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

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Abstract. In this paper we consider a model for a fed-batch fermentation process which describes the biosynthesis of penicillin. Firstly, we solve the problem numerically by using a direct 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 an earlier paper by 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 technique. It turns out, however, that this bvp is sensitive, which is due to the rigid behaviour of the specific growth rate functions. By relaxation of the characteristic parameters we obtain a more simple bvp, which can be solved by using the predicted control structure due to Lim et al. (1986). Now, by path continuation methods, the parameters are aggravated up to the original values. Thus, we obtain a solution which satisfies all first 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.

AMS (MOS) subject classifications. 49M05, 49M35, 65C20, 65K05, 65K10, 65L10, 80A32, 92E20.

1. Introduction

In recent years, the problem of determining optimal fed-batch fermentation controls has become an important field of interest in biochemical processes. In these fermentation processes the substrate is fed into the fermentor intermittently or continuously during the whole process. 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 (1974). More recently the model has been considered intensively by Modak et al. (1985), Lim et al. (1985), Hong (1986), Cuthrell, Biegler (1989) and by Luus (1993).

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 $V(t)$. Control variable is the feed rate $u(t)$ of substrate with the concentration s_F. The problem is to determine the final time t_f and a piecewise continous control history $u(t)$, $0 \le t \le t_f$, such that the product output

$$\tilde{J}(u, t_f) = P(t_f) \tag{1.1}$$

is maximized subject to the state equation

$$\begin{aligned} \frac{d}{dt}X(t) &= \mu(X,S,V)\,X(t)\,, \\ \frac{d}{dt}P(t) &= \pi(X,S,V)\,X(t) - k\,P(t)\,, \\ \frac{d}{dt}S(t) &= -\,\sigma(X,S,V)\,X(t) + s_F\,u(t)\,, \\ \frac{d}{dt}V(t) &= u(t)\,, \end{aligned} \tag{1.2}$$

the boundary conditions

$$\begin{aligned} X(0) &= 10.5\,\mathrm{g}\,, \\ P(0) &= 0\,\mathrm{g}\,, \\ S(0) &= 0\,\mathrm{g}\,, \\ V(0) &= 7\,l\,, \qquad V(t_f) = 10\,l\,, \end{aligned} \tag{1.3}$$

and the control constraints

$$0 \le u(t) \le u_{\max} = 0.1\,l\,\mathrm{h}^{-1}. \tag{1.4}$$

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

Most important for the control structure of the solution are the specific growth rate functions μ, π and σ. We choose these model functions according to Cuthrell and Biegler (1989):

$$\begin{aligned}
\mu &= \mu_{\max} \frac{S}{\mu_1 X + S}, \\
\pi &= \pi_{\max} \frac{S V}{\pi_1 V^2 + S (V + \pi_2 S)}, \\
\sigma &= \frac{\mu}{\sigma_1} + \frac{\pi}{\sigma_2} + \sigma_3 \frac{S}{\pi_1 V + S}.
\end{aligned} \tag{1.5}$$

The parameters are given by

$$\begin{aligned}
\mu_{\max} &= 0.11\,\mathrm{h}^{-1}, & \mu_1 &= 0.006, \\
\pi_{\max} &= 0.0055\,\mathrm{h}^{-1}, & \pi_1 &= 0.0001\,\mathrm{g}/l, \\
\pi_2 &= 10\ l\,\mathrm{g}^{-1}, & \sigma_1 &= 0.47, \\
\sigma_2 &= 1.2, & \sigma_3 &= 0.029\,\mathrm{h}^{-1}.
\end{aligned} \tag{1.6}$$

Note that the papers of Lim et al. (1986) and Luus (1993) contain certain inconsistencies with respect to these approximations which affect the solution of the control problem considerably.

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 $x := X/V$, $p := P/V$, $s := S/V$, and $v := V$. Taking into account that the final volume is prescribed, the problem is given as follows

Problem 1.

We seek for a minimizer (u, t_f) of the functional

$$J(u, t_f) = -p(t_f) \tag{1.7}$$

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

$$\begin{aligned}
x' &= h_1(x,s)\,x - \frac{x}{v} u, \\
p' &= h_2(x,s)\,x - k\,p - \frac{p}{v} u, \\
s' &= -h_3(x,s)\,x + \frac{s_F - s}{v} u, \\
v' &= u,
\end{aligned} \tag{1.8}$$

the boundary conditions

$$x(0) = 1.5\,,\ p(0) = 0\,,\ s(0) = 0\,,\ v(0) = 7\,, \tag{1.9}$$

$$v(t_f) = 10\,, \tag{1.10}$$

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

$$\begin{aligned} h_1 &= 0.11\,\frac{s}{\mu_1\,x + s}\,, \\ h_2 &= 0.0055\,\frac{s}{\pi_1 + s\,(1 + 10\,s)}\,, \\ h_3 &= \frac{h_1}{0.47} + \frac{h_2}{1.2} + 0.029\,\frac{s}{\pi_1 + s}\,, \end{aligned} \tag{1.11}$$

with the parameters $\mu_1 = 0.006$, and $\pi_1 = 0.0001$, as given in Eq.(1.6).

2. Numerical Results by a Direct Method

In this section we present numerical results for Problem 1 obtained by a direct method for optimal control problems. We follow the ideas used in Luus (1993) and apply the following rather simple discretization of the control variable.

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

$$u(t) = u_k + (u_{k+1} - u_k) * (t - t_k) * m/t_f\,,\ \text{ for } t_k \le t \le t_{k+1}. \tag{2.1}$$

Substituting this control function into the Eqs.(1.8), we solve the initial value problem (1.8), (1.9). The numerical integration is obtained applying the stiff initial-value-problem solver RADAU5; cf. Hairer et al.(1991).

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

Problem 2.

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

$$J_D(\boldsymbol{U}^{(m)}, t_f) \;=\; -p(t_f; \boldsymbol{U}^{(m)}, t_f) \tag{2.2}$$

subject to the constraints

$$\begin{aligned} v(t_f; \boldsymbol{U}^{(m)}, t_f) \;&=\; 10, \\ 0 \;\leq\; u_k \;&\leq\; 0.1\,, \;\; k = 0, \ldots, m\,. \end{aligned} \tag{2.3}$$

The numerical solution of Problem 2 is obtained using a standard SQP method from the NAG Fortran library (algorithm E04UCF). Figure 2.1 shows the solution obtained by the described method with discretization parameter $m = 40$.

