# OPTIMAL CONTROL FOR A NONLINEAR TIME-DELAY SYSTEM IN FED-BATCH FERMENTATION*

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**Abstract:** The main control goal in fed-batch fermentation is to maximize yield of target product and reduce operation costs. In this paper, we propose a controlled nonlinear time-delay system, in which the flow rate of glycerol is taken as the control function and the terminal time of the fermentation as the optimization variable, to model the 1,3-propanediol (1,3-PD) production in fed-batch process. Taking the mass of 1,3-PD per unit time as the performance index, we formulate a constrained optimal control model with free terminal time to optimize the production process. Using a time-scale transformation, the optimal control problem is equivalently transcribed into the one with fixed terminal time. A computational approach is then developed to seek the optimal control and the optimal terminal time. This method is based on the control parametrization in conjunction with an improved differential evolution algorithm. Numerical results show that the mass of 1,3-PD per unit time is increased considerably and the duration of the fermentation is shorted greatly compared with previous results.

**Key words:** *nonlinear time-delay system, constrained optimal control, control parametrization, improved differential evolution, fed-batch fermentation*

**Mathematics Subject Classification:** *49M37,93C23*

## 1 Introduction

Fed-batch cultivation technique is a mode of bioreactor operation that provides distinct advantages over the other operation modes and often used in industry due to its ability to overcome the catabolite repression, which usually occurred during production of fine chemicals [14, 25]. Concentration of substrate in cultivation medium can be externally manipulated by using the appropriate feed-rate profiles. This gives the challenge to control and optimize the fed-batch processes. As a result, optimal control of feeding rates in fed-batch fermentation has received extensive attention [1, 29, 31].

1,3-Propanediol (1,3-PD) is one of important products used in chemical industry, in particular for polyesters production (e.g. polyethers and polyurethanes). Microbial fermentation of glycerol to produce 1,3-PD is a good solution from both an economical and ecological viewpoint. Among several strains [3, 35], *Klebsiella pneumoniae* has been widely investigated since 1980s due to its high yield [27,48]. The experimental investigations showed

that the fermentation is a complex bioprocess since the microbial growth is subjected to multiple inhibitions of substrate and products. Regarding the fermentation modes, the most efficient cultivation method appears to be a fed-batch fermentation [49]. The fed-batch process begins with a batch cultivation, then batch-fed glycerol and alkali are poured into the reactor in order to provide sufficient nutrients and maintain a suitable environment for cells growth. During the whole fed-batch process, the products remain in the containment until the end of the run.

Modelling fermentation process has aroused much interest for decades since using non-accurate model in calculation of the optimal feeding rate may lead to undesirable results. Initially, unstructured and nonsegregational models have been used to model fed-batch process. The models have been used for optimal control studies by a number of researchers [23, 38]. Recently, impulsive systems, multistage systems and switched systems have been explored to formulate the fed-batch process [19, 20, 41]. The optimal control problems for these systems are subsequently investigated [8, 18, 21]. Numerical results showed that, by employing obtained optimal strategies, the concentration of 1,3-PD at the terminal time can be increased considerably compared with the experimental results. Although the achieved results are interesting, time delays are ignored in the above researches.

On the other hand, time delays exist in the fermentation process [26, 46] since a cell has to undergo some change or growth process for which it needs some time before it reacts with others. In this paper, considering the existence of time-delays in the fermentation process, we propose a controlled nonlinear time-delay system, in which the flow rate of glycerol is taken as the control function and the terminal time as the optimization variable, to formulate the fed-batch process. Some important properties are also discussed. The main goal of control the fermentation is to maximize the yield of 1,3-PD and reduce operation costs [22]. Thus, the mass of 1,3-PD per unit time is regarded as the performance index. By the way, many studies have considered the same performance index in optimal control of fermentation process [11, 13, 34]. Then, we formulate an optimal control problem with free terminal time involving the proposed nonlinear time-delay system and subject to continuous state constraints and control constraints to optimize the fermentation process. Incidentally, optimal control of time-delay systems with fixed terminal time have attracted the attention of many researchers [9, 15, 44, 45]. In contrast, optimal control problems with free terminal time are more difficult than those with fixed terminal time because they require an initial estimation of the unknown terminal time [32]. For this type of optimal control problems involving dynamical systems without time-delays, many interesting theoretical results can be found in [24, 28, 37]. For numerical computation, several successful families of algorithms have been developed, see, for example [4, 5, 17, 39]. Nevertheless, optimal control problems of nonlinear time-delay systems with free terminal time are rarely considered.

In this paper, using a time-scale transformation, we equivalently transcribe the constrained optimal control problem with free terminal time into the one with fixed terminal time. Furthermore, the transformed optimal control problem is approximated by a sequence of parameter optimization problems using the control parametrization method. In addition, the constraint transcription technique is applied to approximating the continuous state constraints by constraints in canonical form. The convergence of this approximation is also established. An improved differential evolution (DE) algorithm is then developed to solve the resultant parameter optimization problems. Numerical results show that the mass of 1,3-PD per unit time is increased considerably and the duration of fermentation is shorted greatly compared with previous results.

This paper is organized as follows. In the next section, Section 2, the controlled nonlinear time-delay system in the fed-batch process is described. Section 3 gives the constrained op-

timal control problem and its equivalent form. Section 4 develops a computational approach to solve the equivalent optimal control problem, while Section 5 illustrates the numerical results. Finally, conclusions are provided in Section 6.

## $\boxed{2}$ Controlled Nonlinear Time-delay Systems

The fed-batch process starts with a batch process, then batch-fed substrate and alkali are poured into the reactor every so often to provide sufficient nutrients and maintain the suitable environment for strains growth. According to the fermentation process, we assume that

($H_1$). The concentrations of reactants are uniform in reactor. Nonuniform space distribution is ignored.

($H_2$). During the process of fed-batch process, only glycerol and alkali are fed into the reactor. Moreover, the feeding velocity ratio of alkali to glycerol $r$ is a constant.

Under the assumptions ($H_1$) and ($H_2$), the following controlled nonlinear time-delay system can be used to describe the fed-batch process

$$\begin{cases} \dot{x}(t) = f(x(t), x(t-\tau), u(t)), \\ u(t) \in U(t), \ t \in (0, T], \\ x(0) = x_0, \\ x(t) = \phi(t), t \in [-\tau, \ 0], \end{cases} \tag{2.1}$$

where $x(t) := (x_1(t), x_2(t), x_3(t), x_4(t), x_5(t), x_6(t))^\top$ is the state vector whose components are, respectively, the extracellular concentrations of biomass, glycerol, 1,3-PD, acetate, ethanol and the volume of culture fluid at $t$ in the fermenter; $x(t-\tau)$ is the delayed state; $\tau$ is a time-delay; $u(t)$ is the control function denoting the flow rate of the glycerol. Moreover, $T$ is the terminal time of the fermentation and is a variable in this work, $x_0$ is a given initial state, and $\phi(t) \in C^1([-\tau, 0], R^6)$ is a given initial function. Here, $C^1([-\tau, 0], R^6)$ is the Banach space of continuously differentiable functions mapping the interval $[-\tau, 0]$ into $R^6$. The delay in (2.1) arises because nutrient metabolization does not immediately lead to the production of new biomass [46]. The dynamics of fed-batch process is given by

$$f(x(t), x(t-\tau), u(t)) = \begin{pmatrix} q_1(x(t))x_1(t-\tau) - D(x(t), u(t))x_1(t) \\ D(x(t), u(t))(\frac{c_{s0}}{1+r} - x_2(t)) - q_2x(t))x_1(t-\tau) \\ q_3(x(t))x_1(t-\tau) - D(x(t), u(t))x_3(t) \\ q_4(x(t))x_1(t-\tau) - D(x(t), u(t))x_4(t) \\ q_5(x(t))x_1(t-\tau) - D(x(t), u(t))x_5(t) \\ (1+r)u(t) \end{pmatrix}. \tag{2.2}$$

In (2.2), $c_{s0} > 0$ denotes the concentration of initial feed of glycerol in the medium, and $r > 0$ is the velocity ratio of adding alkali to glycerol. The dilution rate $D(x(t), u(t))$ is defined by

$$D(x(t), u(t)) = \frac{(1+r)u(t)}{x_6(t)}. \tag{2.3}$$

On the basis of the previous work [47], the specific growth rate of cells $q_1(x(t))$ is expressed as

$$q_1(x(t)) = \Delta_1 \frac{x_2(t)}{x_2(t) + k_1} \prod_{\ell=2}^{5} \left(1 - \frac{x_\ell(t)}{x_\ell^*}\right), \tag{2.4}$$

where $\Delta_1$ is the maximum specific growth rate, $k_1$ is the Monod saturation constant, and $x_\ell^*$ are the critical concentrations for cells growth. The specific consumption rate of substrate $q_2(x(t))$ is

$$q_2(x(t)) = m_2 + \frac{q_1(x(t))}{Y_2} + \Delta_2 \frac{x_2(t)}{x_2(t) + k_2}. \tag{2.5}$$

In (2.5), $m_2$ is the maintenance term of substrate consumption under substrate-limited conditions, $Y_2$ is the maximum growth yield, $\Delta_2$ is the maximum increment of substrate consumption rate under substrate-sufficient conditions, and $k_2$ is the saturation constant for substrate. The specific formation rates of 1,3-PD and acetate $q_\ell(x(t)), \ell = 3, 4$, are defined as

$$q_\ell(x(t)) = m_\ell + q_1(x(t))Y_\ell + \Delta_\ell \frac{x_2(t)}{x_2(t) + k_\ell}, \tag{2.6}$$

where $m_\ell$ are the maintenance terms of product formations under substrate-limited conditions, $Y_\ell$ are the maximum product yields, $\Delta_\ell$ are the maximum increments of product formation rates under substrate-sufficient conditions, and $k_\ell$ are saturation constants for products. Moreover, the specific formation rate of ethanol $q_5(x(t))$ is described as

$$q_5(x(t)) = q_2(x(t))(\frac{c_1}{c_2 + q_1(x(t))x_2(t)} + \frac{c_3}{c_4 + q_1(x(t))x_2(t)}), \tag{2.7}$$

in which $c_1, c_2, c_3$ and $c_4$ are parameters for determination of yield of ethanol on glycerol.

Due to the fed-batch addition of glycerol in the fermentation process, we denote $t_{2j}$, the moment of ending the flow of glycerol at which the fermentation process switches into a batch process from a feeding process, and $t_{2j+1}$, the moment of adding glycerol at which the fermentation process switches to a feeding process from a batch process, $j = 0, 1, \ldots, N$. Note that these moments are decided a priori in the experiment. Now, define

$$U_i = \begin{cases} [a_i, b_i], & \text{if } i \text{ is even,} \\ \{0\}, & \text{if } i \text{ is odd,} \end{cases} \tag{2.8}$$

where $a_i$ and $b_i$ are positive constants denoting the minimal and the maximal rates of adding glycerol, respectively. Let $U(t) := U_i, t \in (t_{i-1}, t_i], i = 1, 2, \ldots, 2N + 1$, and assume the terminal time of the fermentation $T$ is also bounded in $[T_{min}, T_{max}]$. Thus, we define the class of admissible control functions as

$$\mathcal{U} := \{u \in L_2([0, T_{max}], R^1) \mid u(t) \in U(t), t \in (0, T]\}, \tag{2.9}$$

where $L_2([0, T_{max}], R^1)$ is the space of square-integrable Lebesgue measurable functions from $[0, T_{max}]$ into $R^1$.

There exist critical concentrations of biomass, glycerol, 1,3-PD, acetate and ethanol, outside which cells cease to grow. Hence, it is biologically meaningful to restrict the concentrations of biomass, glycerol and products within a set $W$ defined as

$$x^\top(t) \in W := \prod_{\ell=1}^{6} [x_{*\ell}, x_\ell^*], \forall\, t \in [0, T]. \tag{2.10}$$

For the system (2.1), some important properties are given in the following theorems.

**Theorem 2.1.** *The function $f(\cdot, \cdot, \cdot)$ defined in (2.2) satisfies the following conditions:*

(a). *$f(\cdot, \cdot, \cdot) : R_+^6 \times R_+^6 \times \bigcup\limits_{i=1}^{2N+1} U_i \to R^6$, together with its partial derivatives with respect to*

$x$, $y$ and $u$, is continuous on $R_+^6 \times R_+^6 \times \bigcup_{i=1}^{2N+1} U_i$.

(b). There exists a constant $K > 0$ such that

$$\|f(x, y, u)\| \leq K(1 + \|x\| + \|y\|), \forall (x, y, u) \in R_+^6 \times R_+^6 \times \bigcup_{i=1}^{2N+1} U_i, \tag{2.11}$$

where $\| \cdot \|$ denotes the Euclidean norm.

*Proof.* (a). This conclusion can be obtained by the expression of $f$ in (2.2).

(b). The result can be proved in a similar manner to the proof that given for Property 1 in [19]. □

**Theorem 2.2.** *For each $u \in \mathcal{U}$ and $T \in [T_{min}, T_{max}]$, the system (2.1) has a unique continuous solution on $[-\tau, T]$ denoted by $x(\cdot|u, T)$. Furthermore, $x(\cdot|u, T)$ satisfies that*

$$x(t|u, T) = x_0 + \int_0^t f(x(s|u, T), x(s - \tau|u, T), u(s))ds, \forall t \in [0, T], \tag{2.12}$$

*and $x(t|u, T) = \phi(t), \forall t \in [-\tau, 0]$.*

*Proof.* The proof can be obtained by Theorem 2.1 and the theory of delay-differential equations [10]. □

**Theorem 2.3.** *Given the initial function $\phi(t) \in C^1([-\tau, 0], R_+^6)$ and the initial condition $x_0$, the unique solution $x(\cdot|u, T)$ of the system (2.1) is uniformly bounded.*

*Proof.* For each $u \in \mathcal{U}$ and $T \in [T_{min}, T_{max}]$, since $\phi(t)$ is continuous on $[-\tau, 0]$, there exists a constant $M' \geq 0$ such that

$$\sup\{\|\phi(t)\| | t \in [-\tau, 0]\} \leq M'.$$

Thus,

$$\|x(t|u, T)\| \leq M', \forall t \in [-\tau, 0].$$

In view of Theorems 2.1 and 2.2, we obtain that

$$\|x(t|u, T)\| \leq \|x_0\| + \int_0^t \|f(x(s|u, T), x(s - \tau|u, T), u(s))\|ds,$$

$$\leq \|x_0\| + \int_0^t K(1 + \|x(s|u, T)\| + \|x(s - \tau|u, T)\|)ds,$$

$$\leq M' + K\tau M' + K \int_0^t (1 + 2\|x(s|u, T)\|)ds, \quad \forall t \in (0, T].$$

By the Gronwall inequality, it follows that

$$\|x(t|u, T)\| \leq (M' + K\tau M' + KT_{max}) \exp(2KT_{max}), \quad \forall t \in (0, T].$$

Therefore,

$$\|x(t|u, T)\| \leq M, \forall t \in [-\tau, T],$$

where $M := (M' + K\tau M' + KT_{max}) \exp(2KT_{max})$. □

## $\boxed{3}$ Constrained Optimal Control Problems

In fed-batch process, it is desired that the value of the target product 1,3-PD should be maximized at the end of the process, and at the same time, the operation costs should be reduced. In particular, both the flow rate of glycerol and the terminal time of the fermentation play key roles in achieving the objective.

Thus, we take the mass of 1,3-PD per unit time in the fed-batch process as the cost functional which can be formulated as

$$J(u, T) := \frac{x_3(T|u, T)x_6(T|u, T)}{T}, \qquad (3.1)$$

where $x_3(T|u, T)$ and $x_6(T|u, T)$ are, respectively, the third and the sixth components of the solution to the system (2.1) at terminal time $T$.

Now, we can formally state the optimal control problem as

**Problem (P).** Given the system (2.1), find a control $u \in \mathcal{U}$ and a terminal time $T \in [T_{min}, T_{max}]$ such that the state constraint (2.10) is satisfied and the cost functional (3.1) is maximized.

Note that Problem (P) is of non-standard feature because it has not fixed terminal time but free terminal time. It is difficult to solve Problem (P) using existing numerical techniques [18, 20, 21]. The main difficulty is the implicit dependence of the system state on the terminal time. We now employ a time-scaling transformation from $t \in [0, T]$ to $s \in [0, 1]$ as follows:

$$t = Ts. \qquad (3.2)$$

Then, let $\tilde{x}(s) := x(t(s)), \tilde{u}(s) := u(t(s)), \tilde{\tau} := \frac{\tau}{T}, h(\tilde{x}(s), \tilde{x}(s - \tilde{\tau}), \tilde{u}(s), T) := Tf(\tilde{x}(s), \tilde{x}(s - \tilde{\tau}), \tilde{u}(s)), \tilde{U}(s) := U(t(s))$ and $\tilde{\phi}(s) := \phi(t(s))$. As a result, the system (2.1) takes the form:

$$\begin{cases} \dot{\tilde{x}}(s) = h(\tilde{x}(s), \tilde{x}(s - \tilde{\tau}), \tilde{u}(s), T), \\ \tilde{u}(s) \in \tilde{U}(s), \ s \in (0, 1], \\ \tilde{x}(0) = x_0, \\ \tilde{x}(s) = \tilde{\phi}(s), s \in [-\tilde{\tau}, 0]. \end{cases} \qquad (3.3)$$

Furthermore, the switching instants $t_i$ in the original time are transcribed into $s_i = \frac{t_i}{T}, i = 1, 2, \ldots, 2N$. Now, let $\tilde{x}(\cdot|\tilde{u}, T)$ be the solution of the transformed system (3.3). Accordingly, the class of admissible control functions can be transcribed into $\tilde{\mathcal{U}}$ and the state constraint (2.10) can be rewritten as

$$\tilde{x}^\top(s|\tilde{u}, T) \in W. \qquad (3.4)$$

Therefore, Problem (P) can be transcribed to the following equivalent problem (EP) with fixed terminal time.

**Problem (EP).** Subject to the system (3.3), find a control $\tilde{u} \in \tilde{\mathcal{U}}$ and a terminal time $T \in [T_{min}, T_{max}]$ such that the state constraint (3.4) is satisfied and the cost functional

$$\tilde{J}(u, T) := \frac{\tilde{x}_3(1|\tilde{u}, T)\tilde{x}_6(1|\tilde{u}, T)}{T} \qquad (3.5)$$

is maximized.

By the similar arguments as those given for Theorem 4.4 in [20], we confirm the existence of the optimal solution for problem (EP).

**Theorem 3.1.** Problem (EP) *has at least one optimal solution.*

## 4 Computational Approaches

Problem (EP) is essentially a constrained optimal control problem. It is known that computational schemes based on the control parametrization technique are normally very efficient in solving optimal control problems [40, 43, 44]. In this section, we will develop a computational method using the control parametrization method in conjunction with an improved DE algorithm to solve Problem (EP).

