the maintenance effect has significant consequences, as observed in Figure 4. The substrate feed profiles not only change quantitatively, but even the trends are different, unlike the batch mode or maximum cell productivity in the fed-batch mode with no penalty for feeding.

One of the disadvantages of this embedding technique is that it does not provide the explicit trajectory of the control vector. However, this is not a major drawback since the state vector trajectory is known and the control vector can be back-calculated. Furthermore, if the control is performed in a feedback fashion then the control vector can be obtained adaptatively to keep the system on the *a priori* known state trajectory. Another problem with this technique is that if the numerical value of ϵ becomes too large, then numerical instabilities are likely to occur in the numerical evaluation of the Euler condition. In spite of these two drawbacks, the advantage of converting the singular control problem into a solvable nonsingular problem is quite desirable. The quadratic augmentation in the control vector guarantees a solution even when no solution exists for the original singular control problem.

Conclusion

The technique of embedding a singular control problem in a converging sequence of nonsingular problems is demonstrated on an optimal fed-batch fermentation system for maximum production of bakers' yeast. The solution thus obtained is identical to the exact solution obtained by a heuristic argument and also by invoking the generalized Legendre-Clebsch convexity condition. The heuristic argument of maximum instantaneous growth rate leading to maximum productivity is substantiated as a valid conversion of the maximum productivity problem.

Notation

D = dilution rate, s^{-1}
F = flow rate, $m^3 \cdot s^{-1}$
H = Hamiltonian functional
J = performance index
K_1, K_2 = Haldane-Monod parameters, $kg \cdot m^{-3}$
m_s = maintenance coefficient, $kg_{subs} \cdot kg^{-1}_{cell}$
q = order of singular arc
S = substrate concentration, $kg \cdot m^{-3}$
s = dimensionless substrate concentration
t = time, s
u = dimensionless feed rate
$\mathbf{u}$ = control vector
V = volume, m^3
v = dimensionless volume
X = cell concentration, $kg \cdot m^{-3}$
x = dimensionless cell concentration
$Y_{x/s}$ = yield coefficient, $kg_{cell} \cdot kg^{-1}_{subs}$

Greek letters

α = state vector
β_1 = dimensionless parameter, K_1/K_2
β_2 = dimensionless parameters, $m_s Y_{x/s}/\mu_m$
θ = dimensionless time, $\mu_m t$
ξ_1 = dimensionless cell mass, $x \cdot v$
ξ_2 = dimensionless substrate mass, $s \cdot v$
ξ_3 = dimensionless volume
μ = growth function, s^{-1}
μ_m = Haldane-Monod parameter, s^{-1}
λ = adjoint state vector or variable
ϵ = augmenting parameter
η = adjoint state vector
η_i = adjoint state of ξ_i
τ = dimensionless time, $\mu_m t$
ω = control variable

Subscripts

i = inlet stream
o = outlet stream
x = cell
s = substrate
v = volume
α = derivative with respect to state vector
ω = derivative with respect to control
θ = derivative with respect to time
0(zero) = initial condition
1 = terminal condition

Literature cited

Balakrishanan, A. V., "On a New Computing Technique in Optimal Control," SIAM J. Control, **6,** 149 (1968).

Bell, D. J., and D. H. Jacobson, *Singular Optimal Control Problems,* Academic Press, New York (1975).

Brockett, R. W., "Lie Theory, Functional Expansion, and Necessary Conditions in Singular Optimal Control," *Mathematical Control Theory,* W. A. Coppel, ed., Springer Verlag, Berlin, 68 (1978).

Bryson, A. E., and Y. C. Ho, *Applied Optimal Control,* Hemisphere, Washington, DC (1975).

Constantinides, A., J. L. Spencer, and E. L. Gaden, "Optimization of Batch Fermentation Processes. I: Development of Mathematical Models for Batch Penicillin Fermentations," *Biotech. Bioeng.,* **12,** 803 (1970a).

———, "Optimization of Batch Fermentation Processes. II: Optimum Temperature Profiles for Batch Penicillin Fermentations," *Biotech. Bioeng.,* **12,** 1081 (1970b).

D'Ans, G., D. Gottlieb, and P. Kokotovic, "Optimal Control of Bacterial Growth," *Automatica,* **8,** 729 (1972).