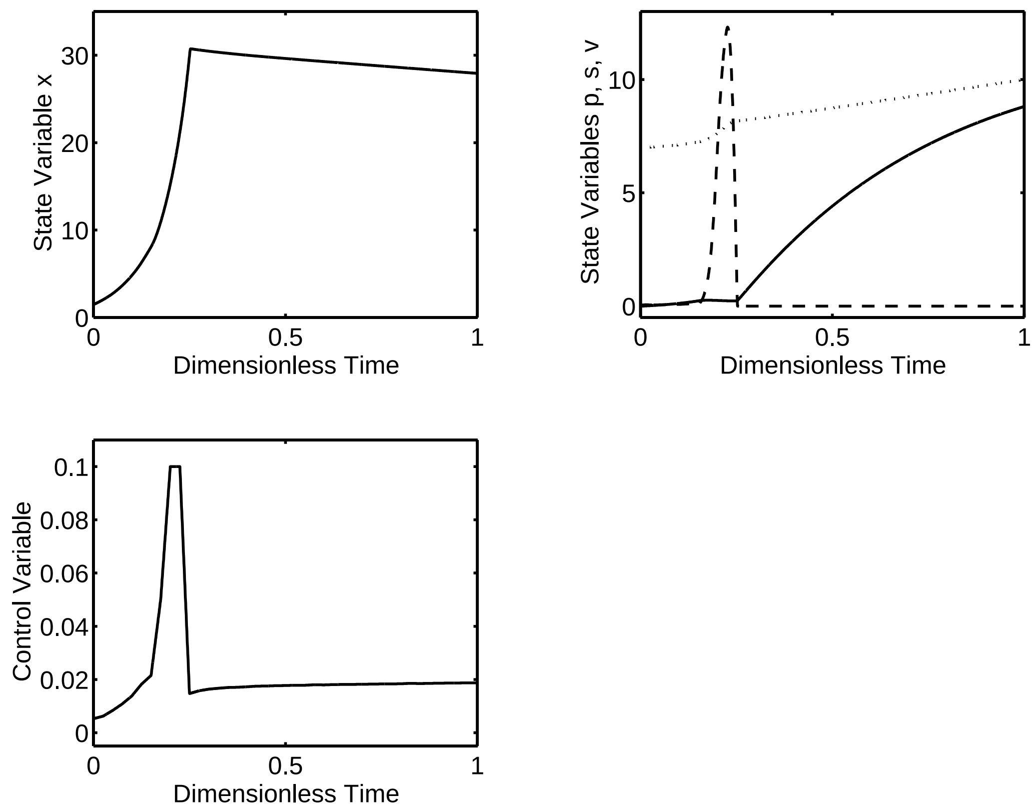

Figure 2.1. Problem 2: State variables and control history for $m = 40$, p: (—), s: (- -), v: ($\cdots$).

For the total output of penicillin production we obtain the value $P(t_f) = 88.07373$g, which improves the numerical results of Cuthrell, Biegler(1989) and Luus(1993) considerably.

Obviously, the reason for this discrepancy is 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 $128\text{h} \le t_f \le 134\text{h}$, whereas we obtain for the free final time the value of $t_f = 137.24115\text{h}$. 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 switching structure of the numerical solutions seems to be dubious. One problem is, that we used a continuous control ansatz, 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 1, cf. Kelley et al. (1967), Strauss (1969), Bryson, Ho (1969), Maurer (1972, 1976). We use the notation of Bryson and Ho. Let (u, t_f) be a solution of the optimal control problem with a piecewise continous control function and the corresponding state variables $\boldsymbol{x}(t) = (x(t), p(t), s(t), v(t))$. 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

$$\begin{aligned} H \; = \; & \lambda_x\,(h_1\,x \; - \; \frac{x}{v}\,u) \; + \; \lambda_p\,(h_2\,x \; - \; k\,p \; - \; \frac{p}{v}\,u) \; + \\ & \lambda_s\,(-\,h_3\,x \; + \; \frac{s_F \; - \; s}{v}\,u) \; + \; \lambda_v\,u \end{aligned} \tag{3.1}$$

the following adjoint differential equations hold

$$\begin{aligned} \lambda_x' \; &= \; -\,(\lambda_x\,h_1 \; + \; \lambda_p\,h_2 \; - \; \lambda_s\,h_3) \; + \; \lambda_x\,\frac{u}{v} \\ & \quad -\,(\lambda_x\,\frac{\partial h_1}{\partial x} \; - \; \lambda_s\,\frac{\partial h_3}{\partial x})\,x \\ \lambda_p' \; &= \; \lambda_p\,(k \; + \; \frac{u}{v}) \\ \lambda_s' \; &= \; -\,(\lambda_x\,\frac{\partial h_1}{\partial s} \; + \; \lambda_p\,\frac{\partial h_2}{\partial s} \; - \; \lambda_s\,\frac{\partial h_3}{\partial s})\,x \; + \; \lambda_s\,\frac{u}{v} \\ \lambda_v' \; &= \; -\,(\lambda_x\,x \; + \; \lambda_p\,p \; - \; \lambda_s\,(s_f - s))\,\frac{u}{v^2}\,. \end{aligned} \tag{3.2}$$

The natural boundary conditions are given as follows

$$\lambda_x(t_f) \;=\; 0 \;,\quad \lambda_p(t_f) \;=\; -1 \;,\quad \lambda_s(t_f) \;=\; 0 \;,\quad H[t_f] \;=\; 0 \;. \tag{3.3}$$

It is worth to note, that the latter condition can be rewritten in the form

$$p'(t_f) \;=\; h_2(x(t_f), s(t_f))\, x(t_f) \;-\; k\, p(t_f) \;=\; 0\,. \tag{3.4}$$