For each $p_i \geq 1, i \in \{1, 2, \ldots, 2N+1\}$, let the subinterval $[s_{i-1}, s_i]$ be partition into $n_{p_i}$ subintervals with $n_{p_i} + 1$ partition points such that

$$s_{i-1} = p_0^i \leq p_1^i, \cdots, \leq p_{n_{p_i}}^i = s_i,$$

where $n_{p_i}$ is chosen such that $n_{p_i+1} \geq n_{p_i}$. Then, the control can be approximated as

$$\tilde{u}^p(s) = \sum_{i=1}^{2N+1} \sum_{k=1}^{n_{p_i}} \sigma^{i,k} \chi_{(p_{k-1}^i, p_k^i]}(s), \tag{4.1}$$

where $\chi_{(p_{k-1}^i, p_k^i]}$ is the indicator function on the interval $(p_{k-1}^i, p_k^i]$ defined by

$$\chi_{(p_{k-1}^i, p_k^i]}(s) = \begin{cases} 1, & s \in (p_{k-1}^i, p_k^i], \\ 0, & \text{otherwise.} \end{cases}$$

Let $\sigma^p = ((\sigma^1)^\top, \ldots, (\sigma^{2N+1})^\top)^\top \in R^l$, where $\sigma^i := (\sigma^{i,1}, \ldots, \sigma^{i,n_{p_i}})^\top$ defines the heights of the approximate control (4.1) and $l = \sum_{i=1}^{2N+1} n_{p_i}$. From (2.9), it is clear that

$$\sigma^{i,k} \in \tilde{U}(s), \ s \in (0, 1]. \tag{4.2}$$

Let $\Xi^p$ be the set of all those $\sigma^p$ satisfying the constraint (4.2). Furthermore, denote the solution of the system (3.3) replacing the control function $\tilde{u}$ with $\tilde{u}^p$ by $\bar{x}(\cdot|\sigma^p, T)$. Accordingly, the state constraint (3.4) becomes

$$\bar{x}^\top(s|\sigma^p, T) \in W. \tag{4.3}$$

Thus, we may specify the approximate problem (EP(p)) as follows.

**Problem (EP(p)).** Given the replaced system (3.3), find a control parameter vector $\sigma^p \in \Xi^p$ and a terminal time $T \in [T_{min}, T_{max}]$ such that the state constraint (4.3) is satisfied and the cost functional

$$\bar{J}(\sigma^p, T) := \frac{\bar{x}_3(1|\sigma^p, T)\bar{x}_6(1|\sigma^p, T)}{T} \tag{4.4}$$

is maximized.

Note that Problem (EP) can be approximated by a sequence of Problems $\{(EP(p))\}_{p=1}^\infty$, each of which is a parameter optimization problem with continuous state inequality constraint (4.3). However, it is difficult to deal with the continuous state inequality constraint in numerically solving the optimization problem. For this reason, let

$$g_\ell(\bar{x}(s|\sigma^p, T)) := x_\ell^* - \bar{x}_\ell(s|\sigma^p, T),$$
$$g_{6+\ell}(\bar{x}(s|\sigma^p, T)) := \bar{x}_\ell(s|\sigma^p, T) - x_{*\ell}, \ \ell = 1, 2, \ldots, 6.$$

Then, the state constraint (4.3) is equivalently transcribed into

$$G(\sigma^p, T) = 0, \tag{4.5}$$

where $G(\sigma^p, T) = \sum_{l=1}^{12} \int_0^1 \min\{0, g_l(\bar{x}(s|\sigma^p, T))\} ds$. However, the equality constraint (4.5) is non-differentiable at the points when $g_l = 0, l \in \{1, 2, \ldots, 12\}$. Using the method given in [39], we approximate the state constraint (4.3) as the following inequality constraint

$$\bar{G}_{\varepsilon,\delta}(\sigma^p, T) := \delta + \sum_{l=1}^{12} \int_0^1 \varphi_\varepsilon(g_l(\bar{x}(s|\sigma^p, T))) ds \geq 0, \tag{4.6}$$

where $\varepsilon > 0$, $\delta > 0$ and

$$\varphi_\varepsilon(\eta) = \begin{cases} \eta, & \text{if } \eta < -\varepsilon, \\ -\dfrac{(\eta - \varepsilon)^2}{4\varepsilon}, & \text{if } -\varepsilon \leq \eta \leq \varepsilon, \\ 0, & \text{if } \eta > \varepsilon. \end{cases} \tag{4.7}$$

It should be noted that this function is obtained by smoothing out the sharp corner of the function $\min\{0, g_l(\bar{x}(s|\sigma^p, T))\}$. Consequently, Problem (EP(p)) is approximated by a sequence of Problems $\{(\text{EP}_{\varepsilon,\delta}(\text{p}))\}$ defined by replacing the state constraint (4.3) with the inequality constraint (4.6). Under appropriate assumptions, it shown in Lemma 8.3.3 of [39] that for all $\varepsilon > 0$, there exists a $\delta(\varepsilon) > 0$ such that for all $\delta, 0 < \delta < \delta(\varepsilon)$, if an admissible pair $(\sigma^p, T) \in \Xi \times [T_{min}, T_{max}]$ satisfies the inequality constraint (4.6), then it also satisfies the state constraint (4.3).

In the numerical computation, the gradients of $\bar{G}_{\varepsilon,\delta}(\sigma^p, T)$ with respect to $\sigma^p$ and $T$ are required. However, the traditional methods for computing the gradients of the constraint $\bar{G}_{\varepsilon,\delta}(\cdot, \cdot)$ involve integrating two systems of differential equations— the state system and the costate system— successively in different directions, which is difficult to implement in computation process [39]. In contrast, we will develop a new scheme for computing the gradients of the constraint $\bar{G}_{\varepsilon,\delta}(\cdot, \cdot)$ with respect to $\sigma^p$ and $T$ in the following theorems.

