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Modelling and pathway identification involving the transport mechanism of a complex metabolic system in batch culture

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ABSTRACT

The bio-dissimilation of glycerol to 1,3-propanediol (1,3-PD) by *Klebsiella pneumoniae* (*K. pneumoniae*) can be characterized by a complex metabolic system of interactions among biochemical fluxes, metabolic compounds, key enzymes and genetic regulation. In this paper, in consideration of the fact that the transport ways of 1,3-PD and glycerol with different weights across cell membrane are still unclear in batch culture, we consider 121 possible metabolic pathways and establish a novel mathematical model which is represented by a complex metabolic system. Taking into account the difficulty in accurately measuring the concentration of intracellular substances and the absence of equilibrium point for the metabolic system of batch culture, the novel approach used here is to define quantitatively biological robustness of the intracellular substance concentrations for the overall process of batch culture. To determine the most possible metabolic pathway, we take the defined biological robustness as cost function and establish an identification model, in which 1452 system parameters and 484 pathway parameters are involved. Simultaneously, the identification model is subject to the metabolic system, continuous state constraints and parameter constraints. As such, solving the identification model by a serial program is a very complicated task. We propose a parallel migration particle swarm optimization algorithm (MPSO) capable of solving the identification model in conjunction with the constraint transcription and smoothing approximation techniques. Numerical results show that the most possible metabolic pathway and the corresponding metabolic system can reasonably describe the process of batch culture.

1. Introduction

The microbial conversion of glycerol by *Klebsiella pneumoniae* (*K. pneumoniae*) to 1,3-propanediol (1,3-PD) in batch culture is of interest to industry because of its environmentally safe, high region specificity, cheaply available feedstock, and relatively high theoretical molar yield [1–5]. Therefore, since the 1980s, many a computational model has been established to describe the process of batch culture. Based on the proposed and modified model by Zeng et al. [6,7], researchers investigated optimal control [8], multistage model [9], parameter identification [10] and stochastic model [11] in batch culture.

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The concentrations of intracellular substances are almost always ignored in any of early batch culture references mentioned above. This is obviously a serious limitation, as intracellular substances arising in real-world applications really exist. In the context of less information about intracellular experiment data, the quantitative description of biological robustness becomes a feasible method to evaluate the validity of the computational concentrations of intracellular substances. Robustness is one of the fundamental characteristics of biological system and it allows a system to sustain its functions in spite of internal and external perturbation [12–14]. Marhl and Perc [15] defined the robustness of the system via a given parameter and a dependant variable, like for example in their case peak and plateau value. Usually, the robustness of the system is evaluated by the sensitivity analysis [16] and jitter [17]. Perc et al. [18,19] studied only the frequency robustness of the system since the amplitude of the new spike is the same as the amplitude of the original spikes. This point of view, which has been observed for a wide variety of experiments [20,21], is being gradually accepted by experts in the field of systems biology. The biological robustness has been quantitatively defined in the approximately stable state of continue culture [22,23]. None of the above literatures, however, quantitatively define the biological robustness of batch culture owing to lack of equilibrium point. Up to now, the biological robustness defined quantitatively is seldom found in batch culture.

In 2008, Sun et al. [24] firstly proposed a novel mathematical model to describe the concentration changes of extracellular and intracellular substances. This model assumed that glycerol passes cell membrane by passive diffusion coupled with facilitated transport and 1,3-PD is transported by passive diffusion. To the best of our knowledge, since there is a small number of reports dealing with the transport ways of glycerol and 1,3-PD of batch culture and it is still not exactly known, the reliability of the model cannot be guaranteed [25].

In this paper, taking into account three possible transport ways of glycerol and 1,3-PD with different weights across cell membranes (passive diffusion, active transport or passive diffusion coupled with active transport), we give 121 possible metabolic pathways and establish a novel mathematical model, which is represented by a complex metabolic system. Some properties of the metabolic system are discussed. Similar to literature [18,19], inspired by the qualitative description of the biological robustness given by Kitano [12–14] and h-stability [26], we first put forward a quantitative definition of biological robustness of intracellular substance concentrations for the batch culture because of less information concerning intracellular substances. The proposed biological robustness, which is defined for the overall process of batch culture due to the absence of equilibrium point, is different from quantitative description of biological robustness of continue culture in the approximately stable state [22,23]. Taking the proposed biological robustness as a cost function, we establish an identification model involving the metabolic system together with subject to continuous state constraints and parameter constraints. The constraint transcription and smoothing approximation techniques [27] are applied to deal with the continuous state constraints in the identification model. The case that the model includes 1452 system parameters and 484 pathway parameters makes solving the identification model for a serial program a very complicated task. With this in mind, we construct a parallel migration particle swarm optimization algorithm to determine the most possible metabolic pathway and corresponding optimal parameters under various initial conditions. Applying the proposed algorithm, in which 9979188 numerical computations of differential equations are involved, to the identification model on 1800 PC-cluster Server, we obtain that both glycerol and 1,3-PD pass cell membranes by active transport and passive diffusion with different weights.

The remainder of this paper is organized as follows. In Section 2, a complex metabolic system is formulated and some important properties are proved. In Section 3, the identification model is proposed via biological robustness. In Section 4, a parallel particle swarm optimization algorithm based on particle migration (MPSO) is constructed to solve the identification model. In Section 5, numerical results are presented. In Section 6, we draw the conclusions and trace the direction for future works.

2. Complex metabolic system

The fermentations of glycerol cover both extracellular and intracellular environments, which are linked by the transports of substrate (glycerol) and products (1,3-PD) across cell membranes. As shown in Fig. 1 [24], the transport ways of glycerol and 1,3-PD across the membrane have not been observed in experiments yet.

Abbreviations: **A**, active transport; **P**, passive diffusion; **AP**, passive diffusion and active transport; **GTW**, transport ways of glycerol; **PDTW**, transport ways of 1,3-PD. Taking three possible transport ways of glycerol and 1,3-PD across cell membranes{**A**,**P**,**AP**} into consideration, let $D := \{(\varsigma, \tau) \in [0,1]^2\}$ be the set of possible metabolic pathways, where ςandτ are **pathway parameters**. Since ς and τ are continuous variables, we can obtain infinite metabolic pathways.

The transport ways of glycerol corresponding to parameter ς are as follow:

$$\begin{cases} \varsigma := 0, \text{ if } \textbf{GTW} \text{ is } \textbf{P}, \\ \varsigma := 1, \text{ if } \textbf{GTW} \text{ is } \textbf{A}, \\ \varsigma \in (0,1), \text{ if } \textbf{GTW} \text{ is } \textbf{AP}. \end{cases}$$

The transport ways of 1,3-PD corresponding to parameter τ are as follow: