Optimal control of a batch fermentation process with nonlinear time-delay and free terminal time and cost sensitivity constraint

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Abstract

In this paper, we consider a nonlinear time-delay dynamic system with uncertain system parameters to characterize the process of batch fermentation. Our goal is to design an optimal control scheme to maximize the productivity of 1,3-propanediol (1,3-PD). Accordingly, we introduce an optimal control problem governed by the nonlinear time-delay dynamic system, in which the control variables are the free terminal time of the batch fermentation process and the initial concentrations of biomass and glycerol. The optimal control problem is subject to a cost sensitivity constraint for ensuring that an acceptable level of the system performance is achieved and continuous state inequality constraints for ensuring that the concentrations of biomass, glycerol, 1,3-PD, acetate, ethanol lie within specified limits. Then, the optimal control problem with free terminal time is transformed, via a hybrid time-scaling strategy, into an equivalent problem with fixed terminal time, which is much preferred for numerical computation. Using the constraint transcription and local smoothing approximation techniques, we approximate these continuous state inequality constraints by conventional inequality constraints to yield an approximate optimal control problem. Because of the highly complex nature of this approximate problem, a parallel algorithm based on the filled function method is constructed to solve this approximate problem. Finally, it is observed that the optimal control obtained is satisfactory through numerical simulations.

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1. Introduction

1,3-Propanediol (1,3-PD) is one of the important products with numerous applications, in particular for production of a new type of polyester, which is referred to as polytrimethylene terephthalate [1]. Currently, the process of producing 1,3-PD can be divided into two types: microbial conversion and chemical synthesis [2]. Compared with chemical synthesis approaches, microbial conversion methods have received attention recently because it is a choice for cheaply renewable feedstock, high region specificity and no harm to environment [3]. From both the economical

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and ecological point of view, it is an effective method to produce 1,3-PD by glycerol bioconversion induced by *Klebsiella pneumonia* (*K. pneumonia*) [4]. At present, there are three microbial conversion methods for producing 1,3-PD: batch, continuous and fed-batch fermentations [5]. In batch fermentation, bacteria and substrate are presented at the beginning of the process, and nothing is added or removed from the fermentor during the process [6]. In continuous fermentation, fresh medium is added continuously to replenish consumed substrate while old medium is removed during the reaction [7, 8]. In fed-batch fermentation, glycerol and alkali are discontinuously added to the reactor at constant rates, so as to keep the substrate concentration and the pH in the desirable levels, without the removal of medium [9, 10]. There are several reasons for the necessity of studying batch fermentation [11]: 1) in batch fermentation, 1,3-PD yield, which is defined as the ratio between the formation of 1,3-PD and the consumption of glycerol, is high. The main reason is that the batch fermentation can be expressed as an excessive metabolism process of glycerol. That is, the high concentration of glycerol leads to the high formation of 1,3-PD and the low formation of by-product in batch fermentation of glycerol. In particular, note that the high target product yield in batch fermentation is only applicable to the bioconversion of glycerol. Not all the batch fermentations are of the high target product yield; 2) batch fermentation is a simple and easy operation mode compared with fed-batch and continuous fermentations; 3) batch fermentation is basic for understanding or controlling fed-batch and continuous fermentations.

In the laboratory, it is impractical to carry out lots of batch experiments to obtain high production concentration and molar yield of 1,3-PD. Consequently, it is necessary to describe the process of batch fermentation through the application of mathematical systems. In [12], a substrate-sufficient kinetic system is proposed to characterize substrate (glycerol) consumption and extracellular substances (1,3-PD, acetate and ethanol) formation in batch fermentation. Robust identification of enzymatic nonlinear dynamical systems for 1,3-PD transport mechanisms in microbial batch fermentation is carried out in [13]. Modelling and pathway identification involving the transport mechanism of a complex metabolic system in batch fermentation is investigated in [14]. Robustness analysis and identification of nonlinear multi-stage dynamical system in batch fermentation are considered in [15, 16, 17]. Parameter identification for a nonlinear enzyme-catalytic dynamic system with multiple time-delays is studied in [18]. The different identification problems for nonlinear hybrid dynamical system in batch fermentation are investigated in [19, 20]. A stochastic model for microbial fermentation process under Gaussian white noise environment is considered in [21]. Joint estimation of batch fermentation is carried out by using unscented kalman filter in [22].

An optimal control problem, in which both process yield and process sensitivity are considered in the objective function, is investigated in [23]. However, there is one limitation: the presence of time-delay, which is always encountered in real-world applications, is ignored in [23]. In [24], a parameter identification for a nonlinear time-delay system is carried out in microbial batch fermentation. The optimal control problem governed by this nonlinear time-delay system is studied in [25]. However, a cost sensitivity corresponding to uncertainty system parameters has not yet been considered. Clearly, a nonlinear dynamic system is an idealized description about the actual behavior of a biological or engineering system. During the life span of the system, the values of some system parameters may change [26, 27]. For an optimal control problem governed by a nonlinear dynamical system, the optimal cost function obtained is under the assumption that these system parameters of the dynamical system are fixed. Given some of these system parameters are subject to variation, the cost sensitivity corresponding to uncertainty system parameters should be taken into consideration [28]. Nonetheless, in the process of microbial fermentation, there are few papers dedicated to the cost sensitivity.

In this paper, we consider a nonlinear time-delay dynamic system to characterize the process of batch fermentation of glycerol bioconversion to 1,3-PD induced by *K. pneumonia*. Our aim is to construct an optimal control to maximize the productivity of 1,3-PD. Therefore, we propose an optimal control problem that depend on system parameters which have some uncertainty as to their exact values. The control variables are the terminal time of the batch fermentation process and the initial concentrations of biomass and glycerol. The optimal control problem governed by a nonlinear time-delay dynamic system, is subject to cost sensitivity (the derivative of the cost function with respect to the uncertain system parameters) constraint for ensuring that an acceptable level of the system performance is achieved and continuous state inequality constraints for ensuring that the concentrations of biomass, glycerol, and reaction products lie within specified limits. Then, the optimal control problem with free terminal time is transformed into an equivalent optimal control problem with fixed terminal time via a hybrid time-scaling strategy that only maps the current state into the new time scale and the delayed state remain in the original time scale. The equivalent problem is much preferred for numerical computation. Through the application of the constraint transcription and local smoothing approximation techniques, we approximate the continuous state inequality constraints by conventional in-

equality constraints to yield an approximate optimal control problem. On account of the highly computing complexity of this approximate problem, the computational cost is **very** high. Thus, a parallel algorithm is proposed to solve it based on the filled function method. Finally, numerical results show that the obtained optimal control is satisfactory.

