MULTISTAGE OPTIMAL CONTROL FOR MICROBIAL FED-BATCH FERMENTATION PROCESS

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Abstract. In this paper, we consider multistage optimal control of bioconversion glycerol to 1,3-propanediol (1,3-PD) in fed-batch fermentation process. To maximize the productivity of 1,3-PD, the whole fermentation process is divided into three stages according to the characteristics of microbial growth. Stages 2 and 3 are discussed mainly. The main aim of stage 2 is to restrict accumulation of 3-hydroxypropionaldehyde and maximize the biomass in the shortest time, and the purpose of stage 3 is to get high productivity of 1,3-PD. With these different objectives, multi-objective optimal control problems are proposed in stages 2 and 3. In order to solve the above optimal control problems, the multi-objective problems are transformed to the corresponding single-objective problems using the mass balance equation of biomass and normalization of the objective. Furthermore, the single-objective optimal control problems are transformed to two-level optimization problems by the control parametrization technique. Finally, numerical solution methods combined an improved Particle Swarm Optimization with penalty function method are developed to solve the resulting optimization problems. Numerical results show that the productivity of 1,3-PD is higher than the reported results.

1. Introduction. 1,3-Propanediol (1,3-PD) is an important chemical material that can be used for synthesizing many polymers with excellent features [1]. In recent decades, the method of converting glycerol to 1,3-PD by microbial fermentation has become the focus of research because it is environment-friendly and uses renewable feedstock [22]. The raw material of the method, glycerol, is inexpensive and renewable. Recently, as a substitute for petroleum, renewable bio-diesel has increased

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rapidly in the past several years, which results in the overproduction of by-product glycerol directly in the same process. Production of 1,3-PD by microbial fermentation using glycerol has attracted much attention throughout the world. Because the microbial fermentation process is more complex than general chemical processes in highly nonlinear, time-varying, stochastic, time delay and so on, an entire fermentation experiment will last more than 30 hours, and it is impossible to optimize the fermentation process relying on the experiment simply. As a result, mathematical methods and tools must be taken into consideration.

An excessive kinetic model for substrate consumption and microbial growth was proposed in 1995 [35]. The effect of metabolic overflow and time-delay on the dynamic behavior of the fermentation system was discussed in [30]. In 2008, considering the enzyme-catalytic reductive pathway and transport of glycerol and 1,3-PD across cell membrane, a mathematical model describing the microbial glycerol fermentation was proposed in [23]. Based on these models, parameter identification, robustness analysis and optimal control have been studied extensively. For batch and continuous cultures, parameter identification problems were discussed in [2, 3, 6, 9, 25]. Analysis and application of biological robustness as performance index were studied in [26]. A measure of concentration robustness in system identification was proposed in [31]. Various optimal control strategies have also been reported such as bi-objective optimization [7], stochastic optimal control [27], robust optimal controls [8, 34], mixed-integer minimax optimization [28] and optimal state-delay control [10]. For fed-batch culture, multistage parameter identification was investigated in [4]. By assuming that transports of glycerol and 1,3-PD across cell membrane are both the active transport and the passive diffusion, parameter identification problem was discussed in [5]. To maximize concentration of 1,3-PD in fed-batch fermentation, optimal switching control [11, 12, 13, 14, 15], multi-objective optimal control [16, 20], robust multi-objective optimal control [17] and time-delayed optimal control [18] were reported. Open loop inputs and pH logic control was considered in [32, 33]. In addition, an uncoupled optimal switching control was studied in [21]. Although the achieved results are interesting, the optimization objective in the above results is either the final concentration or the productivity of 1,3-PD.

In this paper, according to the characteristics of microbial growth, the whole fermentation process is divided into 3 stages. Unlike previous literatures, the accumulation of 3-HPA and multiple objectives are involved in the formulation of the optimal control problems at stages 2 and 3. The multi-objective optimal control problems are transformed to single-objective optimal control problems. To solve the resulting optimal control problems, optimization algorithms are developed based on an improved Particle Swarm Optimization (PSO) [11], control parametrization, and penalty function method. Numerical results show that the optimal productivity of 1,3-PD is higher than the reported results.