**Theorem 4.1.** *For each $\varepsilon > 0$ and $\delta > 0$, the gradients of the constraint $\bar{G}_{\varepsilon,\delta}(\sigma^p, T)$ defined in (4.6) with respect to $\sigma^p$ are*

$$\frac{\partial \bar{G}_{\varepsilon,\delta}(\sigma^p, T)}{\partial \sigma^{i,k}} = \sum_{l=1}^{12} \int_0^1 \frac{\partial \varphi_\varepsilon(g_l(\bar{x}(s|\sigma^p, T)))}{\partial g_l} \frac{\partial g_l(\bar{x}(s|\sigma^p, T))}{\partial \bar{x}} \xi^{i,k}(s) ds$$

$$k = 1, 2 \ldots, n_{p_i}, \ i = 1, 2, \ldots, 2N + 1, \tag{4.8}$$

*where $\xi^{i,k}(s)$ are the solutions of the following time-delay systems:*

$$\dot{\xi}^{i,k}(s) = (1 - \upsilon_i)(1 - \varsigma_{i,k}(s)) \left\{ \frac{\partial h(\bar{x}(s|\sigma^p, T), \bar{x}(s - \tilde{\tau}|\sigma^p, T), \sigma^p, T)}{\partial \bar{x}(s)} \xi^{i,k}(s) \right.$$

$$+ \frac{\partial h(\bar{x}(s|\sigma^p, T), \bar{x}(s - \tilde{\tau}|\sigma^p, T), \sigma^p, T)}{\partial \bar{x}(s - \tilde{\tau})} \xi^{i,k}(s - \tilde{\tau}) +$$

$$\left. \frac{\partial h(\bar{x}(s|\sigma^p, T), \bar{x}(s - \tilde{\tau}|\sigma^p, T), \sigma^p, T)}{\partial \sigma^{i,k}} \right\}, \ \forall s \in (s_{i-1}, s_i], \tag{4.9}$$

*with*

$$\xi^{i,k}(s) = 0, \ s \in [-\tilde{\tau}, 0], \tag{4.10}$$

$$\upsilon_i = \begin{cases} 1, & i \ is \ odd, \\ 0, & otherwise, \end{cases} \tag{4.11}$$

*and*

$$\varsigma_{i,k}(s) = \begin{cases} 1, & s \le s^i_{k-1}, \\ 0, & otherwise. \end{cases} \tag{4.12}$$

*Proof.* For each $\epsilon \ge 0$, define

$$\sigma^{p,\epsilon} = ((\sigma^1)^T, \ldots, (\sigma^{i,1}, \ldots, \sigma^{i,k} + \epsilon, \ldots, \sigma^{i,n_{p_i}}), \ldots, (\sigma^{2N+1})^T)^T \in \Xi.$$

For brevity, let $\bar{x}(s)$ and $\bar{x}^\epsilon(s)$, $\forall s \in (s_{i-1}, s_i]$, denote the solutions of the system (3.3) with $u^p$ corresponding to $\sigma^p$ and $\sigma^p(\epsilon)$, respectively. Clearly, we have

$$\bar{x}(s) = x_0 + \int_0^s h(\bar{x}(\vartheta), \bar{x}(\vartheta - \tilde{\tau}), \sigma^p, T) d\vartheta$$

and

$$\bar{x}^\epsilon(s) = x_0 + \int_0^s h(\bar{x}^\epsilon(\vartheta), \bar{x}^\epsilon(\vartheta - \tilde{\tau}), \sigma^{p,\epsilon}, T) d\vartheta.$$

Consequently, if $i$ is odd or $s \le s^i_{k-1}$, then

$$\frac{\partial \bar{x}(s)}{\partial \sigma^{i,k}} = 0. \tag{4.13}$$

Otherwise,

$$\frac{\partial \bar{x}(s)}{\partial \sigma^{i,k}} = \int_{s^i_{k-1}}^s \left\{ \frac{\partial h(\bar{x}(\vartheta), \bar{x}(\vartheta - \tilde{\tau}), \sigma^p, T)}{\partial \bar{x}(\vartheta)} \frac{\partial \bar{x}(\vartheta)}{\partial \sigma^{i,k}} + \frac{\partial h(\bar{x}(\vartheta), \bar{x}(\vartheta - \tilde{\tau}), \sigma^p, T)}{\partial \bar{x}(\vartheta - \tilde{\tau})} \right.$$
$$\left. \times \frac{\partial \bar{x}(\vartheta - \tilde{\tau})}{\partial \sigma^{i,k}} + \frac{\partial h(\bar{x}(\vartheta), \bar{x}(\vartheta - \tilde{\tau}), \sigma^p, T)}{\partial \sigma^{i,k}} \right\} d\vartheta. \tag{4.14}$$

Differentiating (4.13) and (4.14) with respect to time yields

$$\frac{d}{ds} \left\{ \frac{\partial \bar{x}(s)}{\partial \sigma^{i,k}} \right\} = (1 - \upsilon_i)(1 - \varsigma_{i,k}(s)) \left\{ \frac{\partial h(\bar{x}(s), \bar{x}(s - \tilde{\tau}), \sigma^p, T)}{\partial \bar{x}(s)} \frac{\partial \bar{x}(s)}{\partial \sigma^{i,k}} + \right.$$
$$\left. \frac{\partial h(\bar{x}(s), \bar{x}(s - \tilde{\tau}), \sigma^p, T)}{\partial \bar{x}(s - \tilde{\tau})} \frac{\partial \bar{x}(s - \tilde{\tau})}{\partial \sigma^{i,k}} + \frac{\partial h(\bar{x}(s), \bar{x}(s - \tilde{\tau}), \sigma^p, T)}{\partial \sigma^{i,k}} \right\},$$
$$\forall s \in (s_{i-1}, s_i], \ i = 1, 2, \ldots, 2N+1,$$

where $\upsilon_i$ and $\varsigma_{i,k}(s)$ are defined in (4.11) and (4.12), respectively. Furthermore,

$$\frac{\partial \bar{x}(0)}{\partial \sigma^{i,k}} = \frac{\partial}{\partial \sigma^{i,k}} \left\{ x_0 \right\} = 0,$$

$$\frac{\partial \bar{x}(s)}{\partial \sigma^{i,k}} = \frac{\partial \tilde{\phi}(s)}{\partial \sigma^{i,k}} = 0, \ s \in [-\tilde{\tau}, 0].$$

Hence, define

$$\xi^{i,k}(s) = \frac{\partial \bar{x}(s)}{\partial \sigma^{i,k}}$$

and differentiate $\bar{G}_{\varepsilon,\delta}(\sigma^p, T)$ with respect to $\sigma^p$, we obtain the conclusion (4.9). $\qquad \square$

