Sensitivity analysis and parameter identification for a nonlinear time-delay system in microbial fed-batch process

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Abstract

Developing suitable dynamic models of bioprocess is a difficult issue in bioscience. In this paper, considering the microbial metabolism mechanism, i.e., the production of new biomass is delayed by the amount of time it takes to metabolize the nutrients, in glycerol bioconversion to 1,3-propanediol, we propose a nonlinear time-delay system to formulate the fed-batch fermentation process. Some important properties are also discussed. Then, in view of the effect of time-delay and the high number of kinetic parameters in the system, the parametric sensitivity analysis is used to determine the key parameters. Finally, a parameter identification model is presented and a global optimization method is developed to seek the optimal key parameters. Numerical results show that the nonlinear time-delay system can describe the fed-batch fermentation process reasonably.

1. Introduction

Time-delay systems are increasingly used in numerous application areas that include physiological kinetics, population dynamics and control problems [1,2]. Parameter identification is usually done by comparing the system output observed in practice with the system output predicted by the model, and then adjusting the parameters accordingly. Works on identification of time-delay systems have shown the complexity of the question [3]. As a result, the problem of identifying delays and parameters in time-delay systems has been extensively studied, see, for example, [4–7].

During the past several decades, there has been growing interest in microbial production of 1,3-propanediol (1,3-PD) throughout the world because of its lower cost, higher production and no pollution [8]. Among various microbial production methods of 1,3-PD, dissimilation of glycerol by Klebsiella pneumoniae (K. pneumoniae) has been widely investigated since 1980s [9]. Glycerol fermentation by K. pneumoniae is a complex bioprocess since the microbial growth is subjected to multiple inhibitions of substrate and products, such as glycerol, 1,3-PD, ethanol and so on [10]. The researches about the fermentation include the quantitative description of the cell growth kinetics, the metabolic overflow kinetics of substrate consumption and product formation as well as the optimization of feed strategy of substrate in fed-batch culture [11–13]. More importantly, time-delays exist in the process of glycerol bioconversion to 1,3-PD [14,15]. Several reasons may be responsible for the occurrence of the delays in the fermentation process: a cell has to undergo some change or growth process for which it needs some time before it reacts with others; the substrate and the products have to be transported across the cell membrane requiring a certain amount of time for transport; sometimes, either because of lack of knowledge or in order to reduce complexity it is appropriate to omit a number of intermediate steps in the reaction system for which the...
processing time is not negligible and has to be implemented as a delay [16,17]. Thus, time-delays have to be incorporated into mathematical models formulating the fermentation process.

Regarding the various fermentation techniques, including batch culture, fed-batch culture and continuous culture, the most efficient cultivation method appears to be a fed-batch culture which corrects pH by alkali addition with glycerol supply [10]. For this reason, modeling, optimization and control of the fermentation process have been extensively studied in the literature [11,18–26]. Unstructured and nonsegregational models were initially used to model fed-batch fermentation. The models have been used for optimal control studies by a number of researchers [18–21]. Recently, based on an assumption that the feed of glycerol only occurs at impulsive instants, nonlinear impulsive systems have been extensively investigated to formulate the fermentation process [22]. After this, 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 [22–24]. 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. In contrast, taking the feed of glycerol as a time-continuous process, a nonlinear multistage system was proposed in [11]. The parameter identification of the nonlinear multistage system was subsequently discussed [27]. Numerical simulations in [27] showed that the nonlinear multistage system could describe the fed-batch process better than the nonlinear impulsive system. However, the parameters in the first batch phase and subsequent feed phase are taken different values and no parametric sensitivity analysis is considered in [27]. Properties and optimization algorithms for the optimal control problem involving the nonlinear multistage system, in which the feeding rate of glycerol is taken as the control function, were then investigated in [11,25,26]. Although the above results are interesting, time-delays are ignored in the above researches.

In this paper, considering the metabolism mechanism of microorganism, i.e., the production of new biomass is delayed by the amount of time it takes to metabolize the nutrients, in the fed-batch culture, we propose a nonlinear time-delay system to formulate the fermentation process. Then, due to the effect of time delay and the high number of the kinetic parameters in the system, the parametric sensitivity analysis is used to determine the key parameters. By the way, a nonlinear time-delay system was proposed to formulate the batch fermentation process [28]. Nonetheless, the parametric sensitivity analysis is not discussed in [28]. Parametric sensitivity analysis, i.e., the study of the influence of the parameters of a model on its solution, plays an important role in design, modeling and parameter identification [29,30]. In particular, the sensitivity analysis of time-delay systems has been investigated in the literature, see, e.g., [31–34]. Nevertheless, calculating the sensitivity functions is a very difficult task.

By solving the sensitivity functions numerically using the auxiliary system method, the key parameters are obtained. On this basis, a parameter identification model involving the nonlinear time-delay system is presented and a global optimization method is developed to seek the optimal key parameters. Numerical results show that the nonlinear time-delay system can describe the fed-batch fermentation process better than the results previously reported.

The remainder of this paper is organized as follows. In Section 2, the nonlinear time-delay system and its properties are discussed. A description is carried out about the nonlinear time-delay system of fed-batch process in Section 2.1, and some important properties of the system are discussed in Section 2.2. Section 3 investigates the parametric sensitivity analysis of the nonlinear time-delay system. Section 3.1 gives the definitions of the sensitivity functions, and Section 3.2 shows the numerical simulation results. The parameter identification problem is discussed in Section 4. The parameter identification model is presented in Section 4.1, a computational procedure to seek the optimal key parameters is developed in Section 4.2, and the numerical results are illustrated in Section 4.3. Finally, conclusions are provided in Section 5.

2. Problem formulation

2.1. Nonlinear time-delay systems

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 continuously added to the fermentor. This helps to maintain a suitable environment for cells growth. At the end of the feed, a batch phase starts again. The above processes repeat until the end of the final batch phase. During the whole fermentation process, the production of new biomass is delayed by the amount of time it takes to metabolize the nutrients. Thus, it is necessary to include time-delays for the biomass formation in modeling the fermentation process. According to the fermentation process, we assume that:

- $\text{(H}_0\text{)}$ The concentrations of reactants are uniform in reactor. Nonuniform space distribution is ignored.
- $\text{(H}_3\text{)}$ During the process of fed-batch culture, only glycerol and alkali are fed into the reactor.
- $\text{(H}_4\text{)}$ The feeding rates of glycerol and alkali are both uniform at various discrete time intervals. Moreover, the feeding velocity ratio of alkali to glycerol $r$ is a constant.
- $\text{(H}_5\text{)}$ Biomass, substrate, 1,3-PD, acetate and ethanol concentrations in reactor at time $t$, are determined by biomass concentration at time $t - \tau$. 

