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An Improved Nonlinear Multistage Switch System of Microbial Fermentation Process in Fed-Batch Culture*

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Abstract This paper considers the fed-batch culture in microbial fermentation process, which consists of batch and continuous culture. The goal is to explore the properties of a novel model which can describe the characteristics of multistage for the population growth of microorganisms in nonlinear switch dynamic system. The improved model is developed based on the experimental data to describe the delayed, developmental and stationary stages well for the phases of batch culture. Then the existence, uniqueness and boundedness of solutions to the nonlinear multistage switch system and the Lipschitz continuity and differentiability of solutions with respect to the initial state is discussed as well. Finally, a numerical simulation is employed for the nonlinear multistage switch system.

Keywords Bioconversion, fed-batch culture, Klebsiella pneumoniae, nonlinear multistage switch system.

1 Introduction

1,3-propanediol (1,3-PD) is an important chemical raw material that can be used as a monomer to synthesize polyesters and polyurethanes. Microbial fermentation has provided a new perspective to produce bulk chemicals such as 1,3-PD. Due to the advantages of relative mild conditions, environmentally friendly use, ease of operation and use of renewable resources, microbial fermentation of 1,3-PD has received considerable attention[1, 2]. The experimental investigations showed that the fermentation of glycerol by Klebsiella pneumoniae is a complex bioprocess, since the microbial growth is subjected to multiple inhibitions of substrate and products, such as glycerol, 1,3-PD, acetate and ethanol[3]. There are three common methods of microbial fermentation: batch culture, continuous culture, and fed-batch culture. In batch culture, the bacteria and substrate are added into the bioreactor. Then, bacteria grows under

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proper conditions (temperature, pH, etc.) as the time goes on and the substrate is consumed simultaneously. Typically, the growth of the bacteria includes three phases, i.e., lag, exponential, stationary phases. The batch fermentation is stopped when the source is sufficiently consumed and the product is collected. In continuous culture, the fresh medium flows into the fermentor continuously, and part of the medium in the reactor is withdrawn from the fermenter at the same flow rate of the inlet flow. Fed-batch culture is a production technique between batch and continuous fermentation and is so called as a semi-continuous system with relative operational simplicity and superior industrial feasibility.

In recent years, nonlinear impulsive, switch and hybrid dynamic systems were respectively proposed for describing the fed-batch culture[4–7]. The researches about the fermentation include the quantitative description of the cell growth kinetics under multiple inhibitions, the metabolic overflow kinetics of substrate consumption and product formation as well as the optimal control of feeding strategy of glycerol in fed-batch culture[8–12]. However, the previous theoretical work was based on Monod kinetics and some of its modifications, which can only be used under very restrictive conditions such as a steady state chemostat[13–15]. Modeling and simulation of microbial cell growth is important both theoretically and practically. Although the Monod model has been the most widely used for the prediction of cell growth, it only fits the exponential growth phase of the growth, without any inhibition[16]. Since the fed-batch culture of glycerol bioconversion to 1,3-PD begins with batch culture and this process will be repeated several times. Therefore, it is a vital factor to describe the characteristics of multistage for the population growth of microorganisms. In view of the errors between observations and numerical simulation results, the author proposed a two-stage dynamic system to formulate the fermentation process in batch culture[17]. Then, they establish a parameter identification model to identify parameters in the system. Numerical results show that the two-stage system can describe the factual fermentation better. So, in this paper, based on the idea of [17], we propose a novel model to describe the batch culture phases in the fed-batch fermentation process. Subsequently, we do some theoretical and numerical analysis to guide the practice.

The rest of the paper is organized as follows. In Section 2, a nonlinear multistage switch dynamic system of fed-batch culture is proposed. The existence, uniqueness, boundedness and regularity of solutions to the nonlinear multistage switch system are proved in Section 3. In Section 4, we present a numerical example to show that the errors can be decreased by using nonlinear multistage switch dynamic system. Discussions and conclusions are present in the Section 5.

2 Nonlinear Multistage Switch Dynamic System

In view of the mechanism of bio-dissimilation of glycerol to 1,3-PD, the following assumptions are hold.

A1 The concentrations of reactants are uniform in reactor, while time delay and non-uniform space distribution are ignored; and

A2 During the process of fed-batch culture, the substrates added to the reactor only include glycerol and alkali; and

A3 The feed rate of glycerol and speed of adding alkali are uniform at various time intervals.

