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Nonlinear dynamical systems of fed-batch fermentation and their optimal control

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In this article, we propose a controlled nonlinear dynamical system with variable switching instants, in which the feeding rate of glycerol is regarded as the control function and the moments between the batch and feeding processes as switching instants, to formulate the fed-batch fermentation of glycerol bioconversion to 1,3-propanediol (1,3-PD). Some important properties of the proposed system and its solution are then discussed. Taking the concentration of 1,3-PD at the terminal time as the cost functional, we establish an optimal control model involving the controlled nonlinear dynamical system and subject to continuous state inequality constraints. The existence of the optimal control is also proved. A computational approach is constructed on the basis of constraint transcription and smoothing approximation techniques. Numerical results show that, by employing the optimal control strategy, the concentration of 1,3-PD at the terminal time can be increased considerably.

Keywords: nonlinear dynamical system; optimal control; continuous state constraint; smoothing approximation; fed-batch fermentation

1. Introduction

Glycerol, a by-product of the soap and detergent industry, can be converted to 1,3-propanediol (1,3-PD) by a number of bacteria, such as Klebsiella pneumoniae (K. pneumoniae), Clostridium butyricum and Citrobacter freundii (Homann, Tag, Biebl, Deckwer, and Schink 1990). This bioconversion process is of technical interest since 1,3-PD has numerous applications in polymers, cosmetics, food, lubricants and medicines. However, compared with chemical production, it is difficult to obtain a high 1,3-PD concentration in the fermentor using the microbial culture. Hence, it is an area of interest to develop improved techniques to increase the productivity of 1,3-PD.

Among microorganisms, K. pneumoniae ferments glycerol to 1,3-PD in a high yield and productivity (Zeng 1996; Menzel, Zeng, and Deckwer 1997; Xiu, Zeng, and An 2000). The fermentation of glycerol by K. pneumoniae under anaerobic conditions is a complex bioprocess since microbial growth is subjected to multiple inhibitions of substrate and products, such as glycerol, 1,3-PD and ethanol (Zeng et al. 1994). With regard to fermentation, almost all existing culture techniques, including batch culture, fed-batch culture and continuous culture, have been practiced. During the bioconversion of glycerol to 1,3-PD, the most efficient cultivation method appears to be a fed-batch culture which corrects pH by alkali addition for glycerol supply (Zeng and Biebl 2002). The fed-batch culture begins with a batch culture. After the exponential growth phase (i.e. a period in which the number of new bacteria appearing per unit time is proportional to the present population), glycerol and alkali are added continuously to the fermentor at some rates. This helps to provide nutrition and maintain a suitable environment for cell growth. At the end of the feeding, another batch phase starts again. The above processes are repeated until the end of the final batch phase. Consequently, it is decisive for improving the productivity of 1,3-PD to optimise the feeding rates and the switching instants between the batch and feeding processes in a fed-batch fermentation process.

Modelling the fermentation process is a premise to carry out optimal control and increase the productivity of 1,3-PD. Recently, based on an assumption that the feeding of glycerol only occurs at the impulsive instants, a nonlinear impulsive system was proposed to formulate the fed-batch fermentation process (Gao, Li, Feng, and Xiu 2006). Subsequently, the properties, parameter identification problem and optimal control
problem (OCP), in which the impulsive magnitudes are taken as the control function, for the system have been investigated (Gao, Feng, Wang, and Xiu 2005; Wang, Feng, and Xiu 2008a,b). However, since the feeding rate of glycerol is finite, it is not reasonable to describe the actual fed-batch fermentation process by the impulsive dynamical system. Moreover, these studies are concentrated on deducing the optimality condition of the impulsive OCP. In contrast, we proposed a multistage system by considering the feeding of glycerol as a time-continuous process to formulate the fed-batch fermentation process (Liu, Gong, Feng, and Yin 2009). Taking the feeding rate of glycerol as the control function, a multistage optimal control model was also presented. For this system, the parameter identification problem was then investigated (Gong 2010). Numerical simulations indicated that this multistage dynamical system could describe the microbial fed-batch fermentation better compared with the impulsive dynamical system. Furthermore, on the basis of the control parameterisation technique, computational approaches were developed to seek the optimal solution of the multistage OCP (Liu 2009; Liu et al. 2009). Numerical results showed that, by employing obtained optimal strategies, the concentration of 1,3-PD at the terminal time can be increased considerably. However, in all of the above models, the switching instants between the batch and feeding processes are decided a priori. In this article, we propose a controlled nonlinear dynamical system with variable switching instants, in which the feeding rate of glycerol is taken as the control function, to formulate glycerol bioconversion to 1,3-PD in fed-batch fermentation. Some important properties of the system are also discussed. Incidentally, the optimisation and control of this type of dynamical system has been an active research area over the past decade, and we direct the interested reader to Xu and Antsaklis (2004), Bengea and DeCarlo (2005) and Seatzu, Corona, Giua, and Bemporad (2006) for information on some recent developments. However, to our knowledge, the OCPs of this kind of system with constraints of continuous state and control have rarely been considered.

