JOURNAL OF OPTIMIZATION THEORY AND APPLICATIONS: Vol. 100, No. 1, pp 1-13, JANUARY 1999

Numerical Computation of Optimal Feed Rates for a Fed-Batch Fermentation Model

H. J. OBERLE[1] AND B. SOTHMANN[2]

Abstract. In this paper, we consider a model for a fed-batch fermentation process which describes the biosynthesis of penicillin. First, we solve the problem numerically by using a direct shooting method. By discretization of the control variable, we transform the basic optimal control problem to a finite-dimensional nonlinear programming problem, which is solved numerically by a standard SQP method. Contrary to earlier investigations (Luus, 1993), we consider the problem as a free final time problem, thus obtaining an improved value of the penicillin output. The results indicate that the assumption of a continuous control which underlies the discretization scheme seems not to be valid. In a second step, we apply classical optimal control theory to the fed-batch fermentation problem. We derive a boundary-value problem (BVP) with switching conditions, which can be solved numerically by multiple shooting techniques. It turns out that this BVP is sensitive, which is due to the rigid behavior of the specific growth rate functions. By relaxation of the characteristic parameters, we obtain a simpler BVP, which can be solved by using the predicted control structure (Lim et al., 1986). Now, by path continuation methods, the parameters are changed up to the original values. Thus, we obtain a solution which satisfies all first-order and second-order necessary conditions of optimal control theory. The solution is similar to the one obtained by direct methods, but in addition it contains certain very small bang-bang subarcs of the control. Earlier results on the maximal output of penicillin are improved.

Key Words. Fed-batch fermentation, optimal control theory, minimum principle, direct methods, multiple shooting techniques.

1. Introduction

In recent years, the problem of determining optimal controls for fed-batch fermentation processes has become an important field of interest in

[1]Professor, Institute of Applied Mathematics, University of Hamburg, Hamburg, Germany.
[2]Diploma Candidate, Institute of Applied Mathematics, University of Hamburg, Hamburg, Germany.

0022-3239/99/0100-0001$16.00/0

biochemical engineering. In these fermentation processes, the substrate is fed into the fermentor intermittently or continuously during the whole process. For many biochemical processes, this technique improves the product output upon the so-called batch-fermentation technique, where the whole substrate is given into the fermentor a priori. The problem is to determine optimal feed rate profiles, such that the final product is maximized. The problem is formulated as an optimal control problem with a linearly appearing, bounded control function.

In this paper, we consider a fed-batch fermentation model which describes the biosynthesis of penicillin and which goes back to Fishman and Biryukov (Ref. 1). More recently, the model has been considered intensively by Modak et al. (Ref. 2), Lim et al. (Ref. 3), Hong (Ref. 4), Cuthrell and Biegler (Ref. 5), and Luus (Ref. 6).

We consider a chemical reactor which, in dependence on time, contains the biomass $X(t)$, the substrate $S(t)$, and the product $P(t)$ at certain concentrations and which has the volume $V(t)$. The control variable is the feed rate of substrate $u(t)$ with concentration s_F. The problem is to determine the final time t_f and a piecewise continuous control history $u(t)$, $0 \le t \le t_f$, such that the product output

$$\tilde{J}(u, t_f) = P(t_f) \tag{1}$$

is maximized subject to the state equations

$$(d/dt)X(t) = \mu(X, S, V)X(t), \tag{2a}$$

$$(d/dt)P(t) = \pi(X, S, V)X(t) - kP(t), \tag{2b}$$

$$(d/dt)S(t) = -\sigma(X, S, V)X(t) + s_F u(t), \tag{2c}$$

$$(d/dt)V(t) = u(t), \tag{2d}$$

the boundary conditions

$$X(0) = 10.5 \text{ g}, \tag{3a}$$

$$P(0) = 0 \text{ g}, \tag{3b}$$

$$S(0) = 0 \text{ g}, \tag{3c}$$

$$V(0) = 7l, \qquad V(t_f) = 10l, \tag{3d}$$

and the control constraints

$$0 \le u(t) \le u_{\max} = 0.1l \text{ h}^{-1}. \tag{4}$$

The so-called hydrolysis rate constant is given by $k = 0.01 \text{ h}^{-1}$; the feed substrate concentration is $s_F = 500 \text{ g}/l$.