The fed-batch culture of glycerol bioconversion to 1,3-PD begins with batch fermentation, then glycerol and alkali are discontinuously added to the reactor in order to keep the concentration of glycerol and pH value in a given range. Therefore, under the assumptions (A1)–(A3), the whole fermentation process includes batch culture in the early stage and later fed-batch culture. Mass balances of biomass, substrate and products in fed-batch cultures are written as follows[17]:

$$\begin{cases} \left.\begin{aligned} &\dot{x}_1(t) = \mu x_1(t), \\ &\dot{x}_2(t) = -q_2 x_1(t), \\ &\dot{x}_i(t) = q_i x_1(t), \qquad i = 3,4,5, \end{aligned}\right\} := f^1(x(t),u(t)), \qquad t \in [0, t_g), \\ \left.\begin{aligned} &\dot{x}_1(t) = \mu \mathrm{e}^{-a_1(t-t_g)} x_1(t), \\ &\dot{x}_2(t) = -q_2 \mathrm{e}^{-a_2(t-t_g)} x_1(t), \\ &\dot{x}_i(t) = q_i \mathrm{e}^{-a_i(t-t_g)} x_1(t), \qquad i = 3,4,5, \end{aligned}\right\} := f^2(x(t),u(t)), \qquad t \in [t_g, t_f], \end{cases}$$

$$x_i(0) = x_{0i}, \quad x_i(t_g^+) = x_i(t_g), \quad i = 1,2,3,4,5,$$

where $x_1(t)$, $x_2(t)$, $x_3(t)$, $x_4(t)$ and $x_5(t)$ are biomass, glycerol, 1,3-PD, acetate and ethanol concentrations at time t in the reactor, respectively; $t_g \in (0, t_f)$ is the moment after which the system reaches the stationary phase; $x_i(t_g^+)$, $i = 1,2,3,4,5$, denote the right limit of concentrations of the corresponding reactants at time t_g; $[0, t_g)$ is the time interval of developmental and growth periods and $[t_g, t_f]$ is the one of stationary phases; a_i, $i = 1,2,3,4,5$, are the stationary factors. The values of t_g and a_i, $i = 1,2,3,4,5$, are given as follows[17].

$$t_g = 4.33, \quad a_1 = 1.804, \quad a_2 = 0.23, \quad a_3 = 0.551, \quad a_4 = 0.12, \quad a_5 = 0.$$

For the batch culture, the specific growth rate of cells μ, specific consumption rate of substrate q_2 and specific formation rate of products q_i, $i = 3,4,5$, are expressed by the following equations on the basis of [17].

$$\mu = \mu_m \left(\frac{x_2(t)}{x_2(t) + k_s} \right) \prod_{i=2}^{5} \left(1 - \frac{x_i(t)}{x_i^*} \right)^{n_i}, \tag{1}$$

$$q_2 = m_2 + \frac{\mu}{Y_2}, \tag{2}$$

$$q_i = m_i + \mu Y_i, \quad i = 3,4,5. \tag{3}$$

In the feeding stage of fed-batch culture, glycerol and alkali are continuously added at constant flow rates, which can be described by the dynamic system of continuous culture. Mass

balances of biomass, substrate and products in continuous culture are given below[18].

$$\begin{cases} \dot{x}_1(t) = (\mu - D)x_1(t), \\ \dot{x}_2(t) = D(C_{s0} - x_2(t)) - q_2 x_1(t), \qquad t \in I_c, \\ \dot{x}_i(t) = q_i x_1(t) - D x_i(t), \quad i = 3, 4, 5, \end{cases} \tag{4}$$

where D is referred to the dilution rate and C_{s0} is the initial glycerol concentration in feed. I_c denotes the time interval of the continuous culture.

For the continuous culture, the specific growth rate of cells μ, specific consumption rate of substrate q_2 and specific formation rate of products q_i, $i = 3, 4, 5$, are expressed by the following equations[4, 5].

$$\mu = \mu_m \left(\frac{x_2(t)}{x_2(t) + k_s} \right) \prod_{i=2}^{5} \left(1 - \frac{x_i(t)}{x_i^*} \right), \tag{5}$$

$$q_2 = m_2 + \frac{\mu}{Y_2} + \Delta_2 \frac{x_2(t)}{x_2(t) + k_2}, \tag{6}$$

$$q_i = m_i + \mu Y_i + \Delta_2 \frac{x_2(t)}{x_2(t) + k_i}, \quad i = 3, 4, \tag{7}$$

$$q_5 = q_2 \left(\frac{b_1}{c_1 + \mu x_2(t)} + \frac{b_2}{c_2 + \mu x_2(t)} \right). \tag{8}$$