To maximise the concentration of 1,3-PD at the terminal time, this article presents an optimal control model involving the nonlinear dynamical system and subject to constraints of continuous state inequality and control. The existence of the optimal control is also proved. OCPs involving continuous state constraints have been extensively studied in the literature. Many interesting theoretical results can be found in Ahmed (1974), Cesari (1983) and Ferreira (2006). For numerical computation, several successful families of algorithms have already been developed (see Sakawaa and Sawaragi 1975; Polak and Myne 1976; Gonzaga, Polak, and Trahan 1980; Polak and Wardi 1982; Jennings and Teo 1990; Teo, Rehbock, and Jennings 1993; Warschat and Wunderlich 1994; Gorbunov and Lutoshkin 2004; Paschedag, Giua, and Seatzu 2010 and references therein). In particular, Teo et al. (1993) developed a computational algorithm using a constraint transcription together with the concept of control parametrisation for solving this class of constrained OCPs. This algorithm is much more stable numerically and its convergence can be guaranteed.

In this article, to deal with the continuous state constraints in the proposed OCP, we firstly transpose the continuous state inequality constraints into an equality constraint by a constraint transcription. The local smoothing technique in Teo et al. (1993) is subsequently applied to approximating the non-smooth equality constraint, and the above equality constraint is slacked to an inequality constraint. As a result, a computational approach is developed to seek the optimal control by solving a sequence of the approximate OCPs. Numerical results show that, by employing the optimal control strategy, the concentration of 1,3-PD at the terminal time can be increased considerably compared with previous results.

The remainder of this article is organised as follows. In Section 2, we give the controlled nonlinear dynamical system in microbial fed-batch fermentation. The properties of the dynamical system and its solution are also discussed. An optimal control model is proposed and the existence of the optimal control is established in Section 3. Section 4 develops a computational approach to solve the optimal control model, while Section 5 illustrates the numerical results. Finally, conclusions are provided in Section 6.

2. Controlled nonlinear dynamical systems

In fed-batch fermentation, the composition of culture medium, cultivation conditions and analytical methods of fermentative products are similar to those previously reported (Chen et al. 2003). According to fermentation process, we assume that

\[(H1)\text{ The concentrations of reactants are uniform in the reactor. Time delay and non-uniform space distribution are ignored.}\]

\[(H2)\text{ During the process of fed-batch culture, only glycerol and alkali are fed into the reactor at some constant velocities. Moreover, the feeding velocity ratio } r \text{ of alkali to glycerol is a constant.}\]

Let \(x(t) := (x_1(t), x_2(t), x_3(t), x_4(t), x_5(t), x_6(t))^T \in \mathbb{R}_+^6, \quad t \in [0, T]\) be the state vector and its components be the concentrations of biomass, glycerol, 1,3-PD, acetate, ethanol and the volume of culture fluid at \(t\) in
fermentor, respectively. Here, $T$ is the terminal time of the fermentation process. Since alkali and glycerol are fed to the fermentor at a proportional constant $r$, the control function, $u(t) \in R^1$, represents the feeding rate of glycerol in the fermentation process. Denote $\tau_{2i+1}$, the moment of adding glycerol, at which the fermentation process switches to continuous culture from batch culture, and $\tau_{2i+2}$, the moment of ending the flow of glycerol, $i \in A_1 := \{0, 1, 2, \ldots, n - 1\}$, at which the fermentation process jumps into batch culture from continuous culture. Note that $0 = \tau_0 < \tau_1 < \tau_2 < \cdots < \tau_{2n} < \tau_{2n+1} = T$, and $n$ is a constant in this article. From the above assumptions $(H1)$ and $(H2)$, mass balances of biomass, substrate and products in fed-batch fermentation can be formulated as the following controlled nonlinear dynamical system:

$$
\begin{align*}
\dot{x}(t) &= f(x(t), u(t)), \\
  u(t) &\in U(t), \quad t \in (0, T], \\
  x(0) &= x_0,
\end{align*}
$$

where

$$

f(x(t), u(t)) := \begin{pmatrix}
(q_1(x(t)) - D(x(t), u(t))x_1(t) \\
D(x(t), u(t))(c_0 + x_2(t)) - q_2(x(t))x_1(t) \\
q_3(x(t))x_1(t) - D(x(t), u(t))x_3(t) \\
q_4(x(t))x_1(t) - D(x(t), u(t))x_4(t) \\
q_5(x(t))x_1(t) - D(x(t), u(t))x_2(t) \\
(1 + r)u(t)
\end{pmatrix},
$$

and $x_0 \in R^6_+$ is a given initial state.