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

$$S \;:=\; \frac{\partial H}{\partial u} \;=\; -\; \frac{\lambda_x\, x \;+\; \lambda_p\, p \;-\; \lambda_s\, (s_f - s)}{v} \;+\; \lambda_v\,. \tag{3.5}$$

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

$$u \;=\; \begin{cases} 0, & \text{if} \quad S > 0, \\ u_{\max} = 0.1, & \text{if} \quad S < 0\,. \end{cases} \tag{3.6}$$

More complicated is the case of a singular control subarc, i.e. a subarc where the switching function vanishes identically; c.f. Kelley et al (1967), Maurer (1976), Oberle (1982). 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 explict 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:

$$\begin{aligned} S^{(1)} \;&=\; -\,\frac{x}{v}\;\tilde{S}^{(1)} \\ \tilde{S}^{(1)} \;&=\; (s_F - s)\,(\lambda_x\, \frac{\partial h_1}{\partial s} \;+\; \lambda_p\, \frac{\partial h_2}{\partial s} \;-\; \lambda_s\, \frac{\partial h_3}{\partial s}) \\ &\quad -\; x\,(\lambda_x\, \frac{\partial h_1}{\partial x} \;-\; \lambda_s\, \frac{\partial h_3}{\partial x})\,. \end{aligned} \tag{3.7}$$

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

$$
\begin{aligned}
\tilde{S}^{(2)} \;=\; & \Big\{ -x\,(h_1 \,+\, (s_F - s)\,\frac{\partial h_1}{\partial s} \,-\, x\,\frac{\partial h_1}{\partial x})\,K_1 \\
& +\, x\,(h_3 \,+\, (s_F - s)\,\frac{\partial h_3}{\partial s} \,-\, x\,\frac{\partial h_3}{\partial x})\,K_3 \\
& -\, x^2\,h_1\,K_{11} \,-\, (s_F - s)\,x\,h_3\,K_{33} \\
& +\, x\,(x\,h_3 \,+\, (s_F - s)\,h_1)\,K_{13} \\
& +\, (x\,\frac{\partial h_1}{\partial x} \,-\, (s_F - s)\,\frac{\partial h_1}{\partial s})\,(\lambda_x\,h_1 + \lambda_p\,h_2 - \lambda_s\,h_3) \\
& +\, (s_F - s)\,k\,\lambda_p\,\frac{\partial h_2}{\partial s} \Big\} \\
& +\, \frac{u_{\text{sing}}}{v}\,\Big\{ x^2\,K_{11} + (s_F - s)^2\,K_{33} - 2\,x\,(s_F - s)\,K_{13} \Big\} \\
& =:\; A \,+\, u_{\text{sing}}\,B \;,
\end{aligned}
\tag{3.8}
$$

where the following abbreviations are used

$$
\begin{aligned}
K_1 \;&:=\; \lambda_x\,\frac{\partial h_1}{\partial x} \,-\, \lambda_s\,\frac{\partial h_3}{\partial x} \;, \\
K_3 \;&:=\; \lambda_x\,\frac{\partial h_1}{\partial s} \,+\, \lambda_p\,\frac{\partial h_2}{\partial s} \,-\, \lambda_s\,\frac{\partial h_3}{\partial s} \;, \\
K_{11} \;&:=\; \lambda_x\,\frac{\partial^2 h_1}{\partial x^2} \,-\, \lambda_s\,\frac{\partial^2 h_3}{\partial x^2} \;, \\
K_{13} \;&:=\; \lambda_x\,\frac{\partial^2 h_1}{\partial x \partial s} \,-\, \lambda_s\,\frac{\partial^2 h_3}{\partial x \partial s} \;, \\
K_{33} \;&:=\; \lambda_x\,\frac{\partial^2 h_1}{\partial s^2} \,+\, \lambda_p\,\frac{\partial^2 h_2}{\partial s^2} \,-\, \lambda_s\,\frac{\partial^2 h_3}{\partial s^2} \;.
\end{aligned}
$$

Note, that according to our numerical computations, B does not vanish along a singular subarc. Therefore, Eq.(3.8) can be used for the numerical evaluation of the singular control

$$
u_{\text{sing}} \;=\; -\,\frac{A}{B}\,. \tag{3.9}
$$

Altogether, we have estabished the following bvp with switching conditions.

