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Research paper

Global behavior analysis for stochastic system of 1,3-PD continuous fermentation

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ABSTRACT

Global behavior for stochastic system of continuous fermentation in glycerol bio-dissimilation to 1,3-propanediol by *Klebsiella pneumoniae* is analyzed in this paper. This bioprocess cannot avoid the stochastic perturbation caused by internal and external disturbance which reflect on the growth rate. These negative factors can limit and degrade the achievable performance of controlled systems. Based on multiplicity phenomena, the equilibriums and bifurcations of the deterministic system are analyzed. Then, a stochastic model is presented by a bounded Markov diffusion process. In order to analyze the global behavior, we compute the control sets for the associated control system. The probability distributions of relative supports are also computed. The simulation results indicate that how the disturbed biosystem tend to stationary behavior globally.

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1. Introduction

In many biological systems, there are multiplicity, bifurcations or even chaos which make the system behavior more complicated but still fellow certain rules. Furthermore, real bioprocess have to endure both internal and external random disturbance. These factors are main reasons that lead to oscillatory and instability. Thus, models that include stochastic noises are more accurate representations of the biology properties when compared to deterministic models. A lot of researches concentrated on how to explore the biosystem characters under the affection of certain noise. In the scale of micro-organisms, the noise can be regarded as small and bounded perturbation.

1,3-propanediol (1,3-PD) has been paid attention in microbial production throughout the world because of its lower cost, higher production and no pollution [29]. A great deal of researches on this bioconversion process of 1,3-PD has been made, including experimental investigation of the multiple inhibitions in the fermentation [35], modeling or parameter identification of this complex bioprocess [11,34], discussion on the multiplicity phenomena which occurred in the experiments [30] and metabolic flux or metabolic pathway analysis. In addition, fermentation used to be classified in view of the mode chosen for the bioprocess [18]: batch culture, where bacteria and substrate are added at the very beginning of the process, and there is no addition or removal from the reactor during the whole process [32,37]; fed-batch culture, where glycerol

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and alkali are added discontinuously to the reactor at constant rates without the removal of medium [3,12,19–21]; and continuous culture, where fresh medium is added continuously to replenish consumed substrate while old medium is removed during the reaction [38]. Compared with batch and feed-batch cultures, the continuous fermentation is an ideal way for large scale industrial production by virtue of high production strength, good quality and high degree of automation. Furthermore, its steady control has become an important part in metabolic engineering. Not only experimental research on the process of continuous culture has been reported recently, including multiple product inhibition, growth modeling [24], parameter identification [11], path identification [36], but also much the nonlinear dynamic behavior of microorganisms has been the objective of a number of theoretical works [22,26]. Since the bioprocess appears more complicate activities under different experimental and industrial conditions, researches that focus on how to take out models which can describe the process more accurately become more and more valuable. Wang [25] introduced a stochastic model with white noise reflecting on the growth rate to describe the oscillatory phenomena but lack of stability analysis. Wang et al. [27] studied the regularity of stopping time by means of adding the adjustment factor into the fluctuation coefficient. However, it still cannot ensure that the termination conditions are consistent with the actual bioprocess. Furthermore, the fact that Gaussian noise is unbounded and as such there is a positive chance of taking large values contradicts the very nature of a real physical quantity which is always bounded [4]. Thus a suitable bounded noise should be considered. By and large, model improvement and global behavior analysis for the stochastic system of 1,3-PD fermentation process are far to be explored.

Because of memorylessness, Markov diffusion perturbation model is widely applied in engineering, science and biosystem. Its system behavior can be studied by using a variety of approaches: Stochastic analysis, compare, e.g., the standard references [28] or [10], Stochastic flows, compare [1], Imbedding of the stationary process into the flow, Connections with control theory via the support theorem of Stroock and Varadhan [23]. In [5] Colonius et al use a combination of the last two approaches to present the study of global behavior and the connection between topological and control techniques via parameter dependence. And in order to describe a transient phenomenon, near invariance is introduced in [7]. The global theory is used in some two dimensional nonlinear dynamic system of stirred tank reactor with respect to their controllability and reachability properties in [6]. The persistence and continuity of attractors of Lorenz equation with perturbation is also discussed in [6]. But there is hardly any report about research on high dimensional case. In this work, a novel model based on a stochastic noise characterized by the Ornstein–Uhlenbeck equation is proposed for studying the global behavior of five-dimensional nonlinear system of 1,3-PD continuous fermentation such as stationarity, ergodicity and near invariance.

The remainder of is organized as follows. In Section 2, we analyze the equilibriums and bifurcations of the deterministic system. In Section 3, we propose a stochastic differential equation model with a bounded Markov diffusion process and introduce its associated control system by connecting with control theorem and the support theorem. In Section 4, we compute the control sets by using improved CS algorithm and discuss the system behavior under deterministic perturbation. In Section 5, the global behavior under stochastic perturbation is analyzed through numerical method. In the last section, we draw the conclusions and trace the direction for future works.

2. Deterministic models and bifurcations

The continuous fermentation consists of a culture vessel or reactor with growing microorganisms. The vessel is continuously supplied with glycerol as fresh medium. The inflowing medium is instantly mixed with the culture liquid by a stirrer which can ensure good homogeneity of the culture. Meanwhile the process of pouring out the broth by an overflow system is continuous with the same rate of adding glycerol. Thus, the volume of the culture is kept constant. Furthermore, the composition of culture medium, cultivation conditions and analytical methods of fermentative products were similar to those previously reported by Zeng [33]. According to the experiment process, we can make some assumptions, including:

(H1) The concentrations of reactants only change over the fermentation time, i.e. they are uniform in bio-reactor;
(H2) During the continuous process of the culture, adding substrate to the reactor only considers glycerol, and exporting the fermentation broth is by a fixed dilution rate D.

With the above assumptions (H1) and (H2), mass balances of biomass, substrate and products in this continuous fermentation can be regarded as differential mass balances. They can be used to generate differential equations that can provide an effective tool for modeling and understanding the target system. The changes of biomass embody bacterial reproduction and death. 1,3-PD is the target product while acetate and ethanol are by-products. The bioprocess can be described as a nonlinear dynamic system [11]:

$$\begin{cases} \dot{x}_1(t) = (\mu - D)x_1 \\ \dot{x}_2(t) = D(c_{s0} - x_2) - q_2 x_1 \qquad t > 0, \\ \dot{x}_i(t) = q_i x_1 - D x_i, \quad i = 3, 4, 5 \end{cases} \tag{1}$$

$$x_i(t) = x_{i0}, \quad i \in I_5 = \{1, 2, 3, 4, 5\}, \qquad t = 0,$$

where $x_1(t)$, $x_2(t)$, $x_3(t)$, $x_4(t)$, $x_5(t)$ are, respectively, biomass, glycerol, 1,3-PD, acetate and ethanol concentrations at t in reactor. x_{i0} denotes the initial value at time t=0. D is the dilution rate. c_{s0} is the the initial glycerol concentration in feed. The

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