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# Analysis and application of biological robustness as performance index in microbial fermentation

Lei Wang [a,*], Guanming Cheng [a], Enmin Feng [a], Tao Su [a], Zhilong Xiu [b]

[a] School of Mathematical Science, Dalian University of Technology, Dalian 116024, Liaoning, China
[b] Department of Biotechnology, Dalian University of Technology, Dalian 116012, Liaoning, China

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ABSTRACT

Robustness is the fundamental organizational principle of biological systems. Understanding robustness and its intrinsic properties will provide us with a more profound understanding of biological systems, their anomalies, and countermeasures. In this paper, for the microbial fermentation case, we generally present a way to design the performance index to identify the system structure by using the qualitative description of biological robustness. In the specific example, we give the numerical results for inferring the possible ways of transport across the cell membrane by using serial and parallel algorithm respectively, which show that biological robustness' power for applications.



## 1. Introduction

Robustness is a property that allows a system to maintain its functions despite external and internal perturbations [1]. This feature has been ubiquitously observed in various biological examples. For instance, Escherichia coli is capable of chemotaxis over a wide range of chemo-attractant concentrations [2]. The similarities and differences between biological and engineering notions of robustness have since been further developed in a series of papers by Kitano and co-workers and subsequently many researchers have sought to develop a general theory of biological robustness, with perhaps the most successful effort in this direction being the work of Wagner on mutational robustness [3].

Microbial fermentation is an important bioprocess and attracts more and more attentions because of its lower cost, higher production and no pollution. Many researches have been carried out including the quantitative description of the cell growth kinetics of multiple inhibitions, the metabolic overflow kinetics of substrate consumption and product formation [4,5], robust analysis [6,7], dynamical behavior [8] for the models of the continuous cultures, feeding strategy of glycerol [9,10], parameter identification [11,12], optimal control [13–15], complex metabolic network [16], multiple Time-Delays [17–20] and multistage modeling in batch [21–24] and fed-batch culture [25,26] and so on.

One of the essential issues in microbial fermentation is identifying fundamental principles that possible ways of transport across the cell membrane at the system level. 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 [27]. This paper, in microbial fermentation case, tries to present a general way to design the performance index to identify the system structure by using the qualitative description of biological robustness. Then, some possible problems we might face in the process of using the algorithm are discussed. In the

* Corresponding author.
*E-mail address:* wanglei@dlut.edu.cn (L. Wang).

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specific example, we give the numerical results for inferring the possible ways of transport across the cell membrane by using serial and parallel algorithm respectively, which show that biological robustness' power for applications.

This paper is organized as follows. In Section 2, in microbial fermentation case, we generally present a way to design the performance index to identify the system structure by using the qualitative description of biological robustness. In Section 3, firstly, we briefly review the mathematical model of the microbial fermentation. Secondly, assuming that the glycerol transported by active transport coupled with passive diffusion, on the basis of the algorithm proposed by Section 2, we give the numerical results and show the differences between serial and parallel algorithm. Conclusions are presented at the end of this paper.

## 2. General algorithm to infer the transport mechanism based on the biological robustness

Understanding the transport mechanism of microbial fermentation is vital for further research on gene regulation. Due to the lack of intracellular information, on the basis of dynamical system, using biological robustness as performance index, we can present a system identification model to infer the most possible transport mechanism. However, cell-level understanding is a rather vague notion that is often hard to define because the system is not a tangible object [27]. So far, inspired by robust control theory and the idea of the invariant quantity in topology theory, we need to find some computation value which is robust to all kinds of perturbation. A general algorithm is constructed to seek the solution of problem as follows.

**Algorithm 1.**

**Step 1.** For one of the possible ways of transport across the cell membrane, give the space of parameters perturbation $U(p,\Delta p)$ .
**Step 2.** For each parameter $p_i \in U(p,\Delta p)$, verify whether the parameters are feasible or not. If they are feasible, then compute for the (asymptotic) steady solution of the dynamical system $x(t_{p_i};p_i)$.
**Step 3.** Choose appropriate norm for the solution space of the dynamical system and compare the "distance" between any two of solutions when they achieve the (asymptotic) steady state. Find the maximum value of the "distance".
**Step 4.** For any of the possible ways of transport across the cell membrane, repeat the Step 1–3. and obtain different maximum values of the corresponding ways of transport across the cell membrane.
**Step 5.** Considering factual aim, we design the performance index with the experimental data and the above results.
**Step 6.** Compute performance index and give the conclusion.

**Remark.**

(1) For Step 1., we can randomly generate sample points by uniform distribution or any other distributions on the basis of the actual demand.
(2) We can use the way of parallel computing to greatly improve the efficiency of the algorithm for the first four steps.
(3) The time of the system solutions achieving the (asymptotic) steady state with different parameters may be not consistent. So, in Step 2., we use $t_{p_i}$ to show the difference.
(4) For Algorithm 1, we can choose to minimize the maximum values of the "distance" as the biological robustness, which can be the part of the performance index. That is a min–max problem, and the matured optimal method will help to solve this problem.

## 3. Case study

The study of 1,3-PD from fermentation of glycerol by microorganisms has caused great focus in the world since 1980s. The traditional macroscopic models of glycerol fermentation are all based on unstructured models in which the cells are just viewed as a catalyst for the conversion of substrates into products without paying much attention to the intracellular behavior [5,28–31]. However, less attempt has been made on the glycerol metabolic system. The available structure of the metabolic network is determined by using the method of metabolic flux analysis through which to check the consistency of the assumed metabolic network with the experimental data [9]. In 2008, Sun et al. [32] proposed a mathematical model to describe the concentration changes of extracellular and intracellular substances. Then, a complex metabolic network and the corresponding nonlinear hybrid dynamical system were proposed to determine the most possible metabolic system [33,34].

Due to less information about intracellular behavior, the quantitative description of biological robustness become a feasible method to overcome the shortcoming. Assuming that the glycerol is transported by active transport coupled with passive diffusion, we aim to infer the most reasonable one from three possible transport mechanisms of 1,3-PD across the cell membrane (active transport, passive diffusion or active transport coupled with passive diffusion), and develop the