The remainder of this paper is organized as follows. In Section 2, a nonlinear time-delay dynamic system is formulated. In Section 3, an optimal control problem subject to a cost sensitivity constraint and continuous state inequality constraints is proposed. In Section 4, computational approaches are constructed to solve the optimal control problem. In Section 5, numerical results are presented. In Section 6, **conclusions and trace the direction for future works are presented.**

2. Nonlinear time-delay dynamic system

Nomenclature

- I_n denotes the set $\{1, 2, \dots, n\}$.
- $\mathbb{R}_+$ denotes the set of nonnegative real numbers.
- $\mathbb{R}$ denotes the set of real numbers.
- A^T denotes the transposition of matrix or vector A .
- $T \in [a_3, b_3]$ is the free terminal time for **the** fermentation process, where a_3 and b_3 are the minimal and the maximal time durations, respectively.
- $[0, T] \subset \mathbb{R}_+$, is the interval of reaction time.
- $x_0 := [x_{01}, \dots, x_{05}]^T \in \mathbb{R}^5$, is the initial state vector.
- a_1 and b_1 are the values of the minimal and the maximal the initial state x_{01} , respectively.
- a_2 and b_2 are the values of the minimal and the maximal the initial state x_{02} , respectively.
- $x(t) := [x_1(t), \dots, x_5(t)]^T \in \mathbb{R}^5$, denotes the continuous state vector (whose components are the state variables), where $x_1(t), \dots, x_5(t)$ denote the concentrations of biomass, glycerol, 1,3-PD, acetate, ethanol at time $t \in [0, T]$, respectively.
- μ_m is the maximum specific growth rate.
- k_1 is the Monod saturation constant.
- m_2 is the maintenance term of substrate consumption under substrate-limited conditions.
- Y_2 is the maximum growth yields.
- $m_i, i = 3, 4, 5$, are the maintenance terms of 1,3-PD, acetate and ethanol under substrate-limited conditions.
- $Y_i, i = 3, 4, 5$, are the maximum 1,3-PD, acetate and ethanol yields.

In the actual experiment, the following conditions are assumed throughout, whether explicitly mentioned or not.

H 1. No medium is pumped inside and outside the bioreactor in the process of batch fermentation.

H 2. The concentrations of reactants are **uniformly distributed in the reactor.**

Under **Assumptions H1** and **H2**, mass balance of biomass, substrate and products in batch fermentation can be described as the following nonlinear time-delay system [24],

$$\begin{cases} \dot{x}(t) = f(x(t), x(t - \tau), \sigma), & t \in (0, T], \\ x(t) = \phi(t), & t \leq 0, \\ x(0) = x_0, \end{cases} \quad (1)$$

where $\tau = 0.26$ is a time-delay for biomass in the model of the fermentation process; $\phi(t)$ is a given initial function; $\sigma \in \mathbb{R}^{10}$ is uncertain system parameter vector (whose components are uncertain system parameters). **Note that these uncertain system parameters are difficult to determine exactly.** Methods for estimating the values of these uncertain system parameters using experimental data are given in [24]. We will use these estimates listed in Table 1 as the nominal values σ^0 of system parameter vector in this paper.

Table 1. The nominal values σ^0 of system parameter vector for system (1) listed in [24].

$\sigma_1^0(h^{-1})$	$\sigma_2^0(mmolL^{-1})$	$\sigma_3^0(mmolg^{-1}h^{-1})$	$\sigma_4^0(mmolg^{-1}h^{-1})$	$\sigma_5^0(mmolg^{-1}h^{-1})$	$\sigma_6^0(mmolg^{-1}h^{-1})$
0.994	0.368	3.24	3.679	0.491	7.309
$\sigma_7^0(mmolg^{-1})$	$\sigma_8^0(mmolg^{-1})$	$\sigma_9^0(mmolg^{-1})$	$\sigma_{10}^0(mmolg^{-1})$		
0.085	76	35.54	14.78		

The dynamics of batch process is expressed by

$$f(x(t), x(t - \tau), \sigma) := [\mu(t)x_1(t - \tau), \sigma], -q_2(t)x_1(t - \tau), q_3(t)x_1(t - \tau), q_4(t)x_1(t - \tau), q_5(t)x_1(t - \tau)]^T. \quad (2)$$

In (2), the specific growth rate of cells can be defined by

$$\mu(t) = \frac{\mu_m x_2(t)}{x_2(t) + k_1} \prod_{j=2}^5 \left(1 - \frac{x_j}{x_j^*}\right). \quad (3)$$

The specific consumption rate of substrate can be expressed by

$$q_2(t) = m_2 + \frac{\mu(t)}{Y_2}. \quad (4)$$

The specific formation rates of 1,3-PD and acetic acid are defined by

$$q_i(t) = -m_i + \mu(t)Y_i, i = 3, 4. \quad (5)$$

The specific formation rate of ethanol can be expressed by

$$q_5(t) = m_5 + \mu(t)Y_5. \quad (6)$$

Let $\sigma := [\mu_m, k_1, m_2, m_3, m_4, m_5, Y_2, Y_3, Y_4, Y_5]^T \in \mathbb{R}^{10}$.

Since each component of the state vector $x(t)$, $t \in [0, T]$ represents a certain substance concentration, the concentrations of biomass, glycerol and products should be restricted in a certain range according to the practical fermentation process. Based on the results in [24], the admissible set W of $x(t)$ is defined by

$$x(t) \in W := [x_*, x^*] = \prod_{i=1}^5 [x_{*i}, x_i^*] \subset \mathbb{R}_+^5, \quad (7)$$

with $x_* = [0.01, 0, 0, 0, 0]^T$, $x^* = [15, 2039, 939.5, 1026, 360.9]^T$.