...
Under the assumptions \((H_1)\)--\((H_4)\), the fed-batch fermentation process can be formulated as the following nonlinear time-delay system

\[
\begin{align*}
x(t) &= f_i(t, x(t), x(t - \tau), p), \\
x(t_{i+1}) &= x(t_i), \quad t \in (t_{i-1}, t_i], \quad i = 1, 2, \ldots, 2N + 1, \\
x(t_0) &= x_0, \\
x(t) &= \phi(t), \quad t \in [-\bar{\tau}, t_0],
\end{align*}
\]

where \(x(t) := (x_1(t), x_2(t), x_3(t), x_4(t), x_5(t))^T \in \mathbb{R}_+^5\) is the system state vector whose components represent the extracellular concentrations of biomass, glycerol, 1,3-PD, acetic acid and ethanol at time \(t\) in the fermentor, respectively. \(t_i, i \in \Lambda := \{1, 2, \ldots, 2N + 1\}\), is the switching instant such that \(0 = t_0 < t_i \in \Lambda\), and \(t_{2N+1} = T\), which is decided a priori in the experiment. In particular, \(t_{2i+1}\) is the moment of adding glycerol, at which the fermentation process switches to a feeding process, and \(t_{2i+2}\) denotes the moment of ending the flow of glycerol, at which the fermentation process switches to a batch process, \(i \in \Lambda_1 := \{0, 1, 2, \ldots, N - 1\}\). \(T\) is the terminal time of the fermentation, \(\bar{\tau} > 0\) is a given real number, \(x_0\) is a given initial state, and \(\phi(t) \in \mathcal{C}^1([-\bar{\tau}, 0], \mathbb{R}_+^5)\) is a given initial function in which \(\mathcal{C}^1([-\bar{\tau}, 0], \mathbb{R}_+^5)\) is the Banach space of continuously differentiable functions mapping the interval \([-\bar{\tau}, 0]\) into \(\mathbb{R}_+^5\). Furthermore, for \(t \in [t_{2i}, t_{2i+1}], i \in \Lambda_2 := \{0, 1, \ldots, N\}\),

\[
f_{i+1}^t(x(t), x(t - \tau), p) = q_1(x(t))x_1(t - \tau), \quad \ell = 1, 3, 4, 5
\]

and

\[
f_{i+2}^t(x(t), x(t - \tau), p) = -q_2(x(t))x_1(t - \tau);
\]

for \(t \in (t_{2i+1}, t_{2i+2}], i \in \Lambda_1,\)

\[
f_{i+2}^{t+1}(x(t), x(t - \tau), p) = q_1(x(t))x_1(t - \tau) - D(t)x_i(t).
\]

and

\[
f_{i+2}^{t+2}(x(t), x(t - \tau), p) = D(t)\left(\frac{c_0}{t + \tau} - x_2(t)\right) - q_2(x(t))x_1(t - \tau).
\]

In \((4)\) and \((5)\), \(r\) is the velocity ratio of adding alkali to glycerol. \(c_0\) denotes the concentration of initial feed of glycerol in the experiment. \(D(t)\) is the dilution rate at time \(t\) defined as

\[
D(t) = \frac{(1 + r)\nu_t}{V(t)},
\]

\[
V(t) = V_0 + \sum_{j=1}^{i-1}(1 + r)\nu_j(t_j - t_{j-1}) + (1 + r)\nu_i(t - t_{i-1}).
\]

In \((6)\) and \((7)\), \(\nu_i \geq 0\) is the feeding rate of glycerol in \((t_{i-1}, t_i], i \in \Lambda\), and \(V_0\) is the initial volume of culture fluid in the fermentor. The specific growth rate of cells \(q_1(x(t))\), the specific consumption rate of substrate \(q_2(x(t))\) and the specific formation rates of products \(q_3(x(t)), \ell = 3, 4, 5\), are expressed as the following equations:

\[
q_1(x(t)) = \frac{\Delta_1 x_2(t)}{x_2(t) + k_1} \prod_{i=2}^{5} \left(1 - \frac{x_i(t)}{x_i^*}\right).
\]

\[
q_2(x(t)) = m_2 + q_1(x(t))Y_2 + \frac{\Delta_2 x_2(t)}{x_2(t) + k_2}.
\]

\[
q_3(x(t)) = -m_3 + q_1(x(t))Y_3 + \frac{\Delta_3 x_2(t)}{x_2(t) + k_3}, \quad \ell = 3, 4.
\]

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

It should be noted that there exist critical concentrations of biomass, glycerol, 1,3-PD, acetate and ethanol, outside which cells cease to growth. Thus, it is biologically meaningful to restrict the concentrations of biomass, glycerol and products within a set \(W\) defined as

\[
x^T(t) \in W := \prod_{i=1}^{5}[x_i, x_i^*], \quad \forall t \in [0, T],
\]
Under anaerobic conditions at 37°C and pH 7.0, the critical concentrations for cells growth are \( x_1 = 0.01 \text{ g L}^{-1}, x_2 = 15 \text{ mmol L}^{-1}, x_3 = 0 \text{ mmol L}^{-1}, \ell = 3, 4, 5, x_1 = 6 \text{ g L}^{-1}, x_2 = 2039 \text{ mmol L}^{-1}, x_3 = 1036 \text{ mmol L}^{-1}, x_4 = 1026 \text{ mmol L}^{-1}, \) and \( x_5 = 360.9 \text{ mmol L}^{-1}, \) respectively [13].

Due to the introduction of time-delay in the mathematical model, the values of kinetic parameters in the system (1) may be different from the previous ones. Hence, the time-delay \( \tau \) and the kinetic parameters, i.e.,
\[
p := (\Lambda_1, k_1, m_2, m_3, m_4, Y_2, Y_3, \Delta_2, \Delta_3, \Delta_4, k_2, k_3, k_4, c_1, c_2, c_3) \in \mathbb{R}^{18}
\]
should be identified. Here, time-delay \( \tau \) is assumed to be non-negative and bounded above by \( \bar{\tau} \), that is,
\[
\tau \in \mathcal{T} := [0, \bar{\tau}].
\]
In addition, the admissible set of the kinetic parameter vectors is defined as
\[
\mathcal{P} := \bigcap_{i=1}^{18} [\hat{p}_i \Delta, \hat{p}_i],
\]
where \( \hat{p}_i \) and \( \hat{p}_i^\ast \) are the lower bound and the upper bound of the kinetic parameter \( p_i \), respectively. The values of \( \hat{p}_i \) and \( \hat{p}_i^\ast \) are obtained by decrements and increments of the kinetic parameters considered in [13,22,27].

2.2. Properties of the nonlinear time-delay system

For the system (1), some important properties, e.g., the existence and uniqueness, boundedness, and differentiability of the solution, are discussed in the subsection.

**Theorem 1.** The function \( f^i : (t_{i-1}, t_i] \times \mathbb{R}_+^5 \times \mathbb{R}_+^5 \times \mathbb{R}^{18} \to \mathbb{R}_+^5 \), \( i \in \Lambda \), defined in (2)–(5) satisfies the following conditions:

(a) \( f^i \) is continuous on \( (t_{i-1}, t_i] \) for each \( (x, y, p) \in \mathbb{R}_+^5 \times \mathbb{R}_+^5 \times \mathbb{R}^{18} \) and is continuously differentiable with respect to each of the components \( x, y \) and \( p \) for each \( t \in (t_{i-1}, t_i] \).

(b) There exists a constant \( K > 0 \) such that
\[
\|f^i(t, x, y, p)\| \leq K(1 + \|x\| + \|y\|), \quad \forall (t, x, y, p) \in (t_{i-1}, t_i] \times \mathbb{R}_+^5 \times \mathbb{R}_+^5 \times \mathcal{P},
\]
where \( \| \cdot \| \) denotes the Euclidean norm.

**Proof.**

(a) This conclusion can be obtained by the expression of \( f^i \) in (2)–(5).

(b) We can complete the proof using a similar method as that given for the proof of Property 1 in [35]. \( \square \)

**Theorem 2.** For each \( (\tau, p) \in \mathcal{T} \times \mathcal{P} \), the system (1) has a unique continuous solution, denoted by \( x(\cdot | \tau, p) \), on \([0, \bar{\tau}] \). Furthermore, \( x(\cdot | \tau, p) \) satisfies that
\[
x(t | \tau, p) = x(t_{i-1} | \tau, p) + \int_{t_{i-1}}^{t} f^i(s, x(s | \tau, p), x(s - \tau | \tau, p), p) ds, \quad \forall t \in (t_{i-1}, t_i], \quad i \in \Lambda,
\]
and \( x(t | \tau, p) = \phi(t) \), \( \forall t \in [-\bar{\tau}, 0] \).

**Proof.** The proof can be obtained by Theorem 1 and the theory of delay-differential equations [36]. \( \square \)

**Theorem 3.** Given the initial function \( \phi(t) \in C^4([-\bar{\tau}, 0], \mathbb{R}_+^5) \) and for all \( (\tau, p) \in \mathcal{T} \times \mathcal{P} \), the unique solution \( x(\cdot | \tau, p) \) of the system (1) is uniformly bounded.

**Proof.** Let \( (\tau, p) \in \mathcal{T} \times \mathcal{P} \). Then since \( \phi(t) \) is continuous on \([-\bar{\tau}, 0] \), there exists a real number \( 0 \leq M < +\infty \) such that
\[
\sup\{\|\phi(t)\| | t \in [-\bar{\tau}, 0]\} \leq M, \quad \forall t \in [-\bar{\tau}, 0].
\]
Hence,
\[
\|x(t | \tau, p)\| \leq M, \quad \forall t \in [-\bar{\tau}, 0].
\]
In view of Theorem 1 and Theorem 2, we obtain that
In addition, identification of the kinetic parameters perhaps can be set as constants in the sequent parameter identification process. Parameters in the dynamical system exerting the most influence on the system state can be established.

Based on Theorem 4 and [29], the sensitivity functions are now defined as the partial derivatives of the system state with respect to the delay and the kinetic parameter, i.e.,

$$\text{S}_c(t) := \frac{\partial x(t, \tau, p)}{\partial \tau}, \quad t \in (0, T],$$

$$\text{S}_p(t) := \frac{\partial x(t, \tau, p)}{\partial p}, \quad t \in (0, T].$$

respectively.

Calculating the sensitivity functions is a very difficult task, the auxiliary system method will be used to deduce the formulae of the sensitivity functions. The main reason is that the auxiliary time-delay systems can be solved simultaneously with the system (1). Define

$$X(t) = \begin{cases} \phi(t), & \text{if } t \leq 0, \\ f(t, X(t), X(t - \tau), p), & \text{if } t \in (t_{i-1}, t_i] \text{ for some } i \in \Lambda. \end{cases}$$

We first give the sensitivity function $S_c(\cdot)$ in terms of the solution of an auxiliary time-delay system in the following theorem.

**Theorem 5.** For each $t \in (0, T]$ and $p \in P$, $S_c(t) = \psi(t, \tau, p)$, $\tau \in T,$

where $\psi(t, \tau, p)$ is the solution of the following auxiliary delay-differential system:
\[
\begin{aligned}
    \dot{\psi}(t) &= \frac{\partial f_i(t,x(t),x(t-\tau(t),p))}{\partial t} \psi(t) + \frac{\partial f_i(t,x(t),x(t-\tau(t),p))}{\partial x} \times \psi(t-\tau) - \frac{\partial f_i(t,x(t),x(t-\tau(t),p))}{\partial p} \chi(t-\tau), \quad \forall \ t \in (t_{i-1}, t_i], \\
    \psi(t_{i-1}+) &= \psi(t_{i-1}), \quad i \in \Lambda,
\end{aligned}
\]

with

\[
    \psi(t) = 0, \quad t \in [-\tilde{\tau}, 0].
\]

**Proof.** Let \( \tau + \epsilon \) be arbitrary but fixed. Define

\[
\tau + \epsilon \in [0, \tilde{\tau}].
\]