Under anaerobic conditions at 37°C and pH=7.0, the maximum specific growth rate of cells $\mu_m = 0.67\text{h}^{-1}$, and Monod saturation constant $k_s = 0.28$mmol/L. The critical concentrations of biomass, glycerol, 1,3-PD, acetate and ethanol for cell growth are $x_1^* = 10$g/L, $x_2^* = 2039$mmol/L, $x_3^* = 939.5$mmol/L, $x_4^* = 1026$mmol/L and $x_5^* = 360.9$mmol/L, respectively. b_1, b_2, c_1, c_2, m_i, Y_i, Δ_i, k_i, $i = 2, 3, 4$, are parameters given in [2, 4, 5]. Since the concentrations of biomass, glycerol and products are restricted in a certain range according to the practical production, we consider the properties of the system on a subset of $\mathbb{R}^5$, $W := \{x \in \mathbb{R}^5 \mid x_1 \in [0.001, x_1^*], x_2 \in [100, x_2^*], x_3 \in [0, x_3^*], x_4 \in [0, x_4^*], x_5 \in [0, x_5^*]\}$.

Under the assumptions (A1)–(A3), the continuous process of adding glycerol and alkali is embedded into the dynamic system of continuous culture and hence the multistage switch system of fed-batch culture can be obtained. Let $x(t) := (x_1(t), x_2(t), x_3(t), x_4(t), x_5(t))^{\mathrm{T}} \in \mathbb{R}^5$ be the state variable; $\xi := (x_{01}, x_{02}, x_{03}, x_{04}, x_{05})^{\mathrm{T}}$ denote the initial state vector; $I := [0, T]$ be the time interval of the whole fermentation process; t_i is the moment of starting the glycerol flow, at which the fermentation process switches to continuous culture from batch culture; t_i' denotes the moment of ending the flow of glycerol from the beginning of time t_i, at which the fermentation process switches into batch culture from continuous culture, and $0 = t_0' < t_1 < t_1' < \cdots < t_n' < t_{n+1} = T, i \in \Lambda_n := \{1, 2, \cdots, n\}$. Let $I_i := [t_{i-1}, t_i']$ be the time interval of batch culture, for the batch culture, based on the analysis in [17], we need to separate I_i into two sub-intervals to describe the different stages of batch culture.

$$I_i = [t_{i-1}, t_i'] := [t_{i-1}, t_{i-1}^g] \cup [t_{i-1}^g, t_i']. \tag{9}$$

$I_i' := [t_i, t_i']$ be the time interval of continuous culture, $i \in \Lambda_n$. Thus, based on System (1), the fed-batch culture can be formulated as the following nonlinear multistage switch system

$$\dot{x}(t) = f(x(t), u(t)), \qquad t \in I, \tag{10}$$

$$x(0) = \xi, \tag{11}$$

where, for each $i \in \Lambda_n$,

$$f(x(t), u(t)) := \begin{cases} f^1(x(t), u(t)), & t \in [t_{i-1}, t_{i-1}^g], \\ f^2(x(t), u(t)), & t \in [t_{i-1}^g, t_i'], \\ f^3(x(t), u(t)), & t \in I_i. \end{cases} \tag{12}$$

where

$$\begin{aligned} f^3(x(t), u(t)) : = \big[&(\mu - u(t))x_1(t), u(t)(x_{20} - x_2(t)) - q_2 x_1(t), q_3 x_1(t) - u(t)x_3(t), \\ &q_4 x_1(t) - u(t)x_4(t), q_5 x_1(t) - u(t)x_5(t)\big]^{\mathrm{T}} \in \mathbb{R}^5, \end{aligned} \tag{13}$$

$$u(t) := \begin{cases} \dfrac{(\rho v_i + u_i)(t - t_i)}{\sum_{j=1}^{i-1} \rho(F_j + v_j) + (\rho v_i + u_i)(t - t_i) + \rho V_0}, & t \in I_i', \\ 0 & t \in I_i. \end{cases}$$

Here u_i(g/s) and v_i(ml/s) are flow rates of adding glycerol and alkali in I_i', respectively. F_j and V_j are the volumes of glycerol and alkali added at t_j before t_i, respectively, $i \in \Lambda_n$. V_0 is the initial volume of fermentation broth and ρ is the density of glycerol in feed. $u(t) \in U \subset L_2[0, T]$ is the dilution rate. The $L_2[0, T]$ norm $\|u\|_2$ is defined by $\|u\|_2 = \sqrt{\langle u, u\rangle_2}$ and the inner product $\langle u, v\rangle_2$ is defined as $\langle u, v\rangle_2 \triangleq \int_0^T u(t)v(t)dt$.

