Modeling and optimal control of a nonlinear dynamical system in microbial fed-batch fermentation

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**ABSTRACT**

The mathematical model and optimal control of microbial fed-batch fermentation is considered in this paper. Since it is decisive for increasing the productivity of 1,3-propanediol (1,3-PD) to optimize the feeding rate of glycerol and the switching instants between the batch and feeding processes in the fermentation process, we propose a new nonlinear dynamical system to formulate the process. In the system, the switching instants are variable and the feed rate of glycerol is regarded as the control function. Some important properties of the proposed system and its solution are then discussed. To maximize the concentration of 1,3-PD at the terminal time, an optimal control model involving the proposed system and subject to continuous state inequality constraints is established. The existence of the optimal control of the model is also proved. Finally, a computational approach is constructed on the basis of constraint transcription and smoothing approximation techniques. Numerical results show that the concentration of 1,3-PD at the terminal time can be increased considerably.

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1. Introduction

1,3-Propanediol (1,3-PD) has numerous applications in polymers, cosmetics, food, lubricants and medicines. Industrial 1,3-PD production has attracted much attention as an important monomer to synthesize a new type of polyester, polytrimethylene terephthalate (PTT) \([1]\). The microbial conversion of glycerol to 1,3-PD is particularly attractive in that the process is relatively easy and does not generate toxic byproducts. Glycerol can be converted to 1,3-PD by several microorganisms \([2,3]\). Among these, *Klebsiella pneumoniae* (*K. pneumoniae*) ferments glycerol to 1,3-PD in a high yield and productivity \([4–6]\). 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.

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, ethanol and so on \([7]\). With regard to fermentation, almost all of the 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 the pH by alkali addition for the glycerol supply \([8]\). 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 the cells’ 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 optimize the feeding rates and the switching instants between the batch and feeding processes in fed-batch fermentation process.

Modeling the fermentation process is a premise to carry out optimal control and to increase the productivity of 1,3-PD. Initially, the batch model is extrapolated to fed-batch cultivation by incorporating the dilution factors. Unstructured and nonsegregational models with specific rates of cell growth rate, metabolite production rate, and substrate consumption rate have been used to model fed-batch fermentation. The models have been used for optimal control studies by a number of researchers [9–12]. The specific rates in the models are allowed to be dependent on the limiting nutrient concentration, normally, the substrate concentration. However, the specific rates are known to be dependent not only on the substrate concentration but also on the metabolite concentration [7,13]. Recently, by introducing the inhibitions of substrate and products to the specific rate of cell growth rate and based on an assumption that the feeding of glycerol only occurs at impulsive instants, nonlinear impulse systems have been extensively investigated to formulate the fermentation process [14]. Subsequently, the properties, parameter identification problem and optimal control problem, in which the impulsive magnitudes are taken as the control function, for the system have been investigated [14–17]. Nonetheless, 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 concentrate on deducing the optimality condition of the impulsive optimal control problem. In contrast, taking the feeding of glycerol as a time-continuous process, we have proposed a nonlinear dynamical system to formulate the fed-batch process [18]. The parameter identification problem for this system has been then discussed in [19]. Properties and algorithms for the optimal control problem involving the nonlinear system are then investigated in [18,20]. However, in all of the above models, the switching instants between the batch and feeding processes are decided a priori.

With this motivation, in this paper we propose a novel nonlinear dynamical system, in which the feeding rate of glycerol is taken as the control function, with variable switching instants to formulate glycerol bioconversion to the production of 1,3-PD in fed-batch fermentation. Some important properties of the system are also discussed. Incidentally, the optimization and control of this type of nonlinear system has been an active research area over the past decade, see, for example [21–24]. Nevertheless, the optimal control problem for this kind of system with continuous state constraints is rarely considered.