**Theorem 4.2.** *For each $\varepsilon > 0$ and $\delta > 0$, the gradient of the constraint $\bar{G}_{\varepsilon,\delta}(\sigma^p, T)$ defined in (4.6) with respect to $T$ is*

$$\frac{\partial \bar{G}_{\varepsilon,\delta}(\sigma^p, T)}{\partial T} \quad = \quad \sum_{l=1}^{12} \int_0^1 \frac{\partial \varphi_\varepsilon(g_l(\bar{x}(s|\sigma^p, T)))}{\partial g_l} \frac{\partial g_l(\bar{x}(s|\sigma^p, T))}{\partial \bar{x}} \zeta^i(s) ds$$
$$i = 1, 2, \ldots, 2N+1, \tag{4.15}$$

*where $\zeta^i(s)$ are the solutions of the following time-delay systems:*

$$\dot{\zeta}^i(s)$$
$$= \frac{\partial h(\bar{x}(s|\sigma^p, T), \bar{x}(s - \tilde{\tau}|\sigma^p, T), \sigma^p, T)}{\partial \bar{x}(s)} \zeta^i(s) + \frac{\partial h(\bar{x}(s|\sigma^p, T), \bar{x}(s - \tilde{\tau}|\sigma^p, T), \sigma^p, T)}{\partial \bar{x}(s - \tilde{\tau})}$$
$$\times \zeta^i(s - \tilde{\tau}) + \frac{\tilde{\tau}}{T} \frac{\partial h(\bar{x}(s|\sigma^p, T), \bar{x}(s - \tilde{\tau}|\sigma^p, T), \sigma^p, T)}{\partial \bar{x}(s - \tilde{\tau})}$$
$$\times h(\bar{x}(s - \tilde{\tau}|\sigma^p, T), \bar{x}(s - 2\tilde{\tau}|\sigma^p, T), \sigma^p, T) + \frac{\partial h(\bar{x}(s|\sigma^p, T), \bar{x}(s - \tilde{\tau}|\sigma^p, T), \sigma^p, T)}{\partial T},$$
$$\forall \ s \in (s_{i-1}, s_i], \ i = 1, 2, \ldots, 2N+1,$$

*with*

$$\zeta^i(s) = 0, \ s \in [-\tilde{\tau}, 0]. \tag{4.16}$$

*Proof.* The proof can be completed using a similar method given for Theorem 4.1. □

Based on the above theorems, Problem (EP) can be solved by a sequence of approximation problems $\{(EP_{\varepsilon,\delta}(p))\}$. Each of $\{(EP_{\varepsilon,\delta}(p))\}$ is a smooth mathematical programming problem which can be solved by gradient-based techniques [4, 5, 39]. However, the gradient-based techniques are only designed to find local optima. Furthermore, in solving $\{(EP_{\varepsilon,\delta}(p))\}$, the evaluation of candidate feeding rate as well as the terminal time is a computationally expensive operation because of solving the system (2.1). As a result, finding the global optimum or a good suboptimal solution with traditional search or optimization techniques based on natural phenomenon such as genetic algorithm [12], evolution strategies [36] and simulation annealing [16] is too consuming, or even impossible within the time available.

DE, a recent optimization technique, is an exceptionally simple and easy to use evolution strategy, which is significantly faster and robust in numerical optimization and is more likely to find a true global optimum [33]. The conventional DE has three major steps executed in each generation. They are the mutation, crossover and selection. These three steps are performed until a stop criterion is not reached. DE algorithm has been used in the recent past to solve many engineering problems, see, for example [7, 42]. When using the DE to optimize a function, an acceptable trad-off between convergence and robustness must generally be determined. To increase the convergence without compromising with the robustness, a modified differential evolution (MDE) is developed to solve unconstrained optimization problems encountered in chemical engineering [2]. The basic operations of MDE are similar to those of conventional DE algorithm. However, it can use a smaller population size to achieve a high probability of obtaining the optimum [2]. Nevertheless, the $(EP_{\varepsilon,\delta}(p))$ is a nonlinear optimization problem with constraints in state and control parameters, which MDE can not be applied directly to solving it. Hence, the following strategies are added to the MDE algorithm in [2].

(I). (Handling the control constraints) If there is a bound violation for a parameter in the

$\iota$th individual at the $\kappa$th step, then that parameter is generated randomly between the given lower and upper bounds using the following equations:

$$\sigma_{\iota J}^{p}(\kappa) = \sigma_{low J}^{p} + r_{\iota J}^{1} \times (\sigma_{upp J}^{p} - \sigma_{low J}^{p}), J = 1, \ldots, l,$$

and

$$T_{\iota}(\kappa) = T_{min} + r_{\iota}^{2} \times (T_{max} - T_{min}), \iota = 1, 2, \ldots, N_{p},$$

where $\sigma_{low}^{p}$ and $\sigma_{upp}^{p}$ are, respectively, the lower and upper bounds of the control parameter which can be obtained by (4.2), and $r_{\iota J}^{1}$ and $r_{\iota}^{2}$ are random numbers taken from $[0, 1]$.
(II). (Dealing with the continuous state constraints) For the parameter of the $\iota$th individual at the $\kappa$th step, test the value of $G(\sigma_{\iota}^{p}(\kappa), T_{\iota}(\kappa))$. If $G(\sigma_{\iota}^{p}(\kappa), T_{\iota}(\kappa)) = 0$, then the parameter is feasible. Otherwise, move the parameter towards the feasible region using the gradient information $\dfrac{\partial \bar{G}_{\varepsilon,\delta}(\sigma_{\iota}^{p}(\kappa), T_{\iota}(\kappa))}{\partial \sigma_{\iota}^{p}(\kappa)}$ and $\dfrac{\partial \bar{G}_{\varepsilon,\delta}(\sigma_{\iota}^{p}(\kappa), T_{\iota}(\kappa))}{\partial T_{\iota}(\kappa)}$ with Armijo line searches.
(III). (Stopping criteria) The algorithm stops when the maximal iteration $M_{p}$ is reached.

In view of Theorems 5 and 6, the following algorithm can now be used to generate an approximate optimal control of Problem (P).

**Algorithm 1.**

Step 1. Choose initial values of $\varepsilon, \delta$ and $(\sigma^{p}, T)$, set parameters $\beta_{1} < 1$, $\beta_{2} < 1$, $\bar{\varepsilon}$ and $\bar{\delta}$.

Step 2. Solve approximate problem $(\text{EP}_{\varepsilon,\delta}(\text{p}))$ using the improved MDE algorithm to give $(\sigma_{\varepsilon,\delta}^{p,*}, T_{\varepsilon,\delta}^{*})$.

