The Results on the Stability of Glycolytic Metabolic Networks in Different Cells

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Abstract. Evolutionary forces will affect the structure of metabolic networks and their dynamic behaviors. To examine this hypothesis, in this work we investigate the relationship between the complexity of the metabolic glycolytic networks and the stability of the networks in different cells. By deriving the stoichiometrix from the FBA methods, we develop the models for Sce, Dmgr, Dsmi and Pic in fungi. Based on these models, we analyze the stability of the networks. The results show that the metabolic networks are more complicated with more stable ones.

Keywords: stability, metabolic networks, glycolysis, FBA methods.

1 Introduction

Cellular metabolism and its regulation represent a large scale dynamical system and complex dynamic behavior has been observed for a wide variety of metabolic pathways (Steuer [1]). Generally, the dynamic properties of cellular regulatory systems are considered to be essential for cellular regulation and constitute the conceptual basis for many physiological properties of living cells. As mentioned in Grimbs et al. [2], the dynamic behavior of metabolic networks is governed by numerous regulatory mechanisms, such as reversible phosphorylation, binding of allosteric effectors or temporal gene expression, by which the activity of the participating enzymes can be adjusted to the functional requirements of the different cells.

With the developments in genomics, more and more information on genetic networks has been provided for several micro-organisms. The next logical step is how to use this information to study the integrated behavior of the cellular networks. One of the most concerned areas has been the study of metabolic networks. The analysis of these networks by using mathematical methods can facilitate applying the research results to the real problems. For example, it can guide the metabolic engineering

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process. It is well known that the stability and robustness of the biological systems are the most popular rules which all the living creatures live on. The research on the stability of biological systems includes very rich contents: linear and nonlinear systems, variable and invariable, and so on. In this research, we initially study some basic contents on systems' stability. Specifically, we will investigate the stability of glycolytic metabolic networks in some fungi cells and the relationship between the stability and the biological evolution.

There are several approaches which have been proposed to study the metabolic networks, including metabolic control analysis, biochemical systems theory, cybernetic modeling and flux balance analysis (FBA). Except of FBA, these approaches require kinetic information of the cellular reactions (Mahadevan et al. [3]). However, the kinetic information is often unavailable for most of biological cells. Therefore, we choose FBA incorporated with mathematical analysis to study the stability of the metabolic networks.

FBA is the method which assumes that the metabolic networks will reach a steady state constrained by the stoichiometry. This assumption is based on the fact that metabolic transients are typically rapid compared to cellular growth rates and environmental changes. The consequence of this assumption is that all metabolic fluxes on the formation and degradation of any metabolite must balance, which is leading to the flux balance equation (Varma & Palsson [4]):

$$S \cdot v = 0 \tag{1}$$

where S is a matrix containing the stoichiometry of the metabolic reactions, v is a vector of the metabolic reaction rates. In general, the above equation is always underdetermined. To deriving a meaningful result, it must recur to combining other mathematical methods.

In 2007, Grimbs et al. [2] proposed a computational approach based on structural kinetic modeling. The authors applied the approach to the metabolism of human erythrocytes and the results showed that the allosteric enzyme regulation significantly enhances the stability of the network.

In this paper, we investigate the relationship between the complexity of the glycolytic metabolic networks and their stability. In our previous study, we found that the yield of the productions of some important metabolites is higher with more complicated metabolic networks. In this work, we assume the similar results about the stability of the network will be obtained. That is, the metabolic networks are more stable with more complicated ones.

2 The Glycolytic Metabolic Networks of Different Cells in Fungi

In this section, after we introduce the mathematical methods which will be used in analyzing the stability of the networks, we depict the metabolic networks of four different cells which we selected to investigate. All of them belong to the class of Fungi. Specifically, they are: Saccharomyces cerevisiae (sce), Saccharomyces mikatae (dsmi), Magnaporthe grisea (dmgr) and Pichia stipicis (pic).

2.1 Mathematical Methods

A metabolic network is combined by a set of coupled chemical reactions and transport processes. Suppose a network which contains m metabolites and r reactions. Based on the FBA formula, the time-dependent changes of the metabolite concentrations can be described by a set of differential equations of the form $\dot{x} = S \cdot v$, where x denotes the m-dimensional vector of metabolite concentrations, S denotes the $m \times r$-dimensional stoichiometric matrix and v denotes an r-dimensional vector of enzyme kinetic reaction rates. If considering a steady state of the system, then the differential equations system converts to equation (1).