In view of **Theorem 2**, \( x(t, \tau, p) \) and \( x(t, \tau + \epsilon, p) \), \( \forall \ t \in (t_{i-1}, t_i], i \in \Lambda \), can be written as

\[
x(t, \tau, p) = x_0 + \sum_{j=1}^{i-1} \int_{t_j}^{t} f^i(s, x(s, \tau, p), x(s-\tau, t, p), p) ds + \int_{t_{i-1}}^{t} f^i(s, x(s, \tau, p), x(s-\tau, t, p), p) ds
\]

and

\[
x(t, \tau + \epsilon, p) = x_0 + \sum_{j=1}^{i-1} \int_{t_j}^{t} f^i(s, x(s, \tau + \epsilon, p), x(s-\tau, t, p), p) ds + \int_{t_{i-1}}^{t} f^i(s, x(s, \tau + \epsilon, p), x(s-\tau, t, p), p) ds,
\]

respectively. Thus, it follows that for \( t \in (t_{i-1}, t_i], i \in \Lambda \),

\[
\begin{aligned}
    \psi(t, \tau, p) &= \frac{d}{de} x(t, \tau + \epsilon, p) \bigg|_{e=0} = \frac{\partial x(t, \tau, p)}{\partial \tau} \bigg|_{i-1 = 0} + \sum_{j=1}^{i-1} \int_{t_j}^{t} \left( \frac{\partial f^i(s, x(s, \tau, p), x(s-\tau, t, p), p)}{\partial (s-\tau)} \psi(s-\tau, t, p) \right) ds \\
    &\quad + \int_{t_{i-1}}^{t} \left( \frac{\partial f^i(s, x(s, \tau, p), x(s-\tau, t, p), p)}{\partial (s-\tau)} \psi(s-\tau, t, p) \right) ds + \int_{t_0}^{t} \left( \frac{\partial f^i(s, x(s, \tau, p), x(s-\tau, t, p), p)}{\partial (s-\tau)} \psi(s-\tau, t, p) \right) ds + \int_{t_{i-1}}^{t} \left( \frac{\partial f^i(s, x(s, \tau + \epsilon, p), x(s-\tau, t, p), p)}{\partial (s-\tau)} \psi(s-\tau, t, p) \right) ds.
\end{aligned}
\]

Furthermore, since the state vector \( x \) is continuous on \([-\tilde{\tau}, T] \) and the switching instant \( t_{i-1}, i \in \Lambda \), is independent of the choice of the time-delay \( \tau \), we have

\[
\psi(t_{i-1}+) = \psi(t_{i-1}).
\]

It is also clear that for \( t \in [-\tilde{\tau}, 0] \),

\[
\psi(t, \tau, p) := \frac{d}{de} x(t, \tau + \epsilon, p) \bigg|_{e=0} = 0.
\]

Obviously, (27) and (28) in conjunction with (29) is the solution of time-delay system (23) and (24). Thereby completing the proof. \( \square \)

The next theorem give the sensitivity function \( S_p(\cdot) \) in terms of the solution of another auxiliary time-delay system.

**Theorem 6.** For each \( t \in (0, T] \) \( \text{and} \ \tau \in T \),

\[
S_p(t) = \phi(t, \tau, p), \ p \in \mathcal{P},
\]

where \( \phi(\cdot, \tau, p) \) is the solution of the following auxiliary delay-differential system

\[
\begin{aligned}
    \dot{\phi}(t) &= \frac{\partial f_i(t,x(t),x(t-\tau(t),p))}{\partial t} \phi(t) + \frac{\partial f_i(t,x(t),x(t-\tau(t),p))}{\partial x} \times \phi(t-\tau) - \frac{\partial f_i(t,x(t),x(t-\tau(t),p))}{\partial p} \chi(t-\tau), \quad \forall \ t \in (t_{i-1}, t_i], \\
    \phi(t_{i-1}+) &= \phi(t_{i-1}), \quad i \in \Lambda,
\end{aligned}
\]

with

\[
\phi(t) = 0, \quad t \in [-\tilde{\tau}, 0].
\]

**Proof.** The proof is similar to the proof that given for **Theorem 5**. \( \square \)

For comparison, the relative sensitivity functions will be used in the numerical simulations because they are non-dimensional and allow for comparing the results for different parameters and states. These functions are defined as
\[ S'_i(t) := \frac{\tau}{x_i(t; \tau, p)} S_i(t), \]  
\[ (33) \]
and
\[ S'_{pl}(t) := \frac{p_l}{x_i(t; \tau, p)} S'_{pl}(t), \]
\[ l = 1, 2, \ldots, 18, \quad \ell = 1, 2, \ldots, 5, \quad t \in [0, T], \]  
\[ (34) \]
respectively. However, for values of \( x_i(t; \tau, p) \) close to zero, a very large relative sensitivity may be obtained due to the division by \( x_i(t; \tau, p) \). Therefore, in the current work, the relative sensitivity values were set to zero for all state values below 0.001.

The relative sensitivity functions (33) and (34) can in principle be obtained by Theorems 5 and 6, respectively. It should, however, be noted that the involving time-delay systems are highly nonlinear. Therefore, it is impossible to obtain analytical solutions of the above systems and one has to resort to numerical simulations.

### 3.2. Numerical simulation results

The parametric sensitivity analysis for concentrations of biomass, glycerol, 1,3-PD, acetic acid and ethanol with respect to time-delay and kinetic parameters is investigated. The solution of the system (1) as well as the sensitivity functions in Theorems 5 and 6 were solved numerically using Matlab 7.10.0 (The Mathworks Inc.) and the intrinsic delay-differential equations (DDEs) with constant delays solver DDE23 which solved DDEs using explicit Runge–Kutta triples [37]. In particular, the relative error tolerance and the absolute error tolerance were set as \( 10^{-8} \) and \( 10^{-8} \), respectively. The cubic spline interpolation method [38] was adopted to construct the fitting curves before zero time point such that they pass through all the experimental data. The parameters needed in computing the solution to the system (1) are listed in Table 1. The feeding process began at \( t_1 = 5.33 \) h. The start of feeding moment \( t_{s1} \), the stop of feeding moment \( t_{s2} \), \( j \in \Lambda_3 := \{0, 1, \ldots, 782\} \), were determined by the experiment. In the computational process, the fermentation process was partitioned into the first batch phase (Bat.Ph.) and phases I-XI (Phs.I-XI) according to the actual experiment. In each one of Phs.I-XI, the same feeding strategy was applied. The feeding rates of glycerol in Phs.I-XI are listed in Table 2. The value \( p = (0.876, 0.28, 0.5953, 4.9029, 0.97, 128.205, 67.69, 33.07, 8.7388, 11.89089, 5.74, 17.7296, 15.50, 85.71, 0.025, 0.06, 5.18, 50.45) \) for the kinetic parameter vector were taken as the initial values of time delay and the kinetic parameters. These values are obtained from previous investigations [1, 27]. The durations of the feeding processes in Phs.I-XI were 5, 7, 8, 7, 6, 4, 3, 2, 1, 2 and 1 s in each 100 s, leaving 95, 93, 92, 93, 96, 97, 98, 99, 98 and 99 s for batch cultures, respectively. It should be mentioned that this approach had been adopted to obtain the experimental data and to identify the parameters of nonlinear multistage system in [27]. Furthermore, by (33) and (34), the relative sensitivity functions \( S'_i(t) \) and \( S'_{pl}(t) \), \( l = 1, 2, \ldots, 18, \quad \ell = 1, 2, \ldots, 5, \) were also computed. For comparison, the relative sensitivities are plotted against time. Figs. 1–5 show the relative sensitivity curves for the concentrations of biomass, glycerol, 1,3-PD, acetic acid and ethanol, respectively. It can be observed from Figs. 1–5 that some curves among the 19 ones stay near zero, that is, the effect of these parameters on the concentration changes can be assumed to be very dimutive, and these parameters can thus be concluded to have low sensitivities. In detail, we assume that if the maximal absolute value of specific sensitivity curve is less than 0.3, the parameter has low sensitivity. Table 3 lists the parameters of high sensitivity for space-convenience. The check marks in Table 3 imply high sensitivities of parameters to certain \( x \) component.