Most important for the control structure of the solution are the specific growth rate functions μ, π, σ. We choose these model functions according to Cuthrell and Biegler (Ref. 5),

$$\mu = \mu_{\max} S/(\mu_1 X + S), \tag{5a}$$

$$\pi = \pi_{\max} SV/[\pi_1 V^2 + S(V + \pi_2 S)], \tag{5b}$$

$$\sigma = \mu/\sigma_1 + \pi/\sigma_2 + \sigma_3 S/(\pi_1 V + S). \tag{5c}$$

The parameters are given by

$$\mu_{\max} = 0.11\ \mathrm{h}^{-1}, \qquad \mu_1 = 0.006, \tag{6a}$$

$$\pi_{\max} = 0.0055\ \mathrm{h}^{-1}, \qquad \pi_1 = 0.0001\ \mathrm{g}/l, \tag{6b}$$

$$\pi_2 = 10 l\ \mathrm{g}^{-1}, \qquad \sigma_1 = 0.47, \tag{6c}$$

$$\sigma_2 = 1.2, \qquad \sigma_3 = 0.029\ \mathrm{h}^{-1}. \tag{6d}$$

For the following considerations, the problem is reformulated using the concentrations of cell mass, product, and substrate, respectively, as new (dimensionless) state variables. We denote these quantities by

$$x := X/V, \qquad p := P/V, \qquad s := S/V, \qquad v := V.$$

Taking into account that the final volume is prescribed, the problem is given as follows.

Problem P1. We seek a minimizer (u, t_f) of the functional

$$J(u, t_f) = -p(t_f), \tag{7}$$

subject to the state equations $(0 \le t \le t_f)$

$$x' = h_1(x, s)x - (x/v)u, \tag{8a}$$

$$p' = h_2(x, s)x - kp - (p/v)u, \tag{8b}$$

$$s' = -h_3(x, s)x + [(s_F - s)/v]u, \tag{8c}$$

$$v' = u, \tag{8d}$$

the boundary conditions

$$x(0) = 1.5, \qquad p(0) = 0, \qquad s(0) = 0, \qquad v(0) = 7, \tag{9}$$

$$v(t_f) = 10, \tag{10}$$

and the control constraints

$$0 \le u(t) \le 0.1.$$

The parameters are $k=0.01$, $s_F=500$. Further, the transformed growth rate functions are given by

$$h_1=0.11\, s/(\mu_1 x+s), \tag{11a}$$

$$h_2=0.0055\, s/[\pi_1+s(1+10\, s)], \tag{11b}$$

$$h_3=h_1/0.47+h_2/1.2+0.029\, s/(\pi_1+s), \tag{11c}$$

with the parameters $\mu_1=0.006$ and $\pi_1=0.0001$ as given in Eqs. (6).

2. Numerical Results by a Direct Method

In this section, we present numerical results for Problem P1 obtained by a direct method for optimal control problems. We follow the ideas used in Luus (Ref. 6) and apply the following rather simple discretization of the control variable.

For an equidistant grid $t_k=kt_f/m$, $k=0,\ldots,m$, and data $U^{(m)}=(u_0,\ldots,u_m)$, we choose the continuous and piecewise linear control function

$$u(t)=u_k+(u_{k+1}-u_k)(t-t_k)m/t_f, \qquad t_k\le t\le t_{k+1}. \tag{12}$$

Substituting this control function into Eqs. (8), we solve the initial-value problem (8), (9). The numerical integration is obtained applying the stiff initial-value-problem solver RADAU5 [cf. Hairer and Wanner (Ref. 7)].