3. Optimal control problem

Let $x(\cdot|x_{01}, x_{02}, T, \sigma) \in \mathbb{R}^5$ denote the **continuous** solution of **system** (1) corresponding to the control variables x_{01}, x_{02}, T and the system parameter vector $\sigma \in \mathbb{R}^{10}$. In batch fermentation, it is desired that the productivity of 1,3-PD should be maximized at terminal time. This is achieved by manipulating the initial concentrations of biomass x_{01} and glycerol x_{02} and the free terminal time T . That is, the cost function is defined by

$$J(x_{01}, x_{02}, T|\sigma) = \frac{x_3(T|x_{01}, x_{02}, T, \sigma)}{T}. \quad (8)$$

In the process of microbial fermentation, we assumed that σ is a given system parameter vector whose components are nominal estimates of **the system parameters in Table 1**. However, this assumption is idealistic since the nominal

estimates are only approximations of the true system parameters. Therefore, inspired by the work in [26, 27, 28], we define the following cost sensitivity corresponding to the control variables x_{01}, x_{02}, T as

$$\left[\frac{\partial J(x_{01}, x_{02}, T|\sigma)}{\partial \sigma} \right] \left[\frac{\partial J(x_{01}, x_{02}, T|\sigma)}{\partial \sigma} \right]^T. \quad (9)$$

Clearly, formula (9) measures the rate at which the process yield changes with small variation of σ . Thus, a low value of the cost sensitivity indicates that the productivity of 1,3-PD is not sensitive to the variation of σ .

Let

$$\begin{aligned} g_j(x(t|x_{01}, x_{02}, T, \sigma)) &:= x_j(t|x_{01}, x_{02}, T, \sigma) - x_j^*, \forall t \in [0, T], j \in I_5, \\ g_{j+5}(x(t|x_{01}, x_{02}, T, \sigma)) &:= x_{j*} - x_j(t|x_{01}, x_{02}, T, \sigma), \forall t \in [0, T], j \in I_5. \end{aligned} \quad (10)$$

Therefore, in batch process, the optimal control problem can be formulated as

$$\begin{aligned} \textbf{Problem (OCP)} : \quad & \max \quad J(x_{01}, x_{02}, T|\sigma) \\ \text{s.t.} \quad & \left[\frac{\partial J(x_{01}, x_{02}, T|\sigma)}{\partial \sigma} \right] \left[\frac{\partial J(x_{01}, x_{02}, T|\sigma)}{\partial \sigma} \right]^T \leq \epsilon, \end{aligned} \quad (11)$$

$$g_j(x(t|x_{01}, x_{02}, T, \sigma)) \leq 0, \forall t \in [0, T], j \in I_{10}, \quad (12)$$

$$(x_{01}, x_{02}, T) \in [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3], \quad (13)$$

where Inequation (11) is a cost sensitivity constraint for ensuring an acceptable level of the system performance is achieved, where ϵ is a given small constant; (12) is termed the *continuous state inequality constraint* [30], which must be satisfied at every point in the time horizon $[0, T]$.

For a given $\sigma \in \mathbb{R}^{10}$, any vector $(x_{01}, x_{02}, T) \in [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3]$ satisfying constraints (11) and (12) is called an *admissible control vector* for system (1). Let $\mathcal{U}$ denote the set of all admissible control vectors. In view of the actual fermentation process, $\mathcal{U}$ is not an empty set. Therefore, we assume that

H 3. $\mathcal{U}$ is not an empty set.

From the definition of the set $\mathcal{U}$, it follows that we have the following property:

Property 1. Under Assumption H3, $\mathcal{U}$ is a compact set.

The existence of the optimal solution to Problem OCP is stated as follows.

Theorem 1. For a given $\sigma \in \mathbb{R}^{10}$, Problem OCP has an optimal solution.

Proof. From (8), we see that the cost function is continuous in $(x_{01}, x_{02}, T) \in \mathcal{U}$. Since the set $\mathcal{U}$ is compact, the proof follows readily. ■

4. Computational approaches

4.1. Hybrid Time-scaling Transformation

In Problem OCP, the direct method to calculating cost sensitivity defined in (9) involves one of the two gradient computation procedures (either the variational approach or the costate approach). It is cumbersome to integrate the state and variational or costate systems numerically when the terminal time T is a decision variable to be optimized [29]. To address the problem caused by the free terminal time T , the time-scaling transformation is proposed in [30, 31]. It is one of the most popular tools to transform Problem OCP into an equivalent problem with fixed terminal time. This time-scaling transformation affects the delay length in a complicated manner. In reality, under this time-scaling transformation, a fixed time-delay in the original time horizon becomes a variable time-delay in the new time horizon. Consequently, in a way, this time-scaling transformation complicates, rather than simplifies, the computation of optimal control problems involving time-delay systems. In [37], a hybrid time-scaling strategy is proposed, where the current state vector is mapped into the new time horizon while the delayed state vector remains in the original time horizon.

This transformation works by introducing a new time variable $s \in [-\tau, 1]$ and relating s to t through the equation

$$t = \bar{\mu}(s|T) = \begin{cases} T, & \text{if } s = 1, \\ T \cdot s, & \text{if } 0 \leq s < 1, \\ s, & \text{if } s < 0, \end{cases} \quad (14)$$

where $\bar{\mu}$ is the so-called *time-scaling function*.

It is easy to verify that the time-scaling function is non-decreasing, continuous and piecewise-linear. Moreover,

$$\frac{d\bar{\mu}(s|T)}{ds} = T, s \in (0, 1). \quad (15)$$

Let $\tilde{x}(s) := x(\bar{\mu}(s|T))$. Then, applying the time-scaling transformation $t = \bar{\mu}(s|T)$ gives the following new differential equation:

$$\begin{cases} \dot{\tilde{x}}(s) = \frac{d}{ds}(\tilde{x}(s)) = \frac{d}{ds}(x(\bar{\mu}(s|T))) = T \frac{dx(\bar{\mu}(s|T))}{dt}, s \in (0, 1], \\ \tilde{x}(s) = \phi(s), s \leq 0, \\ \tilde{x}(0) = x_0, s = 0. \end{cases} \quad (16)$$

Note that the delayed argument $\bar{\mu}(s|T) - \tau$, depends on s and T . Let $s_{delay} = s_{delay}(s, T)$ and $t_{delay} = t_{delay}(s, T)$ denote the delayed time points **in the new time horizon $[0, 1]$ and the original time horizon $[0, T]$** , respectively. Then, the relationship between s_{delay} and t_{delay} is given by the following fundamental equation:

$$\bar{\mu}(s_{delay}|T) = t_{delay} = \bar{\mu}(s|T) - \tau. \quad (17)$$

Thus, for $s \geq 0$, we have

$$x(t - \tau) = x(\bar{\mu}(s|T) - \tau) = x(\bar{\mu}(s_{delay}|T)) = \tilde{x}(s_{delay}). \quad (18)$$

Then, by substituting (1) into (18) and (16), we obtain

$$\begin{cases} \dot{\tilde{x}}(s) = \tilde{f}(\tilde{x}(s), \tilde{x}(s_{delay}), \sigma, T) = Tf(\tilde{x}(s), \tilde{x}(s_{delay}), \sigma), \quad \bar{\mu}(s_{delay}|T) \in (0, T], s \in (0, 1], \\ \tilde{x}(s) = \phi(s), s \leq 0, \\ \tilde{x}(0) = x_0, s = 0. \end{cases} \quad (19)$$

The difficulty **of** solving (19) is that s_{delay} depends on s and T .