Let the parameters that have high sensitivities in at least one of Figs. 1–5 be key parameters. Specifically, they are \( \tau, \Lambda_1, m_3, m_3, Y_3, Y_3, \Lambda_2, \Lambda_1, c_3, c_4 \) and \( c_4 \). For low sensitivity parameters, substituting values in [27] should be adequate. More correct and reliable values are necessary only for high sensitivity parameters. As a result, the key parameters to be identified are simplified to time-delay \( \tau \) and \( p = (\Lambda_1, m_3, m_3, Y_3, Y_3, \Lambda_2, \Lambda_1, c_3, c_4) \). Notice that the number of parameters to be identified reduces to 10 from the original 19.

### 4. Parameter identification problems

The parameter identification problem for a time-delay system is generally to adjust values of time-delay and the parameters so that the discrepancy between predicted and observed system output is as small as possible. A parameter identifi-
cation problem may be resolved by fitting parameterized solutions to experimental data through minimizing a least squares objective function. In this section, the key parameters obtained in the previous section will be taken as the parameters to be identified and the other parameters in \( p \) are regarded as constants whose values take from [27].

### Table 2
The feeding rates of glycerol in Phs.I-XI.

<table>
<thead>
<tr>
<th>Phases</th>
<th>I-II, IV-V</th>
<th>III</th>
<th>VI</th>
<th>VII</th>
<th>VIII-XI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding rates [mLs(^{-1})]</td>
<td>0.2103</td>
<td>0.1992</td>
<td>0.2214</td>
<td>0.24365</td>
<td>0.2548</td>
</tr>
</tbody>
</table>

### Table 3
The key parameters in the system (1).

<table>
<thead>
<tr>
<th>( x_1 )</th>
<th>( x_2 )</th>
<th>( x_3 )</th>
<th>( x_4 )</th>
<th>( x_5 )</th>
<th>( \tau )</th>
<th>( \Delta_1 )</th>
<th>( m_2 )</th>
<th>( m_3 )</th>
<th>( Y_2 )</th>
<th>( Y_3 )</th>
<th>( \Delta_2 )</th>
<th>( \Delta_3 )</th>
<th>( c_3 )</th>
<th>( c_4 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>√</td>
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<td>√</td>
</tr>
</tbody>
</table>

### Fig. 1
The relative sensitivities of biomass concentration with respect to delay and kinetic parameters.

### Fig. 2
The relative sensitivities of glycerol concentration with respect to delay and kinetic parameters.
4.1. Parameter identification models

In the fed-batch fermentation process, we have measured $n$ experimental data. However, since the byproducts of acetic acid and ethanol can change the pH values, alkali is fed into the fermentor to maintain a suitable environment for cells growth. The measured concentrations of acetic acid and ethanol are inaccurate due to this feed. As a result, the experimental concentrations of biomass, glycerol and 1,3-PD are only used to identify the key parameters. First of all, we denote the concentrations of biomass, glycerol and 1,3-PD measured at the moment $t_ı$ in the experiment by $y_ı^1$, $y_ı^2$ and $y_ı^3$, respectively. Furthermore, let $x(t_ı | τ, p)$ be the solution of the system (1) corresponding to a pair $(τ, p)\in \mathcal{T} \times \mathcal{P}$, where $\mathcal{P}$ is the corresponding range for the key parameter vector $p$ in $\mathcal{P}$. Now, we consider the following cost function
\begin{equation}
J(τ, p) := \sum_{ı=1}^{n} \sum_{i=1}^{3} (x_i(t_ı | τ, p) - y_ı^i)^2,
\end{equation}
(35)
to evaluate the errors between the computational values $x(t_ı | τ, p)$ and the experimental data $y_ı^i$ at the moment $t_ı$.

Given the system (1), our purpose is to find a $(τ, p)\in \mathcal{T} \times \mathcal{P}$ such that the constraint (12) is satisfied and the cost function (35) is minimized. Hence, the parameter identification model can be stated formally as

\begin{align}
&\text{(PIM) } \min_{(τ, p)} J(τ, p) \\
&\text{s.t. } x(t | τ, p) \in W, t \in [0, T], \\
&(τ, p) \in \mathcal{T} \times \mathcal{P}.
\end{align}
The existence of the optimal solution for the parameter identification model (PIM) can be established as follows.

**Theorem 7.** (PIM) has an optimal solution, that is, there exists \((\tau^*, p^*) \in \tau \times \tilde{P}\) such that

\[ J(\tau^*, p^*) \leq J(\tau, p), \quad \forall (\tau, p) \in \tau \times \tilde{P}. \]  

(36)

**Proof.** Define the admissible set of the key parameters as

\[ \mathcal{F} := \{ (\tau, p)|x(\tau, p) \text{ is the solution of the system (1) on } [-\tau, T] \} \]  

and \(x(t|\tau, p) \in W \text{ for } t \in [0, T]\).  