Let the solution of this initial-value problem be denoted by $\mathbf{x}(t;\, U^{(m)},\, t_f)=[x(t;\, U^{(m)},\, t_f), p(t;\, U^{(m)},\, t_f), s(t;\, U^{(m)},\, t_f), v(t;\, U^{(m)},\, t_f)]$. Now, the discretized finite-dimensional optimal control problem can be formulated as a nonlinear programming problem as follows:

Problem P2. Determine a minimizer $(U^{(m)},\, t_f)$ of the function

$$J_D(U^{(m)},\, t_f)=-p(t_f;\, U^{(m)},\, t_f), \tag{13}$$

subject to the constraints

$$v(t_f;\, U^{(m)},\, t_f)=10, \tag{14a}$$

$$0\le u_k\le 0.1, \qquad k=0,\ldots,m. \tag{14b}$$

The numerical solution of Problem P2 is obtained using a standard SQP method from the NAG Fortran library (Algorithm E04UCF, Ref. 8). Figure

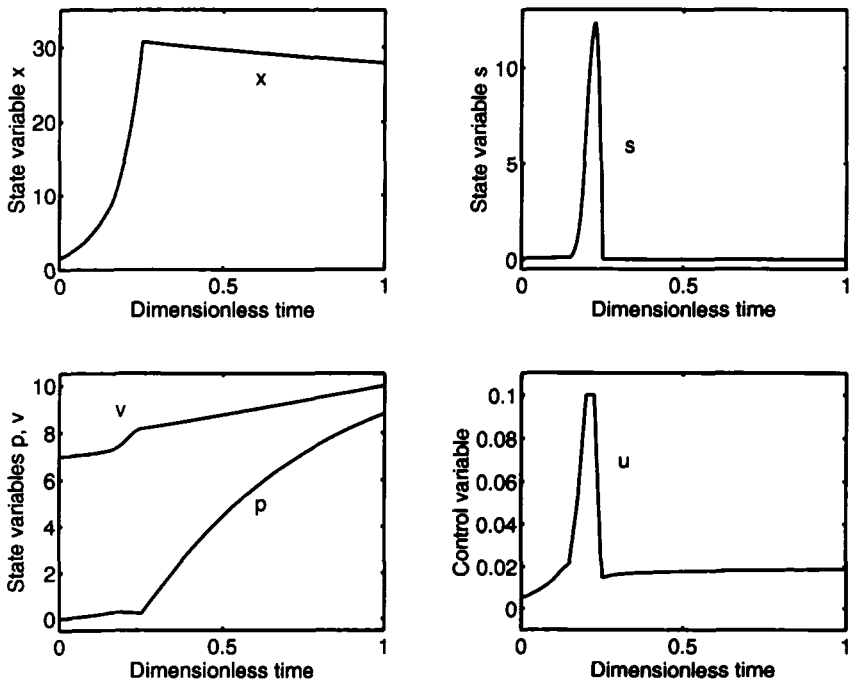

Fig. 1. Problem P2: State variables and control history for $m=40$.

1 shows the solution obtained by the method described with discretization parameter $m=40$.

For the total output of penicillin production, we obtain the value $P(t_f)=$ 88.07373 g, which improves the numerical results of Cuthrell and Biegler (Ref. 5) and Luus (Ref. 6). The reason for this discrepancy seems to be the fact, that in the earlier papers, the problem is solved for a fixed final time, which is varied separately in a second step. So, Luus considered final times in the region $128\text{ h} \leq t_f \leq 134\text{ h}$, whereas we obtain for the free final time the value of $t_f = 137.24115$ h. Therefore, it seems that, by transformation into a finite-dimensional problem, nonoptimal local minima are produced, which are situated in the neighborhood of the real optimum.

Nevertheless, the control sequence of the numerical solutions seems to be dubious. One problem is that we used a continuous control approximation, although for mixed bang-bang and singular subarcs the optimal control in general is discontinuous. Therefore, it seems to be necessary to look more carefully for the necessary conditions of optimal control theory.