According to the actual fermentation process, the state of the system (1) does not undergo a jump at the switching instants. In (2), $r > 0$ is the velocity ratio of adding alkali to glycerol. $c_0 > 0$ denotes the initial concentration of glycerol in feed. Since $u(t) \geq 0$, $x_0(t)$ is non-decreasing and $x_0(t) > 0$ due to the positivity of $x_0(0)$, then, $D(x(t), u(t))$ is the dilution rate defined as

$$
D(x(t), u(t)) = \frac{(1 + r)u(t)}{x_0(t)}.
$$

The specific growth rate of cells $q_1(x(t))$, specific consumption rate of substrate $q_2(x(t))$ and specific formation rates of products $q_i(x(t))$, $i = 3, 4, 5$, are expressed by the following equations on the basis of previous work (Xiu et al. 2000).

$$
q_1(x(t)) = \frac{\Delta_1 x_2(t)}{x_2(t) + k_1},
$$

$$
q_2(x(t)) = m_i + q_1(x(t))Y_i + \frac{\Delta_1 x_2(t)}{x_2(t) + k_1}, \quad i = 2, 3, 4,
$$

$$
q_5(x(t)) = q_2(x(t)) \left( \frac{c_1}{c_2 + q_1(x(t))x_2(t)} + \frac{c_3}{c_4 + q_1(x(t))x_2(t)} \right).
$$

Under anaerobic conditions at 37°C and pH 7.0, the kinetic parameters in (4)–(6) (Liu 2009) are listed in Table 1.

Since biological considerations limit the rate of switching, there are maximal and minimal time durations that are spent on each of the batch and feeding processes. On this basis, define the set of admissible switching instants as

$$
\Gamma := \left\{ (\tau_1, \tau_2, \ldots, \tau_{2n}) \in R^{2n} | \tau_i - \tau_{i-1} \leq \rho_i, \quad i = 1, 2, \ldots, 2n + 1 \right\},
$$

where $\tau_0 = 0$, $\tau_{2n+1} = T$, $\rho_i$ and $\varrho_i$ are the minimal and the maximal time durations of the $i$th process, respectively. Accordingly, any $\tau \in \Gamma$ is regarded as an admissible vector of switching instants.

According to the actual fermentation process, the control function $u$ is a piecewise constant function over $[0, T]$ with jumps at $\tau_1, \ldots, \tau_{2n}$, that is, $u(t)$ can be expressed as

$$
u(t) = \sum_{i=1}^{2n+1} v_i \chi(\tau_{i-1}, \tau_i), \quad t \in [0, T],
$$

where $v_i, i = 1, 2, \ldots, 2n + 1$, are the parameters to be optimised and $\chi_I$ denotes the indicator function of $I$ defined as

$$
\chi_I(t) = \begin{cases}
1, & \text{if } t \in I, \\
0, & \text{otherwise}.
\end{cases}
$$

<table>
<thead>
<tr>
<th>$\ell$</th>
<th>$m_\ell$</th>
<th>$Y_\ell$</th>
<th>$\Delta_\ell$</th>
<th>$k_\ell$</th>
<th>$c_\ell$</th>
<th>$x_\ell$</th>
<th>$x_\ell^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>0.67</td>
<td>0.28</td>
<td>0.025</td>
<td>0.01</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>2.20</td>
<td>113.636</td>
<td>13.35</td>
<td>16.69</td>
<td>0.06</td>
<td>15</td>
<td>2039</td>
</tr>
<tr>
<td>3</td>
<td>-2.69</td>
<td>67.69</td>
<td>15.06</td>
<td>15.50</td>
<td>5.18</td>
<td>0</td>
<td>1036</td>
</tr>
<tr>
<td>4</td>
<td>-0.97</td>
<td>33.07</td>
<td>5.74</td>
<td>85.71</td>
<td>50.45</td>
<td>0</td>
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<td></td>
<td>0</td>
<td>60.9</td>
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<td>6</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>
Let \( U_1 := \{0\} \) and \( U_2 := [a_{2t+1}, b_{2t+1}] \). Then, \( U(t) := [\xi_n(t), \xi^{(i)}(t)] \) is \( U_2 \) on \( (\tau_{2t+1}, \tau_{2t+2}] \), \( i \in \Lambda_1 \) and \( U_1 \) on \( (\tau_{2t}, \tau_{2t+1}] \), \( i \in \Lambda_2 := \{0, 1, \ldots, n\} \), where \( a_{2t+1} \) and \( b_{2t+1} \), \( i \in \Lambda_2 \), are positive constants which denote the minimal and the maximal rates of adding glycerol, respectively. Thus, we define the class of admissible control functions as

\[
U := \{u|v_i \in U(t), t \in (\tau_{i-1}, \tau_i), i = 1, 2, \ldots, 2n + 1\}.
\]

(9)

Proof: This conclusion can be obtained from Theorem 2.1 and the theory of ordinary differential equations (ODEs; Arrowsmith and Place 1982).