2. Dynamic system of microbial fed-batch fermentation. The fed-batch culture of glycerol bio-conversion to 1,3-PD begins with a batch culture, then glycerol and alkali are intermittently fed into the reactor. In other words, fed-batch fermentation consists of batch fermentation and feeding fermentation. In this paper, two fermentation modes are distinguished according to whether the feeding rates are zero or not. We assume that the concentrations of reactants are uniform in the reactor, and time delay is ignored.
Based on [5], mass balances of biomass, substrate and products in the fed-batch fermentation can be formulated as follows.

\[
\begin{align*}
\dot{x}_1(t) &= [\mu - D(t, u(t))]x_1(t), \\
\dot{x}_2(t) &= D(t, u(t))(c_{s0} - x_2(t)) - q_2x_1, \\
\dot{x}_3(t) &= q_3x_1(t) - D(t, u(t))x_3(t), \\
\dot{x}_4(t) &= q_4x_1(t) - D(t, u(t))x_4(t), \\
\dot{x}_5(t) &= q_5x_1(t) - D(t, u(t))x_5(t), \\
\dot{x}_6(t) &= \frac{1}{p_6} \left[ \frac{p_7x_2(t)}{x_2(t) + p_8} - \frac{m_2Y_2 + \mu}{Y_2} \right] - \frac{\Delta_3x_2(t)}{x_2(t) + k_2^*} - \mu x_6(t), \\
\dot{x}_7(t) &= \frac{p_{10}x_6(t)}{x_6(t) + k_1 + k_1 \frac{x_7(t)}{p_{11}}} - \frac{p_{12}x_7(t)}{x_7(t) + k_2 + \frac{x_7(t)}{p_{13}}} - \mu x_7(t), \\
\dot{x}_8(t) &= \frac{p_{12}x_7(t)}{x_7(t) + k_2 + \frac{x_7(t)}{p_{15}}} - \frac{p_{14}x_8(t)}{x_8(t) + p_{15}} - \mu x_8(t) \\
&\quad - \frac{\Delta_3x_7(t)}{x_7(t) + k_2^*} - \mu x_8(t),
\end{align*}
\]

(1)

where \( t \in [0, T] \); \( T \) is a given terminal time; \( x_1(t), x_2(t), \ldots, x_7(t) \) and \( x_8(t) \) are the concentrations of biomass, extracellular glycerol, extracellular 1,3-PD, acetic acid, ethanol, intracellular glycerol, intracellular 3-hydroxypropionaldehyde (3-HPA), and intracellular 1,3-PD, respectively; and \( D(t, u(t)) \) is the dilution rate at time \( t \) defined by

\[
D(t, u(t)) = \frac{(1 + r)u(t)}{V_0 + \int_0^t (1 + r)u(s)ds},
\]

(2)

Here, the feeding ratio of alkali to glycerol \( r \), the initial volume of the reactor \( V_0 \), and the concentration of feeding glycerol \( c_{s0} \) are given positive constants.

In (1), the feeding rate of glycerol \( u(t) \) is the control. Let \( U_{ad} \) be the admissible set of controls defined as

\[
U_{ad} := \{ u(t) \in L_\infty([0, T], R) | 0 \leq u(t) \leq v_{max} \},
\]

(3)

where \( v_{max} \) is the maximal feeding rate of glycerol; and \( L_\infty([0, T], R) \) is the Banach space of the essentially bounded functions from \([0, T]\) into set \( R \). Note that when \( u(t) \neq 0 \), dynamic system (1) describes the feeding fermentation process; when \( u(t) = 0 \), dilution rate \( D(t, u(t)) = 0 \), at this time no glycerol or alkali is fed, and dynamic system (1) describes the batch fermentation process.