3. Necessary Conditions Derived by Optimal Control Theory

In the following, we apply the necessary conditions of optimal control theory to the previous Problem P1 [cf. Kelley et al. (Ref. 9), Strauss (Ref. 10), Bryson and Ho (Ref. 11), Maurer (Refs. 12–13)]. We use the notation of Bryson and Ho. Let (u, t_f) be a solution of the optimal control problem with a piecewise continuous control function and the corresponding state variables

$$\mathbf{x}(t) = (x(t), p(t), s(t), v(t)).$$

Then, there exist (piecewise continuously differentiable) adjoint variables

$$\boldsymbol{\lambda}(t) = (\lambda_x(t), \lambda_p(t), \lambda_s(t), \lambda_v(t))$$

such that, with the Hamilton function

$$\begin{aligned} H = {} & \lambda_x[h_1 x - (x/v)u] + \lambda_p[h_2 x - kp - (p/v)u] \\ & + \lambda_s\{-h_3 x + [s_F - s)/v]u\} + \lambda_v u, \end{aligned} \tag{15}$$

the following adjoint differential equations hold:

$$\lambda_x' = -(\lambda_x h_1 + \lambda_p h_2 - \lambda_s h_3) + \lambda_x u/v - (\lambda_x \partial h_1/\partial x - \lambda_s \partial h_3/\partial x)x, \tag{16a}$$

$$\lambda_p' = \lambda_p(k + u/v), \tag{16b}$$

$$\lambda_s' = -(\lambda_x \partial h_1/\partial s + \lambda_p \partial h_2/\partial s - \lambda_s \partial h_3/\partial s)x + \lambda_s u/v, \tag{16c}$$

$$\lambda_v' = -[\lambda_X x + \lambda_p p - \lambda_s(s_f - s)]u/v^2. \tag{16d}$$

The natural boundary conditions are given as follows:

$$\lambda_x(t_f) = 0, \qquad \lambda_p(t_f) = -1, \qquad \lambda_s(t_f) = 0, \qquad H(t_f) = 0. \tag{17}$$

It is worth noting that the latter condition can be rewritten in the form

$$p'(t_f) = h_2(x(t_f), s(t_f))x(t_f) - kp(t_f) = 0. \tag{18}$$

This condition can easily be derived if one assumes that the optimal control history ends with a small batch mode subarc ($u = 0$).

Now, we have to determine the optimal control function by means of the minimum principle. First, the switching function is given by

$$S := \partial H/\partial u = -[\lambda_x x + \lambda_p p - \lambda_s(s_f - s)]/v + \lambda_v. \tag{19}$$

Thus, according to the minimum principle, one has the bang-bang control law

$$u=\begin{cases}0, & \text{if } S>0,\\ u_{\max}=0.1, & \text{if } S<0.\end{cases} \tag{20}$$

More complicated is the case of a singular control subarc, i.e., a subarc where the switching function vanishes identically; cf. Kelley et al. (Ref. 9), Maurer (Ref. 13), and Oberle (Ref. 14). The singular control case is most important for the fed-batch fermentation process. So, for our model, about 90% of the process takes place in this singular mode.

For the computation of the singular control function, we use the second total time derivative of the switching function. The fact that this derivative vanishes identically on a singular subarc can be used to obtain an explicit expression for u_{sing} by elimination. For the sake of completeness, we give these rather complicated expressions in the following.

On a singular subarc, the first derivative of the switching function is given by

$$S^{(1)}=-(x/v)\tilde{S}^{(1)}, \tag{21a}$$

$$\tilde{S}^{(1)}=(s_F-s)(\lambda_x\partial h_1/\partial s+\lambda_p\partial h_2/\partial s-\lambda_s\partial h_3/\partial s) - x(\lambda_x\partial h_1/\partial x-\lambda_s\partial h_3/\partial x). \tag{21b}$$

Now, for the computation of u_{sing}, it suffices to build up the derivative of $\tilde{S}^{(1)}$. One obtains

$$\begin{aligned}\tilde{S}^{(2)}=&-x(h_1+(s_F-s)\partial h_1/\partial s-x\partial h_1/\partial x)K_1\\ &+x[h_3+(s_F-s)\partial h_3/\partial s-x\partial h_3/\partial x]K_3-x^2h_1K_{11}\\ &-(s_F-s)xh_3K_{33}+x[xh_3+(s_F-s)h_1]K_{13}\\ &+[x\partial h_1/\partial x-(s_F-s)\partial h_1/\partial s](\lambda_x h_1+\lambda_p h_2-\lambda_s h_3)\\ &+(s_F-s)k\lambda_p\partial h_2/\partial s\\ &+(u_{\text{sing}}/v)\{x^2K_{11}+(s_F-s)^2K_{33}-2x(s_F-s)K_{13}\}\\ =:&A+u_{\text{sing}}B,\end{aligned} \tag{22}$$

