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Sensitivity analysis and identification of kinetic parameters in batch fermentation of glycerol

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ABSTRACT

A nonlinear dynamical system was established in our preceding work to describe the batch and continuous bioconversions of glycerol to 1,3-propanediol by *Klebsiella pneumoniae*. The purpose of this article is to analyze the sensitivity of kinetic parameters of the dynamical system and identify their values from experiment. A global sensitivity analysis approach is constructed by combining the local technique with the Monte Carlo method. With only those parameters of higher sensitivity as design variables, we propose a parameter identification model and solve it by a gradient-based simulated annealing algorithm. Numerical results show that our methods are feasible and efficient.

1. Introduction

The bioconversion of glycerol by *Klebsiella pneumoniae* (*K. pneumoniae*) to 1,3-propanediol (1,3-PD) is of interest to industry because of the increasing glycerol surplus on the market and the potential uses of 1,3-PD [1]. Since the 1980s, several mathematical models have been established to describe this bioconversion process [2–5].

In our preceding work [6], a novel mathematical model was proposed to describe the batch and continuous fermentations of glycerol, in which the enzyme-catalytic kinetics on the reductive pathway, the transport mechanisms of glycerol and 1,3-PD across cell membrane, together with the inhibition of 3-hydroxypropionaldehyde (3-HPA) to glycerol dehydratase (GDHt) and 1,3-PD oxydoreductase (PDOR) are all taken into consideration. More influence factors in the fermentation process gives rise to more kinetic parameters, which usually are set to their expected values or fitted to experimental data. However, it is difficult to identify or optimize the kinetic parameters for such an over parameterized model. In consideration of the fact that not all parameters have a significant influence on the behavior of the model, sensitivity analysis technique is needed to identify whether parameters are "significant".

Sensitivity analysis deals with the influence that small changes in nominal values of model parameters exerts on model results [7]. An important classification of the existing methods refers to the way that the parameters are treated. In local sensitivity analysis (or called "one-factor-at-a-time" analysis), only one parameter at-a-time is varied to a given percentage of its expected values while keeping all other model parameters fixed to their expected value [8]. This approach means that the analysis concentrates on estimating the local impact of a parameter on the model output. Opposed to this, global techniques analyze the whole parameter space at once.

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A local analysis method can be integrated to a global one by various methods [9,10], one of which is the sampling-based approach. The Monte Carlo method is one of global sampling methods, which scans in a random or systematic way the entire range of possible parameter values and possible parameter sets [10]. Therefore, combining with Monte Carlo methods, local sensitivity analysis gets integrated to a global sensitivity analysis approach, which is both effective and widely used [11,12].

Up to date, there are a large number of researches developed for parameter identification of kinetic models in glycerol fermentation [13–15]. However, work concerning parameter sensitivity analysis is scarce.

In the present work, a nonlinear dynamical system presented in our preceding work is investigated. To assess the influences of the kinetic parameters on the behavior of the nonlinear dynamical system, we develop a global sensitivity analysis method by combining an existing local technique with Monte Carlo sampling of the parameter space. For the purpose of determining those parameters of higher sensitivity, a parameter identification model is proposed, in which the continuous state inequality constraints are dealt with via the constraint transformation and local smoothing technique, and solved by a gradient-based simulated annealing algorithm, where the gradients of the constraint functions are calculated. Finally, the proposed methods are carried out on the basis of four groups of real experiments in batch culture.

This paper is organized as follows. In Section 2, we briefly introduce the nonlinear dynamical system of glycerol batch fermentation. Section 3 explores a novel global sensitivity analysis technique. A parameter identification model is presented in Section 4. In Section 5, a gradient-based algorithm is developed. Section 6 shows numerical results. Conclusions are presented at the end of the paper.