The specific growth rate of biomass \( \mu \), the specific consumption rate of substrate glycerol \( q_2 \) and the specific formation rates of products \( q_i (i = 3, 4, 5) \) are expressed...
as
\[
\mu = \mu_m \frac{x_2(t)}{x_2(t) + k_2} \prod_{i=2}^{5} \left( 1 - \frac{x_i(t)}{x_i^*} \right)^{n_i},
\]
\[q_2 = m_2 + \frac{\mu}{Y_2} + \frac{\Delta_2 x_2(t)}{x_2(t) + k_2^*} + p_1 x_6(t) \frac{x_6(t) + p_2}{x_6(t)} + p_3 \max \{x_2(t) - x_6(t), 0\},
\]
\[q_3 = m_3 + \mu Y_3 + \frac{\Delta_3 x_3(t)}{x_3(t) + k_3^*} + \frac{p_4 x_8(t)}{x_8(t) + p_5} + p_{17} \max \{x_8(t) - x_3(t), 0\},
\]
\[q_4 = m_4 + \mu Y_4 + \frac{\Delta_4 x_4(t)}{x_4(t) + k_4^*},
\]
\[q_5 = m_5 + \mu Y_5.
\]

Under anaerobic conditions at 37°C and pH 7.0, the critical concentrations of biomass, glycerol, 1,3-PD, acetate and ethanol, intracellular glycerol, 3-HPA, intracellular 1,3-PD and kinetic parameters in (1)-(8) are listed in Table 1[5].

| Table 1. The critical concentrations and kinetic parameters in system (1) [5]. |
|---|
| $x_1^*$ | $x_2^*$ | $x_3^*$ | $x_4^*$ | $x_5^*$ | $x_6^*$ | $x_7^*$ | $x_8^*$ |
| 10 | 2039 | 2000 | 1026 | 360 | 2039 | 275 | 2000 |
| $m_2$ | $m_3$ | $m_4$ | $m_5$ | $Y_2$ | $Y_3$ | $Y_4$ | $Y_5$ |
| 2.2 | -2.69 | -0.97 | 5.26 | 0.0082 | 67.69 | 33.07 | 11.66 |
| $k_2^*$ | $k_3^*$ | $k_4^*$ | $\Delta_2$ | $\Delta_3$ | $\Delta_4$ | $n_2$ | $n_3$ |
| 11.43 | 15.50 | 85.71 | 28.58 | 26.59 | 5.74 | 1 | 3 |
| $n_4$ | $n_5$ | $k_5$ | $V_0$ | $r$ | $p_1$ | $p_2$ | $p_3$ |
| 3 | 3 | 0.28 | 5 | 0.75 | 30.0688 | 3.8179 | 679.913 |
| $p_4$ | $p_5$ | $p_6$ | $p_7$ | $p_8$ | $p_9$ | $p_{10}$ | $p_{11}$ |
| 58.5244 | 3.9251 | 8.3591 | 59.266 | 2.2919 | 2478.52 | 19.6651 | 136.563 |
| $p_{12}$ | $p_{13}$ | $p_{14}$ | $p_{15}$ | $p_{16}$ | $p_{17}$ | $k_1$ | $k_2$ |
| 22.4736 | 0.7205 | 5.6354 | 5.5999 | 1.7492 | 1.4570 | 0.53 | 0.14 |

Let $x(t) = (x_1(t), x_2(t), \ldots, x_8(t))^T$, and $f(x(t), u(t))$ be the right-hand side of system (1). Then the system (1) can be written as the following vector form:
\[
\begin{align*}
\dot{x}(t) &= f(x(t), u(t)), \quad t \in [0, T], \\
x(0) &= x_0.
\end{align*}
\]

For a given $x_0$, and $u(t) \in U_{ad}$, system (9) has a unique solution denoted by $x(\cdot|u)$ [29]. Let $S_0$ is the solution set of system (9) corresponding to $u \in U_{ad}$ and $x_0$.

3. Multistage optimal control model. It is well known that there are three stages in the microbial growth. They are the adaptation period, the logarithmic growth period and the stable period. At the first stage (i.e., the adaptation period), microorganisms adapt to the environment, and grow and metabolize slowly. The fermentation horizon is denoted by $[0, t_1]$, where $t_1$ is a fixed empirical value. This is a batch fermentation process. Next, we will discuss the fed-batch fermentation process in the second and third stage in detail.
At stage 2 $[t_1, t_2]$, namely logarithmic growth period, microbial growth and metabolism are rapid. At the same time, metabolites and intermediate product 3-HPA also accumulate rapidly with substrate glycerol being consumed rapidly. Therefore, glycerol needs to be fed, reasonable alkali is also fed in order to neutralize acetic acid. However, a little bit higher glycerol concentration will cause a high accumulation of intermediate product 3-HPA. 3-HPA is toxic and can inhibit cell growth and metabolism. Too high concentration of 3-HPA will lead to abnormal termination of fermentation \[19, 23\]. Thus the feeding rate and the concentration of glycerol should not be too high at this stage. In this paper, we restrict the concentration of glycerol in $[0, H_{cg}]$, where $H_{cg}$ is a given positive constant. The aim of stage 2 is to allow the biomass to grow rapidly in a shortest time to the maximum and control the accumulation of 3-HPA. As a result, there are three objectives at stage 2: $\max x_1(t_2)$, $\min t_2$, $\min \int_{t_1}^{t_2} x_7(t)dt$. Taking the feeding rate of glycerol $u(t)$ as the control, the optimal control problem (PL1) with free termination $t_2$ can be stated as follows.

\[
(PL1) \quad \min (-x_1(t_2), \quad t_2, \quad \int_{t_1}^{t_2} x_7(t)dt) \\
\text{s.t.} \quad \dot{x}(t) = f(x(t), u(t)), \\
x_2(t) \leq H_{cg}, \\
u(t) \in U_{ad}, \\
t \in [t_1, t_2].
\]

For convenience, the solution of the system (9) is denoted as $x(t)$ in the sequel. Because the concentration of each substance in the reactor is nonnegative, and it cannot exceed its critical concentration $x^*_i (i = 1, 2, \ldots, 8)$, the solution of dynamic system (9) must belong to the following set $W$:

\[
W = \{x(t) \in C^1([0, T], R^8) \mid 0 \leq x_i(t) \leq x^*_i, i = 1, 2, \ldots, 8, \forall t \in [0, T]\}. \quad (10)
\]

Recall that the inequality constraint $x_2(t) \leq H_{cg}$ in (PL1) is merely bound constraint. Thus, define

\[
W_L = \{x(t) \in W \mid 0 \leq x_2(t) \leq H_{cg}, \forall t \in [0, T]\}. \quad (11)
\]

Then, the admissible state set of (PL1) is

\[
S_L = S_0 \cap W_L, \quad (12)
\]

and the feasible control set is

\[
U_L = \{u(t) \in U_{ad} \mid x(\cdot \mid u(t)) \in S_L\}, \quad (13)
\]

where $S_0$ is the solution set of system (9).

In (PL1), $x_1(t)$ reaches the maximum at the moment $t_2$. It follows from system (1) and $x_1(t_2) > 0$ that

\[
\dot{x}_1(t) \mid_{t=t_2} = [\mu - D(t, u(t))] \mid_{t=t_2} = 0. \quad (14)
\]