where the following abbreviations are used:

$$K_1:=\lambda_x\partial h_1/\partial x-\lambda_s\partial h_3/\partial x, \tag{23a}$$

$$K_3:=\lambda_x\partial h_1/\partial s+\lambda_p\partial h_2/\partial s-\lambda_s\partial h_3/\partial s, \tag{23b}$$

$$K_{11}:=\lambda_x\partial^2 h_1/\partial x^2-\lambda_s\partial^2 h_3/\partial x^2, \tag{23c}$$

$$K_{13}:=\lambda_x\partial^2 h_1/\partial x\partial s-\lambda_s\partial^2 h_3/\partial x\partial s, \tag{23d}$$

$$K_{33}:=\lambda_x\partial^2 h_1/\partial s^2+\lambda_p\partial^2 h_2/\partial s^2-\lambda_s\partial^2 h_3/\partial s^2. \tag{23e}$$

Note that according to our numerical computations, B does not vanish along a singular subarc, i.e., the singular subarcs are of first order. Therefore, Eq. (22) can be used for the numerical evaluation of the singular control,

$$u_{\text{sing}} = -A/B. \tag{24}$$

Altogether, we have established the following BVP with switching conditions.

Problem P3. This problem is represented by the relations below:

(i) Differential equations: Eqs. (8), (16), and $t_f' = 0$.
(ii) Boundary conditions: Eqs. (9), (10), (17), or (18), respectively.
(iii) Control variable: The control variable has to be substituted according to an estimated control structure, where the singular control is evaluated by Eqs. (22), (24).
(iv) Switching conditions: The (unknown) switching points are determined, such that the switching function vanishes at these points; for a singular subarc, in addition its first derivative (21) does so.

4. Numerical Results by Multiple Shooting Technique

For the numerical solution of the BVP with switching conditions, we apply multiple shooting techniques [cf. Bulirsch (Ref. 15), Stoer and Bulirsch (Ref. 16)]. Especially, we use the multiple shooting code BNDSCO [cf. Oberle (Ref. 14, 17)], which is able to handle switching conditions. Again, for the numerical solution of the initial-value problems, the stiff solver RADAU5 is applied [cf. Hairer and Wanner (Ref. 7)].

The basis for the solution of Problem P3 is the correct estimation of the control sequence, i.e., the number and the relative position of singular and bang-bang subarcs. It turns out, however, that this estimation is not easy to get for the above optimal control problem. Due to Lim et al. (Ref. 3), one should expect the control sequence

$$u_{\max} \to 0 \to u_{\text{sing}} \to 0, \tag{25}$$

but first we did not succeed in solving the BVP with this estimation. Therefore, we relaxed the parameters μ_1 and π_1 in the growth rate functions (11) to the values