Obviously, \(\mathcal{F}\) is non-empty. Moreover, \(\mathcal{F} \subseteq \tau \times \tilde{P}\) is a bounded set due to the compactness of the set \(\tau \times \tilde{P}\). Then, for any sequence \(((\tau^i, p^i))_{i=1}^\infty \subseteq \mathcal{F}\), there exists at least one subsequence \(((\tau^i, p^i))_{i=1}^\infty \subseteq ((\tau^i, p^i))\) such that \((\tau^i, p^i) \to (\check{\tau}, \check{p})\) as \(i \to \infty\). Now, for each \(i\), suppose \(x(\cdot|\tau^i, p^i)\) is the solution of the system (1) and \(x^i(t|\tau^i, p^i) \in W\) for all \(t \in [0, T]\), then \(x(\cdot|\tau^i, p^i)\) is also a solution of the system (1) and \(x^i(\cdot|\tau^i, p^i) \in W\) in view of Theorem 4 and the compactness of the \(W\). Namely, \((\tau, p) \in \mathcal{F}\), which implies the closeness of the set \(\mathcal{F}\). Furthermore, since the cost function \(J(\tau, p)\) is continuous in \(\tau \times \tilde{P}\), we confirm that (PIM) has an optimal pair \((\tau^*, p^*)\) such that (36) holds. This completes the proof. \(\square\)

### 4.2. A computational procedure

(PIM) is in essence a parameter optimization problem. However, since the constraint (12) in (PIM) is a continuous state inequality constraint, (PIM) can be viewed as a semi-infinite programming problem. An efficient algorithm for solving this type of optimization problems was discussed in [39]. We will briefly discuss the application of this algorithm to (PIM).

To begin with, let

\[
\begin{align*}
g_t(x(t|\tau, p)) &:= x^t - x_t(t|\tau, p), \\
g_{s,\ell}(x(t|\tau, p)) &:= x_{s,\ell}(t|\tau, p) - x_{s,\ell}, \quad \ell = 1, 2, \ldots, 5.
\end{align*}
\]

The condition \(x^t(t|\tau, p) \in W\) is equivalently transcribed into

\[ G(\tau, p) = 0, \]  

where \(G(\tau, p) := \sum_{i=1}^{10} \int_0^T \min\{0, g_i(x(t|\tau, p))\} dt\). However, the equality constraint (38) is non-differentiable at the points where \(g_i = 0\). We replace (38) with

\[ \tilde{G}_{c,\ell}(\tau, p) := \gamma + \sum_{i=1}^{10} \int_0^T \pi_c(g_i(x(s|\tau, p))) ds \geq 0, \]  

(39)

where \(\varepsilon > 0, \gamma > 0\) and

\[ \pi_c(\eta) = \begin{cases} 
\eta, & \text{if } \eta < -\varepsilon, \\
-\frac{\eta^2}{2\varepsilon^2}, & \text{if } -\varepsilon \leq \eta \leq \varepsilon, \\
0, & \text{if } \eta > \varepsilon.
\end{cases} \]  

(40)

\begin{figure}[ht]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{The relative sensitivities of ethanol concentration with respect to delay and kinetic parameters.}
\end{figure}
Thus, (PIM) is approximated by a sequence of nonlinear programming problems (PIM$e,c$) defined by replacing constraint (38) with (39). Clearly, for each $e$ and $\gamma$, (PIM$e,c$) is a mathematical programming in canonical form.

The next theorem shows that for any $e > 0$, if $\gamma$ is chosen sufficiently small, the solution of the corresponding problem (PIM$e,c$) will satisfy the continuous state inequality constraint (12).

**Theorem 8.** For each $e > 0$, there exists a $\gamma(e) > 0$ such that if (39) with $\gamma < \gamma(e)$ is satisfied for some $(\tau, \bar{p}) \in \mathcal{T} \times \mathcal{P}$, then the original constraint (12) is also satisfied at $(\tau, \bar{p}) \in \mathcal{T} \times \mathcal{P}$.

The proof of Theorem 8 can be found in Chapter 8 of [39]. On the basis of this theorem, (PIM) can be solved through solving a sequence of problems ((PIM$e,c$)). In the computational process, the gradients of constraint $G_{e,c}(\tau, \bar{p})$ with respect to each key parameter are needed. However, the traditional methods for computing the gradient of the constraint $G_{e,c}(\tau, \bar{p})$ involve integrating two systems of differential equations—the state system and the costate system—successively in different directions, which is difficult to implement in computational process [39]. In contrast, we will develop a new scheme for computing these gradients of the constraint $G_{e,c}(\tau, \bar{p})$ on the basis of Theorems 5 and 6.

**Theorem 9.** For each $e > 0$ and $\gamma > 0$, the gradient of the constraint $G_{e,c}(\tau, \bar{p})$ defined in (39) with respect $\tau$ is

$$
\frac{\partial G_{e,c}(\tau, \bar{p})}{\partial \tau} = \sum_{i=1}^{10} \int_{0}^{T} \frac{\partial \tau_{i}(x(t, \tau, \bar{p}))}{\partial g_{i}} \frac{\partial g_{i}(x(t, \tau, \bar{p}))}{\partial x} \zeta(t) dt,
$$

where $\zeta(\tau)$ is the solution of the following time-delay system

$$
\begin{cases}
\dot{\zeta}(t) = \frac{\partial f^{g}(x(t, \tau, \bar{p}), x(t-\tau, \bar{p}))}{\partial x} \dot{\zeta}(t) + \frac{\partial f^{g}(x(t, \tau, \bar{p}), x(t-\tau, \bar{p}))}{\partial x} \zeta(t-\tau) - \frac{\partial f^{g}(x(t, \tau, \bar{p}), x(t-\tau, \bar{p}))}{\partial x} \zeta(t-\tau), & \forall t \in (t_{i-1}, t_{i}],
\end{cases}
$$

with $\zeta(t) = 0, \quad t \in [-1, 0]$.

**Theorem 10.** For each $e > 0$ and $\gamma > 0$, the gradient of the constraint $G_{e,c}(\tau, \bar{p})$ defined in (39) with respect $\bar{p}$ is

$$
\frac{\partial G_{e,c}(\tau, \bar{p})}{\partial \bar{p}} = \sum_{i=1}^{10} \int_{0}^{T} \frac{\partial \tau_{i}(x(t, \tau, \bar{p}))}{\partial g_{i}} \frac{\partial g_{i}(x(t, \tau, \bar{p}))}{\partial x} \zeta(t) dt,
$$

where $\zeta(\tau)$ is the solution of the following time-delay system

$$
\begin{cases}
\dot{\zeta}(t) = \frac{\partial f^{g}(x(t, \tau, \bar{p}), x(t-\tau, \bar{p}))}{\partial x} \dot{\zeta}(t) + \frac{\partial f^{g}(x(t, \tau, \bar{p}), x(t-\tau, \bar{p}))}{\partial x} \zeta(t-\tau) + \frac{\partial f^{g}(x(t, \tau, \bar{p}), x(t-\tau, \bar{p}))}{\partial \bar{p}}, & \forall t \in (t_{i-1}, t_{i}],
\end{cases}
$$

with $\zeta(t) = 0, \quad t \in [-1, 0]$.