As a result, the objective $\max x_1(t_2)$ in (PL1) can be transformed to the constraint $[\mu - D(t, u(t))] \mid_{t=t_2} = 0$. At the same time, the objectives $t_2$ and $\int_{t_1}^{t_2} x_7(t)dt$ are
normalized. Then the multi-objective optimal control problem (PL1) can be transformed to the following single-objective problem (PL):

\[
\begin{align*}
\text{(PL)} & \quad \min \quad \frac{t_2}{T} + \frac{\int_{t_1}^{t_2} x_7(t) \, dt}{(t_2 - t_1)x_7^2} \\
& \text{s.t.} \quad [\mu - D(t, u(t))] |_{t=t_2} = 0, \\
& \quad x(t) \in S_L, \\
& \quad u(t) \in U_L, \\
& \quad t \in [t_1, t_2].
\end{align*}
\]

Stage 3 is the stable period \([t_2, T]\). Since \(T\) is a given time in the experiment, 1,3-PD may not always reach the maximum at \(T\). Let \(t_3 \in [t_2, T]\) be the moment at which 1,3-PD reaches the maximum. Then, stage 3 is restricted in \([t_2, t_3]\). The concentration of microorganism will not change greatly, and the accumulation of 3-HPA is weak. It is the phase to get the maximal yield of 1,3-PD by increasing the concentration of glycerol in shortest time. As a result, an optimal control problem (PS1) with free final time \(t_3\) can be stated as follows.

\[
\text{(PS1)} \quad \max \quad \left( x_3(t_3), \frac{1}{t_3} \right) \\
\text{s.t.} \quad \dot{x}(t) = f(x(t), u(t)), \\
& \quad u(t) \in U_{ad}, \\
& \quad t \in [t_2, t_3] \subset [t_2, T].
\]

Let \(S_s = S_0 \cap W, U_s = \{u(t) \in U_{ad} | x(t) \in S_s\}\) with \(S_0\) being the solution set of system (9) and \(W\) being defined by (10). Then, \(S_s\) and \(U_s\) are, respectively, the feasible state set and feasible control set of (PS1). The vector objective \(\max(x_3(t_3), \frac{1}{t_3})\) is replaced by \(\max \frac{x_3(t_3)}{t_3}\), which yields the following single-objective optimal control problem:

\[
\text{(PS)} \quad \max \quad \frac{x_3(t_3)}{t_3} \\
\text{s.t.} \quad x(t) \in S_s, \\
& \quad u(t) \in U_s, \\
& \quad t \in [t_2, t_3] \subset [t_2, T].
\]

Now, (PL) and (PS) are the single-objective optimal control problems corresponding to (PL1) and (PS1). Note that the objective functions in (PL) and (PS) are continuous, and the feasible domains are compact sets. Thus, (PL) and (PS) exist the optimal solutions.

4. **Numerical solution methods.** (PL) and (PS) are the optimal control problems with free terminal time. Furthermore, there is an equality constraint in (PL). Thus, it is impossible to solve the problems analytically. In this section, the infinite-dimensional controls in two problems will be parameterized and discretized according to the feeding processes of glycerol and alkali, and numerical solution methods will be developed to solve the above two problems.
4.1. **Control parameterization.** In the experiment, glycerol and alkali are usually added to the fermenter at constant rates \( v_l \) and \( rv_l \), simultaneously. The feeding will last a few seconds, and then the system begins batch fermentation in next few seconds. The feeding process and batch fermentation will occur alternately \( N \) times till the 2nd stage terminating at \( t_2 \). In order to make experiment operation easier, we assume that feeding time and batch fermentation time are fixed instead of varying, and they are denoted by \( \triangle \tau_1 \) and \( \triangle \tau_2 \). Then, the control variable \( u(t) \) is determined by the parameters \( N, \triangle \tau_1, \triangle \tau_2, v_l \), and it can be rewritten as

\[
 u(t) = \begin{cases} v_l, & t \in [t_1 + k(\triangle \tau_1 + \triangle \tau_2), t_1 + k(\triangle \tau_1 + \triangle \tau_2) + \triangle \tau_1], \\
 0, & t \in (t_1 + k(\triangle \tau_1 + \triangle \tau_2) + \triangle \tau_1, t_1 + (k + 1)(\triangle \tau_1 + \triangle \tau_2)), 
\end{cases}
\]

where \( k = 0, 1, 2, \ldots, N - 1; \) and the feeding times \( N \in \mathbb{Z}^+ \). When the 2nd stage stops, \( t_2 = t_1 + (N - 1)(\triangle \tau_1 + \triangle \tau_2) + \triangle \tau_1 \).

Generally speaking, \( \triangle \tau_1 \) and \( \triangle \tau_2 \) will be less than 5 minutes in the experiment. Let \( \tau = (\triangle \tau_1, \triangle \tau_2), \Gamma = [0, 0.084] \times [0, 0.084] \), then \( \tau \in \Gamma, v_l \in B = [0, v_{\text{max}}], N \in \mathbb{Z}^+ \). For a positive integer \( N \), the problem (PL) can be transformed to the following two-level optimization problem (PL-TL):

\[
(\text{PL-TL}) \quad \min_{N \in \mathbb{Z}^+} \min_{\tau \times v_l \in \Gamma \times B} \quad \frac{t_2}{T} + \frac{\int_{t_1}^{t_2} x_7(t)dt}{(t_2 - t_1)x_7^2} \\
\text{s.t.} \quad |\mu - D(t, u(t))| \big|_{t = t_2} = 0, \\
\quad x(t) \in S_L, \\
\quad t \in [t_1, t_2].
\]

4.2. **Penalty function method.** For the equality constraint in (PL-TL), penalty function method will be used. Thus, the problem (PL-TL) can be transformed to the following problem:

\[
(\text{PL-TL-M}) \quad \min_{N \in \mathbb{Z}^+} \min_{\tau \times v_l \in \Gamma \times B} \quad \frac{t_2}{T} + \frac{\int_{t_1}^{t_2} x_7(t)dt}{(t_2 - t_1)x_7^2} + M|\mu - D(t, \tau, v_l)|^2 \big|_{t = t_2} \\
\text{s.t.} \quad x(t) \in S_L, \\
\quad t \in [t_1, t_2],
\]

where \( M > 0 \) is a penalty factor.

Define the inner layer optimization of (PL-TL-M) as follows.

\[
(\text{I-PL-M}) \quad JL(N) = \min_{\tau \times v_l \in \Gamma \times B} \quad \frac{t_2}{T} + \frac{\int_{t_1}^{t_2} x_7(t)dt}{(t_2 - t_1)x_7^2} + M|\mu - D(t, \tau, v_l)|^2 \big|_{t = t_2}^2 \\
\text{s.t.} \quad x(t) \in S_L, \\
\quad t \in [t_1, t_2].
\]

Then, (PL-TL-M) is equivalent to the following optimization problem:

\[
(\text{O-PL}) \quad \min_{N \in \mathbb{Z}^+} \quad JL(N)
\]
At stage 3, by using the similar technique with the feeding rate \( v_s \in B = [0, v_{max}] \), (PS) can be transformed to the following optimal control problem:

\[
(PS-TL) \max_{N \in \mathbb{Z}^+} \max_{\tau \times v_s \in \Gamma \times B} \frac{x_3(t_3)}{t_3} \\
\text{s.t.} \quad x(t) \in S_s, \\
\quad t \in [t_2, t_3],
\]

where the initial time \( t_2 \) is determined by (PL). Similarly, the inner layer optimization of (PS-TL) can be defined as follows.

\[
(I-PS) \quad JS(N) = \max_{\tau \times v_s \in \Gamma \times B} \frac{x_3(t_3)}{t_3} \\
\text{s.t.} \quad x(t) \in S_s, \\
\quad t \in [t_2, t_3].
\]

Then, (PS-TL) is equivalent to the following problem:

\[
(O-PS) \max_{N \in \mathbb{Z}^+} JS(N)
\]

Now, optimal control problems (PL) and (PS) have been transformed to (O-PL) and (O-PS), which are easier to be solved.