2. Nonlinear hybrid dynamical system

Let $\mathbf{x} = (x_1, x_2, \ldots, x_8)^T$, the components of which represent the concentrations of biomass (g/L), extracellular glycerol (mmol/L), extracellular 1,3-PD (mmol/L), acetate (mmol/L), ethanol (mmol/L), intracellular glycerol (mmol/L), 3-HPA (mmol/L), intracellular 1,3-PD (mmol/L) in the reactor, respectively. In our preceding work [6], we concluded that there exists a facilitated mechanism for 1,3-PD across cell membranes. Therefore, we assume that both glycerol and 1,3-PD pass the cell membrane by passive diffusion coupled with facilitated transport in this paper. For any positive integer n, we use the notation I_n to represent the set $\{1, 2, \ldots, n\}$. The nonlinear dynamical system of glycerol batch fermentation under this assumption can be described by

$$\dot{\mathbf{x}} = \mathbf{F}(\mathbf{x}, \mathbf{u}), \tag{1}$$

where $\mathbf{u}$ denotes the kinetic parameter vector to be identified. The right hand side of (1) is of the form $\mathbf{F}(\mathbf{x}, \mathbf{u}) = (f_1(\mathbf{x}, \mathbf{u}), \ldots, f_8(\mathbf{x}, \mathbf{u}))^T$ with the components defined as

$$f_1(\mathbf{x}, \mathbf{u}) = \mu x_1, \tag{2}$$

$$f_2(\mathbf{x}, \mathbf{u}) = -q_2 x_1, \tag{3}$$

$$f_3(\mathbf{x}, \mathbf{u}) = q_3 x_1, \tag{4}$$

$$f_4(\mathbf{x}, \mathbf{u}) = q_4 x_1, \tag{5}$$

$$f_5(\mathbf{x}, \mathbf{u}) = q_5 x_1, \tag{6}$$

$$f_6(\mathbf{x}, \mathbf{u}) = \frac{1}{k_7}\left(k_8 \frac{x_2}{x_2 + k_9} + k_{10}(x_2 - x_6) N_{R_+}(x_2 - x_6) - q_{20}\right) - \mu x_6, \tag{7}$$

$$f_7(\mathbf{x}, \mathbf{u}) = k_{11} \frac{x_6}{K_m^G\left(1 + \frac{x_7}{k_{12}}\right) + x_6} - k_{13} \frac{x_7}{K_m^P + x_7\left(1 + \frac{x_7}{k_{14}}\right)} - \mu x_7, \tag{8}$$

$$f_8(\mathbf{x}, \mathbf{u}) = k_{13} \frac{x_7}{K_m^P + x_7\left(1 + \frac{x_7}{k_{14}}\right)} - k_{15} \frac{x_8}{x_8 + k_{16}} - k_{17}(x_8 - x_3) N_{R_+}(x_8 - x_3) - \mu x_8. \tag{9}$$

Here, K_m^G and K_m^P are Michaelis–Menten constants. $N_{R_+}(\cdot)$, the indicator function of a real number ξ, is defined as

$$N_{R_+}(\xi) = \begin{cases} 1, & \xi > 0, \\ 0, & \xi \le 0. \end{cases}$$

The specific cell growth rate μ, the specific consumption rate of extracellular glycerol q_2 and the specific formation rate of extracellular 1,3-PD q_3 are expressed in [6]

$$\mu = \mu_m \frac{x_2}{x_2 + K_s}\left(1 - \frac{x_2}{x_2^*}\right)\left(1 - \frac{x_3}{x_3^*}\right)\left(1 - \frac{x_4}{x_4^*}\right)\left(1 - \frac{x_5}{x_5^*}\right), \tag{10}$$

$$q_2 = k_1 \frac{x_2}{x_2 + k_2} + k_3(x_2 - x_6) N_{R_+}(x_2 - x_6), \tag{11}$$

$$q_3 = k_4 \frac{x_8}{x_8 + k_5} + k_6(x_8 - x_3) N_{R_+}(x_8 - x_3), \tag{12}$$