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Pathway identification using parallel optimization for a nonlinear hybrid system in batch culture

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ABSTRACT

The complex bio-process for the bioconversion of glycerol to 1,3-propanediol (1,3-PD) can be characterized by a nonlinear hybrid dynamical system of enzyme-catalytic kinetics and genetic regulation. In this paper, in consideration of the possible ways that 3-hydroxypropionaldehyde (3-HPA) inhibits the cell growth, various possible transports and inhibition mechanisms, we consider 576 possible metabolic pathways and establish a fourteen-dimensional nonlinear hybrid dynamical system with uncertain system parameters and pathway parameters for describing the process of batch culture. Some important properties of the hybrid system are discussed. Taking into account the difficulty in accurately measuring the concentration of intracellular substances and the absence of equilibrium points for the hybrid system, we quantitatively define biological robustness of the intracellular substance concentrations for the overall process of batch culture. Our goal is to determine the most possible metabolic pathway and corresponding system parameters. To this end, taking the relative error between the experimental data and the computational values of the extracellular substances together with the proposed biological robustness of the intracellular substances as a cost function, we establish an identification model, in which 17 280 system parameters and 5760 pathway parameters are involved. Furthermore, the identification model is subject to the hybrid system, continuous state constraints and parameter constraints. As such, it is a very complicated task to solve the identification model by a serial program. With this in mind, we propose a parallel improved differential evolution algorithm (P-IDE), based on the constraint transcription and smoothing approximation techniques, for solving the identification model. An illustrative numerical example shows the appropriateness of the most possible metabolic pathway and the corresponding system parameters as well as the effectiveness of the parallel algorithm.

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1. Introduction

The microbial conversion of glycerol by *Klebsiella pneumoniae* (*K. pneumoniae*) to 1,3-propanediol (1,3-PD) is of interest to industry because of its environmental safety, high region specificity, cheaply available feedstock, and relatively high theoretical molar yield [1–5]. Bioprocesses, which are involved in producing different pharmaceutical products, may be classified in view of the mode chosen for the process: either batch, fed-batch or continuous [6]. A comparison of batch culture with fed-batch culture [7] and continuous culture [8] can obtain the highest production concentration and molar yield 1,3-PD to glycerol [9]. Not only the nonlinear dynamic behaviour of microorganisms has been the objective of a number of theoretical works [10,11], but also much experimental research on the process of batch culture has been reported recently, including multiple product inhibition and growth modelling [12], a model for product formation [13], optimal control [14], multistage model [15,16], sensitivity analysis [17], parameter identification [18], stochastic model [19], time-delay system [20] and joint estimation [21]. In 2008, Sun [22] firstly proposed a nonlinear dynamical system involving concentration changes of three intracellular substances and two key enzymes. However, the global regulation of gene expression is not yet clear.

In glycerol metabolism process, four key enzymes including 1,3-PD oxydoreductase (PDOR), glycerol dehydratase (GDHt), glycerol dehydrogenase (GDH) and dihydroxyacetone kinase I (DHAK I), are coordinately expressed and induced by glycerol or dihydroxyacetone (DHA). The genes for these four enzymes are organized as a cluster on the chromosome and called the *dha regulon* [23,24]. The four key enzymes are regulated by the *dha regulon*. The intermediate 3-HPA will repress the expression of the *dha regulon* [25]. These make the *dha regulon* be the key factor in the process of glycerol metabolism. None of the above literatures, involve the global regulation of gene expression. Until 2012, a fourteen-dimensional nonlinear dynamical system of enzyme-catalytic kinetics and genetic regulation [26] was established to describe the microbial batch culture better. However, there are still some uncertain factors in the fermentation, especially whether 3-HPA inhibits the formation of other intracellular substances or such intracellular substances exert influence on the formation of 3-HPA. This leads to the uncertainty of metabolic mechanism of fermentation process. With this in mind, the key problem of our paper is to determine the true metabolic mechanism.

Little attention is paid to intracellular substances in any of early batch culture references. This obviously suffers from some limitations, as there really exist intracellular substances in fermentation processes. In view of the difficulties in measuring the concentrations of intracellular substances, we judge the reliability of numerical solution for the concentrations of intracellular substances in terms of some basic characteristics of biological system. Kitano argued that biological robustness is a property of the system whose purpose is to maintain a certain function despite external and internal perturbations that is ubiquitously observed in various aspects of biological systems [27–29]. Stelling deemed that robustness is a fundamental feature of living systems where its relationship with evolution—trade-offs among robustness, fragility, resource demands, and performance—provides a possible framework for how biological systems have evolved and been organized [30]. Perc and Marhl defined the biological robustness, which is usually evaluated by the sensitivity analysis [31] and frequency [32]. In continuous culture, some researchers have quantitatively defined the biological robustness in the approximately steady state [33,34]. In our previous work [9], we quantitatively defined the biological robustness of batch culture. However, such definition ignores the influence of the global regulation of gene expression.

During the glycerol metabolism by *K. pneumoniae*, it is most reasonable for 1,3-PD to pass the cell membrane by passive diffusion coupled with facilitated transport [35]. In addition, the intracellular 1,3-PD concentration depends on the conversion of 3-HPA, whereas the accumulation of 3-HPA during fermentation of glycerol possibly causes growth cessation [22]. However, there are still some uncertain factors in the fermentation, especially whether 3-HPA inhibits the formation of other intracellular substances or such intracellular substances exert influence on the formation of 3-HPA. With this in mind, the metabolic process consisting of the uncertainty of metabolic mechanism is actually a hybrid process [36], which can be described by a nonlinear hybrid dynamical system.

In this paper, taking into account the above mentioned factors, we give 576 possible metabolic pathways and establish a fourteen-dimensional nonlinear hybrid dynamical system with uncertain system parameters and pathway parameters, for characterizing the batch culture of the expression of gene–mRNA–enzyme-product according to the repression of the *dha regulon* by 3-HPA. Some properties of the hybrid system are discussed. Due to the lack of information concerning intracellular substances, similar to literature [31,32], enlightened by the qualitative description of the biological robustness given by Kitano [27–29] and h-stability [37], we propose a quantitative definition of biological robustness for intracellular substance concentrations in batch culture. Such biological robustness, which is defined for the overall process of batch culture on account of the absence of equilibrium points, is different from quantitative description of biological robustness for continue culture in the approximately steady state [33,34]. Our aim is to determine the most possible metabolic pathway and corresponding system parameters of the hybrid system. To this end, taking the relative error between the experimental data and the computational values of the extracellular substances together with the proposed biological robustness of the intracellular substances as a cost function, we establish an identification model subject to the hybrid system, parameter constraints and continuous state inequality constraints that restrict the state variables at an infinite number of time points. The identification model is transformed by constraint transcription and local smoothing approximate techniques [38]. Moreover, the model includes 17 280 system parameters and 5760 pathway parameters. This makes it a very complicated task to solve the identification model by a serial program. With this in mind, we propose a parallel improved differential evolution algorithm to determine the most possible metabolic pathway under various initial conditions. Applying the proposed algorithm, in