4.3. Optimization algorithms. A heuristic approach frame is developed to solve two-level optimization problem (PL-TL) and (PS-TL) as follows.

Step 1: Set an initial switching number \( N_0 \), and error \( \epsilon > 0 \).

Step 2: Solve the inner optimization problems (I-PL) and (I-PS).

Step 3: \( N := N + d \), where \( d \) is a positive integer.

Step 4: If \( |JL(N) - JL(N - d)| < \epsilon \), (and \( |JS(N) - JS(N - d)| < \epsilon \)), then stop.

Otherwise, go to Step 2.

Remark 1. The key for above frame is to solve the inner layer optimization problems (I-PL) and (I-PS) with bounded constraints, the improved PSO algorithm with cross border policy [11] can be used.

Considering the penalty factor \( M \) in (I-PL), an optimization algorithm combined penalty function method with PSO is developed to solve (PL-TL) as shown in Algorithm 1.

Remark 2. Since there is only bound constraints in (I-PS), the improved PSO algorithm can be used directly. Algorithm AS for solving (PS-TL) become available by removing sub-loop from Algorithm AL. Algorithm AS will not be listed for brevity.

5. Numerical results. All computations are performed in Visual C++ on a Lenovo-Think T430 coreTM i5-3210m machine. Parameters in Algorithm 1 are taken as \( N_0 = 20, d = 5, M_0 = 2, C = 2, Hcg = 400, v_{max} = 0.6Lh^{-1} \), and \( v_{max} = 1.5Lh^{-1} \). Other parameters in the improved PSO are same as those ones in [11].

At stage 1, let \( u(t) = 0, t_1 = 5.33h \). Euler method is used to solve the system (9) with the step length \( h_1 = 0.01 \), initial value \( x(0) \) and error \( \epsilon = 10^{-4} \). Then \( x(t_1) \) is computed, and both \( x(0) \) and \( x(t_1) \) are listed in Table 2.

At stages 2 and 3, Euler method is used to solve the system (9), and the step length \( h = (k \Delta \tau_1, k \Delta \tau_2)/k \). Here, \( k \in Z^+ \), \( k \Delta \tau_i \in Z^+ (i = 1, 2) \), \( (k \Delta \tau_1, k \Delta \tau_2) \) is the greatest common divisor of \( k \Delta \tau_1 \) and \( k \Delta \tau_2 \).
Algorithm 1 Algorithm AL to solve (PL-TL)

Step 1: Set integers $N^0 > 0$ and $d > 0$, parameter $C > 0$, and error $\varepsilon > 0$, let $i = 0$.

Step 2: Suppose current switching number is $N^i$, enter following sub-loop to solve (I-PL).

Step 2.1: Set penalty factor $M_0 > 0, k := 0$.

Step 2.2: Solve (I-PL-M) using improved PSO algorithm. Its optimal solution is denoted by $(\tau^k, v^k_l)$, optimal index by $JL(N^i)$.

Step 2.3: If $M_i |(\mu - D(t, \tau^k, v^k_l))|_{t = t_2}^2 < \varepsilon$, then $(\tau^k, v^k_l)$ is the optimal solution of (I-PL), and go to Step 3. Otherwise, go to Step 2.4.

Step 2.4: Set $M_{k+1} = CM_k, k := k + 1$, and go to Step 2.2.

Step 3: Set $N^{i+1} = N^i + d, i := i + 1$, and go to Step 2. Otherwise, go to Step 4.

Step 4: If $|JL(N^{i-1}) - JL(N^{i})| < \varepsilon$, then $N^{i-1}$ is the optimal switching number, and $(\tau^k, v^k_l)$ is the optimal solution of (PL-TL), stop. Otherwise, set $N^{i+1} = N^i + d, i := i + 1$, and go to Step 2.

Taking $x(t_1)$ and $x(t_2)$ as the initial value, Algorithm AL and Algorithm AS are used to solve (PL-TL) and (PS-TL), the numerical results are listed in Table 3.

