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Sensitivity analysis and parameter identification for a nonlinear time-delay system in microbial fed-batch process

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ABSTRACT

Developing suitable dynamic models of bioprocess is a difficult issue in bioscience. In this paper, considering the microbial metabolism mechanism, i.e., the production of new biomass is delayed by the amount of time it takes to metabolize the nutrients, in glycerol bioconversion to 1,3-propanediol, we propose a nonlinear time-delay system to formulate the fed-batch fermentation process. Some important properties are also discussed. Then, in view of the effect of time-delay and the high number of kinetic parameters in the system, the parametric sensitivity analysis is used to determine the key parameters. Finally, a parameter identification model is presented and a global optimization method is developed to seek the optimal key parameters. Numerical results show that the nonlinear time-delay system can describe the fed-batch fermentation process reasonably.

1. Introduction

Time-delay systems are increasingly used in numerous application areas that include physiological kinetics, population dynamics and control problems [1,2]. Parameter identification is usually done by comparing the system output observed in practice with the system output predicted by the model, and then adjusting the parameters accordingly. Works on identification of time-delay systems have shown the complexity of the question [3]. As a result, the problem of identifying delays and parameters in time-delay systems has been extensively studied, see, for example, [4–7].

During the past several decades, there has been growing interest in microbial production of 1,3-propanediol (1,3-PD) throughout the world because of its lower cost, higher production and no pollution [8]. Among various microbial production methods of 1,3-PD, dissimilation of glycerol by *Klebsiella pneumoniae* (*K. pneumoniae*) has been widely investigated since 1980s [9]. Glycerol fermentation by *K. pneumoniae* is a complex bioprocess since the microbial growth is subjected to multiple inhibitions of substrate and products, such as glycerol, 1,3-PD, ethanol and so on [10]. The researches about the fermentation include the quantitative description of the cell growth kinetics, the metabolic overflow kinetics of substrate consumption and product formation as well as the optimization of feed strategy of substrate in fed-batch culture [11–13]. More importantly, time-delays exist in the process of glycerol bioconversion to 1,3-PD [14,15]. Several reasons may be responsible for the occurrence of the delays in the fermentation process: a cell has to undergo some change or growth process for which it needs some time before it reacts with others; the substrate and the products have to be transported across the cell membrane requiring a certain amount of time for transport; sometimes, either because of lack of knowledge or in order to reduce complexity it is appropriate to omit a number of intermediate steps in the reaction system for which the

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processing time is not negligible and has to be implemented as a delay [16,17]. Thus, time-delays have to be incorporated into mathematical models formulating the fermentation process.

Regarding the various fermentation techniques, including batch culture, fed-batch culture and continuous culture, the most efficient cultivation method appears to be a fed-batch culture which corrects pH by alkali addition with glycerol supply [10]. For this reason, modeling, optimization and control of the fermentation process have been extensively studied in the literature [11,18–26]. Unstructured and nonsegregational models were initially used to model fed-batch fermentation. The models have been used for optimal control studies by a number of researchers [18–21]. Recently, based on an assumption that the feed of glycerol only occurs at impulsive instants, nonlinear impulsive systems have been extensively investigated to formulate the fermentation process [22]. After this, the properties, parameter identification problem and optimal control problem, in which the impulsive magnitudes are taken as the control function, for the system have been investigated [22–24]. Nonetheless, since the feeding rate of glycerol is finite, it is not reasonable to describe the actual fed-batch fermentation process by the impulsive dynamical system. In contrast, taking the feed of glycerol as a time-continuous process, a nonlinear multistage system was proposed in [11]. The parameter identification of the nonlinear multistage system was subsequently discussed [27]. Numerical simulations in [27] showed that the nonlinear multistage system could describe the fed-batch process better than the nonlinear impulsive system. However, the parameters in the first batch phase and sequent feed phase are taken different values and no parametric sensitivity analysis is considered in [27]. Properties and optimization algorithms for the optimal control problem involving the nonlinear multistage system, in which the feeding rate of glycerol is taken as the control function, were then investigated in [11,25,26]. Although the above results are interesting, time-delays are ignored in the above researches.

In this paper, considering the metabolism mechanism of microorganism, i.e., the production of new biomass is delayed by the amount of time it takes to metabolize the nutrients, in the fed-batch culture, we propose a nonlinear time-delay system to formulate the fermentation process. Then, due to the effect of time delay and the high number of the kinetic parameters in the system, the parametric sensitivity analysis is used to determine the key parameters. By the way, a nonlinear time-delay system was proposed to formulate the batch fermentation process [28]. Nonetheless, the parametric sensitivity analysis is not discussed in [28]. Parametric sensitivity analysis, i.e., the study of the influence of the parameters of a model on its solution, plays an important role in design, modeling and parameter identification [29,30]. In particular, the sensitivity analysis of time-delay systems had been investigated in the literature, see, e.g., [31–34]. Nevertheless, calculating the sensitivity functions is a very difficult task.

By solving the sensitivity functions numerically using the auxiliary system method, the key parameters are obtained. On this basis, a parameter identification model involving the nonlinear time-delay system is presented and a global optimization method is developed to seek the optimal key parameters. Numerical results show that the nonlinear time-delay system can describe the fed-batch fermentation process better than the results previously reported.

The remainder of this paper is organized as follows. In Section 2, the nonlinear time-delay system and its properties are discussed. A description is carried out about the nonlinear time-delay system of fed-batch process in Section 2.1, and some important properties of the system are discussed in Section 2.2. Section 3 investigates the parametric sensitivity analysis of the nonlinear time-delay system. Section 3.1 gives the definitions of the sensitivity functions, and Section 3.2 shows the numerical simulation results. The parameter identification problem is discussed in Section 4. The parameter identification model is presented in Section 4.1, a computational procedure to seek the optimal key parameters is developed in Section 4.2, and the numerical results are illustrated in Section 4.3. Finally, conclusions are provided in Section 5.

2. Problem formulation

2.1. Nonlinear time-delay systems

The fed-batch culture begins with a batch culture. After the exponential growth phase (i.e., a period in which the number of new bacteria appearing per unit time is proportional to the present population), glycerol and alkali are continuously added to the fermentor. This helps to maintain a suitable environment for cells growth. At the end of the feed, a batch phase starts again. The above processes repeat until the end of the final batch phase. During the whole fermentation process, the production of new biomass is delayed by the amount of time it takes to metabolize the nutrients. Thus, it is necessary to include time-delays for the biomass formation in modeling the fermentation process. According to the fermentation process, we assume that.

(H_2) The concentrations of reactants are uniform in reactor. Nonuniform space distribution is ignored.
(H_2) During the process of fed-batch culture, only glycerol and alkali are fed into the reactor.
(H_3) The feeding rates of glycerol and alkali are both uniform at various discrete time intervals. Moreover, the feeding velocity ratio of alkali to glycerol r is a constant.
(H_4) Biomass, substrate, 1,3-PD, acetate and ethanol concentrations in reactor at time t, are determined by biomass concentration at time $t - \tau$.