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Sensitivity analysis and parameter identification of nonlinear hybrid systems for glycerol transport mechanisms in continuous culture

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HIGHLIGHTS

- A fourteen-dimensional hybrid dynamic system for glycerol transport mechanisms is described.
- A global sensitivity analysis approach of parameters is constructed.
- A parameter identification model concerning robustness of system is proposed.
- A parallel algorithm is constructed to solve the model.

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ABSTRACT

In this paper, we establish a modified fourteen-dimensional nonlinear hybrid dynamic system with genetic regulation to describe the microbial continuous culture, in which we consider that there are three possible ways for glycerol to pass the cell's membrane and one way for 1,3-PD (passive diffusion and active transport). Then we discuss the existence, uniqueness, continuous dependence of solutions and the compactness of the solution set. We construct a global sensitivity analysis approach to reduce the number of kinetic parameters. In order to infer the most reasonable transport mechanism of glycerol, we propose a parameter identification model aiming at identifying the parameter with higher sensitivity and transport of glycerol, which takes the robustness index of the intracellular substance together with the relative error between the experimental data and the computational values of the extracellular substance as a performance index. Finally, a parallel algorithm is applied to find the optimal transport of glycerol and parameters.

1. Introduction

The bioconversion of glycerol to 1,3-propanediol (1,3-PD) has caused more attention due to its advantages, such as low cost, high production and no pollution (Homann et al., 1990; Biebl et al., 1999). However, its production of 1,3-propanediol is low compared with the traditional chemical production. Hence, many researchers have tried to research the kinetic model of fermentation to improve the productivity of 1,3-PD. Since 1980s glycerol bioconversion to 1,3-PD by *Klebsiella pneumoniae* has been widely investigated (Menzel et al., 1997).

Zeng and Deckwer (1995) proposed a five-dimensional dynamical system, in which the bioconversion of glycerol to 1,3-PD was described by an excess kinetic model. In 2000, the improved model by Zhilong et al. (2000) has become more feasible to describe phenomena of oscillation in continuous fermentation. Then Gao et al. (2005) and Li et al. (2006) investigated the parameter identification, stability of equilibrium and optimal control of the model. Lately, Wang et al. (2012), Wang et al. (2013) and Yuan et al. (2014) made some further research about complex metabolic network in batch and Fed-Batch culture.

Sun et al. (2008) firstly proposed an eight-dimensional nonlinear dynamical system involving concentration changes of three intracellular substances (glycerol, 1,3-PD and 3-hydroxypropionaldehyde (3-HPA)) and two key enzymes (1,3-PD oxydoreductase (PDOR) and glycerol dehydratase (GDHt)) in glycerol fermentation to 1,3-PD by *K. pneumoniae*. In 2011, based on Sun's model, Wang et al. (2011) inferred that the most possible ways across the cell membrane of glycerol and 1,3-PD are both passive diffusion and active transport, considering that the transport mechanisms of glycerol and 1,3-PD are still exactly unknown. Yaqin et al. (2012) proposed a fourteen-dimensional nonlinear dynamic system concerning the repression of the dha regulon and two key enzymes by 3-HPA to describe the continuous culture, which is more accurate than eight-dimensional model.

However, exact transport mechanisms of glycerol and 1,3-PD in the continuous culture are still unknown, although there are some literatures (Wang et al., 2011; Zhai et al., 2011) which inferred the

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most reasonable transport mechanisms of glycerol and 1,3-PD in the eight-dimensional dynamical system about continuous culture. So for the fourteen-dimensional nonlinear hybrid dynamical system in this paper, we assumed that 1,3-PD passes the cell membrane by both passive diffusion and active transport in terms of Juan Wang's (2011) paper and we considered all three possible transport mechanisms of glycerol (active transport, passive transport and the combination of the two ways).

In addition, although there are many works (Wang et al., 2011; Zhai et al., 2011; Shen et al., 2012) on parameter identification in continuous culture, these works are not considered about parameter sensitivity analysis. Considering that the fourteen-dimensional model involved more parameters than before, we propose a novel global sensitivity analysis method to reduce the parameters in this paper because of the high computational cost for the parameter identification model as follows.

In this paper, some properties of the system are discussed. To infer the most reasonable transport mechanism of glycerol, a parameter identification model is proposed for the parameter with higher sensitivity and transport of glycerol, which takes the robustness index of the intracellular substance together with the relative error between the experimental data and the computational values of the extracellular substance as a performance index. Finally, a parallel algorithm is constructed to solve the identification model. Then, we obtain the optimal transport of glycerol and parameters of the corresponding system.