Table 2. The initial state and final state in three stages.

| $x(0)$ | $x(t_1)$ | $x(t_2)$ | $x(t_3)$ |
|--------|----------|----------|----------|
| $(2.7, 217.4, 0, 0, 0, 0, 0, 0)^T$ | $(3.125, 26.557, 121.263, 40.906, 20.783, 15.887, 13.143, 92.883)^T$ | $(8.007, 82.786, 492.433, 120.359, 88.621, 53.972, 110.348, 456.382)^T$ | $(7.763, 223.007, 1321.761, 180.664, 102.715, 202.643, 126.896, 1135.526)^T$ |

Table 3. The obtained optimal control.

| stage | terminal time | feeding and batch time | feeding rate | switch times |
|-------|--------------|------------------------|--------------|--------------|
| 2     | $t_2 = 15.171$ | $\tau = (0.006, 0.042)^T$ | $v_l = 0.538$ | $N = 205$ |
| 3     | $t_3 = 24.292$ | $\tau = (0.018, 0.058)^T$ | $v_s = 1.264$ | $N = 120$ |

Our main results, the final concentration of 1,3-PD $x_3(t_3)$, total fermentation time $t_3$, and the productivity of 1,3-PD $x_3(t_3)/t_3$, are listed in Table 4. For comparison, the results in [13, 21, 32] are also listed in Table 4. From Table 4, we can see that the final concentration of 1,3-PD in this paper is 35.52% higher than the one in [13], and is nearly twice as that in [32]. Furthermore, the fermentation time in this paper is the middle among the previous literatures. More importantly, the productivity of 1,3-PD in this paper is 19.5%–49.8% higher than the ones in [13, 21, 32].

Table 4. The comparison between our results and previous results.

|                  | result in [13] | result in [21] | result in [32] | our result |
|------------------|----------------|----------------|----------------|------------|
| 1,3-PD concentration | 975.319        | 1416.7         | 679.22         | 1321.761   |
| fermentation time            | 24.16          | 39             | 14.9167        | 24.292     |
| 1,3-PD productivity            | 40.3691        | 36.3256        | 45.5342        | 54.4114    |
Figure 1. The concentrations of biomass, 1,3-PD and 3-HPA under the obtained optimal control.

Under the optimal control in Table 3, the concentrations of biomass, 1,3-PD and 3-HPA are plotted in Figure 1. From Figure 1, we can see that the concentration of 1,3-PD in stage 3 rises a lot faster than that in stage 2. Thus, 1,3-PD is produced mainly in stage 3. It is effective to promote the concentration or the productivity of 1,3-PD by avoiding the rapid accumulation period of 3-HPA.

The concentration of glycerol under the optimal control in Table 3 is plotted in Figure 2. From Figure 2, we can see that the concentration of glycerol in stage 2 rises slower than that in stage 3, it is coincide with the role of the concentration of 1,3-PD with respect to fermentation time. The reason is that controls $v_l > v_s$.

Figure 3 shows that the index of (O-PL) declines with respect to the switch times $N$, while the index of (O-PS) rises.

6. Conclusions. This paper has considered multistage optimal control problems in microbial fed-batch fermentation. In order to get high productivity of 1,3-PD, the whole fermentation process is divided into 3 stages. Multi-objective optimal control problems are proposed in stages 2 and 3 and then they are transformed to single-objective optimal control problems. To the best our knowledge, this is the first work in the literature for optimizing the fed-batch process in stages 2 and 3 with multi-objective formulation in each stage. Solution method based on
Figure 2. The concentration of glycerol under the obtained optimal control.

Figure 3. The indices of (O-PL) and (O-PS)
control parametrization, penalty function method and the improved PSO have been
developed to solve the resulting optimal control problems. Finally, numerical results
show that the productivity of 1,3-PD is increased considerably. In future research, it
will be interest to quantify the inhibition of 3-HPA in 1,3-PD fed-batch production.

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