Dunn, I. J., and J. R. Mor, "Variable Volume Continuous Cultivation," *Biotech. Bioeng.,* **15,** 1805 (1975).

Edge, E. R., and W. F. Powers, "Function-Space Quasi-Newton Algorithms for Optimal Control Problems with Bounded Controls and Singular Arcs," *J. of Optimiz. Theory and Appl.,* **20**(4), 455 (1976).

Fleming, W. H., and R. W. Rishel, *Deterministic and Stochastic Optimal Control,* Springer-Verlag, New York (1975).

Fiechter, A., G. F. Fuhrmann, and O. Käppeli, "Regulation of Glucose Metabolism in Growing Yeast Cells," *Advances in Microbial Physiology,* A. H. Rose and J. G. Morris, eds., **22,** 123 (1981).

Jacobson, D. H., S. B. Gershwin, and M. M. Lele, "Computation of Optimal Singular Controls," *IEEE Trans. Auto. Cont.,* **AC15**(1), 67 (1970).

Johansen, D. E., "Convergence Properties of the Method of Gradients," *Advances in Control Systems,* C. T. Leondes, ed., **4,** 279 (1966).

King, R. E., J. Aragona, and A. Constantinides, "Specific Optimal Control of a Batch Fermentor," *Int. J. Control,* **20**(5), 869 (1974).

Lim, H. C., B. J. Chen, and C. C. Creagan, "An Analysis of Extended and Exponentially Fed Batch Cultures," *Biotech. Bioeng.,* **19,** 425 (1977).

Mehra, R. K., and R. E. Davis, "A Generalized Gradient Method for Optimal Control Problems with Inequality Constraints and Singular Arcs," *IEEE Trans. Auto. Cont.,* **AC17**(1), 69 (1972).

Menawat, A., "Modeling of Baker's Yeast Growth and Singular Optimal Control of Bioreactors," Ph. D. Thesis, Dept. Chem. Eng., Drexel Univ., Philadelphia (1986).

Ohno, H., E. Nakanishi, and T. Takamatsu, "Optimal Control of a Semibatch Fermentation," *Biotech. Bioeng.,* **18,** 847 (1976).

Ohno, H., E. Nakanishi, and T. Takamatsu, "Optimum Operating Mode for a Class of Fermentation," *Biotech. Bioeng.,* **20,** 625 (1978).

Rai, V. R., and A. Constantinides, "Mathematical Modeling and Optimization of the Gluconic Acid Fermentation," *AIChE Symp. Ser,* **132,** 114 (1973).

Shmueli, K., and A. M. Steinberg, "Numerical Solution of a Relaxed Control Problem by the Epsilon Method," *JOTA,* **35**(1), 45 (1981).

Sirisena, H. R., and F. S. Chou, "Convergence of the Control Parameterization Ritz Method for Nonlinear Optimal Control Problems," *J. of Optimiz. Theory and Appl.,* **29**(3), 369 (1979).

Takamatsu, T., I. Hashimoto, S. Shioya, K. Mizuhara, T. Koike, and H. Ohno, "Theory and Practice of Optimal Control in Continuous Fermentation Process," *Automatica,* **11,** 141 (1975).

Taylor, J. M., and C. T. Constantinides, "Optimization: Application of the Epsilon Method," *IEEE Trans. Auto. Cont.,* **AC17,** 128 (1972a).

———, "A Computation Aspect of the Epsilon Method," *IEEE Trans. Auto. Cont.,* **AC17,** 738 (1972b).

Weigand, W. A., "Computer Applications to Fermentation Processes," *Annual Reports on Fermentation Processes,* **2,** Academic Press, New York (1978).

———, "Maximum Cell Productivity by Repeated Fed-Batch for Constant Yield Case," *Biotech. and Bioeng.,* **23,** 249 (1981).

Weigand, W. A., H. C. Lim, C. C. Creagan, and R. D. Mohler, "Optimization of a Repeated Fed-Batch Reactor for Maximum Cell Productivity," *Biotech. and Bioeng. Symp.,* **9,** 335 (1979).

Zabriskie, D. W., "Real-time Applications of Computers in Fermentation Processes," *Annals NY Acad. Sci.,* **223** (1979).

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