The rest of this paper is organized as follows: in Section 2, a fourteen-dimensional nonlinear dynamical system is presented; in Section 3, the existence, uniqueness and the continuity of solutions are discussed; in Section 4, a global sensitivity analysis approach is proposed to reduce the parameter to be identified; in Section 5, a quantitative description of the material about the system robustness, the identification model and feasible parallel algorithm to it are presented; in Section 6, the numerical result of the parameter identification model is given; conclusions are presented at the end of the paper.

2. Nonlinear dynamical system with genetic regulation

During the glycerol metabolism by *K. pneumoniae*, considering that the transport mechanism of glycerol across cell membrane in the reductive pathway is still unclear, we take into consideration all three possible transport mechanisms of glycerol. And the key problem is to infer the most possible transport mechanism of glycerol.

According to the model in Yaqin et al. (2012), let $\mathbf{x}(t)=(x_1(t),x_2(t),x_3(t),\ldots,x_{14}(t))^T\in\mathbb{R}^{14}$ be the state vector, where $x_1(t),x_2(t),x_3(t),\ldots,x_5(t)$ are the concentrations of biomass of *K. pneumoniae*, extracellular glycerol, extracellular 1,3-PD, acetate and ethanol, and $x_6(t),x_7(t),x_8(t),\ldots,x_{14}(t)$ denote the intracellular concentrations of glycerol, 3-HPA, 1,3-PD, m_R, free repressor, m_{GDHt}, GDHt, m_{PDOR} and PDOR at time t respectively. To simplify notations, let $I_n:=\{1,2,\ldots,n\}$.

Then, the nonlinear dynamical system of glycerol fermentation in a continuous culture, denoted by $NDS(D,C_{s_0},\mathbf{u},\ell)$, can be described by

$$\begin{cases}\dot{\mathbf{x}}(t)=\mathbf{f}(\mathbf{x}(t),\mathbf{u}^{(k)},\ell^{(k)}), & t\in I:=[0,t_f]\\ \mathbf{x}(t_0)=\mathbf{x}_0\end{cases} \tag{1}$$

where $\mathbf{u}^{(k)}$ denotes the kinetic parameter vector to be identified, $k\in I_3$. Denoting $\ell^{(k)}=(l_1^{(k)},l_2^{(k)})^T\in D_l:=\{\ell^{(1)},\ell^{(2)},\ell^{(3)}\}=\{(0,1)^T,(1,0)^T,(1,1)^T\}$ as the kth transport mechanism of glycerol across cell membrane, $k\in I_3$. $I:=[0,t_f]$ is the interval of reaction time, and $\mathbf{x}_0$ is the initial state. To simplify notation, we denote $\mathbf{u}^{(k)}$ as $\mathbf{u}$ and $\ell^{(k)}$ as ℓ if there is no confusion.

The right hand side of (1) is of the form $\mathbf{f}(\mathbf{x}(t),\mathbf{u},\ell):=(f_1(\mathbf{x}(t),\mathbf{u},\ell),\ldots,f_{14}(\mathbf{x}(t),\mathbf{u},\ell))^T$ with the components defined as

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

$$f_2(\mathbf{x}(t),\mathbf{u},\ell)=D(C_{s_0}-x_2(t))-q_2(\mathbf{x})x_1(t) \tag{3}$$

$$f_3(\mathbf{x}(t),\mathbf{u},\ell)=q_3(\mathbf{x})x_1(t)-Dx_3(t) \tag{4}$$

$$f_4(\mathbf{x}(t),\mathbf{u},\ell)=q_4(\mathbf{x})x_1(t)-Dx_4(t) \tag{5}$$

$$f_5(\mathbf{x}(t),\mathbf{u},\ell)=q_5(\mathbf{x})x_1(t)-Dx_5(t) \tag{6}$$

$$\begin{aligned}f_6(\mathbf{x}(t),\mathbf{u},\ell)=&\frac{1}{u_7}\Big(l_1u_8\frac{x_2(t)}{x_2(t)+u_9}+l_2u_{10}(x_2(t)-x_6(t))N_+(x_2(t)\\&-x_6(t))-q_2^0(\mathbf{x})\Big)-\mu(\mathbf{x})x_6(t)\end{aligned} \tag{7}$$

$$\begin{aligned}f_7(\mathbf{x}(t),\mathbf{u},\ell)=&\frac{u_{11}x_{12}(t)x_6(t)}{K_M^G\left(1+\frac{x_7(t)}{u_{12}}\right)+x_6(t)}-\frac{u_{13}x_{14}(t)x_7(t)}{K_M^P+x_7(t)\left(1+\frac{x_7(t)}{u_{14}}\right)}\\&-\mu(\mathbf{x})x_7(t)-\frac{u_{15}u_{16}^2u_{17}x_7(t)}{x_7(t)+u_{18}}\end{aligned} \tag{8}$$

$$\begin{aligned}f_8(\mathbf{x}(t),\mathbf{u},\ell)=&\frac{u_{13}x_{14}(t)x_7(t)}{K_M^P+x_7(t)\left(1+\frac{x_7(t)}{u_{14}(t)}\right)}-\frac{u_{19}x_8(t)}{x_8(t)+u_{20}}-\mu(\mathbf{x})x_8(t)\\&-u_{21}(x_8(t)-x_3(t))N_+(x_8(t)-x_3(t))\end{aligned} \tag{9}$$

$$f_9(\mathbf{x}(t),\mathbf{u},\ell)=\frac{x_7(t)+u_{18}}{x_9(t)+u_{18}+u_{22}x_7(t)}-(u_{23}+\mu(\mathbf{x}))x_9(t) \tag{10}$$

$$f_{10}(\mathbf{x}(t),\mathbf{u},\ell)=u_{24}x_7(t)-(u_{25}+\mu(\mathbf{x}))x_{10}(t)-u_{15}u_{16}u_{17}\frac{x_7(t)}{x_7(t)+u_{18}} \tag{11}$$

$$f_{11}(\mathbf{x}(t),\mathbf{u},\ell)=\frac{x_7(t)+u_{18}}{x_7(t)+u_{18}+u_{22}x_7(t)}-(u_{26}+\mu(\mathbf{x}))x_{11}(t) \tag{12}$$

$$f_{12}(\mathbf{x}(t),\mathbf{u},\ell)=u_{27}x_{11}(t)-(u_{28}+\mu(\mathbf{x}))x_{12}(t) \tag{13}$$

$$f_{13}(\mathbf{x}(t),\mathbf{u},\ell)=\frac{x_7(t)+u_{18}}{x_7(t)+u_{18}+u_{22}x_7(t)}-(u_{29}+\mu(\mathbf{x}))x_{13}(t) \tag{14}$$

$$f_{14}(\mathbf{x}(t),\mathbf{u},\ell)=u_{30}x_{13}(t)-(u_{31}+\mu(\mathbf{x}))x_{14}(t) \tag{15}$$

where D and C_{s_0} denote the dilution rate and the glycerol concentration respectively. ${K_M}^G$ and ${K_M}^P$ denote Michaelis–Menten constants of enzymes GDHt and enzymes PDOR, with 0.53 mmol L^{-1} and 0.14 mmol L^{-1} respectively.

The specific cell growth rate can be expressed based on Gao et al. (2005) as follows:

$$\mu(\mathbf{x})=\mu_m\frac{x_2(t)}{x_2(t)+K_s}\prod_{i=2}^{5}\left(1-\frac{x_i(t)}{\overline{x_i}(t)}\right) \tag{16}$$

where μ_m is the maximum specific growth rate of biomass with 0.67 h^{-1}, K_s is the Monod saturation constant with 0.28 mmol L^{-1}. $\overline{x_i}(t)$ $(i=2,3,4,5)$ denotes the upper bound of $x_i(t)$.

While the uptake of extracellular glycerol is considered as a "black box" model, its specific consumption rate can be expressed by

$$q_2^0(\mathbf{x})=m_2+\frac{\mu(\mathbf{x})}{Y_2}+\triangle q_2\frac{x_2(t)}{x_2(t)+K_2^*} \tag{17}$$

Considering three possible transport mechanisms of glycerol across cell membrane, the specific consumption rate of extracellular glycerol can be given by (Wang et al., 2011)

$$q_2(\mathbf{x})=l_1u_1\frac{x_2(t)}{x_2(t)+u_2}+l_2u_3(x_2(t)-x_6(t))N_+(x_2(t)-x_6(t)) \tag{18}$$