Problem 3.

Differential equations: Eqs.(1.8), (3.2) and $t'_f = 0$.

Boundary conditions: Eqs.(1.9), (1.10), (3.3), or (3.4), respectively.

Control variable: The control variable has to be substituted according to an estimated control structure, where the singular control is evaluated by Eqs.(3.8), (3.9).

Switching conditions: The (unknown) switching points are determined, such that the switching functions vanishes at these points, and for a singular subarc, in addition it's first derivative (3.7) 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 (1971), Stoer, Bulirsch (1990). Especially, we use the multiple shooting code BNDSCO, cf. Oberle (1982, 1989), 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, Wanner (1991).

Basis for the solution of Problem 3 is the correct estimation of the switching structure, 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.(1986) one should expect the switching structure

$$u = u_{\max} \; - \; u = 0 \; - \; u = u_{\text{sing}} \; - \; u = 0 \,, \tag{4.1}$$

but first, we didn't succeed in solving the bvp with this estimation. Therefore, we relaxed the parameters μ_1 and π_1 in the growth rate functions (1.11) to the values $\mu_1 = 0.6\,,\ \pi_1 = 0.1$.

For these data the bvp can be solved with the control estimation (4.1) rather easily. Figure 4.1 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 (homotopie method) in order to decrease the parameters μ_1 and π_1 up to its former values $\mu_1 = 0.006$, and $\pi_1 = 0.0001$. The homotopy path, we used is defined as follows

$$\mu_1(\theta) \;:=\; 0.6\,(1 \;-\; 0.99 \cdot \theta)\,,\ \ \pi_1(\theta) \;:=\; 0.1\,(1 \;-\; 0.999 \cdot \theta)\,, \tag{4.2}$$

where θ is increased form 0 to 1.

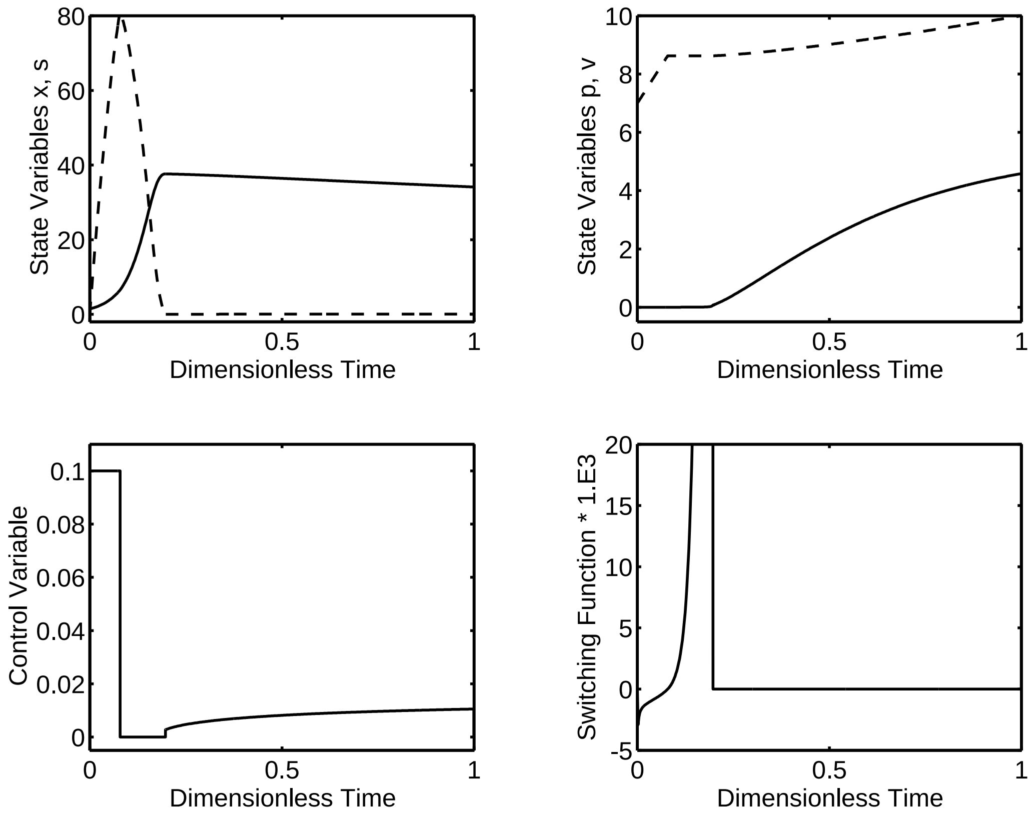

Figure 4.1. Problem 3: State variables, control variable and switching function for the relaxed growth rate functions; x, p, u, S: (—), s, v: (- -).