In this paper, to maximize the concentration of 1,3-PD at the terminal time, we then present an optimal control model involving the dynamical system and subject to constraints of continuous state and control. The existence of the optimal control is also proved. Due to the complex nature of the control problem, it is not possible to derive an analytical solution. Thus, it is necessary to rely on numerical methods for solving the problem. To deal with the continuous state constraints, we first transcribe the continuous state inequality constraints into an equality constraint by a constraint transcription. The local smoothing technique in [25] is subsequently applied to approximating the non-smooth equality constraint, and the above equality constraint is slack off to an inequality constraint. As a result, a computational approach is developed to seek the optimal control by solving a sequence of the approximately optimal control problems. 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 rest of the paper is organized as follows. The nonlinear dynamical system is formulated to describe a microbial fed-batch fermentation process in Section 2. In Section 3, some important properties of the nonlinear system is discussed. An optimal control model is proposed and the existence of the optimal control is also established in Section 4. Section 5 develops a computational approach to solve the optimal control model, while Section 6 illustrates the numerical results. Finally, conclusions are provided in Section 7.

2. Problem formulation

The fed-batch culture of glycerol bioconversion to 1,3-PD begins with a batch culture. After the exponential growth phase, glycerol and alkali are continuously fed into the reactor. After the feeding ends, another batch culture starts again. According to fermentation process, we assume that

\begin{align*}
(H_1): \quad & \text{The concentrations of reactants are uniform in the reactor. Time delay and nonuniform space distribution are ignored.} \\
(H_2): \quad & \text{During the process of the fed-batch culture, only glycerol and alkali are fed into the reactor at some constant velocities. Moreover, the feeding velocity ratio } \tau \text{ of alkali to glycerol is a constant.}
\end{align*}

Under the above assumptions (H1) and (H2), mass balances of biomass, substrate and products in fed-batch fermentation can be formulated as the following nonlinear dynamical system:

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

where \( x := (x_1, x_2, x_3, x_4, x_5, x_6)^T \in \mathbb{R}^6 \) and \( u \in \mathbb{R}^1 \) are, respectively, the state and control vectors. The components of the state vector denote the concentrations of biomass, glycerol, 1,3-PD, acetate and ethanol and the volume of culture fluid at \( t \) in fermentor and the control function represents the feeding rate of glycerol in the fermentation process. Moreover, \( x_0 \in \mathbb{R}^6_+ \) is a given initial state and \( T \) is the terminal time of the fermentation process. Let the switching instants be \( \tau_{2i+1}, \) the moment
of adding glycerol, at which the fermentation process switches to continuous culture from the batch culture, and \( T_{2i+2} \), the moment of ending the flow of glycerol, \( i \in \mathbb{A}_1 := \{0, 1, 2, \ldots, n - 1\} \), 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 paper. Furthermore,

\[
f(x(t), u(t)) = \begin{pmatrix}
(q_1(x(t)) - D(x(t), u(t)))x_1(t) \\
D(x(t), u(t)) \left( \frac{c_0}{1 + r} - x_2(t) \right) - q_2(x(t))x_1(t) \\
q_3(x(t))x_1(t) - D(x(t), u(t))x_3(t) \\
q_4(x(t))x_1(t) - D(x(t), u(t))x_4(t) \\
q_5(x(t))x_1(t) - D(x(t), u(t))x_5(t) \\
(1 + r)u(t)
\end{pmatrix}.
\]  

In (2), \( r \) is the velocity ratio of adding alkali to glycerol. \( c_0 \) denotes the initial concentration of glycerol in feed. \( D(x(t), u(t)) \) is the dilution rate defined as

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

On the basis of previous work [5], the specific growth rate of cells \( q_1(x(t)) \), the specific consumption rate of the substrate \( q_2(x(t)) \) and the specific formation rates of products \( q_3(x(t)), q_4(x(t)), q_5(x(t)) \), \( \ell = 3, 4, 5 \), are expressed by the following equations.

\[
q_1(x(t)) = \frac{\Delta_1x_2(t)}{x_2(t) + k_1 \prod_{i=2}^{n} \left( 1 - \frac{x_i(t)}{x_i^*} \right)}^{m_1},
\]

\[
q_\ell(x(t)) = m_\ell + q_1(x(t))\ell_\ell + \frac{\Delta_1x_2(t)}{x_2(t) + k_\ell}, \quad \ell = 2, 3, 4,
\]

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

Under anaerobic conditions at 37°C and pH 7.0, the kinetic parameters and the critical concentrations \( x_a \) and \( x^* \) in (4)–(6) are listed in Table 1.

There are maximal and minimal time durations that are spent on each of the batch and feeding processes because biological considerations limit the rate of switching. Therefore, define the set of admissible switching instants as

\[
\Gamma := \{(\tau_1, \tau_2, \ldots, \tau_{2n})^T \in \mathbb{R}^{2n} | \rho_1 \leq \tau_i - \tau_{i-1} \leq \rho_0, i = 1, 2, \ldots, 2n + 1\},
\]

where \( \tau_0 = 0, \tau_{2n+1} = T, \rho_1 \) and \( \rho_0 \) are the minimal and 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 \( \tau_1, \tau_2, \ldots, \tau_{2n} \), that is,

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

where \( \nu_i, i = 1, 2, \ldots, 2n + 1 \) are the parameters to be optimized and \( \chi_{(a, b]} \) denotes the indicator function of \( I \) defined by

\[
\chi_{(a, b]}(t) = \begin{cases} 
1, & \text{if } t \in I, \\ 
0, & \text{otherwise}.
\end{cases}
\]

Let \( U(t) := [c(t), \gamma^*(t)] \) be \( U_1 := \{0\} \) on \( (\tau_2, \tau_{2i+1}] \), \( i \in \mathbb{A}_1 := \{1, 2, \ldots, n\} \) and \( U_2 := [b_{2i+1}, b_{2i+2}] \) on \( (\tau_{2i+1}, \tau_{2i+2}] \), \( i \in \mathbb{A}_1 \), where \( a_{2i+1} \) and \( b_{2i+1} \), \( i \in \mathbb{A}_2 \), are positive constants which denote the minimal and the maximal rates of adding glycerol, respectively. Now, we define the class of admissible control functions as

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

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<th>( \gamma_\ell )</th>
<th>( k_\ell )</th>
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Table 1: The values of parameters and critical concentrations in the system (1).
Let \( \theta = (\tau^T, v^T)^T \in \mathbb{R}^{4n+1} \), where \( v := (v_1, v_2, \ldots, v_{2n+1})^T \), and \( \Theta \) be a subset of \( \mathbb{R}^{4n+1} \) which consists of all those vectors \( \theta \) such that the corresponding \( r \) and \( v \) satisfy (7) and (9), respectively. Thus, any control function \( u \) in \( \mathcal{U} \), for brevity, can be written as
\[
u(\cdot|\theta).
\]

There exist critical concentrations, outside which cells cease to grow, of biomass, glycerol, 1,3-PD, acetate and ethanol. Hence, it is biologically meaningful to restrict the concentrations of biomass, glycerol, products and the volume of culture fluid in a set \( W \) defined as
\[
x_t^W(t) \in W := \bigcap_{\ell=1}^6 [x_s, x_{s}^\ell], \quad \forall \ t \in [0, T].
\]

3. Properties of nonlinear dynamical system

In this section we will prove some properties of the solutions to the system (1), such as the existence and uniqueness, uniform boundedness and so on. First, we prove some properties of the function \( f \).

**Property 1.** The function \( f(\cdot, \cdot) \) defined in (2) satisfies the following conditions:
(a) \( f(\cdot, \cdot) : \mathbb{R}^n_+ \times \mathcal{U}_1 \cup \mathcal{U}_2 \to \mathbb{R}^n \), together with their partial derivatives with respect to \( x \) and \( u \), are continuous on \( \mathbb{R}^n_+ \times \mathcal{U}_1 \cup \mathcal{U}_2 \) for each \( t \in [0, T] \).
(b) There exists a constant \( K > 0 \) such that
\[
\|f(x(t), u(t|\theta))\| \leq K(1 + \|x(t)\|), \quad \forall (x(t), u(t|\theta)) \in \mathbb{R}^n_+ \times \mathcal{U}_1 \cup \mathcal{U}_2, \ t \in [0, T].
\]

**Proof.** (a) This conclusion can be obtained by the expression of \( f \) in (2).
(b) We can complete the proof using a method similar to the proof of Property 1 in [26].

**Theorem 1.** For each \( u(\cdot|\theta) \in \mathcal{U} \), the nonlinear dynamical system (1) has a unique continuous solution denoted by \( x(\cdot|\theta) \). Furthermore, \( x(\cdot|\theta) \) satisfies the following integral equation
\[
x(t|\theta) = x(0) + \int_0^t f(x(s|\theta), u(s|\theta)), \quad \forall \ t \in [0, T].
\]

and is continuous in \( \theta \).

**Proof.** This conclusion can be obtained from **Property 1** and the theory of ordinary differential equations [27].

**Theorem 2.** 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 **Property 1** and **Theorem 1**, we obtain that, for each \( u(\cdot|\theta) \in \mathcal{U} \),
\[
\|x(t|\theta)\| \leq \|x_0\| + \int_0^t \|f(x(s|\theta), u(s|\theta))\|ds,
\]
\[
\leq \|x_0\| + K \int_0^T (\|x(s|\theta)\| + 1)ds.
\]
By the Gronwall inequality, it follows that
\[
\|x(t|\theta)\| \leq M_1, \quad \forall \ t \in [0, T],
\]
where \( M_1 := (\|x_0\| + KT) \exp(KT). \)

4. Optimal control model

The optimal control model is presented and the existence of the optimal control is also discussed in this section. First, the set of solutions to the system (1), \( \delta_0 \), is defined as
\[
\delta_0 := \{ x(\cdot|\theta)|x(t|\theta) \text{is a continuous solution to the system (1) with } u(\cdot|\theta) \in \mathcal{U} \text{ for all } t \in [0, T] \}.
\]
Since the concentrations of biomass, glycerol and products are restricted in \( W \), we denote the set of the admissible solutions by
\[
\delta := \{ x(\cdot|\theta) \in \delta_0 | x(t|\theta) \in W \text{ for all } t \in [0, T] \}.
\]
Furthermore, the set of the feasible control functions can be defined as
\[
\mathcal{F} := \{ u(\cdot|\theta) \in \mathcal{U}| x(\cdot|\theta) \in \delta \}.
\]
In fed-batch fermentation of glycerol bio-dissimilation to 1,3-PD, the aim of adding glycerol and optimizing the switching instants is to obtain as much 1,3-PD as possible. Hence, the performance criterion is the concentration of 1,3-PD at the
terminal time, that is
\[ J(\theta) := x_3(T|\theta), \quad (18) \]
where \( x_3(\cdot|\theta) \) is the third component of the solution to the system \((1)\). So we establish the optimal control model of fed-batch fermentation:
\[ (OCM) \quad \text{max } J(\theta) \quad \text{s.t. } u(\cdot|\theta) \in \mathcal{F}. \]

The existence theorem of the optimal control for \((OCM)\) can be obtained in the following theorem.

**Theorem 3.** \((OCM)\) has at least one optimal solution.

**Proof.** In view of the definition of the set of the feasible controls \((17)\), we know that the feasible set of parameters can be defined as
\[ \hat{\Theta} := \{ \theta \in \Theta | u(\cdot|\theta) \in \mathcal{F} \}. \quad (19) \]
Since the set \( \Theta \) is compact, we conclude that \( \hat{\Theta} \subseteq \Theta \) is a bounded set. Moreover, for any sequence \( \{ \theta^i \}_{i=1}^{\infty} \subseteq \hat{\Theta} \), there exists at least one subsequence \( \{ \theta^{i_k} \} \subseteq \{ \theta^i \} \) such that \( \theta^{i_k} \to \bar{\theta} \) as \( i \to \infty \). It follows from **Theorem 1** that \( x(\cdot|\bar{\theta}) \) is a solution of the system \((1)\) and for all \( t \in [0, T], x(t|\theta) \in W \) due to the compactness of \( W \). That is, \( u(\cdot|\bar{\theta}) \in \mathcal{F} \), which implies \( \bar{\theta} \in \hat{\Theta} \) and the closeness of \( \hat{\Theta} \). Hence, \( \hat{\Theta} \) is a compact set. Furthermore, since the cost functional \( J(\theta) \) is continuous in \( \theta \), we conclude that \((OCM)\) has at least one optimal solution. \( \square \)

5. A computational procedure

\((OCM)\) is essentially an optimization problem subject to continuous state constraints. Several successful families of algorithms for solving this class of problems have been developed [25,28–32]. In particular, we would like to mention a computational approach base on a constraint transcription and local smoothing technique in [25]. Now, a computational procedure for solving \((OCM)\) may be stated as follows.