Step 3. Check the value of $G(\sigma_{\varepsilon,\delta}^{p,*}, T_{\varepsilon,\delta}^{*})$.

Step 4. If $G(\sigma_{\varepsilon,\delta}^{p,*}, T_{\varepsilon,\delta}^{*}) = 0$, then go to Step 6. Otherwise, set $\delta = \beta_{1}\delta$. If $\delta < \bar{\delta}$, then go to Step 5. Otherwise go to Step 2.

Step 5. Set $\varepsilon = \beta_{2}\varepsilon$. If $\varepsilon \geq \bar{\varepsilon}$, then go to Step 3. Otherwise go to Step 6.

Step 6. If $\min\limits_{i \in \{1,2,\ldots,2N+1\}} n_{p_{i}} \geq \bar{P}$, where $\bar{P}$ is a predefined positive constant, then go to Step 7. Otherwise, go to Step 2 with $n_{p_{i}}$ increased to $n_{p_{i}+1}$ for each $i$.

Step 7. Construct $(u^{p,*}, T^{*})$ from $(\sigma_{\varepsilon,\delta}^{p,*}, T_{\varepsilon,\delta}^{*})$ by (4.1) and (3.2) and stop.

At the conclusion of Steps 1-7, $(u^{p,*}, T^{*})$ is an approximate optimal solution of Problem (P).

## 5 Numerical Results

In numerical simulation, the reactant composition, cultivation conditions, and the determination of biomass, substrate and metabolites have been reported in [6]. Under anaerobic conditions at 37°C and pH 7.0, the critical concentrations $x_{*}$ and $x^{*}$ for cells growth and the system parameters in (2.4)-(2.7) are listed in Table 1. Moreover, to numerically solve the system (2.1), the initial state, the velocity ratio of adding alkali to glycerol, the concentration of initial feed glycerol and time-delay are $x_{0} = (0.1115\text{gL}^{-1}, 495\text{mmolL}^{-1}, 0, 0, 0, 5\text{L})^{\top}$, $r = 0.75$, $c_{s0} = 10762\text{mmolL}^{-1}$, and $\tau = 0.217\text{h}$, respectively. In addition, the initial function $\phi(t)$ is interpolated by the cubic spline [30] of the experimental data, $T_{min} = 11\text{h}$, and $T_{max} = 24.16\text{h}$.

Table 1: The critical concentrations and the system parameters in (2.4)-(2.7).

| $\ell$ | $m_\ell$ | $Y_\ell$ | $\Delta_\ell$ | $k_\ell$ | $c_\ell$ | $x_{*\ell}$ | $x_\ell^*$ |
|---|---|---|---|---|---|---|---|
| 1 | - | - | 0.67 | 0.28 | 0.025 | 0.01 | 6 |
| 2 | 2.20 | 0.0082 | 28.58 | 11.43 | 0.06 | 15 | 2039 |
| 3 | -2.69 | 67.69 | 26.59 | 15.50 | 5.18 | 0 | 1036 |
| 4 | -0.97 | 33.07 | 5.74 | 85.71 | 50.45 | 0 | 1026 |
| 5 | - | - | - | - | - | 0 | 360.9 |
| 6 | - | - | - | - | - | 4 | 7 |

Table 2: The bounds of feeding rates in Phs. I-IX [20].

| Phases | I-II | III | IV-V | VI | VII | VIII-IX |
|---|---|---|---|---|---|---|
| Upper bounds[mLs$^{-1}$] | 0.2524 | 0.2390 | 0.2524 | 0.2657 | 0.2924 | 0.3058 |
| Lower bounds[mLs$^{-1}$] | 0.1682 | 0.1594 | 0.1682 | 0.1771 | 0.1949 | 0.2038 |

In computational process, we use the same switching instants and feeding rate settings as those used to obtain the experimental results [41] to optimize the feeding rates and the terminal time. More specifically, the maximal duration of fed-batch process is partitioned into the first batch phase (Bat. Ph.) and phases I-IX (Phs. I-IX) according to the number of switchings. The same feeding strategies are adopted in each one of Ph. I to Ph. IX. Furthermore, $t_1 = 5.33$h, the feeding moment $t_{2j+1}$ and the end of the feeding moment $t_{2j+2}$ are determined by the experiment. Namely, the durations of the feeding processes in Phs. I-IX are $5, 7, 8, 7, 6, 4, 3, 2$ and $1$ seconds in each $100$ seconds, leaving $95, 93, 92, 93, 96, 97, 98$ and $99$ seconds for batch processes, respectively. This is also done for the computational time consideration since there are total 1355 switchings in the maximal duration of fed-batch process. Moreover, the bounds of feeding rates in Phs. I-IX are listed in Table 2.

In the improved DE algorithm, the size of population $Np$, the maximal iteration $Mp$, the scaling factor $F$, and the crossover constant $CR$ are, respectively, 100, 200, 0.5 and 0.8. In Algorithm 1, the initial values of $u$ and $T$ are chosen as those in [20], in which the corresponding $N = 677$. The other parameters $\varepsilon, \delta, \beta_1, \beta_2, \bar{\varepsilon}, \bar{\delta}$ and $\bar{P}$ are chosen as $0.1, 0.01, 0.1, 0.01, 1.0 \times 10^{-8}, 1.0 \times 10^{-7}$ and $1$, respectively.

Applying Algorithm 1 to Problem (P), we obtain the optimal terminal time $T^* = 11.11$h which is much shorter than 19.83h in the experiment [41] and 21.1078h in [20]. Moreover, under the optimal terminal time, the corresponding optimal number of switchings is $N^* = 209$. This is very interesting for the biochemical engineer to reduce the operation costs in the fed-batch process. As a result, the optimal feeding rates of glycerol in Phs. I-IV are shown in Figure 1. Here, all the computations are performed in Microsoft Visual C++ 6.0 and numerical results are plotted by MATLAB 7.10.0. In particular, the combination of the fourth-order Runge-Kutta integration scheme with the cubic spline interpolation [30] is used to integrate the delay-differential equations with the relative error tolerance $10^{-6}$. In detail, the blue line in the first subfigure of Figure 1 indicates the feeding rate of glycerol, which is identically equal to zero, and the time duration in the Bat. Ph. Accordingly, the blue lines in the next 4 subfigures illustrate the feeding rates of glycerol in conjunction with time durations of a feeding process and its succeeding batch process in Ph. I to Ph. IV,