When $\bar{\mu}(s_{delay}|T) < 0$, it follows from (14) that $s_{delay} < 0$, and thus

$$s_{delay} = \bar{\mu}(s_{delay}|T) = \bar{\mu}(s|T) - \tau. \quad (20)$$

When $\bar{\mu}(s_{delay}|T) \geq 0$, it follows from (14) and (17) that s_{delay} satisfies the following equation:

$$T \cdot s - \tau = T \cdot s_{delay}. \quad (21)$$

To obtain value of the delayed state $\tilde{x}(s_{delay}|x_{01}, x_{02}, T, \sigma)$, the delay time s_{delay} is needed to be found. Note that s_{delay} is a variable, which is determined **through** solving (21) at each time point s . Thus, to calculate a single cost function value, it is required to solve this equation at least T/h times, where h , which is usually taken as $1/3600$, is the maximum step length, when solving the time-delay differential equations. Clearly, it is computationally expensive to solve the new problem, defined on the new time horizon. Thus, another way is needed to get the value of $\tilde{x}(s_{delay}|x_{01}, x_{02}, T, \sigma)$ and then solve (21).

To overcome the difficulties of determining s_{delay} , explicitly, we use the following identity:

$$\tilde{x}(s_{delay}) = x(\bar{\mu}(s_{delay}|T)) = x(t_{delay}). \quad (22)$$

Substituting (17) and (22) into (19) yields the following dynamic system:

$$\begin{cases} \dot{\tilde{x}}(s) = \tilde{f}(\tilde{x}(s), x(t_{delay}), \sigma, T) = Tf(\tilde{x}(s), x(t_{delay}), \sigma, T), \quad t_{delay} \in (0, T], s \in (0, 1], \\ \tilde{x}(s) = \phi(s), s \leq 0, \\ \tilde{x}(0) = x_0, s = 0. \end{cases} \quad (23)$$

Let $\tilde{x}(\cdot|x_{01}, x_{02}, T, \sigma)$ denote the solution of **system** (23) corresponding to the admissible triple (x_{01}, x_{02}, T) .

Since t_{delay} (unlike s_{delay}) can be determined explicitly at all points by using the equation $t_{\text{delay}} := \bar{\mu}(s|T) - \tau$, there is no difficulty in evaluating the delay in **system** (23). Nonetheless, the right-hand side of **system** (23) relies on two coupled time-delay systems—one defined on the original time scale, the other defined on the new time scale. Therefore, this new time-scaling transformation is a hybrid transformation that combines information of the new and the old time horizons.

For a given triple $(x_{01}, x_{02}, T) \in [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3]$, $\tilde{x}(\cdot|x_{01}, x_{02}, T, \sigma)$ can be determined as follows. By the initial condition of **system** (23), $\tilde{x}(s|x_{01}, x_{02}, T, \sigma) = \phi(s)$, for $s \leq 0$. For $s > 0$, we need to determine $\tilde{x}(s|x_{01}, x_{02}, T, \sigma)$ solving **system** (23) numerically. When solving this differential equation, $x(t_{\text{delay}})$ on the right-hand side of **system** (23) is obtained using the previous values of $\tilde{x}(s|x_{01}, x_{02}, T, \sigma)$. More specifically, to determine the state value at $t_{\text{delay}} := \bar{\mu}(s|T) - \tau$, we first find the unique past time point t_ℓ on the original time horizon such that $t_\ell \leq t_{\text{delay}} \leq t_{\ell+1}$. Such knot points must exist because $\bar{\mu}(s|T)$ is continuous and strictly increasing on $(-\infty, 1]$. The value of $x(t_{\text{delay}})$ can be obtained by interpolating the values of $x(t_\ell)$ and $x(t_{\ell+1})$.

Correspondingly, **formula** (10) and Problem **OCP** are transformed as follows, respectively

$$\begin{aligned} \tilde{g}_j(\tilde{x}(s|x_{01}, x_{02}, T, \sigma)) &:= \tilde{x}_j(s|x_{01}, x_{02}, T, \sigma) - x_j^*, \forall s \in [0, 1], j \in I_5, \\ \tilde{g}_{j+5}(\tilde{x}(s|x_{01}, x_{02}, T, \sigma)) &:= x_{j^*} - \tilde{x}_j(s|x_{01}, x_{02}, T, \sigma), \forall s \in [0, 1], j \in I_5, \end{aligned} \quad (24)$$

and

$$\textbf{Problem } \widetilde{\textbf{OCP}} : \quad \max \quad \tilde{J}(x_{01}, x_{02}, T|\sigma) := \frac{\tilde{x}_3(1|x_{01}, x_{02}, T, \sigma)}{T} \quad (25)$$

$$s.t. \quad \left\| \frac{\partial \tilde{J}(x_{01}, x_{02}, T|\sigma)}{\partial \sigma} \right\| \left\| \frac{\partial \tilde{J}(x_{01}, x_{02}, T|\sigma)}{\partial \sigma} \right\|^T \leq \epsilon, \quad (26)$$

$$\tilde{g}_j(\tilde{x}(s|x_{01}, x_{02}, T, \sigma)) \leq 0, \forall s \in [0, 1], j \in I_{10}, \quad (27)$$

$$(x_{01}, x_{02}, T) \in [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3]. \quad (28)$$

4.2. Computing cost sensitivity

We now derive a formula for the cost sensitivity of Problem **OCP** in the following theorem.