**Theorem 2.3**: If \( x(\cdot|\theta) \) is a solution of the system (1) with given initial state \( x_0 \), then it is uniformly bounded.

Proof: In view of Theorems 2.1 and 2.2, we obtain that, for each \( u(\cdot|\theta) \in U \),

\[
\|x(t|\theta)\| \leq \|x_0\| + \int_0^t \|f(x(s), u(s|\theta))\|ds,
\]

\[
\leq \|x_0\| + K \int_0^T (\|x(s)\| + 1)ds.
\]

By the Gronwall inequality, it follows that

\[
\|x(t|\theta)\| \leq (\|x_0\| + KT) \exp(KT) \quad \forall t \in [0, T],
\]

which gives a value,

\[
M_T = (\|x_0\| + KT) \exp(KT),
\]

for the uniformly bounded property.

3. Optimal control models

Now, define the set of the solutions to the system (1), \( S_0 \), as

\[
S_0 := \{x(\cdot|\theta) \mid x(t|\theta) \text{ is a continuous solution to the system (1) with } u(\cdot|\theta) \in U \text{ for all } t \in [0, T]\}.
\]

(13)

Since the concentrations of biomass, glycerol, products and the volume of culture fluid are restricted in \( W \), we denote the set of the admissible solutions by

\[
S := \{x(\cdot|\theta) \in S_0 \mid x(t|\theta) \in W \text{ for all } t \in [0, T]\}. \quad (14)
\]

Furthermore, the set of the feasible control functions can be defined as

\[
\mathcal{F} := \{u(\cdot|\theta) \in U \mid x(\cdot|\theta) \in S\}.
\]

(15)

Then, the problem of optimising the feeding rate of glycerol and the switching instants between the batch and feeding processes to obtain as much 1,3-PD as possible at the terminal time can be described as follows:

\[
\text{OCP} \quad \min J(\theta) := -x_3(T|\theta)
\]

s.t. \( u(\cdot|\theta) \in \mathcal{F} \),

where \( x_3(\cdot|\theta) \) is the third component of the solution to the system (1).

In view of the special structure of the control function as given in (10), the existence theorem of the optimal control for OCP can be obtained as follows.
Theorem 3.1: OCP has an optimal solution.

Proof: Define the feasible set of parameters $\theta$ as

$$\tilde{\Theta} := \{\theta \in \Theta \mid u(\cdot|\theta) \in \mathcal{F}\}.$$  

Considering the compactness of the set $\Theta$, we obtain that $\tilde{\Theta}$ is a bounded set. In addition, for any sequence $\{\tilde{\theta}^i\}_{i=1}^{\infty} \subseteq \Theta$, there exists at least one subsequence $\{\tilde{\theta}^i\} \subseteq \{\tilde{\theta}^i\}$ such that $\tilde{\theta}^i \to \tilde{\theta}^i$ as $i \to \infty$. It follows from Theorem 2.2 that $x(t|\tilde{\theta}^i)$ is a solution of the system (1) and for all $i \in [0, T]$, $x(t|\tilde{\theta}^i) \in W$ due to the compactness of $W$. That is, $u(\cdot|\tilde{\theta}^i) \in \mathcal{F}$, which implies $\tilde{\theta}^i \in \tilde{\Theta}$ and the closeness of $\tilde{\Theta}$. Hence, $\tilde{\Theta}$ is a compact set. Furthermore, since the cost functional $J(\theta)$ is continuous in $\theta$, we conclude that OCP has an optimal solution. The proof is completed. 

4. Computational approaches

In fact, OCP is an optimisation problem subject to continuous state inequality constraints. In this section, we shall develop a computational method inspired by Teo et al. (1993) to solve our proposed optimal control model.

To begin with, let

$$g_{c}(x(t|\theta)) := x_1^2 - x_1(t|\theta),$$
$$g_{b+c}(x(t|\theta)) := x_1(t|\theta) - x_{b+c}, \quad \ell = 1, 2, \ldots, 6.$$  

The condition $x(t|\theta) \in W \forall t \in [0, T]$ is equivalently transcribed into

$$G(\theta) := 0,$$  

where $G(\theta) := \sum_{i=1}^{12} \int_0^T \min\{0, g_{i}(x(t|\theta))\}dt$. However, $G(\theta)$ is non-smooth and the non-differentiable points are at $g_{i} = 0$, $i = 1, 2, \ldots, 12$. Consequently, standard optimisation routines would have difficulties in dealing with this type of equality constraints. The following smoothing technique introduced in Jennings and Teo (1990) is to replace $\min\{0, g_{i}(x(t|\theta))\}$ with $\hat{g}_{i,c}(x(t|\theta))$, where

$$\hat{g}_{i,c}(x(t|\theta)) = \begin{cases} 
    g_{i}(x(t|\theta)), & \text{if } g_{i}(x(t|\theta)) < -\epsilon, \\
    \frac{(g_{i}(x(t|\theta)) - \epsilon)^2}{4\epsilon}, & \text{if } -\epsilon \leq g_{i}(x(t|\theta)) \leq \epsilon, \\
    0, & \text{if } g_{i}(x(t|\theta)) > \epsilon, 
\end{cases}$$

where $\epsilon > 0$ is an adjustable parameter controlling the accuracy of the approximation. Then, the equality constraint (16) now can be approximated by

$$G_{e}(\theta) := 0,$$  

where $G_{e}(\theta) := \sum_{i=1}^{12} \int_0^T \hat{g}_{i,c}(x(t|\theta))dt$. In fact, (18) is slacked to the following inequality constraint in the computation

$$G_{e,c}(\theta) \geq 0,$$  

where $G_{e,c}(\theta) := \gamma + G_{e}(\theta)$, $\gamma > 0$ is an adjustable parameter controlling the feasibility of the constraint (11). As stated in Teo et al. (1993), the remarkable feature about the constraint transcription (19) is that the constraint qualification is not violated. Consequently, the algorithm developed on the basis of this kind of constraint transcription is much more stable numerically.

Let

$$\mathcal{F}_{e,c} := \{u(\cdot|\theta) \mid x(\cdot|\theta) \in S_0 \text{ and } \gamma + G_{e,c}(\theta) \geq 0\}.$$  

Then, OCP can be approximated by the following approximate OCP:

$$\text{OCP}_{e,c} \quad \min J(\theta) := -x_3(T|\theta)$$
$$\text{s.t. } u(\cdot|\theta) \in \mathcal{F}_{e,c}. $$  

For each $\epsilon > 0, \gamma > 0$, the problem OCP$_{e,c}$ can be solved as a nonlinear mathematical programming problem in the control parameters. This nonlinear mathematical programming problem can be solved using any efficient optimisation technique, such as the sequential quadratic programming routine (Nocedal and Wright 1999). For this, we need the gradient formulae for the cost functional and the constraint functional with respect to the control parameters.

The gradient formulae of the cost functional with respect to the control parameter vector $\theta \in \Theta$ are given in the following theorem.

Theorem 4.1: For each $\epsilon > 0$, and $\gamma > 0$, the derivatives of the cost functional (21) with respect to the control parameters are defined as

$$\frac{\partial J(\theta)}{\partial \theta_i} = \int_{t_{i-1}}^{t_i} \frac{\partial \tilde{H}(t)}{\partial u} dt, \quad i = 1, 2, \ldots, 2n + 1,$$  

$$\frac{\partial J(\theta)}{\partial t_j} = \tilde{H}(t_{j-}) - \tilde{H}(t_{j+}), \quad j = 1, 2, \ldots, 2n,$$  

where

$$\tilde{H}(t) = \tilde{H}(x(t|\theta), u(t|\theta), \tilde{\lambda}(t)), $$
$$\tilde{H}(x(t|\theta), u(t|\theta), \tilde{\lambda}(t)) = \tilde{\lambda}(t)^T f(x(t|\theta), u(t|\theta)), $$
and

$$\tilde{\lambda}(t) = (\tilde{\lambda}_1(t), \tilde{\lambda}_2(t), \tilde{\lambda}_3(t), \tilde{\lambda}_4(t), \tilde{\lambda}_5(t), \tilde{\lambda}_6(t))^T$$

is the solution of the costate system

$$\dot{\tilde{\lambda}}(t) = -\left(\frac{\partial \tilde{H}(x(t|\theta), u(t|\theta), \tilde{\lambda}(t))}{\partial x}\right)^T,$$
with the boundary conditions

\[ \tilde{\lambda}(T) = (0, 0, -1, 0, 0, 0)^T, \]  

\[ \tilde{\lambda}(\tau_j-) = \tilde{\lambda}(\tau_j+), \quad j = 1, 2, \ldots, 2n. \]  

**Proof:** Let \( \theta \in \Theta \) be an arbitrary but fixed vector. For \( i \in \{1, 2, \ldots, 2n + 1\}, j \in \{1, 2, \ldots, 2n\}, w_i \) and \( t_j \) are two arbitrary real numbers. Define

\[ \theta^i_\varepsilon := (v_i, \ldots, v_i + \varepsilon w_i, \ldots, v_{2n+1}, t_1, \ldots, t_{2n})^T, \]

\[ \theta^{i,j}_\varepsilon := (v_i, \ldots, v_{2n+1}, t_1, \ldots, t_j + \varepsilon t_j, \ldots, t_{2n})^T, \]

where \( \varepsilon \) is sufficiently small such that

\[ v_i + \varepsilon w_i \in U(t), \quad t \in (\tau_{j-1}, \tau_j), \]

and

\[ \tau_{j-1} < t_j + \varepsilon t_j < \tau_{j+1}. \]