Let
\[ g_\ell(x(t|\theta)) := x_\ell(t|\theta) - x_\ell^*, \]
\[ g_{\ell+1}(x(t|\theta)) := x_{\ell+1} - x_\ell(t|\theta), \quad \ell = 1, 2, \ldots, 6. \]
Then, the condition \((11)\) is equivalently transcribed into
\[ G(\theta) = 0, \quad (20) \]
where \( G(\theta) := \sum_{\ell=1}^{12} \int_0^T \max(0, g_\ell(x(t|\theta))) dt \). However, \( G(\theta) \) is non-smooth in \( \theta \). Consequently, standard optimization routines would have difficulties in dealing with this type of equality constraint. The following smoothing technique is to replace \( \max(0, g_\ell(x(t|\theta))) \) with \( \hat{g}_{\ell, \epsilon}(x(t|\theta)) \), where
\[ \hat{g}_{\ell, \epsilon}(x(t|\theta)) := \begin{cases} 0, & \text{if } g_\ell(x(t|\theta)) < -\epsilon, \\ (g_\ell(x(t|\theta)) + \epsilon)^2, & \text{if } -\epsilon \leq g_\ell(x(t|\theta)) \leq \epsilon, \\ \frac{4\epsilon}{g_\ell(x(t|\theta))}, & \text{if } g_\ell(x(t|\theta)) > \epsilon, \end{cases} \quad (21) \]
where \( \epsilon > 0 \) is an adjustable parameter controlling the accuracy of the approximation. Note that
\[ \hat{G}_\epsilon(\theta) := \sum_{\ell=1}^{12} \int_0^T \hat{g}_{\ell, \epsilon}(x(t|\theta)) dt \quad (22) \]
is a smooth function in \( \theta \). The equality constraint \((20)\) now can be approximated by
\[ \hat{G}_\epsilon(\theta) = 0. \quad (23) \]
In fact, \((23)\) is slacked off to the following inequality constraint in the computation
\[ \hat{G}_{\epsilon, \gamma}(\theta) := \gamma + \hat{G}_\epsilon(\theta) \geq 0, \quad (24) \]
where \( \gamma > 0 \) is an adjustable parameter controlling the feasibility of the constraint \((23)\).
Let
\[ \mathcal{F}_{\epsilon, \gamma} := \{ u(\cdot|\theta)|x(\cdot|\theta) \in \delta_0 \text{ and } \gamma + \hat{G}_\epsilon(\theta) \geq 0 \}. \quad (25) \]
Then, (OCM) can be approximated by the approximately optimal control problem as follows:

\[
(\text{OCM}_{\epsilon, \gamma}) \quad \begin{array}{l}
\text{max } J(\theta) := x_3(T|\theta) \\
\text{s.t. } u(\cdot|\theta) \in F_{\epsilon, \gamma}
\end{array}
\]  \quad (26)

To solve the optimal control model (OCM), we need to solve a sequence of problems \(\{\text{OCM}_{\epsilon, \gamma}\}\). While each (OCM\(_{\epsilon, \gamma}\)) can be solved as a nonlinear mathematical programming problem in the control parameters. This nonlinear mathematical programming problem can be solved using any efficient optimization technique, such as the sequential quadratic programming routine (see, for example, [33]). For this, we need the gradient formulae for the cost functional and the constraint functionals with respect to the control parameters. The derivation of these gradients is given below.

**Theorem 4.** For each \(\epsilon > 0\), and \(\gamma > 0\), the derivatives of the cost functional (26) with respect to the control parameters are, respectively, given by

\[
\frac{\partial J(\theta)}{\partial \tau_i} = \dot{H}(\tau_i^-) - \dot{H}(\tau_i^+), \quad i = 1, 2, \ldots, 2n,
\]

\[
\frac{\partial J(\theta)}{\partial v_j} = \int_{\tau_{j-1}}^{\tau_j} \frac{\partial H(t)}{\partial u} \, dt, \quad j = 1, 2, \ldots, 2n + 1,
\]

where

\[
\dot{H}(t) = \dot{H}(x(t|\theta), u(t|\theta), \hat{\lambda}(t)),
\]

\[
\dot{H}(x(t|\theta), u(t|\theta), \hat{\lambda}(t)) = \dot{\lambda}^T(t)f(x(t|\theta), u(t|\theta)),
\]

and

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

is the solution of the costate system

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

with the boundary conditions

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

\[
\dot{\lambda}(\tau_i-) = \dot{\lambda}(\tau_i^+), \quad j = 1, 2, \ldots, 2n.
\]