$$\mu_1 = 0.6, \qquad \pi_1 = 0.1.$$

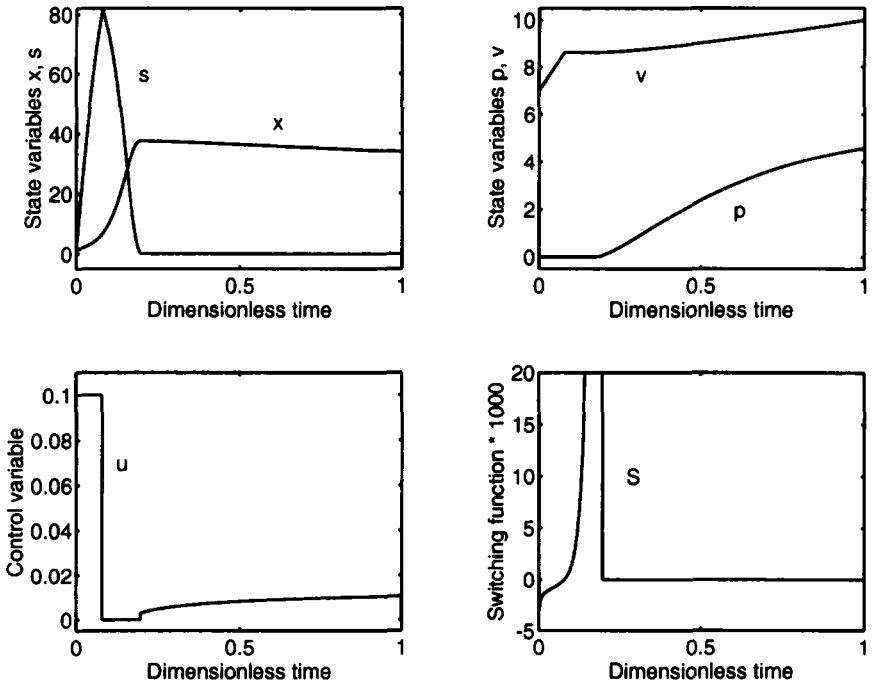

Fig. 2. Problem P3: State variables, control variable, and switching function for the relaxed growth rate functions.

For these data, the BVP can be solved with the control estimation (25) rather easily. Figure 2 shows the history of the state variables, the corresponding optimal control, and of the switching function as well. One observes that the minimum principle is satisfied for this solution.

Now, we use a path continuation method (homotopy method) in order to decrease the parameters μ_1 and π_1 up to its former values

$$\mu_1 = 0.006, \qquad \pi_1 = 0.0001.$$

The homotopy path that we used is defined as follows:

$$\mu_1(\theta) := 0.6(1 - 0.99\theta), \qquad \pi_1(\theta) := 0.1(1 - 0.999\theta), \tag{26}$$

where θ is increased from 0 to 1.

If one performs this homotopy chain without regard to the correctness of the control sequence (i.e., without test of the minimum principle), one obtains a solution of the BVP which does not satisfy the minimum principle. In fact, the structure corresponds to the structure proposed by Lim et al. (1986), but the switching function indicates that this solution cannot be

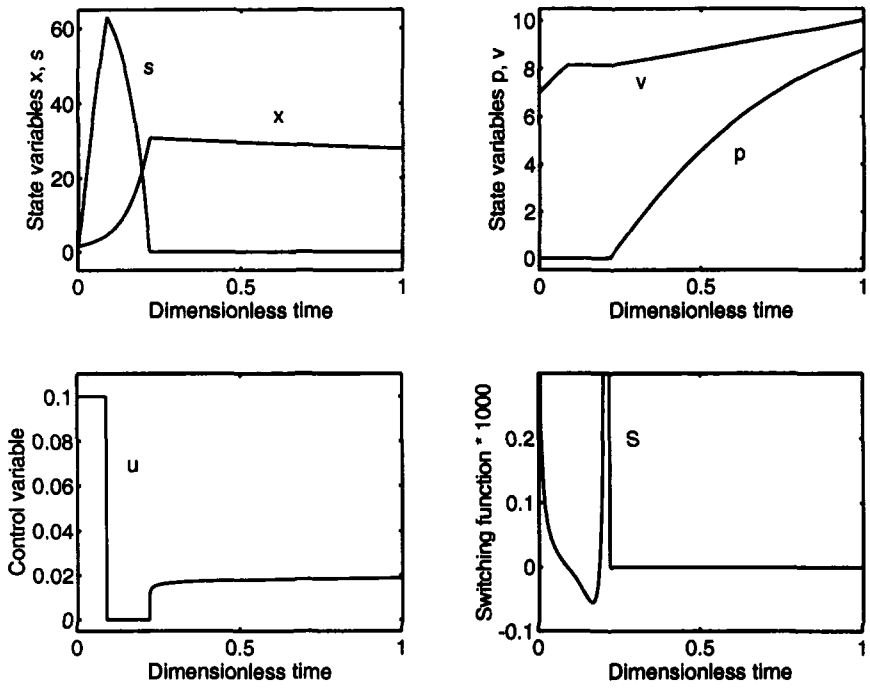

Fig. 3. Problem P3: State variables, control variable, and switching function for the original data; incorrect switching structure.

optimal. In Fig. 3, the time history of this trajectory including the control history and the switching function is shown.