Now, \( J(\theta^i_\varepsilon) \) and \( J(\theta^{i,j}_\varepsilon) \) can be expressed as

\[ J(\theta^i_\varepsilon) = -\chi_3(T | \theta^i_\varepsilon) \]

\[ + \int_0^T (\tilde{\lambda}(t))^T (f(x(t | \theta^i_\varepsilon), u(t | \theta^i_\varepsilon)) - \dot{x}(t | \theta^i_\varepsilon)) dt, \]

and

\[ J(\theta^{i,j}_\varepsilon) = -\chi_3(T | \theta^{i,j}_\varepsilon) \]

\[ + \int_0^T (\tilde{\lambda}(t))^T (f(x(t | \theta^{i,j}_\varepsilon), u(t | \theta^{i,j}_\varepsilon)) - \dot{x}(t | \theta^{i,j}_\varepsilon)) dt, \]

respectively, where \( \tilde{\lambda} \in \mathbb{R}^6 \) is yet arbitrary. Thus, it follows that

\[ \Delta J(\theta^i_\varepsilon) := \frac{dJ(\theta^i_\varepsilon)}{d\varepsilon} \bigg|_{\varepsilon=0} = \frac{\partial J(\theta)}{\partial v_i} w_i \]

\[ = (0, 0, -1, 0, 0, 0) \Delta x(T | \theta) \]

\[ + \int_0^T \left\{ \frac{\partial \tilde{H}(t)}{\partial x} \Delta x(t | \theta) + \frac{\partial \tilde{H}(t)}{\partial u} w_i \chi_{[\tau_{j-1}, \tau_j]} \right. \]

\[ \left. - \tilde{\lambda}^T(t) \Delta \dot{x}(t | \theta) \right\} dt, \]  

(30)

and

\[ \Delta J(\theta^{i,j}_\varepsilon) := \frac{dJ(\theta^{i,j}_\varepsilon)}{d\varepsilon} \bigg|_{\varepsilon=0} = \frac{\partial J(\theta)}{\partial t_j} t_j \]

\[ = (0, 0, -1, 0, 0, 0) \Delta x(T | \theta) \]

\[ + \int_0^T \left\{ \frac{\partial \tilde{H}(t)}{\partial x} \Delta x(t | \theta) - \tilde{\lambda}^T(t) \Delta \dot{x}(t | \theta) \right\} dt \]

\[ + (\tilde{H}(\tau_j-) - \tilde{H}(\tau_j+)) t_j, \]  

(31)

where \( \tilde{H}(t) \) is defined as in (24). Integrating (30) and (31) by parts and combining (25)–(29), we have

\[ \frac{\partial J(\theta)}{\partial v_i} w_i = \int_{\tau_{j-1}}^\tau \frac{\partial \tilde{H}(t)}{\partial u} w_i dt, \]

\[ \frac{\partial J(\theta)}{\partial t_j} t_j = (\tilde{H}(\tau_j-) - \tilde{H}(\tau_j+)) t_j. \]

Since \( w_i \) and \( t_j \) are arbitrary, the conclusions (22) and (23) of the theorem follow. \( \square \)

Using a similar technique as that given for the proof of Theorem 4.1, the gradient formulæ of the constraint with respect to the control parameter vector \( \theta \in \Theta \) are given in the following theorem.

**Theorem 4.2:** For each \( \epsilon > 0 \), and \( \gamma > 0 \), the derivatives of the constraint functional \( G_{\epsilon,\gamma}(\theta) \) with respect to the control parameters are, respectively,

\[ \frac{\partial G_{\epsilon,\gamma}(\theta)}{\partial v_i} = \int_{\tau_{j-1}}^\tau \frac{\partial \tilde{H}(t)}{\partial u} dt, \quad i = 1, 2, \ldots, 2n + 1, \]

\[ \frac{\partial G_{\epsilon,\gamma}(\theta)}{\partial t_j} = \tilde{H}(\tau_j-) - \tilde{H}(\tau_j+), \quad j = 1, 2, \ldots, 2n, \]

where

\[ \tilde{H}(t) = \sum_{j=1}^{12} \tilde{\gamma}_j x(t | \theta) + \tilde{\lambda}^T(t) f(x(t | \theta), u(t | \theta)), \]

and

\[ \tilde{\lambda}(t) = (\tilde{\lambda}_1(t), \tilde{\lambda}_2(t), \tilde{\lambda}_3(t), \tilde{\lambda}_4(t), \tilde{\lambda}_5(t), \tilde{\lambda}_6(t))^T \]

is the solution of the costate system

\[ \check{\dot{x}}(t) = -\left( \frac{\partial \tilde{H}(x(t | \theta), u(t | \theta), \check{\lambda}(t))}{\partial x} \right)^T, \]

with the boundary conditions

\[ \check{\lambda}(0) = \tilde{\lambda}(T) = (0, 0, 0, 0, 0, 0)^T, \]

\[ \check{\lambda}(\tau_j-) = \tilde{\lambda}(\tau_j+), \quad j = 1, 2, \ldots, 2n. \]

In view of Theorems 4.1 and 4.2, the following algorithm can now be used to generate an approximately optimal solution of the OCP.

