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Robust optimization for nonlinear time-delay dynamical system of *dha regulon* with cost sensitivity constraint in batch culture

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ABSTRACT

Time-delay dynamical systems, which depend on both the current state of the system and the state at delayed times, have been an active area of research in many real-world applications. In this paper, we consider a nonlinear time-delay dynamical system of *dha-regulon* with unknown time-delays in batch culture of glycerol bioconversion to 1,3-propanediol induced by *Klebsiella pneumonia*. Some important properties and strong positive invariance are discussed. Because of the difficulty in accurately measuring the concentrations of intracellular substances and the absence of equilibrium points for the time-delay system, a quantitative biological robustness for the concentrations of intracellular substances is defined by penalizing a weighted sum of the expectation and variance of the relative deviation between system outputs before and after the time-delays are perturbed. Our goal is to determine optimal values of the time-delays. To this end, we formulate an optimization problem in which the time delays are decision variables and the cost function is to minimize the biological robustness. This optimization problem is subject to the time-delay system, parameter constraints, continuous state inequality constraints for ensuring that the concentrations of extracellular and intracellular substances lie within specified limits, a quality constraint to reflect operational requirements and a cost sensitivity constraint for ensuring that an acceptable level of the system performance is achieved. It is approximated as a sequence of nonlinear programming sub-problems through the application of constraint transcription and local smoothing approximation techniques. Due to the highly complex nature of this optimization problem, the computational cost is high. Thus, a parallel algorithm is proposed to solve these nonlinear programming sub-problems based on the filled function method. Finally, it is observed that the obtained optimal estimates for the time-delays are highly satisfactory via numerical simulations.

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1. Introduction

The microbial conversion of glycerol induced by *Klebsiella pneumonia* (*K. pneumonia*) to 1,3-propanediol (1,3-PD) is particularly attractive to industry since it is environmentally safe and has renewable feedstock [1–5]. The fermentation process can be divided into three types: batch culture (all substrate is added to the fermentor at the beginning of the reaction); continuous culture (substrate is added continuously during the reaction); and fed-batch cultures (the process switches between batch and continuous modes) [6,7]. There are three reasons for the necessity of studying batch culture [8]. First, batch culture lays an experimental foundation for fed-batch or continuous culture. In other words, batch culture is a part of fed-batch or continuous cultures. Second, batch culture compared to fed-batch or continuous culture can obtain the highest conversion rates because it can express the process of the excess metabolism for the bioconversion of glycerol, while other cultures fail to achieve this. Finally, the waste water, in which the concentration of glycerol is relatively low for the lipidic chemical or biodiesel company, is appropriate to the process of batch culture. In the laboratory, it is impractical to carry out a sufficient number of experiments so as to obtain high production concentration and molar yield 1,3-PD to glycerol. Thus, the need for the mathematical model or system, which describes this microbial process, is evident. In [9], a substrate-sufficient kinetic system is presented to describe substrate (glycerol) consumption and extracellular substances (1,3-PD, acetate and ethanol) formation in batch culture. A nonlinear dynamical system involving concentration changes of three intracellular substances and two key enzymes is proposed in [10]. Based on these mathematical models, batch culture has become a hot research topic, including suboptimal control problems [11], robust optimal control problems [12], multi-stage system [13–15], sensitivity analysis [16], robust identification problems [17], pathway identification problems [18], stochastic model [19] joint estimation [20] and hybrid system [21].

However, for all the papers mentioned above, the global regulation of gene expression is not taken into consideration. There are four typical key enzymes for the glycerol metabolism process, including 1,3-PD oxydoreductase (PDOR), glycerol dehydratase (GDHt), glycerol dehydrogenase (GDH) and dihydroxyacetone kinase I (DHAK I). These enzymes are coordinately expressed and induced by glycerol or dihydroxyacetone (DHA). The genes, which are called the *dha regulon* [22,23], are organized as a cluster on the chromosome for these four enzymes. The *dha regulon* can regulate the four key enzymes. The expression of the *dha regulon* will be repressed by the intermediate 3-HPA [24]. These facts make the *dha regulon* the key factor in the process of glycerol metabolism. In [25], a fourteen-dimensional nonlinear dynamical system was established to describe the batch culture including enzyme-catalytic kinetics and genetic regulation. More recently in [26], a pathway identification for a nonlinear hybrid system is studied on the basis of the results in [25].

Unfortunately, in [26], there is one limitation: time-delay is not considered. Time-delay systems are frequently encountered in a multitude of real-world applications over the past decade, for example, see [27–36] and the references cited therein. Several reasons may be responsible for the occurrence of the delays in the fermentation process: (i) a cell has to undergo some change or growth process for which it needs some time before it reacts with others; (ii) the substrate and the products have to be transported across the cell membrane requiring a certain amount of time for transport; (iii) 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 processing time is not negligible and has to be implemented as a delay [37]. Thus, time-delays have to be incorporated into mathematical models formulating the fermentation process. In many systems, however, the time-delays are not known exactly [38]. Hence, time-delay estimation is one of the key issues in the study of time-delay systems [39]. A parameter identification problem for a nonlinear time-delay system behaves as follows: at each time t , the system's instantaneous rate of change depends not only on its current state, but also on its state at times $t-\tau_i, i=1,\ldots,m,$ where each τ_i is a so-called state-delay [40].

Considering the difficulties in measuring the concentrations of intracellular substances, biological robustness is a popular concept to judge the reliability of numerical solution for the concentrations of intracellular substances [41]. Perc and Marhl [42,43] defined the biological robustness, which is usually evaluated by the sensitivity analysis and frequency. Stelling [44] 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. Kitano [45,46] argued that biological robustness is a property that allows a system to maintain its functions despite external and internal perturbations. With this motivation, we quantitatively defined the biological robustness of batch culture in our previous work [26], which has one limitation: such definition only considers the expectation of the relative deviation between system outputs before and after system parameters are perturbed. One of our contributions in the paper overcomes this limitation.

Generally, a nonlinear dynamic system is an idealized description of the actual behavior of a biological or engineering system [47]. During the life span of the system, the values of some of its coefficients may change [48]. For an optimization problem governed by a nonlinear dynamical system, the optimal cost function obtained is under the assumption that the coefficients of the dynamical system are fixed [49]. Given some of these system coefficients are subject to variation, the sensitivity of the variation of these coefficients should be taken into consideration [50]. However, in microbial fermentation, there are few papers dedicated to this important issue.

In the paper, in batch culture of glycerol bioconversion to 1,3-PD induced by *K. pneumonia*, we consider a nonlinear time-delay dynamical system of *dha-regulon* with unknown time-delays. Some important properties and strong positive