Theorem 2.

$$\left\| \frac{\partial \tilde{J}(x_{01}, x_{02}, T|\sigma)}{\partial \sigma} \right\| \left\| \frac{\partial \tilde{J}(x_{01}, x_{02}, T|\sigma)}{\partial \sigma} \right\|^T = \sum_{k=1}^{10} \left\{ \frac{\lambda_3^k(1|x_{01}, x_{02}, T, \sigma)}{T} \right\}^2, \quad (29)$$

where $\lambda(s|x_{01}, x_{02}, T, \sigma) = (\lambda_j^k(s|x_{01}, x_{02}, T, \sigma))_{5 \times 10} \in \mathbb{R}^{5 \times 10}$, $s \in [0, 1]$, is the solution of the following auxiliary delay-differential system:

$$\begin{aligned} \dot{\lambda}(s|x_{01}, x_{02}, T, \sigma) &= \frac{\partial \tilde{f}(\tilde{x}(s), x(t_{\text{delay}}), \sigma, T)}{\partial \tilde{x}} \lambda(s|x_{01}, x_{02}, T, \sigma) + \frac{\partial \tilde{f}(\tilde{x}(s), x(t_{\text{delay}}), \sigma, T)}{\partial x} \lambda(s_{\text{delay}}|x_{01}, x_{02}, T, \sigma) \\ &\quad + \frac{\partial \tilde{f}(\tilde{x}(s), x(t_{\text{delay}}), \sigma, T)}{\partial \sigma}, \forall s \in [0, 1], \end{aligned} \quad (30)$$

with

$$\lambda(s|x_{01}, x_{02}, T, \sigma) = \mathbf{0} \in \mathbb{R}^{5 \times 10}, \quad \forall s \leq 0. \quad (31)$$

Proof. Let $(x_{01}, x_{02}, T) \in [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3]$ be an admissible triple. By Theorem 3.2 in [36], we have

$$\frac{\partial \tilde{x}_j(1|x_{01}, x_{02}, T, \sigma)}{\partial \sigma_k} = \lambda_j^k(1|x_{01}, x_{02}, T, \sigma), j \in I_5, k \in I_{10},$$

where $\lambda(s|x_{01}, x_{02}, T, \sigma) = (\lambda_j^k(s|x_{01}, x_{02}, T, \sigma))_{5 \times 10} \in \mathbb{R}^{5 \times 10}$ is the solution of the systems (30) and (31). Thus, differentiating $\tilde{J}(x_{01}, x_{02}, T|\sigma)$ with respect to σ_k yields

$$\frac{\partial \tilde{J}(x_{01}, x_{02}, T|\sigma)}{\partial \sigma_k} = \frac{\partial}{\partial \sigma_k} \left\{ \frac{\tilde{x}_3(1|x_{01}, x_{02}, T, \sigma)}{T} \right\} = \frac{1}{T} \frac{\partial \tilde{x}_3(1|x_{01}, x_{02}, T, \sigma)}{\partial \sigma_k} = \frac{\lambda_3^k(1|x_{01}, x_{02}, T, \sigma)}{T}, k \in I_{10}.$$

Hence,

$$\left[\frac{\partial \tilde{J}(x_{01}, x_{02}, T|\sigma)}{\partial \sigma} \right] \left[\frac{\partial \tilde{J}(x_{01}, x_{02}, T|\sigma)}{\partial \sigma} \right]^T = \sum_{k=1}^{10} \left\{ \frac{\partial \tilde{J}(x_{01}, x_{02}, T|\sigma)}{\partial \sigma_k} \right\}^2 = \sum_{k=1}^{10} \left\{ \frac{\lambda_3^k(1|x_{01}, x_{02}, T, \sigma)}{T} \right\}^2. \quad \square$$

4.3. Approximate problem

Problem $\widetilde{\text{OCP}}$ involves an infinite number of constraints (i.e. the continuous state inequality constraints imposed at every point in $[0, 1]$ (see (27))). Thus, Problem $\widetilde{\text{OCP}}$ can be viewed as a semi-infinite mathematical programming problem. **The constraint transcription in conjunction with local smoothing approximation techniques** are used to solve this type of optimal control problem in [30]. We will briefly discuss the application of **these techniques** to Problem $\widetilde{\text{OCP}}$.

Constraints (27) can be transcribed equivalently to

$$G^j(x_{01}, x_{02}, T|\sigma) = 0, j \in I_{10}, \quad (32)$$

where $G^j(x_{01}, x_{02}, T|\sigma) := \int_0^1 \max \{0, \tilde{g}_j(\tilde{x}(s|x_{01}, x_{02}, T, \sigma))\} ds, j \in I_{10}$. However, $G^j(x_{01}, x_{02}, T|\sigma), j \in I_{10}$, are non-smooth in $(x_{01}, x_{02}, T) \in [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3]$. Hence, we replace (32) with **the following functional inequality constraints**.

$$\tilde{G}^j(x_{01}, x_{02}, T|\sigma) := \int_0^1 \varphi_{\varepsilon, j}(\tilde{g}_j(\tilde{x}(s|x_{01}, x_{02}, T, \sigma))) ds \geq \gamma, j \in I_{10}, \quad (33)$$

where $\varepsilon > 0, \gamma > 0$ are adjustable parameters and

$$\varphi_{\varepsilon, j}(\tilde{g}_j(\tilde{x}(s|x_{01}, x_{02}, T, \sigma))) := \begin{cases} \tilde{g}_j(\tilde{x}(s|x_{01}, x_{02}, T, \sigma)), & \text{if } \tilde{g}_j(\tilde{x}(s|x_{01}, x_{02}, T, \sigma)) \in (\varepsilon, +\infty), \\ \frac{[\tilde{g}_j(\tilde{x}(s|x_{01}, x_{02}, T, \sigma)) + \varepsilon]^2}{4\varepsilon}, & \text{if } \tilde{g}_j(\tilde{x}(s|x_{01}, x_{02}, T, \sigma)) \in [-\varepsilon, \varepsilon], \\ 0, & \text{if } \tilde{g}_j(\tilde{x}(s|x_{01}, x_{02}, T, \sigma)) \in (-\infty, -\varepsilon). \end{cases}$$

Hence, with this approximation scheme, constraints (27) in Problem $\widetilde{\text{OCP}}$ are approximated by constraints (33), which are standard constraints and can be readily handled using the computational method described in Section 4.4.