**Algorithm 1:**

**Step 1:** Choose initial values of \( \epsilon^0, \gamma^0 \) and \( \theta^0_{\epsilon^0, \gamma^0} \in \Theta \), set parameters \( \alpha > 0 \), \( \beta > 0 \), \( M_1 > 0 \) and \( M_2 > 0 \), and set \( h_1 = 0 \) and \( h_2 = 0 \).

**Step 2:** Solve OCP\( _{\epsilon^0, \gamma^0} \) using sequential quadratic programming (Nocedal and Wright 1999) with an initial \( \theta^0_{\epsilon^0, \gamma^0} \) to give \( \theta^0_{\epsilon^0, \gamma^0} \).

**Step 3:** Check feasibility of \( G(\theta^*_{\epsilon^0, \gamma^0}) = 0 \). If \( G(\theta^*_{\epsilon^0, \gamma^0}) \) is feasible, then go to Step 4. Else set \( \gamma^{h+1} = \alpha \gamma^h \) and
h_3 = h_2 + 1. If \( \gamma^{h_3} \leq M_1 \), then go to Step 4. Else set \( \theta_{\gamma^{h_3}, \gamma^{h_2}} = \theta_{\gamma^{h_2}-1, \gamma^{h_2}} \) and go to Step 2.

**Step 4:** Set \( e^{h_1} = \beta e^{h_1} \) and \( h_5 = h_1 + 1 \). If \( e^{h_1} > M_2 \), set \( \theta_{e^{h_5}, \gamma^{h_3}} = \theta_{e^{h_1}-1, \gamma^{h_1}} \) and go to Step 2. Else output \( u_{e^{h_5-1}, \gamma^{h_3}} \) from \( \theta_{e^{h_1}-1, \gamma^{h_1}} \) by (8) and stop.

Then, \( u_{e^{h_5-1}, \gamma^{h_3}} \) is an approximately optimal solution of OCP.

**Remark 1:** In the algorithm, \( \epsilon \) is a parameter controlling the accuracy of the smoothing approximation. \( \gamma \) is a parameter controlling the feasibility of the constraint (11). \( M_1 \) and \( M_2 \) are two predefined parameters ensuring the termination of the algorithm.

**Remark 2:** It is important for the validity of the above algorithm to choose the parameters \( \alpha \), \( \beta \), \( M_1 \), and \( M_2 \). Typically, the parameters \( \alpha \) and \( \beta \) must be chosen less than 1. \( M_1 \) and \( M_2 \) are two sufficiently small values such that the algorithm can be terminated.

**5. Numerical results**

Based on the reactant composition, cultivation conditions, determination of biomass, substrate and metabolites were reported in Chen et al. (2003). The parameters needed in the computation of the solution to the system (1) are listed in Table 2. Note that these parameters are the same as the ones used in Liu et al. (2009). In addition, the ODEs in the computation process are numerically integrated by the fourth order Runge-Kutta method with the relative error tolerance \( 10^{-4} \).

To save computational time, the fermentation process is partitioned into the first batch phase (Bat. Ph.) and phases I–IX (Ph. I to Ph. IX) according to the switching times. The same time durations of feeding processes (resp. batch processes) and the same feeding strategies are adopted in each one of Ph. I to Ph. IX. Furthermore, the time durations for two adjacent processes, i.e., a feeding process and its succeeding batch process, in Ph. I to Ph. IX are equal and assumed to be \( \frac{3600 \times (T-n)}{3} \) s. It should be mentioned that this approach had been adopted to obtain the experimental data in the actual fermentation process (Chen et al. 2003). These bounds of the time durations in each of the phases are listed in Table 3 (Liu and Feng 2010). The bounds of feeding rates in Ph. I to Ph. IX are given in Table 4 (Liu et al. 2009).