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where θ is increased form 0 to 1.

If one performs this homotopy chain without regard to the correctness of the switching structure (i.e. without test of the minimum principle), one obtains a solution of the bvp which does not satisfy the minimum principle. The structure in fact, corresponds to the structure proposed by Lim et al.(1986), but the switching function indicates that this solution cannot be optimal. In Figure 4.2 the time history of this trajectory including the control history and the switching function is shown.

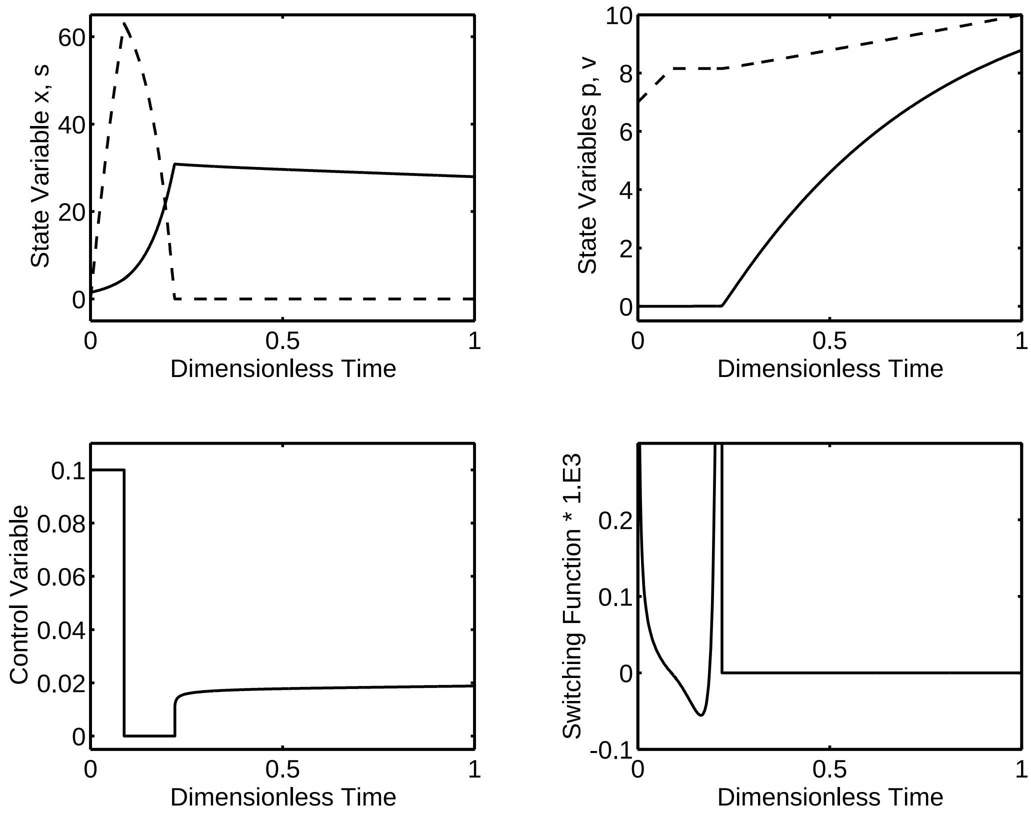

Figure 4.2. Problem 3: State variables, control variable and switching function for the original data; incorrect switching structure; x, p, u, S: (—), s, v: (- -).