In the final step, we follow the homotopy path, testing in each step the minimum principle, i.e., the sign of the switching function. It turns out that for the homotopy parameter $\theta \approx 0.936$, the switching structure changes. There occurs an additional singular subarc, which grows rapidly with increase of the homotopy parameter. In Fig. 4, the final solution is shown ($\theta = 1$). The control sequence of this solution is given by

$$u_{\max} \to u_{\text{sing}} \to u_{\max} \to 0 \to u_{\text{sing}} \to 0. \tag{27}$$

In Fig. 4, the time histories of the solution, the optimal control, and the switching function are shown. The characteristic quantities of the two solutions, Fig. 3 (nonoptimal) and Fig. 4 (optimal), are given in Table 1. Note that the final penicillin production of the first solution (Fig. 3), nearly coincides with the results of Cuthrell and Biegler (Ref. 5) and Luus (Ref. 5), whereas the final penicillin production of the second solution (Fig. 4)

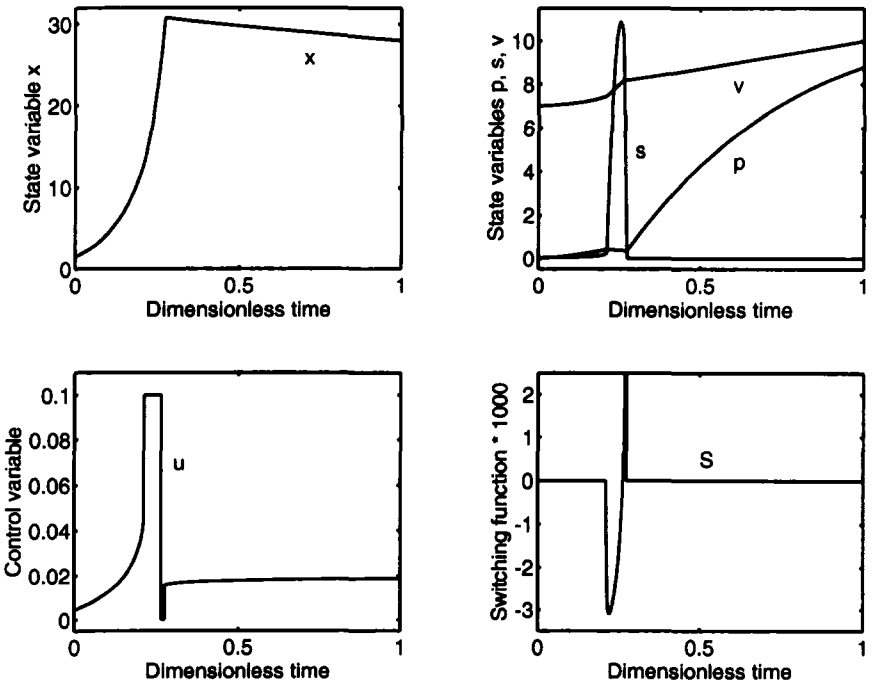

Fig. 4. Problem P3: State variables, control variable, and switching function for the original data; correct switching structure.

improves our results obtained by a direct method (cf. Section 2). Of course, one can assume that the results of Section 2 may be improved too if one uses a more sophisticated direct method. However, it seems to be necessary to allow discontinuities of the control variable at a certain number of discretization nodes.

Table 1. Problem P3, characteristic quantities of two trajectories.

	Trajectory of Fig. 3	Trajectory of Fig. 4
Final time [h]	132.48314	139.24621
Switching points [h]	11.55939	0.0042168
	29.07368	29.43797
	132.48143	36.77577
		38.25831
		139.24450
Penicillin production [g]	87.88065	88.10622

5. Conclusions

In this paper, a fed-batch fermentation model which describes the biosynthesis of pencillin has been reconsidered. By application of a direct method for optimal control problems, solutions are obtained which improve earlier results published in the literature. This is due to the fact that the free final time is treated as an additional variable in the discretized nonlinear programming problem.