**Proof.** The derivation of the gradients of the cost functional \(J(\theta)\) with respect to \(\tau_i\), \(i \in \{1, 2, \ldots, 2n\}\), and \(v_j\), \(j \in \{1, 2, \ldots, 2n + 1\}\), is similar. Thus, only the derivation of the gradient of the cost function \(J(\theta)\) with respect \(\tau_i\) is given below. Let \(\theta \in \Theta\) be an arbitrary but fixed vector and \(t_i, i \in \{1, 2, \ldots, 2n\}\), an arbitrary real number. Define

\[
\theta^L_e := (v_1, \ldots, v_{2n+1}, \tau_1, \ldots, \tau_i + \epsilon t_i, \ldots, \tau_{2n})^T,
\]

where \(\epsilon > 0\) is an arbitrarily small real number such that

\[
\tau_{i-1} < \tau_i + \epsilon t_i < \tau_{i+1}.
\]

Thus, \(J(\theta^L_e)\) can be expressed as

\[
J(\theta^L_e) := x_3(T|\theta^L_e) + \int_0^T \dot{\lambda}^T(t)(f(x(t|\theta^L_e), u(t|\theta^L_e)) - \dot{x}(t|\theta^L_e)) \, dt,
\]

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

\[
\Delta J(\theta^L_e) = \frac{dJ(\theta^L_e)}{d\theta} \bigg|_{\theta = 0} = \frac{\partial J(\theta)}{\partial \tau_i} t_i
\]

where

\[
\hat{H}(t) := \dot{H}(x(t|\theta), u(t|\theta), \hat{\lambda}(t)),
\]

\[
\dot{H}(x(t|\theta), u(t|\theta), \hat{\lambda}(t)) = \dot{\lambda}^T(t)f(x(t|\theta), u(t|\theta)),
\]

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

is the solution of the costate system

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

with the boundary conditions

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

\[
\dot{\lambda}(\tau_i-) = \dot{\lambda}(\tau_i^+), \quad j = 1, 2, \ldots, 2n.
\]
Since \( t_i \) is arbitrary, the conclusion (27) of the theorem follows. The gradient formula (28) can be derived similarly. The proof is completed. \( \square \)

Using the similar technique as that given for the proof of the above theorem, the gradient formulae of the constraints with respect to the control parameters are given in the following theorem.

**Theorem 5.** For each \( \epsilon > 0 \), and \( \gamma > 0 \), the derivatives of the constraint functional \( \tilde{G}_{c, \gamma}(\theta) \) with respect to the control parameters are, respectively,

\[
\frac{\partial \tilde{G}_{c, \gamma}(\theta)}{\partial t_i} = \tilde{H}(t_i) - \bar{H}(t_i), \quad i = 1, 2, \ldots, 2n,
\]

\[
\frac{\partial \tilde{G}_{c, \gamma}(\theta)}{\partial v_j} = \int_{t_{j-1}}^{t_j} \frac{\partial \bar{H}(t)}{\partial u} \, dt, \quad j = 1, 2, \ldots, 2n + 1,
\]

where

\[
\bar{H}(t) = \sum_{i=1}^{12} \bar{g}_c(x(t|\theta)) + \tilde{\lambda}^T(t)f(x(t|\theta), u(t|\theta)),
\]

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

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

with the boundary conditions

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

\[
\tilde{\lambda}(t_j) = \tilde{\lambda}(t_j), \quad i = 1, 2, \ldots, 2n.
\]

In view of Theorems 4 and 5, the following algorithm can now be used to generate an approximately optimal solution of (OCM).

**Algorithm**

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

Step 2. Solve (OCM) using sequential quadratic programming [33] with an initial \( \theta^0_{e, \gamma, 0} \) to give \( \theta^*_{e, \gamma, 0} \).

Step 3. Check the feasibility of \( G(\theta^*_{e, \gamma, 0}) = 0 \). If \( G(\theta^*_{e, \gamma, 0}) \) is feasible, then go to Step 4. Otherwise set \( \gamma = \gamma + 1 \) and \( h = h + 1 \). If \( \gamma = M_2 \), set \( \theta^0_{e, \gamma} = \theta^0_{e, \gamma-1} \) and go to Step 2.