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 Figure 4.3 the final solution is shown ($\theta = 1$). The switching structure of this solution is given by

$$u_{\max} - u_{\text{sing}} - u_{\max} - 0 - u_{\text{sing}} - 0\,, \tag{4.4}$$

In Figure 4.3 the time histories of the solution, the optimal control and of the switching function is shown. The characteristic quantities of the two solutions, Fig. 4.2 (nonoptimal) and Fig.4.3 (optimal), are given in the following Table 1. Note, that the final penicillin production of the first solution, Fig. 4.2, nearly coincide with the results of Cuthrell, Biegler(1989) and Luus(1993), whereas the final penicillin production of the second solution,

Fig. 4.3, 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 sofisticated direct method. However, it seems to be necessary to allow discontinuities of the control variable at certain number of discretization knotes.

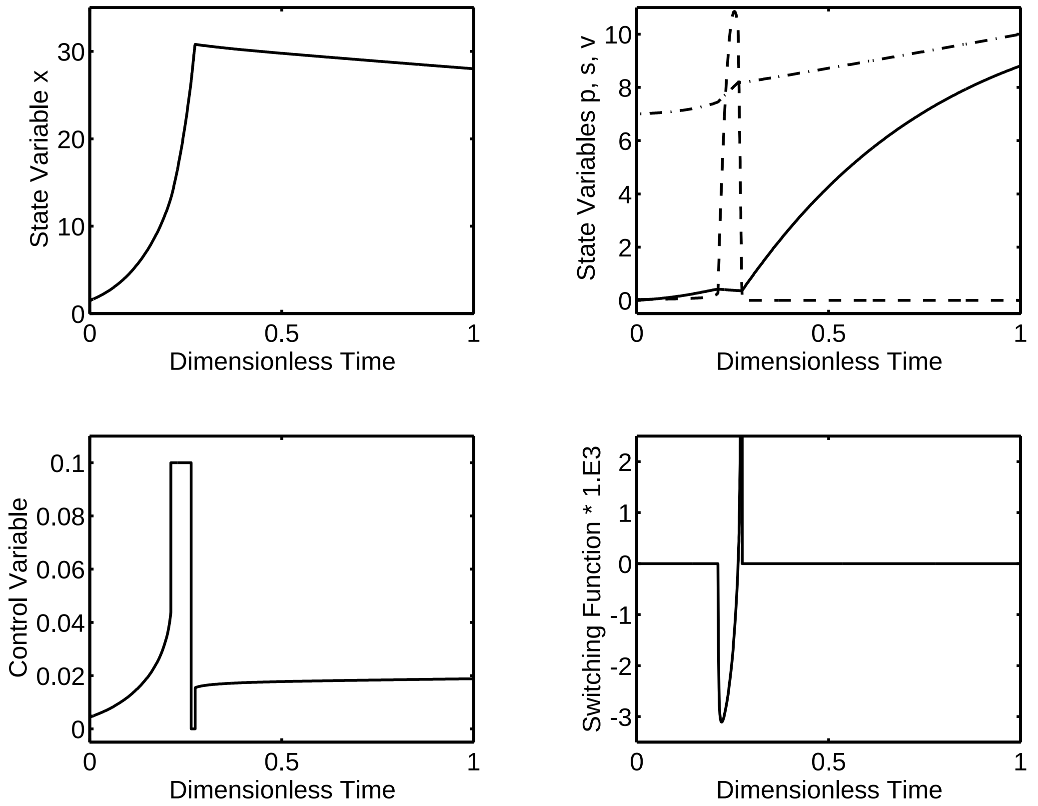

Figure 4.3. Problem 3: State variables, control variable and switching function for the original data; correct switching structure; x, p, u, S: (—), s: (- -), v: (-·-).

Table 1. Characteristic quantities of the two trajectories.

	Trajec., Fig. 4.2	Trajec., Fig. 4.3
Final Time [h]	132.48314	139.24621
Switching Points [h]	11.55939 29.07368 132.48143	0.0042168 29.43797 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 penicillin, 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 technique, two solutions are obtained. The first nonoptimal solution, characterized by an earlier proposed switching structure, fails to satisfy the minimum principle. Whereas, the second solution, with a more complicated structure, satisfy the necessary conditions of optimal control theory and improves the previous results for the penicillin output.

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