By means of classical optimal control theory, the necessary conditions are derived. Especially, we presented an explicit expression for the computation of the singular control function of this model. Applying multiple shooting techniques, two solutions are obtained. The first nonoptimal solution, characterized by an earlier proposed control sequence, fails to satisfy the minimum principle, whereas the second solution, with a more complicated structure, satisfies the necessary conditions of optimal control theory and improves the previous results for the penicillin output.

References

1. FISHMAN, V. M., and BIRYUKOV, V. V., *Kinetic Model of Secondary Metabolite Production and Its Use in the Computation of Optimal Conditions*, Biotechnology and Bioengineering Symposium, Vol. 4, pp. 647–662, 1974.
2. MODAK, J. M., LIM, H. C., and TAYEB, Y. J., *General Characteristics of Optimal Feed Rate Profiles for Various Fed-Batch Fermentation Processes*, Biotechnology and Bioengineering, Vol. 28, pp. 1396–1407, 1986.
3. LIM, H. C., TAYEB, T. J., MODAK, J. M., and BONTE, P., *Computational Algorithms for Optimal Feed Rates for a Class of Fed-Batch Fermentation: Numerical Results for Penicillin and Cell Mass Production*, Biotechnology and Bioengineering, Vol. 28, pp. 1408–1420, 1986.
4. HONG, J., *Optimal Substrate Feeding Policy for a Fed-Batch Fermentation with Substrate and Product Inhibition Kinetics*, Biotechnology and Bioengineering, Vol. 28, pp. 1421–1431, 1986.
5. CUTHRELL, J. E., and BIEGLER, L. T., *Simultaneous Optimization and Solution Methods for Batch Reactor Control Profiles*, Computers and Chemical Engineering, Vol. 13, pp. 49–62, 1989.
6. LUUS, R., *Piecewise Linear Continuous Optimal Control by Iterative Dynamic Programming*, Industrial and Engineering Chemistry Research, Vol. 32, pp. 859–865, 1993.
7. HAIRER, E., and WANNER, G., *Solving Ordinary Differential Equations, II: Stiff and Differential-Algebraic Problems*, Springer Verlag, Heidelberg, Germany, 1991.

8. ANONYMOUS, *The NAG Fortran Library Manual, Mark 15*, Vol. 4, E04, Minimizing or Maximizing a Function, Numerical Algorithms Group, Oxford, England, 1991.
9. KELLEY, H. J., KOPP, R. E., and MOYER, H. G., *Singular Extremals*, Topics in Optimization, Edited by G. Leitmann, Academic Press, New York, New York, pp. 63–101, 1967.
10. STRAUSS, A., *An Introduction to Optimal Control Theory*, Lecture Notes in Operations Research and Mathematical Economics, Springer, New York, New York, Vol. 3, 1968.
11. BRYSON, A. E., and HO, Y. C., *Applied Optimal Control*, Ginn and Company, Waltham, Massachusetts, 1969.
12. MAURER, H., *Zur numerischen Berechnung optimaler singulärer Steuerungen*, Doctoral Thesis, University of Köln, Köln, Germany, 1972.
13. MAURER, H., *Numerical Solution of Singular Control Problems Using Multiple Shooting Techniques*, Journal of Optimization Theory and Applications, Vol. 18, pp. 235–257, 1976.
14. OBERLE, H. J., *Numerische Berechnung optimaler Steuerungen von Heizung und Kühlung für ein realistisches Sonnenhausmodell*, Habilitationsschrift, University of Technology, München, Germany, 1982.
15. BULIRSCH, R., *Die Mehrzielmethode zur numerischen Lösung von nichtlinearen Randwertaufgaben und Aufgaben der optimalen Steuerung*, Report of the Carl Cranz Gesellschaft, Oberpfaffenhofen, Germany, 1971.
16. STOER, J., and BULIRSCH, R., *Introduction to Numerical Analysis*, 2nd Edition, Texts in Applied Mathematics, Springer, New York, New York, 1990.
17. OBERLE, H. J., and GRIMM, W., *BNDSCO: A Program for the Numerical Solution of Optimal Control Problems*, Report 515, Institut for Flight Systems Dynamics, German Aerospace Research Establishment DLR, Oberpfaffenhofen, Germany, 1989.