3 Existence, Uniqueness, Boundedness and Regularity Properties

In this section, we study the existence, uniqueness and boundedness of solutions to system (10)–(11). Here, we will denote the solution of (10)–(11) corresponding to the initial condition $\xi \in \mathbb{R}^5$ by $x^\xi(\cdot)$.

In order to overcome the discontinuities of the system, the Skorohod topology is induced and a specific form of λ is constructed to prove the main results in [19]. In this paper, the dynamic system is a switch system which is alternately switched among functions f^j, $j = 1, 2, 3$. When we discuss properties of the multistage dynamic system (10)–(11), the properties of the system at the switch times require extra attention. Similar to those done in [19], we can obtain our desired results at the switch times of the system. Therefore, for the following propositions and theorems, we only need to consider the properties of each function f^j, $j = 1, 2, 3$, in their corresponding stages.

Lemma 3.1 *Suppose $\xi \in \mathbb{R}^5$. Then, given any absolutely continuous function $y : I \to \mathbb{R}^5$, there exists a solution $x^\xi(\cdot) \in C_b(I, \mathbb{R}^5)$ such that, for all $t \in I$,*

$$\|x^\xi(t) - y(t)\| \le \mathrm{e}^K \varepsilon(y, \xi),$$

with $K > 0$, and

$$\varepsilon(y,\xi) := \|y(0)-\xi\| + \int_0^1 \|\dot{y}(t) - f(y(t),u(t))\|dt.$$

Proof See Picard Lemma 5.6.3 in [20]. ∎

Proposition 3.2 *For each $j = 1,2,3$, the function $f^j(x,u)$ defined in (12) satisfies that*

i) *$f^j(\cdot,\cdot)$ is twice continuously differential,*

ii) *$f^j(\cdot,\cdot)$ satisfies linear growth conditions in x, that is, there exists a constant $K' \in (0,\infty)$ such that for all $x \in W$ and $u \in U$,*

$$\|f^j(x,u)\| \le K'(\|x\|+1).$$

Proof i) It is easy to verify that the function $f^j(\cdot,\cdot)$, $j = 1,2,3$, is twice continuously differentiable by the corresponding definitions.

ii) Since $u(t) = 0$ for all $t \in I_i$, we only need to prove the case of $j = 3$. For any $u \in U$, it follows from (13) that

$$\|f^3(x,u)\| = \left[\sum_{i=1}^{5}(f_i^3(x,u))^2\right]^{1/2} \le \sum_{i=1}^{5}\left|f_i^3(x,u)\right|.$$

Setting $K_1 := \mu_m + \rho_{\max}$, $L_2 := |m_2| + |1/Y_2| + |\Delta_2|$ and $K_2 := \max\{L_2 + \rho_{\max}, \rho_{\max}C_{s0}\}$, we can obtain that

$$|f_1^3(x,u)| = |(\mu - u(t))x_1| \le |\mu + u(t)||x_1| \le (\mu_m + \rho_{\max})\|x\| \le K_1(1+\|x\|),$$
$$|f_2^3(x,u)| = |u(t)(C_{s0} - x_2(t)) - q_2x_1| \le |u(t)||C_{s0} - x_2(t)| + |q_2||x_1| \le K_2(1+\|x\|).$$

Similarly, let

$$L_i := m_i + \mu_m Y_i + \Delta_i, \quad i = 3,4,$$
$$L_5 := C_2\left(\frac{b_1}{c_1} + \frac{b_2}{c_2}\right),$$
$$K_i := \rho_{\max} + C_i, \quad i = 3,4,5.$$

Thus, for $i = 3,4,5$, we have

$$|f_i^3(x,u)| = |q_ix_1 - u(t)x_i| \le L_i|x_1| + \rho_{\max}|x_i| \le K_i(1+\|x\|).$$

Finally, set $K' := \max\{K_1, K_2, \cdots, K_5\}$, then we can obtain that

$$\|f^3(x,u)\| \le K'(\|x\|+1).$$

The proof is completed. ∎

Proposition 3.3 *For each $j = 1, 2, 3$, the function $f^j(x, u)$ defined in (12) satisfies that there exists a constant $K \geq 1$ such that for all $x_1, x_2 \in W$, and $u_1, u_2 \in U$, the following three relations hold:*

$$\|f^j(x_1, u_1) - f^j(x_2, u_2)\| \leq K(\|x_1 - x_2\| + \|u_1 - u_2\|_2),$$
$$\|f^j_x(x_1, u_1) - f^j_x(x_2, u_2)\| \leq K(\|x_1 - x_2\| + \|u_1 - u_2\|_2),$$
$$\|f^j_u(x_1, u_1) - f^j_u(x_2, u_2)\| \leq K(\|x_1 - x_2\| + \|u_1 - u_2\|_2).$$