Then, by virtue of the results in [30], we obtain an approximate problem of Problem $\widetilde{\text{OCP}}$ as given below.

$$\begin{aligned} \text{Problem } \widetilde{\text{NOCP}} : \quad & \max \quad \tilde{J}(x_{01}, x_{02}, T|\sigma) = \frac{\tilde{x}_3(1|x_{01}, x_{02}, T, \sigma)}{T} \\ & s.t. \quad \left[\frac{\partial \tilde{J}(x_{01}, x_{02}, T|\sigma)}{\partial \sigma} \right] \left[\frac{\partial \tilde{J}(x_{01}, x_{02}, T|\sigma)}{\partial \sigma} \right]^T \leq \epsilon, \\ & \quad \tilde{G}^j(x_{01}, x_{02}, T|\sigma) \geq \gamma, j \in I_{10}, \\ & \quad (x_{01}, x_{02}, T) \in [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3]. \end{aligned} \quad (34)$$

4.4. A parallel filled function algorithm

Since system (23) is **highly nonlinear**, Problem $\widetilde{\text{NOCP}}$ is too complicated to solve analytically. **Problem $\widetilde{\text{NOCP}}$ is a smooth problem that can be solved using the gradient-based algorithms (see, for example, [32]).** However, these techniques are designed to **search for** local optimal solutions.

The main difficulty for global optimization is to escape from the current local minimizer and to find a better one. One of the most popular approaches is the filled function method, the conception of which was first proposed by Ge at the Dundee Biennial Conference on Numerical Analysis in 1983 and finally published in [33]. However, the traditional filled function methods are often non-differentiable and sensitive to **some adjustable** parameters, or contain ill-conditioned terms and more than one adjustable parameter needing to be controlled [35]. To overcome these limitations, a new filled function method is proposed in [34].

Because of the highly complex nature of Problem $\widetilde{\text{NOCP}}$, we design a parallel filled function approach. On each slave processor, we can construct a filled function. Before the next iteration, on the master processor, we can obtain the optimal triple (x_{01}, x_{02}, T) and use it to update the current triple (x_{01}, x_{02}, T) on each slave processor. Then, on each slave processor, we can sequentially compute until the algorithm has a successful exit.

For convenience, Problem $\widetilde{\text{NOCP}}$ can now be equivalently transformed by the following optimal control problem called Problem $\overline{\text{NOCP}}$

$$\text{Problem } \overline{\text{NOCP}} : \min \tilde{J}(x_{01}, x_{02}, T|\sigma) := -\frac{\tilde{x}_3(1|x_{01}, x_{02}, T, \sigma)}{T} \quad (35)$$

$$s.t. \left[\frac{\partial \tilde{J}(x_{01}, x_{02}, T|\sigma)}{\partial \sigma} \right] \left[\frac{\partial \tilde{J}(x_{01}, x_{02}, T|\sigma)}{\partial \sigma} \right]^T \leq \epsilon, \quad (36)$$

$$\begin{aligned} \tilde{G}^j(x_{01}, x_{02}, T|\sigma) &\geq \gamma, j \in I_{10}, \\ (x_{01}, x_{02}, T) &\in [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3]. \end{aligned} \quad (37)$$

The parameters in Algorithm 1 are defined below.

- Let u denote (x_{01}, x_{02}, T) .
- p is the slave processor index.
- $\tilde{N}$ is the number of slave processors.
- k is the iteration index.
- $\mathcal{K}$ is the maximal iteration of k .
- δ is a nonnegative adjustable parameter satisfying

$$0 < \delta < \min \left\{ \frac{1}{L^2}, \min \left\{ \tilde{J}(u_p^k|\sigma) - \tilde{J}(\hat{u}_p^k|\sigma) : \hat{u}_p^k \in S_2 \text{ is a minimizer of } \tilde{J}(u|\sigma) \text{ in (35)} \right\} \right\}, 0 < L < \infty \text{ is a constant,}$$

with

$$S_2 \leftarrow S_{21} \bigcup S_{22},$$

$$S_{21} \leftarrow \left\{ u \in [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3] \mid \tilde{J}(u_p^k|\sigma) > \tilde{J}(u|\sigma) > \tilde{J}(u_p^k|\sigma) - \delta \right\}$$

and

$$S_{22} \leftarrow \left\{ u \in [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3] \mid \tilde{J}(u|\sigma) < \tilde{J}(u_p^k|\sigma) - \delta \right\}.$$

- A is a nonnegative adjustable parameter controlling the accuracy of the filled function method.
- $A_{\max}$ is an upper bound of parameter A .
- $\delta_{\min}$ is a lower bound of parameter δ .
- $\tilde{\mathcal{K}}$ is an integer for testing convergence (if the value of the cost function has not changed after $\tilde{\mathcal{K}}$ iterations, then we terminate the algorithm).
- ϵ is the convergence tolerance of a cost sensitivity constraint for ensuring an acceptable level of the system performance is achieved.
- $\tilde{\epsilon}$ is the convergence tolerance of the cost function.

- u_g^k is the best control variables found by any member of the slave processor set at the end of the k th iteration.
- $\tilde{J}(u_g^k)$ is the value of the cost function found by any member of the slave processor set at the end of the k th iteration.
- u_p^k is the control variables found by the p th member of the slave processor set at the end of the k th iteration.
- $\tilde{J}(u_p^k)$ is the value of the cost function found by the p th member of the slave processor set at the end of the k th iteration.

Algorithm 1:

Step 1 : Initialize and broadcast data.

- **Step 1.1 :** Read known data such as $\epsilon, \tilde{\epsilon}, \tilde{\mathcal{K}}, \tilde{N}, W, a_1, b_1, a_2, b_2, a_3, b_3$ and $\mathcal{K}$ on master processor.
- **Step 1.2 :** Broadcast (**MPI_Broad**) data on master processor to all slave processors.

Step 2 : Execute the following procedure on each slave processor and denote the ID of process as $p \in I_N$.

- **Step 2.1 :** Choose $u_p^1 \in [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3]$, $\delta_{\min} \leftarrow 10^{-10}$, $A_{\max} \leftarrow 10^5$, $k \leftarrow 1$.
- **Step 2.2 :** Set $A \leftarrow 10$, $\delta \leftarrow 10^{-5}$, $h_1 \leftarrow 0$, $h_2 \leftarrow 0$. If $k > \mathcal{K}$, then the algorithm has an abnormal exit.
- **Step 2.3 :** Check and adjust.