In Algorithm 1, the smoothing and feasible parameters were initially selected as \( \theta^0 = 0.1 \) and \( \gamma^0 = 0.01 \), and then subsequently adjusted according to the guidelines in Algorithm 1. In particular, the parameters \( \alpha \) and \( \beta \) were chosen as 0.1 and 0.01 until the solution obtained was feasible for the original problem. The process was terminated when \( M_1 = 1.0 \times 10^{-8} \) and \( M_2 = 1.0 \times 10^{-7} \). It is worth mentioning that, in the former stage of iterations, a small value of \( \gamma \) was required to ensure feasibility. After that, the \( \gamma \) hardly changed as \( \epsilon \) was decreased. The components \( e^{h_1} \) and \( \theta_{e^{h_1}, \gamma^{h_1}} \) of the initial vector \( \theta_{e^{h_1}, \gamma^{h_1}} \) are chosen as those in Liu et al. (2009).

All computations are performed in Visual C++ 6.0 and numerical results are plotted by MATLAB 6.5 on an AMD Athlon 64 X2 Dual Core Processor TK-57 1.90 GHz machine. Applying the proposed Algorithm 1 to the OCP, we obtain the optimal switching instants listed in Table 5 and the optimal feeding strategies shown in Figure 1. In detail, the blue line in the first subfigure of Figure 1 indicates the feeding rate, which is identically equal to zero, of glycerol and the time duration in the Bat. Ph. Accordingly, the blue lines in the next nine subfigures illustrate the feeding rates in conjunction with time durations of a feeding process and its succeeding batch process, in Ph. I to Ph. IX, respectively.

<table>
<thead>
<tr>
<th>Phases</th>
<th>Bounds</th>
<th>Values (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bat.</td>
<td>( \rho_1 )</td>
<td>19,080</td>
</tr>
<tr>
<td></td>
<td>( \theta_1 )</td>
<td>19,440</td>
</tr>
<tr>
<td>I</td>
<td>( \rho_2 )</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>( \theta_{2+1} )</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>( \theta_2 )</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>( \theta_{2+1} )</td>
<td>98</td>
</tr>
<tr>
<td>II–V</td>
<td>( \rho_2 )</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>( \theta_{2+1} )</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>( \theta_2 )</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>( \theta_{2+1} )</td>
<td>96</td>
</tr>
<tr>
<td>VI–VIII</td>
<td>( \rho_2 )</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>( \theta_{2+1} )</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>( \theta_2 )</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>( \theta_{2+1} )</td>
<td>99</td>
</tr>
<tr>
<td>IX</td>
<td>( \rho_2 )</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>( \theta_{2+1} )</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>( \theta_2 )</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>( \theta_{2+1} )</td>
<td>99</td>
</tr>
</tbody>
</table>

**Table 2.** The parameters in computation of the solution to the system (1) (Liu et al. 2009).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>( x_0 )</td>
<td>(0.1115 g L(^{-1}), 495 mmol L(^{-1}), 0, 0, 0, 5 L)(^T)</td>
</tr>
<tr>
<td>( n )</td>
<td>677</td>
</tr>
<tr>
<td>( r )</td>
<td>0.75</td>
</tr>
<tr>
<td>( c_{s0} )</td>
<td>10672 mmol L(^{-1})</td>
</tr>
<tr>
<td>( T )</td>
<td>24.16 h</td>
</tr>
</tbody>
</table>
Under the obtained optimal switching instants and optimal feeding rates, the computational concentration of 1,3-PD at the terminal time is 1017.04 mmol L\(^{-1}\), which is increased by 27.57\% in comparison with the experimental result 797.23 mmol L\(^{-1}\) appearing in Wang et al. (2008a) for numerical simulation. Furthermore, compared with the obtained 1,3-PD concentration of 925.127 mmol L\(^{-1}\) in Liu et al. (2009), which is computed in case that the same number of phases is considered and the switching instants between the batch and feeding processes are decided \textit{a priori}, the concentration of 1,3-PD at the terminal time obtained in this article is increased by 9.935\%. Hence, it is decisive for enhancing the productivity of 1,3-PD to optimise the feeding rate of glycerol and the switching instants between the batch and feeding processes in fed-batch fermentation of glycerol to 1,3-PD. In particular, the concentration change of 1,3-PD with respect to fermentation time under the optimal switching and control scheme is shown in Figure 2. For the purpose of comparison, the 1,3-PD concentration obtained in Liu et al. (2009) and the experimental data appearing in Wang et al. (2008a) are also shown in Figure 2. From these curves in Figure 2, we conclude that the obtained 1,3-PD concentration at the terminal time in this article is actually higher than the ones previously reported.

6. Conclusions

In this article, a controlled nonlinear dynamical system to describe the fed-batch fermentation of glycerol bioconversion to 1,3-PD was proposed. Taking the feed rate of glycerol as the control function and the switching instants as optimisation variables, we presented an optimal control model involving a nonlinear dynamical system and subject to the constraints of continuous state and control. A computational method was developed based on constraint transcription and smoothing approximation techniques. Numerical results showed that, by employing the optimal control policy, the concentration of 1,3-PD at the terminal time could be increased considerably.
Figure 1. The optimal feeding strategy of glycerol in fed-batch fermentation process.
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References