Proof Let $x_2 = x_1 + \Delta x$ and $u_2 = u_1 + \Delta u$. It follows from the Mean Value Theorem that, for each $j = 1, 2, 3$,

$$\begin{aligned}\|f^j(x_2, u_2) - f^j(x_1, u_1)\| &= \left\|\frac{\partial f^j}{\partial x}(x_1 + \theta_1\Delta x, u)\Delta x\right\| + \left\|\frac{\partial f^j}{\partial u}(x_1, u + \theta_2\Delta u)\Delta u\right\| \\ &\leq \left\|\frac{\partial f^j}{\partial x}(x_1 + \theta_1\Delta x, u)\right\|\|\Delta x\| + \left\|\frac{\partial f^j}{\partial u}(x_1, u_1 + \theta_2\Delta u)\right\|\|\Delta u\|.\end{aligned}$$

The continuous differentiability of the function f^j implies the existence of positive constants M_1 and M_2 such that

$$\left\|\frac{\partial f^j}{\partial x}(x_1 + \theta_1\Delta x, u)\right\| \leq M_1, \qquad \left\|\frac{\partial f^j}{\partial u}(x_1, u_1 + \theta_2\Delta u)\right\| \leq M_2.$$

Hence, letting $K_1' := \max\{M_1, M_2, 1\}$, we can obtain that

$$\|f^j(x_2, u_2) - f^j(x_1, u_1)\| \leq K_1'(\|x_2 - x_1\| + \|u_2 - u_1\|_2).$$

The twice continuously differentiable of f^j, $j = 1, 2, 3$, in Proposition 3.2 implies that $\|\partial^2 f^j/\partial x^2\|$, $\|\partial^2 f^j/\partial u^2\|$ and $\|\partial^2 f^j/\partial x\partial u\|$ are all bounded. It is clear that we can prove that there exist $K_2', K_3' > 1$, such that

$$\|f^j_x(x_1, u_1) - f^j_x(x_2, u_2)\| \leq K_2'(\|x_1 - x_2\| + \|u_1 - u_2\|_2),$$
$$\|f^j_u(x_1, u_1) - f^j_u(x_2, u_2)\| \leq K_3'(\|x_1 - x_2\| + \|u_1 - u_2\|_2).$$

Finally, letting $K = \max\{K_1', K_2', K_3'\}$, we can obtain the desired result. ∎

Let $C_b([0, T], \mathbb{R}^5)$ denote the space of continuous bounded functions on $[0, T]$ with values in $\mathbb{R}^5$, equipped with the sup norm topology, that is, for $z \in C_b([0, T], \mathbb{R}^5)$, $\|z\|_c = \sup\{\|z(t)\|, t \in [0, T]\}$.

Theorem 3.4 *For any $\xi \in \mathbb{R}^5$, System (10)–(11) has a unique solution $x^\xi(\cdot) \in C_b(I, \mathbb{R}^5)$.*

Proof First, it follows from Lemma 3.1 that the existence of solutions is proved. Subsequently, we will verify the uniqueness. Let $x_1^\xi(t)$ and $x_2^\xi(t)$ be two solutions of (10)–(11). For all $t \in I$, we can conclude that

$$\begin{aligned}\|x_1^\xi(t) - x_2^\xi(t)\| &\leq \int_0^t \|f(x_1^\xi(s), u(s)) - f(x_2^\xi(s), u(s))\|ds \\ &\leq K\int_0^t \|x_1^\xi(s) - x_2^\xi(s)\|ds.\end{aligned}$$

Bellman Gronwall inequality is applied to the above inequality, which implies that, for all $t \in I$, $\|x_1^\xi(t) - x_2^\xi(t)\| = 0$. Thus, the solution of (10)–(11) is unique. ∎

Next, we explore the question of Lipschitz continuity of solutions relative to the initial condition.