1. Based on Theorem 2 and formula (33), check the values of $\left[\frac{\partial \tilde{J}(u_p^k | \sigma)}{\partial \sigma} \right] \left[\frac{\partial \tilde{J}(u_p^k | \sigma)}{\partial \sigma} \right]^T$ and $\tilde{G}^j(u_p^k | \sigma)$, $j \in I_{10}$.
2. If $\left[\frac{\partial \tilde{J}(u_p^k | \sigma)}{\partial \sigma} \right] \left[\frac{\partial \tilde{J}(u_p^k | \sigma)}{\partial \sigma} \right]^T > \epsilon$ or $\exists j \in I_{10}$ such that $\tilde{G}^j(u_p^k | \sigma) < \gamma$ (i.e., u_p^k is infeasible for Problem **NOCP**), then perform a gradient-descend search (minimizing $\left[\frac{\partial \tilde{J}(u_p^k | \sigma)}{\partial \sigma} \right] \left[\frac{\partial \tilde{J}(u_p^k | \sigma)}{\partial \sigma} \right]^T$) or a gradient-ascent search (maximizing $\tilde{G}^j(u_p^k | \sigma)$) to obtain a feasible point $\check{u}_p^k$ for Problem **NOCP** (i.e., $\left[\frac{\partial \tilde{J}(\check{u}_p^k | \sigma)}{\partial \sigma} \right] \left[\frac{\partial \tilde{J}(\check{u}_p^k | \sigma)}{\partial \sigma} \right]^T \leq \epsilon$ and $\forall j \in I_{10}, \tilde{G}^j(\check{u}_p^k | \sigma) \geq \gamma$) and set $u_p^k \leftarrow \check{u}_p^k$.

$$\text{If } \begin{cases} h_2 = 0 \\ h_2 = 1, \end{cases} \begin{cases} h_1 = 0, \\ h_1 = 1, \end{cases} \begin{array}{l} \text{then goto Step 2.4,} \\ \text{then goto Step 2.5,} \\ \text{then goto Step 2.10.} \end{array}$$

- **Step 2.4 :** Use the gradient-based algorithms with initial value u_p^k to obtain local optimal solution of Problem **NOCP**, still denoted by itself u_p^k , set $h_1 \leftarrow 1$ and goto Step 2.3.
- **Step 2.5 :** If $A > A_{\max}$, then u_p^k is taken as a global minimizer of $\tilde{J}(u | \sigma)$ in (35), set $h_2 \leftarrow 1$ and goto Step 2.3; otherwise, goto Step 2.6.
- **Step 2.6 :** Based on [34], for $u \in [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3]$, construct

$$FF_{u_p^k, A, \delta}(u) \leftarrow \min \left\{ -\|u - u_p^k\|^2 - \frac{\tilde{J}^2(u | \sigma)}{A}, \min \{A(\tilde{J}(u | \sigma) - \tilde{J}(u_p^k | \sigma)), -\delta\}(\tilde{J}(u | \sigma) - \tilde{J}(u_p^k | \sigma))^2 \right\}.$$

- **Step 2.7 :** Minimize $FF_{u_p^k, A, \delta}(u)$ from $2|u|$ initial points, where $|u|$ is the dimension of vector u . Let v^* denote the minimizer of $FF_{u_p^k, A, \delta}(u)$.
- **Step 2.8 :** If $\tilde{J}(v^* | \sigma) < \tilde{J}(u_p^k | \sigma)$, then set $u_p^k \leftarrow v^*$, goto Step 2.6; **otherwise, goto Step 2.9.**
- **Step 2.9 :** **Let $\delta \leftarrow 0.1\delta$. If $\delta > \delta_{\min}$, goto Step 2.5; otherwise, let $A \leftarrow 10A$ and goto Step 2.5.**

- **Step 2.10** : Compute the cost function (35), denoted by $\tilde{J}(u_p^k|\sigma)$. Send (**MPI_Send**) $\tilde{J}(u_p^k|\sigma)$ and u_p^k to master processor and Barrier (**MPI_Barrier**) until all slave processors complete the work in the k th iteration.

Step 3 : Assign the master processor to execute the tasks: receive (**MPI_Recv**) $\tilde{J}(u_p^k|\sigma)$ and u_p^k from the p th processor; compute

$$\tilde{J}(u_g^k) \leftarrow \min_{p=1,\dots,\tilde{N}} \tilde{J}(u_p^k|\sigma), \quad u_g^k \leftarrow \arg \min_{p=1,\dots,\tilde{N}} \tilde{J}(u_p^k|\sigma).$$

Then, Broadcast (**MPI_Broad**) u_g^k to all slave processors and set $\tilde{J}_{best}^k \leftarrow \tilde{J}(u_g^k)$.

Step 4 : Execute the following procedure on each slave processor: based on broadcasted u_g^k in master processor, obtain u_g^k ; then, use u_g^k to replace u_p^{k+1} .

Step 5 : Assign the master processor to execute the tasks: If $k \geq \tilde{\mathcal{K}}$, $|\tilde{J}_{best}^{k-\tilde{\mathcal{K}}+1} - \tilde{J}_{best}^k| < \tilde{\epsilon}$, then report results and the algorithm has a successful exit; otherwise, set $k \leftarrow k + 1$ and goto Step 2.2.

Remark 1. In Step 2.2 and Step 5, the algorithm stops when any of the following conditions holds:

1. The maximal iteration $\mathcal{K}$ is reached;
2. The deviation between the best fitness of current iteration and that of the $\tilde{\mathcal{K}}$ th previous iteration is less than $\tilde{\epsilon}$.

Remark 2. Recall from Theorems 2.1 and 2.3 in [34] that the value of A should be selected large enough and the value of δ should be selected small enough. Otherwise, there could be no minimizer of $FF_{u_p^k, A, \delta}(u)$ in a better basin.

1. The value of δ should be selected small enough. We set the initial adjustable parameter δ of 10^{-5} in Step 2.2. Thus, the value of δ is reduced successively in Step 2.9 when certain step fails. If the adjustable parameter δ reaches its lower bound and we cannot find the better local minimizer, we increase the value of A .
2. The value of A should be selected large enough. We set the initial adjustable parameter A of 10 in Step 2.2. Afterwards, the value of A is increased successively in Step 2.9 if no better solution is found when minimizing the filled function. If the adjustable parameter A reaches its upper bound and we cannot find the better local minimizer, the algorithm is terminated and the current local minimizer is taken as the global minimizer.