Now, each of problems ((PIM$e,c$)) can be solved by gradient-based optimization methods [39]. Nevertheless, all those techniques are only designed to find local optimal solutions. The need of global optimization techniques to avoid the spurious solutions often found by traditional gradient-based local methods had been highlighted in [28,40,41]. An improved Particle Swarm Optimization (PSO) algorithm was developed to solve the optimal control problems with control and state constraints and its effectiveness was demonstrated in [11]. Therefore, we will solve each problem (PIM$e,c$) using the improved PSO algorithm [11]. As a result, we may recall some improved strategies added to the original PSO proposed in [42]. To overcome local convergence, a new updating strategy about velocity and position and a craziness operator are introduced. A reflection strategy is also introduced to handle the bounds of the identified parameters. The state constraints are very difficult to handle. By a way, although there exist many constraint handling techniques in the evolutionary computation [43,44], the treatment of continuous state constraints is rarely considered. Basing on Theorems 9 and 10, we present a handling technique for this type of constraints in the sequel. Consider $N$ particles in the evolutionary process, the position and velocity of the ith particle can be represented by $\sigma_i = (\tau_i, p_{i1}, \ldots, p_{iN})^T$ and $\nu_i = (v_{i1}, v_{i2}, \ldots, v_{iN})^T$, respectively. Furthermore, denote the lower bound and upper bound of the position by $\sigma_{low}$ and $\sigma_{upp}$ obtained by (14) and (15), respectively. At the $(k + 1)$th iteration, the improved evolutionary strategies of the particle $i$ are as follows.

1. **Updating strategy** In the former stage of iterations, velocity and position are updated by the following modifications to balance exploration and exploitation

   $$
   \begin{align*}
   \nu_{ij}(k + 1) &= r_{ij}^{\phi} \nu_{ij}(k) + c_1 r_{ij}^{\phi} (p_{ij} - \sigma_{ij}(k)) + c_2 r_{ij}^{\phi} (g_{ij} - \sigma_{ij}(k)), \\
   \sigma_{ij}(k + 1) &= r_{ij}^{\phi} \sigma_{ij}(k) + (1 - r_{ij}^{\phi}) \nu_{ij}(k + 1),
   \end{align*}
   $$

   with $r_{ij}^{\phi}$ being a random number in $[0, 1]$. Here, $c_1$ and $c_2$ are called the learning factors, $r_{ij}^{\phi}$ is a random factor, and $\sigma_{ij}$ and $\nu_{ij}$ are the position and velocity of the ith particle, respectively.
where \( p_i = (p_{i1}, p_{i2}, \ldots, p_{i10})^T \) is the best position that particle \( i \) has ever found, \( gb = (gb_1, gb_2, \ldots, gb_{10})^T \) is the best position that the group has ever found, \( c_1^p \) and \( c_2^p \) are two positive constants, \( r_1^g, r_2^g, r_3^g \) and \( r_4^g \) are random parameters chosen uniformly from \([0, 1]\).

(2) (Craziness operator) To keep the diversity of particles, when the number of iterations is larger than \( M^p_i \), the velocity of the \( i \)th particle is adjusted as

\[
\nu_{ij}(k+1) = \begin{cases} 
\nu_{ij}(k), & \text{if } r_5 \leq P_{cr} \\
2\text{Rand}_i(r_5) - 1, & \text{otherwise}
\end{cases}
\]

(47)

where \( r_5 \) is a random number taken uniformly from \([0, 1]\). \( \text{Rand}_i(r) \) is a function used to randomly generate the \( j \)th component of the velocity of the \( i \)th particle, \( P_{cr} \) is a predefined probability.

(3) (Dealing with parameter bounds) At the \((k+1)\)th step, assume that the \( j \)th component of position of the \( i \)th particle violates parameter bound constraint, then it is reflected back from the bound by the amount of violation

\[
\sigma_{ij}(k+1) = \begin{cases} 
2\sigma_{\text{low},j} - \sigma_{ij}(k+1), & \text{if } \sigma_{ij}(k+1) < \sigma_{\text{low},j} \\
2\sigma_{\text{upp},j} - \sigma_{ij}(k+1), & \text{if } \sigma_{ij}(k+1) > \sigma_{\text{upp},j}
\end{cases}
\]

(48)

(4) (Dealing with state constraints) For the position of the \( i \)th particle at the \((k+1)\)th step, test the value of \( G(\sigma_i(k+1)) \). If \( G(\sigma_i(k+1)) = 0 \), then the position is feasible. Otherwise, that is, \( G(\sigma_i(k+1)) > 0 \), move the position towards the feasible region in the direction of \(-\frac{\Delta(x_i(k+1))}{\|\Delta(x_i(k+1))\|}\) with Armijo line search.

(5) (Stopping criterions) The algorithm stops when any of the following conditions holds:

- the maximal iteration \( M^p \) is reached;
- the maximal deviation between the group's best fitness values in the last \( M^p_i \) iterations is less than \( \varepsilon^p \), where \( \varepsilon^p \) is a predefined constant.

On the basis of Theorems 8–10 and the above improved PSO, the following algorithm to solve the (PIM) can be developed.

**Algorithm 4.1.**

Step 1. Set \( \varepsilon > 0, \gamma > 0, \beta_1 > 0, \beta_2 > 0, \bar{\epsilon} > 0 \) and \( \bar{\gamma} > 0 \).
Step 2. Solve (PIM) using the improved PSO algorithm to give \((\tau_{i,j}^*, p_{i,j}^*)\).
Step 3. Check feasibility of \( g_{j}(x(t)|\tau_{i,j}^*, p_{i,j}^*) \geq 0 \) for \( t \in [0, T] \) and \( i = 1, 2, \ldots, 10 \).
Step 4. If \((\tau_{i,j}^*, p_{i,j}^*)\) is feasible, go to Step 5. Otherwise, set \( \gamma = \beta_1 \gamma \). If \( \gamma < \bar{\gamma} \), go to Step 6. Else go to Step 2.
Step 5. Set \( \bar{\epsilon} = \beta_2 \bar{\epsilon} \). If \( \bar{\epsilon} \geq \bar{\gamma} \), go to Step 3. Else go to Step 6.
Step 6. Output \((\tau_{i,j}^*, p_{i,j}^*)\) and stop.