Theorem 3.5 *For all $\xi, \xi' \in \mathbb{R}^5$ and all $t \in I$, there exists a constant $L \in (0, \infty)$ such that*

$$\|x^\xi(t) - x^{\xi'}(t)\| \le L\|\xi - \xi'\|.$$

Proof First, we let $y(t) := x^{\xi'}(t)$. Next, by Theorem 3.4, the solution of (10)–(11) is unique, so we can deduce from Lemma 3.1 that, for all $t \in I$, $\|x^\xi(t) - x^{\xi'}(t)\| \le \mathrm{e}^K \varepsilon(x^{\xi'}(t), \xi)$. Now we find that

$$\begin{aligned}\varepsilon(x^{\xi'}(t), \xi) &= \|\xi - \xi'\| + \int_0^1 \|f(x^\xi(t), u(t)) - f(x^{\xi'}(t), u'(t))\|dt \\ &\le \|\xi - \xi'\| + K\int_0^1 |u(t) - u'(t)|dt.\end{aligned}$$

By Schwartz inequality and Hölder inequality, we can have

$$\begin{aligned}&\int_0^1 |u(t) - u'|dt \le \left(\int_0^1 1dt\right)^{1/2}\left(\int_0^1 |u(t) - u'|^2 dt\right)^{1/2}, \\ &\varepsilon(x^{\xi'}(t), \xi) \le \|\xi - \xi'\| + K\|u - u'\|_2 \le \sqrt{2}K\|\xi - \xi'\|.\end{aligned}$$

Letting $L := \sqrt{2}K\mathrm{e}^K$, we complete the proof. ∎

Proposition 3.6 *For any $\xi \in \mathbb{R}^5$, the solution of System* (10)–(11) *satisfies that*

$$\|x^\xi(\cdot)\| \le (1 + \|\xi\|)\mathrm{e}^{K'},$$

with K' as in Proposition 3.2.

Proof Now, we prove the boundedness of solutions to System (10)–(11). By the definition of solutions of differential equation, it suffices to show that the solutions of the following integral equation:

$$x^\xi(t) = \xi + \int_0^t f(x^\xi(s), u(s))ds, \quad t \in I \tag{14}$$

are bounded. From the above equation (14) and Proposition 3.2, we can have that

$$\|x^\xi(t)\| \le \|\xi\| + \int_0^t \|f(x^\xi(s), u(s))\|ds \le \|\xi\| + K'\int_0^t \|[x^\xi(s) + 1]\|ds.$$

Letting $y(t) := \|x^\xi(t)\| + 1$, we conclude that

$$y(t) \le y(0) + K'\int_0^t y(s)ds.$$

By Bellman Gronwall inequality, for all $t \in I$, we can obtain $y(t) \le y(0)\mathrm{e}^{K'}$ and hence, that $\|x^\xi(t)\| \le (1 + \|\xi\|)\mathrm{e}^{K'}$. ∎

4 Numerical Results and Discussion

For numerical simulation, we use the 6th Runge-Kutta method to calculate the numerical results of the nonlinear multistage switch dynamic system. The medium composition, cultivation conditions, determination of biomass, substrate and metabolites have been reported[4, 5]. The initial value $\xi = (0.115\text{g/L}, 494.5\text{mmol/L}, 0, 0, 0)^{\mathrm{T}}$. Fed-batch began at $t_1 = 5.33\text{h}$. The flow time t_i, the flow stopping time t_i', and the speeds u_i and v_i of adding glycerol and alkali, $i \in \Lambda_{785}$, are determined by the experiment.

Since intermittent feeding of alkali into the reactor to maintain the pH value at 7 or so greatly affects the extracellular concentrations of acetic acid and ethanol, this work is only concerned with the relative error between the experimental data and computational values of the first three substances. Figures 1–3 show the comparisons for the concentrations of biomass, substrate and 1,3-PD between experimental data and computational results, where the stars denote the experimental values, written as $y(\tau_j) = (y_1(\tau_j), y_2(\tau_j), y_3(\tau_j)), \tau_j = 2jh, j \in \Lambda_{16}$, the dashing lines denote the computational curves in [4], and the red real lines denote the computational curves $x_k(t), k \in \Lambda_3$ in this work. Define relative errors as follows:

$$e_k := \frac{\sum_{i=1}^{16} \left| x_k(\tau_i) - y_k(\tau_i) \right|}{\sum_{i=1}^{16} y_k(\tau_i)}, \qquad k \in \Lambda_3.$$