5. Numerical results

The optimal productivity of 1,3-PD and the corresponding optimal control in Problem $\widetilde{\text{NOCP}}$ are obtained by Algorithm 1 on Lenovo DeepComp 1800 PC-cluster Server composed of 16 nodes. Each node is equipped with two Intel 5420 CPU (4 Core, 64-bit, clocked at 2.5 GHz) and 8 GB memory. The parameters chosen in Algorithm 1, derived empirically after numerous experiments, are listed in Table 2. The initial state is $x_0 = (0.102, 418.26087, 0, 0, 0)$. The initial terminal time is $T = 4$. The initial function $\phi(t)$ is obtained based on [24]. System (23) is solved by using Euler method with a step size of $1/3600$.

In Fig. 1, three axes respectively represent the initial concentration of extracellular biomass x_{01} , glycerol x_{02} , and the value of the cost function with various initial state x_{01} and x_{02} . Following the observation of Fig. 1, all the peaks are contained in a polyhedron and the cost function $\tilde{J}(x_{01}, x_{02}, T|\sigma)$ can reach the maximum value when $(x_{01}, x_{02}, T) \in [a_1, b_1] \times [a_2, b_2] \times [a_3, b_3]$. Thus, it is confident to draw the conclusion that the cost function $\tilde{J}(x_{01}, x_{02}, T|\sigma)$ is optimal when x_{01} is 0.9985, x_{02} is 404.034 and the optimal terminal time is 4.82. More accurately, the optimal control and the corresponding cost function for Problem $\widetilde{\text{NOCP}}$ are, respectively, $u^* = (0.9985, 404.034, 4.82)$ and $\tilde{J}(u^*|\sigma) = 81.10$.

The ranges of uncertain system parameter vector perturbations applied to get the results in Figs. 2 and 3 belong to $[0.5\sigma_k, 1.5\sigma_k], k = 1, 2, \dots, 10$. To investigate the cost sensitivity of individual uncertain system parameters $\sigma_k, k = 1, 2, \dots, 10$, for box plots drew in Fig. 2, we randomly generated 200 perturbations of individual uncertain system parameters $\sigma_k, k = 1, 2, \dots, 10$, with the initial control strategy $u = (0.102, 418.26087, 4)$. It turns out that the 7th component of σ , i.e., Y_2 , is the most critical system parameter in terms of cost sensitivity: $(\partial\tilde{J}/\partial\sigma_7)^2 = (\partial\tilde{J}/\partial Y_2)^2$ is the dominant term in the sensitivity values in Fig. 2. As another demonstration, we generated the perturbed system

parameter vector as follows: for $k \neq 7$, we perturbed σ_k by 50% (in the negative and positive direction); for $k = 7$, we perturbed σ_7 from the disturbance intervals

$$(0, 5\%), (5\%, 10\%), \dots, (45\%, 50\%).$$

where the upper limit of each interval is referred to as the "disturbance percentage". For each disturbance percentage (5%, 10%, ..., 45%, 50%), we generated 200 random system parameter vector according to the above procedure and calculated the corresponding value of the cost sensitivity under σ^0 and initial state **vector** x_0 and initial terminal time T . Our results are shown as box plots in Fig. 3. From Fig. 3, we can see that the 7th component of σ , i.e., Y_2 is the sensitive system parameter.

In our simulations, we generated the perturbed system parameter vector as follows: for $k \neq 7$, we perturbed σ_k by 10% (in the negative and positive direction); for $k = 7$, we perturbed σ_7 from the disturbance intervals

$$[0.065, 0.067], [0.069, 0.071], \dots, [0.099, 0.101], [0.103, 0.105].$$

For each disturbance intervals, we generated 1,000 random system parameter vector according to the above procedure and calculated the corresponding value of the cost function under the optimal control strategy u^* for including constraint (11) and excluding constraint (11) in Fig. 4. The first thing to note is that the value of the cost function to Problem **NOCP excluding** constraint (11) is very sensitive with respect to changes in σ_7 . For example, a change of 2×10^{-3} in the value of σ_7 causes the value of the cost function to over 30%. The change in the value of the cost function to Problem **NOCP including** constraint (11), however, is much smaller. The value of the cost function to Problem **NOCP including** constraint (11) under optimal **control** u^* hardly changes when σ_7 is changed.

From Fig. 5, the continuous inequality constraints (12) is satisfied for $t \in [0, T]$.

Under the obtained optimal control strategy, we obtained the optimal yield of 1,3-PD at the optimal terminal time is 81.10 mmol h⁻¹, which is increased by 3.76% compared to the result (78.16 mmol h⁻¹) in [25]. Compared to the result (41.13 mmol h⁻¹) in [24], our result is increased by 97.2%.

Table 2. The parameters chosen in Algorithm 1.

τ	a_1	a_2	b_1	b_2	c_1	c_2	ϵ	$\tilde{\epsilon}$	$\tilde{N}$	$\mathcal{K}$	$\tilde{\mathcal{K}}$	ϵ	γ
0.26	0.01	1	200	1700	2	10	20	0.1	79	600	50	0.01	0.01

6. Discussions and conclusions

In this paper, we consider a nonlinear time-delay dynamic system with uncertain system parameters to characterize the process of batch fermentation. To maximize the concentration of 1,3-PD at the terminal time, we introduce an optimal control problem governed by the nonlinear time-delay dynamic system, subject to a cost sensitivity constraint and continuous state inequality constraints. Then, the optimal control problem with varying terminal time is transformed. Using **some techniques**, we approximate the continuous state inequality constraints by **conventional inequality constraints** to yield an approximate optimal control problem. A parallel algorithm is proposed to solve the approximate optimal control problem based on the filled function method. Finally, numerical simulation results verified the effectiveness of the numerical solution method.

In fact, optimal control problems involved nonlinear time-delay system appear in various industrial processes. Future studies will generalize the mathematical model to other processes and demonstrate the validity of the numerical solution method.

Fig. 1. The value of the cost function $J(x_{01}, x_{02}, T|\sigma)$ for various initial state x_{01} and x_{02} . (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 2. The cost sensitivity for individual system parameter uncertainty $\sigma_k, k = 1, 2, \dots, 10$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 3. The cost sensitivity under all uncertain system parameters disturbance. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 4. Variation in the value of the cost function due to the variation of $\sigma_7(Y_2)$. *I* : (red) Problem **OCP** including (11), *E* : (blue) Problem **OCP** excluding (11). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 5. $g_j(t) = x_j(t|u^*, \sigma) - x_j^*$, $g_{j+5}(t) = x_{j+5}(t|u^*, \sigma) - x_{j+5}^*$, $j \in I_5$, under $u^* = [x_{01}^*, x_{02}^*, T^*]$ in batch culture process in $t \in [0, T^*]$.

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