**Remark 2.** In the algorithm, \( \bar{\epsilon} \) is a parameter controlling the accuracy of the smoothing approximation. \( \gamma \) is a parameter controlling the feasibility of the constraint (12). \( \bar{\epsilon} \) and \( \gamma \) are two predefined parameters ensuring the termination of the algorithm.

**Remark 3.** It is important for the validity of the above algorithm to choose the parameters \( \beta_1, \beta_2, \bar{\epsilon} \) and \( \bar{\gamma} \). Especially, the parameters \( \beta_1 \) and \( \beta_2 \) must be chosen less than 1. \( \bar{\epsilon} \) and \( \bar{\gamma} \) are two sufficient small values such that the algorithm can be terminated.

### 4.3. Numerical results

In the numerical computation, the medium composition cultivation conditions, determinations of biomass, substrate and metabolites have been reported [45]. Algorithm 4.1 was applied to seeking the optimal key parameters in (PIM) and all computations were implemented in Matlab 7.10.0. Here, the establishment of the initial function \( \phi(t) \), the parameters needed in solving the system (1) and the feeding rate of glycerol were the same as the ones used in Section 3.2. The start and stop moments of glycerol and alkali adding were determined by the experiment. The lower bounds and the upper bounds of the key parameter \( p \) were \( \bar{p}_x = (0.438, 0.5, 2.45145, 0.0039, 33.845, 5.945445, 8.8648, 2.59, 25.225)^T \) and \( p^* = (1.314, 3.3, 7.35435, 0.0117, 101.535, 17.836335, 26.5944, 7.77, 75.675)^T \), respectively [13,22,27]. In addition, the smoothing and feasible parameters were initially selected as \( \bar{\epsilon} = 0.1 \) and \( \gamma = 0.01 \). The parameters \( \beta_1 \) and \( \beta_2 \) were chosen as 0.1 and 0.01 until the solution obtained was feasible for the original problem. The process terminated when \( \bar{\epsilon} = 1.0 \times 10^{-8} \) and \( \gamma = 1.0 \times 10^{-7} \). In the improved PSO algorithm, the number of initial particles swarm \( N^p \), the maximal iteration \( M^p \), and the parameters \( c_1^p, c_2^p, P_{cr}, M^p_1 \) and \( \varepsilon^p \) were, respectively, 50, 200, 2, 2, 0.5, 100, 20, and \( 10^{-4} \). These parameters are derived empirically after numerous experiments.

By applying **Algorithm 4.1**, we obtained the optimal key parameter \( \tau^* = 0.4652h \) and \( p^* = (0.8, 1.927, 3.2819, 0.0063, 80.6096, 6.8489, 10.3687, 2.81, 65.5226)^T \). In particular, strategy of dealing with state constraints by Theorem 9
Table 4
The relative errors between the computational values and the experimental data.

<table>
<thead>
<tr>
<th></th>
<th>(e_1(%))</th>
<th>(e_2(%))</th>
<th>(e_3(%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonlinear time-delay system</td>
<td>3.989</td>
<td>5.531</td>
<td>4.03</td>
</tr>
<tr>
<td>Nonlinear multistage system [27]</td>
<td>7.46</td>
<td>11.46</td>
<td>5.35</td>
</tr>
</tbody>
</table>

Fig. 6. The concentration changes of biomass with respect to fermentation time.

Fig. 7. The concentration changes of glycerol with respect to fermentation time.

Fig. 8. The concentration changes of 1,3-PD with respect to fermentation time.
was performed for eight times in the computation process. The performance of the system (1) is compared with that of the nonlinear multistage system which is an ordinary differential equation model in [27]. The relative errors $e_{i}, i = 1, 2, 3$, between the computational values and the experimental data for the two models were listed in Table 4. The relative errors are defined as

$$e_{i} = \frac{\sum_{j=1}^{n}|y_{ij} - z_{ij}|}{\sum_{j=1}^{n}z_{ij}},$$

where $y_{ij}$ is the $i$th component of the solution to the system (1) under the optimal key parameters. From Table 4, we conclude that the relative errors are decreased compared with the ones in the nonlinear multistage system [27]. In particular, the concentration changes of biomass, glycerol and 1,3-PD with respect to the optimal key parameters for the system (1) were respectively shown in Figs. 6–8. The simulation for the nonlinear multistage system in [27] and the experimental data were also presented in these figures for comparison. As a result, the system (1) fits the experimental data better than the one previously reported.

Furthermore, under the optimal key parameters $\tau^{*}$ and $\rho^{*}$, we recalculated the system (1) and obtained the predictive concentrations of biomass, glycerol, 1,3-PD, acetic acid and ethanol at time 27.83 h which are 4.533 g L$^{-1}$, 174.79 mmoll$^{-1}$, 1011.86 mmolL$^{-1}$, 203.65 mmoll$^{-1}$ and 195.58 mmoll$^{-1}$, respectively. In comparison with the experimental concentrations of biomass, glycerol, 1,3-PD, acetic acid and ethanol, i.e., 4.38 g L$^{-1}$, 186.85 mmolL$^{-1}$, 1035.0 mmoll$^{-1}$, 182.5 mmoll$^{-1}$ and 174.35 mmoll$^{-1}$, we can see that the predictive concentrations of biomass, glycerol and 1,3-PD can well consistent with the experimental data. Nevertheless, the predictive concentrations of acetic acid and ethanol deviate from the experimental data about 11.59% and 12.18%, respectively. The reasons why the deviations occurred might be that the experimental concentrations of acetic acid and ethanol were not incorporated in the parameter identification problem. This also verified the inaccuracies of the experimental concentrations of acetic acid and ethanol due to the feed of the alkali.

In all, from the numerical results, we can see that the proposed system introducing the time-delay in modeling the fed-batch fermentation process is reasonable.

5. Conclusion

A nonlinear time-delay system was proposed to describe the fed-batch fermentation process. To determine the time-delay effect and decrease the number of the kinetic parameters, the parametric sensitivity analysis was investigated. On this basis, a parameter identification model was presented and a computational procedure was developed to seek the optimal key parameters. Numerical results verified the validity of the mathematical model and the effectiveness of the computational method.

Acknowledgments

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