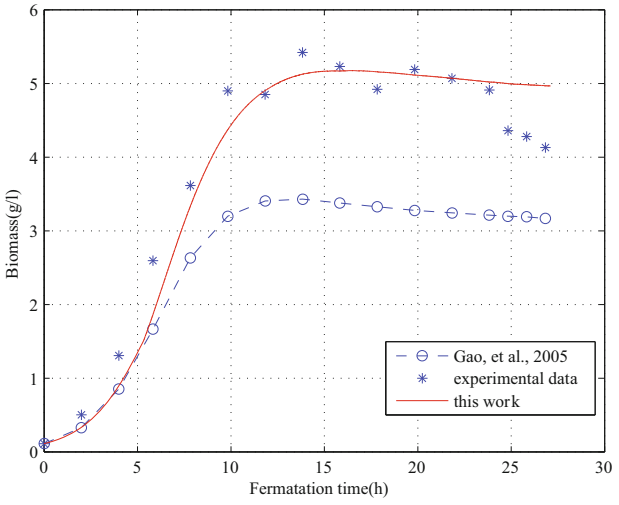

Figure 1 Comparison for the concentration of biomass between experimental data and computational results

We obtain the errors $e_1 = 6.21\%$, $e_2 = 10.27\%$, $e_3 = 6.98\%$. Actually, about the numerical results, in this paper, there is no manifest distinction from [7]. However, in [7], the key parameters t_l and t_m may be different for each different batch culture stages. So, it may cause potential difficulty to do further study on the parameter identification and optimal control problems since there are more than 300 batch culture stages in the experiment. In this paper, however, we

have 3 different switch functions corresponding to the different stages and the most important advantages is that stationary factors a_i, $i = 1, 2, 3, 4, 5$, in function $f^2(x(t), u(t))$ are fixed in each corresponding stage. This advantage will help us to do further research especially in terms of genetic engineering and metabolism mechanisms in the future.

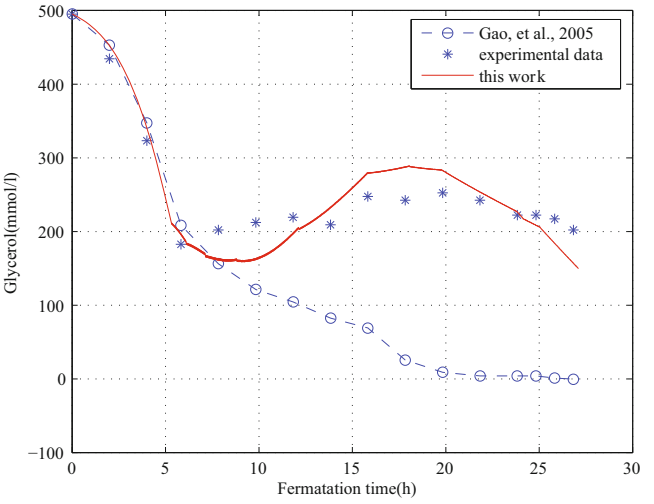

Figure 2 Comparison for the concentration of glycerol between experimental data and computational results

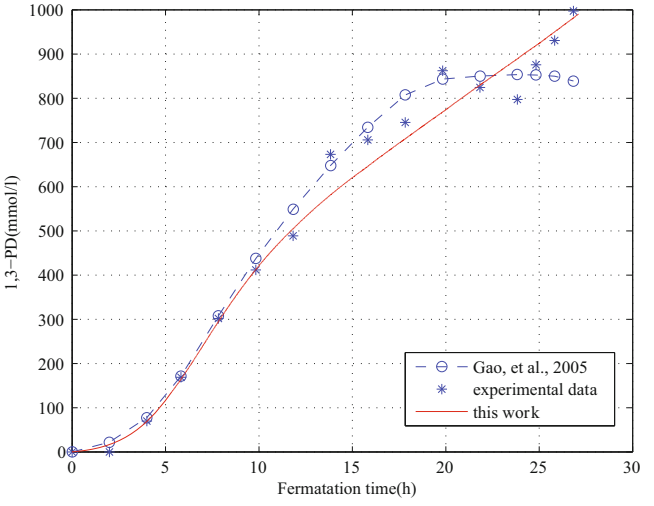

Figure 3 Comparison for the concentration of 1,3-PD between experimental data and computational results

5 Conclusions

In this paper, we have presented a novel nonlinear multistage switch dynamic system for describing the fed-batch culture. We then demonstrated the existence, uniqueness, boundedness and regularity of solutions to the nonlinear multistage switch system. Then, a numerical simulation for the nonlinear multistage switch system illustrates the improvements between our efforts and those in [4, 5, 7]. Our future work will involve parameter identification and the optimal control problems of nonlinear multistage switch system. It will be a challenge since the system is a highly nonlinear, multistage and switch system.

References

[1] Bibel H, Memzel K, and Zeng A P, Microbial production of 1,3-propanediol, *Appl. Microbiol. Biotechnol.*, 1999, **52**: 289–297.