respectively. To show the feeding rates of glycerol for Ph. I to Ph. IV better, 4 small subfigures are also incorporated in the corresponding 4 subfigures, respectively.
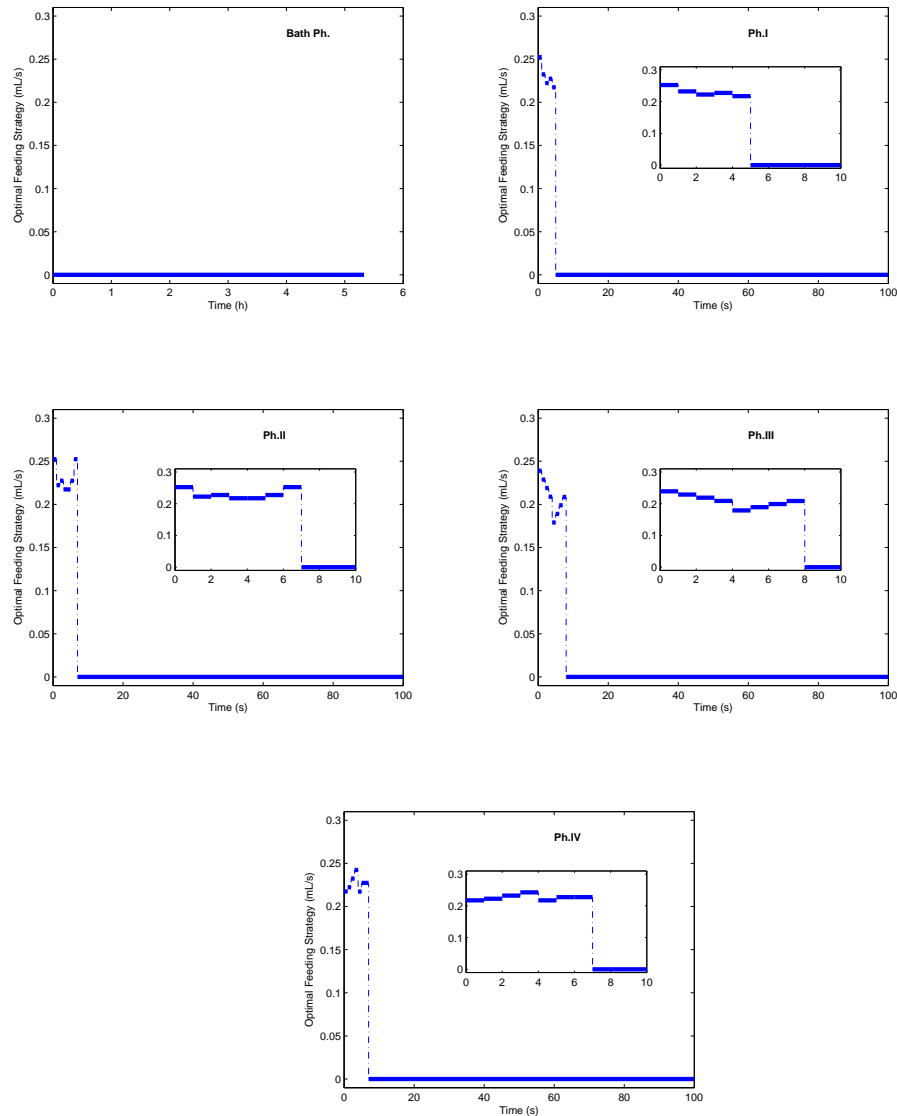


Figure 1: The optimal feeding strategy of glycerol in fed-batch process.

Under the obtained optimal feeding rates and the optimal terminal time, the mass of 1,3-PD per unit time is $297.786 \text{mmolh}^{-1}$ which is increased by 11.74% in comparison with experimental result $266.496 \text{mmolh}^{-1}$ in [41] and by 9.954% compared with the computational result $270.827 \text{mmolh}^{-1}$ in [20]. The optimal computed profile of the mass of 1,3-PD per unit time is depicted by solid curve in Figure 2. In addition, the computational result in [20] and the experimental data (data points) are also shown in Figure 2 for comparison. From Figure 2, we observe that the optimal terminal time is really shorter and the mass of 1,3-PD per unit time at the optimal terminal time is actually higher than previous results.
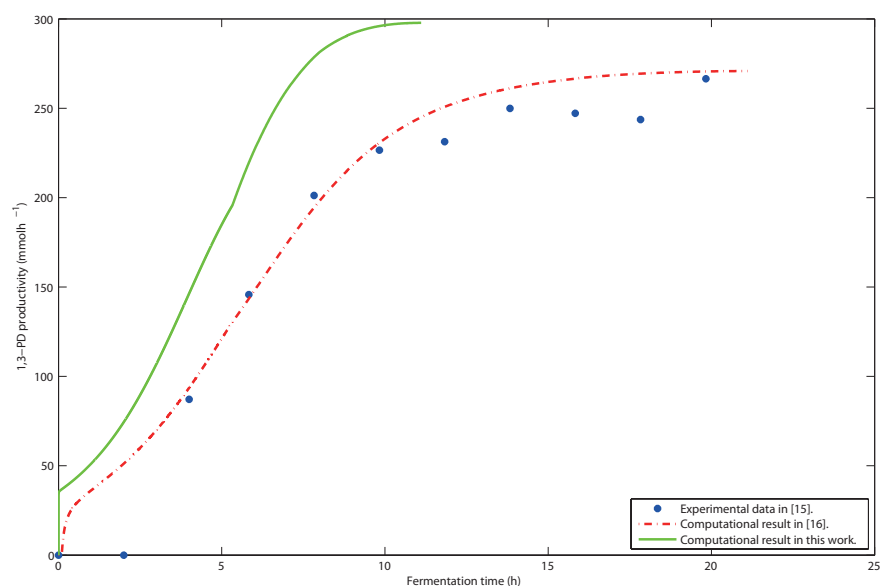
Figure 2: The mass of 1,3-PD per unit time with respect to fermentation time.

## 6 Conclusions

In this paper, we investigated the optimal control problem in fed-batch process. We firstly proposed the nonlinear time-delay system to model the fermentation process. We then presented the optimal control model and its equivalent form. By the control parameterization technique and the improved DE algorithm, we developed the solution approach to solve the optimal control problem. Numerical results showed the validity of the proposed model and the effectiveness of the developed numerical algorithm.

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