Step 4. Set \( \theta^*_{e, \gamma, 0} = \beta \theta^*_{e, \gamma, 0} \) and \( h = h + 1 \). If \( \theta^0_{e, \gamma, 0} \) from \( \theta^*_{e, \gamma-1, \gamma} \) by (8) and stop.

Then, \( \theta^*_{e, \gamma-1, \gamma} \) is an approximately optimal solution of (OCM).

6. Numerical results

Based on the reactant composition, cultivation conditions, determination of biomass, substrate and metabolites were reported in [34]. The initial state, the switching times, the velocity ratio of adding alkali to glycerol, the initial concentration of glycerol in feed, and fermentation time are \( x_0 = (0.1115 \, \text{gL}^{-1}, 495 \, \text{mmolL}^{-1}, 0, 0, 0, 5 \, \text{L})^T \), \( 2n = 1332, r = 0.75, c_{d0} = 10762 \, \text{mmolL}^{-1} \), and \( T = 857.88 \, \text{s} \), respectively. In the Algorithm, the initial values \( \epsilon^0, \gamma^0 \), the parameters, \( \alpha, \beta, M_1 \) and \( M_2 \) needed in the computation are, respectively, 0.1, 1, 0.1, 0.1, 10^{-8}, 10^{-7}. These parameters are derived empirically after numerous experiments. The components \( \theta^0_{e, \gamma, 0} \) and \( \theta^0_{e, \gamma, 0} \) of the initial vector \( \theta^0_{e, \gamma, 0} \) are chosen as those in [18].

In order to save the computational time, the fermentation process is partitioned into the first batch phase (Bat. Ph.) and phases I–VIII according to the switching times. The same time durations of feeding processes (resp. batch processes) are adopted in each one of phases I–VIII. It should be mentioned that this approach had been adopted to obtain the experimental data in the actual fermentation process [34]. These bounds of the time durations in each of phases are listed in Table 1. Table 2 reports the bounds of feeding rates of glycerol in phases I–VIII. Note that these bounds in Tables 1 and 2 had been used in the previous work [18].

Applying the algorithm to solving (OCM), we obtain the optimal switching instants listed in Table 3 and the optimal feeding rates shown in Fig. 1. Here, all the computations are performed in Visual C++ 6.0 and numerical results are plotted.
by MATLAB 6.5. In particular, the corresponding Cauchy problems in the computation are integrated by the fourth order Runge-Kutta method with the relative error tolerance $10^{-4}$. In detail, the blue line in the first subfigure of Fig. 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 8 subfigures illustrate the feeding rates in conjunction with time durations of a feeding process and its succeeding batch process, in phases I–VIII, respectively. Under the optimal feeding rates and the optimal switching instants, we get the concentration of 1,3-PD at the terminal time, which is the final goal, is $1010.52 \text{ mmolL}^{-1}$. It is also noticeable that the 1,3-PD concentration at the terminal time is 26.79% greater than the experimental data $797 \text{ mmolL}^{-1}$ and is 9.23% greater than the one mentioned in [18]. These are due to using the optimal feeding rates of glycerol and the optimal switching instants between the batch and feeding processes. Furthermore, the concentration change of 1,3-PD under the optimal feeding rates
of glycerol and the optimal switching instants is shown in Fig. 2. The experimental data and the result in [18] are also depicted in Fig. 2 for the purpose of comparison. From Fig. 2, we can see that the simulation result in this work is actually better than the ones previously reported [18].
verified the validity of the mathematical model and the effectiveness of the computational method. Numerical results involving 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. An optimal control model involving nonlinear dynamical system and variable switching instants was first proposed. Taking the feeding rate of glycerol as the control function and the switching instant as optimization variable, we then presented an optimal control model involving 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 verified the validity of the mathematical model and the effectiveness of the computational method.