[2] Menzel K, Zeng A P, and Deckwer W D, High concentration and productivity of 1,3-propanediol from continuous fermentation of glycerol by Klebsiella pneumoniae, *Enzyme Microb. Technol.*, 1997, **20**: 82–86.

[3] Zeng A P and Biebl H, Bulk-chemicals from biotechnology: The case of 1,3-propanediol production and the new trends, *Adv. Biochem. Eng. Biotechnol.*, 2002, **74**: 239–259.

[4] Gao C X, Li K Z, et al., Nonlinear impulsive system of fed-batch culture in fermentative production and its properties, *Chaos Soliton. Fract.*, 2006, **28**: 271–277.

[5] Wang G, Feng E M, and Xiu Z L, Modeling and parameter identification of microbial bioconversion in fed-batch cultures, *J. Process Contr.*, 2008, **18**: 458–464.

[6] Gong Z H, et al., Modelling and optimization for a switched system in microbial fed-batch culture, *Appl. Math. Model.*, 2011, **35**: 3276–3284.

[7] Wang L, Ye J X, Feng E M, Wang G, and Xiu Z L, An improved nonlinear complex system of microbial bioconversion process in fed-batch culture, *Dynam. Cont. Dis. Ser. B.*, 2012, **19**(6): 697–707.

[8] Gong Z H, et al., Infer objective function of glycerol metabolism in klebsiella pneumoniae basing on bilevel programming, *Journal of Systems Science and Complexity*, 2010, **23**(2): 334–342.

[9] Ye J X, Feng E M, Yin H C, and Xiu Z L, Modelling and well-posedness of a nonlinear hybrid system in fed-batch production of 1,3-propanediol with open loop glycerol input and pH logic control, *Nonlinear Anal. Real World*, 2011, **12**(1): 364–376.

[10] Ye J X, Zhang Y D, Feng E M, Xiu Z L, and Yin H C, Nonlinear hybrid system and parameter identification of microbial fed-batch culture with open loop glycerol input and pH logic control, *Appl. Math. Model.*, 2012, **36**(1): 357–369.

[11] Ye J X, Xu H L, Feng E M, and Xiu Z L, Optimization of a fed-batch bioreactor for 1,3-propanediol production using hybrid nonlinear optimal control, *Journal of Process Control*, 2014, **24**(10): 1556–1569.

[12] Cheng G M, Wang L, Loxton R, and Lin Q, Robust suboptimal control of a microbial batch culture process, *J. Optim. Theory Appl.*, doi: 10.1007/s10957-014-0654-z.

[13] Xiu Z L, Zeng A P, and Deckwer W D, Mulitiplicity and stability anlysis of Microorganisms

in continuous culture: Effects of metabolic overflow and growth inhibition, *Biotechnol. Bioeng.*, 1998, **5**: 251–261.

[14] Wang L, Ye J X, Feng E M, and Xiu Z L, An improved model for multistage simulation of glycerol fermentation in batch culture and its parameter identification, *Nonlinear Anal. Hybrid Syst.*, 2009, **3**(4): 455–462.

[15] Wang L, Xiu Z L, Gong Z H, and Feng E M, Modeling and parameter identification for multistage simulation of microbial bioconversion in batch culture, *Int. J. Biomath.*, 2012, **5**: Article ID. 1250034, doi: 10.1142/S179352451100174X.

[16] Lin J, Lee S, et al., Modeling of typical microbial cell growth in batch culture, *Biotechnol. Bioprocess. Eng.*, 2000, **5**: 382–385.

[17] Gong Z H, Liu C Y, and Feng E M, Modeling in microbial batch culture and its parameter identification, *Decision and Control,* 2009 *Held Jointly with the* 2009 28*th Chinese Control Conference, CDC/CCC* 2009*, Proceedings of the* 48*th IEEE Conference on. IEEE*, 2009, 6213–6217.

[18] Liu C Y, Gong Z H, Feng E M, and Yin H C, Modelling and optimal control for nonlinear multistage dynamical system of microbial fed-batch cultrue, *J. Ind. Manag. Optim.*, 2009, **5**: 835–850.

[19] Wang L, Modelling and regularity of nonlinear impulsive switching dynamical system in fed-batch culture, *Abst. Appl. Anal.*, 2012, **2012**: Article ID 295627, doi: 10.1155/2012/295627.

[20] Polak E, *Optimization: Algorithms and Consistent Approximations*, Springer-Verlag, New York, 1997.