### Table 2
The bounds of time durations in the Bat, Ph, and phases I–VIII.

<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>19080</td>
</tr>
<tr>
<td></td>
<td>$\varrho_1$</td>
<td>19440</td>
</tr>
<tr>
<td>I ($t = 1, \ldots, 28$)</td>
<td>$\rho_2$</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>$\varrho_2$</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>$\rho_2+1$</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>$\varrho_2+1$</td>
<td>98</td>
</tr>
<tr>
<td>II–V ($t = 29, \ldots, 378$)</td>
<td>$\rho_3$</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>$\varrho_3$</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>$\rho_3+1$</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>$\varrho_3+1$</td>
<td>96</td>
</tr>
<tr>
<td>VI–VIII ($t = 379, \ldots, 666$)</td>
<td>$\rho_4$</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>$\varrho_4$</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>$\rho_4+1$</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>$\varrho_4+1$</td>
<td>99</td>
</tr>
</tbody>
</table>

### Table 3
The bounds of feeding rates in phases I–VIII.

<table>
<thead>
<tr>
<th>Phases</th>
<th>I–II</th>
<th>III</th>
<th>IV</th>
<th>V–VII</th>
<th>VIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper bounds (mL s$^{-1}$)</td>
<td>0.3058</td>
<td>0.2924</td>
<td>0.2657</td>
<td>0.2524</td>
<td>0.2390</td>
</tr>
<tr>
<td>Lower bounds (mL s$^{-1}$)</td>
<td>0.2038</td>
<td>0.1949</td>
<td>0.1771</td>
<td>0.1682</td>
<td>0.1992</td>
</tr>
</tbody>
</table>

### Table 4
The optimal switching instants in the fed-batch fermentation process.

<table>
<thead>
<tr>
<th>Phases</th>
<th>Switching instants</th>
<th>Optimal values (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bat.</td>
<td>$t_1$</td>
<td>19081.6</td>
</tr>
<tr>
<td>I ($t = 1, \ldots, 28$)</td>
<td>$t_2$</td>
<td>19087.7 + 100.16($t - 1$)</td>
</tr>
<tr>
<td></td>
<td>$t_2+1$</td>
<td>19081.6 + 100.16($t - 1$)</td>
</tr>
<tr>
<td>II ($t = 29, \ldots, 65$)</td>
<td>$t_3$</td>
<td>21885 + 100.16($t - 29$)</td>
</tr>
<tr>
<td></td>
<td>$t_3+1$</td>
<td>21886.1 + 100.16($t - 28$)</td>
</tr>
<tr>
<td>III ($t = 66, \ldots, 126$)</td>
<td>$t_4$</td>
<td>25599.8 + 100.16($t - 66$)</td>
</tr>
<tr>
<td></td>
<td>$t_4+1$</td>
<td>25592 + 100.16($t - 65$)</td>
</tr>
<tr>
<td>IV ($t = 127, \ldots, 245$)</td>
<td>$t_5$</td>
<td>31711.7 + 100.16($t - 127$)</td>
</tr>
<tr>
<td></td>
<td>$t_5+1$</td>
<td>31701.7 + 100.16($t - 126$)</td>
</tr>
<tr>
<td>V ($t = 246, \ldots, 378$)</td>
<td>$t_6$</td>
<td>43627.5 + 100.16($t - 246$)</td>
</tr>
<tr>
<td></td>
<td>$t_6+1$</td>
<td>43620.8 + 100.16($t - 245$)</td>
</tr>
<tr>
<td>VI ($t = 379, \ldots, 459$)</td>
<td>$t_7$</td>
<td>56943.6 + 100.16($t - 379$)</td>
</tr>
<tr>
<td></td>
<td>$t_7+1$</td>
<td>56942 + 100.16($t - 378$)</td>
</tr>
<tr>
<td>VII ($t = 460, \ldots, 522$)</td>
<td>$t_8$</td>
<td>65055 + 100.16($t - 460$)</td>
</tr>
<tr>
<td></td>
<td>$t_8+1$</td>
<td>65054.9 + 100.16($t - 459$)</td>
</tr>
<tr>
<td>VIII ($t = 523, \ldots, 666$)</td>
<td>$t_9$</td>
<td>71366 + 100.16($t - 523$)</td>
</tr>
<tr>
<td></td>
<td>$t_9+1$($t \neq 666$)</td>
<td>71365 + 100.16($t - 522$)</td>
</tr>
</tbody>
</table>

### 7. Conclusions

In this paper, the mathematical model and optimal control of microbial fed-batch fermentation was considered (Table 4). A nonlinear dynamical system with variable switching instants was first proposed. Taking the feeding rate of glycerol as the control function and the switching instant as optimization variable, we then presented an optimal control model involving 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 verified the validity of the mathematical model and the effectiveness of the computational method.
Acknowledgements

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References