Given a metabolic state characterized by x^0 and v^0, the system of differential equations can be approximated by a Taylor series expansion as follows:

$$\frac{dx}{dt} = S \cdot v(x^0) + S \cdot \frac{\partial v}{\partial x}\Big|_{x^0} \left(x - x^0\right) + \ldots \tag{2}$$

where the first item describes the steady state properties of the system, as exploited by FBA to constrain the stoichiometrically feasible flux distributions. Let the second item $S \cdot \frac{\partial v}{\partial x}\Big|_{x^0} = J$, then the structure of the Jacobian matrix J constrains the possible dynamics of the system at each metabolic state. Evaluating the eigenvalues of J, then if the largest real part of the eigenvalues is positive, it implies the instability of the metabolic state. And only if all the eigenvalues have a negative real part, the metabolic state is stable. For detailed explanation of the methods, please refer to Grimbs et al. [2].

2.2 The Glycolytic Networks of Sce, Dmgr, Dsmi and Pic

We select four kinds of cells in Fungi to continue our research. Specially, the cells are Sce, Dmgr, Dsmi and Pic.

The metabolic network considered for modeling the glycolysis of Sce is shown in Fig 1. The network consists of 14 metabolites and 12 reactions, in which all the metabolites are:

$$\begin{aligned}
&x_1 = G6P, \quad x_2 = F6P, \quad x_3 = FBP, \quad x_4 = DHAP,\\
&x_5 = GAP, \quad x_6 = 1{,}3-BPG, \quad x_7 = PEP, \quad x_8 = PYR,\\
&x_9 = ACA, \quad x_{10} = ETOH, \quad x_{11} = NAD^+, \quad x_{12} = ATP,\\
&x_{13} = AMP, \quad x_{14} = GLC.
\end{aligned}$$

Where the substrate is Glucose (GLC), and the important product is Ethanol (ETOH). For the meaning of other abbreviations in Fig 1, please refer to Hynne et al. [5].

Remember that, in our models, the substrate Glc is not included in the metabolic vector x, but treated as a constant input of the network. For Sce, set the concentration of Glc equals to 1mmol per gram (Dry Weight). For the metabolic glycolytic networks of Dmgr, Dsmi and Pic, please refer to the reference [6].

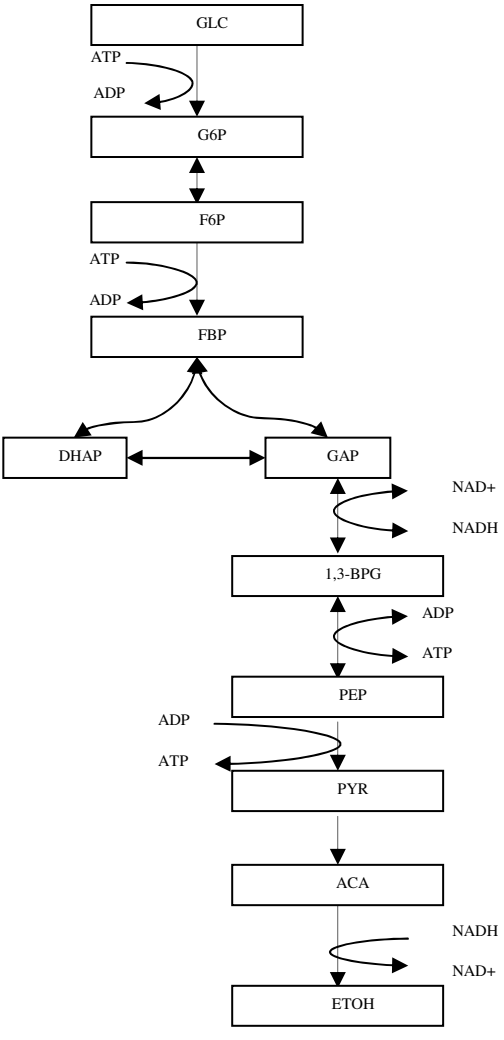

Fig. 1. The glycolytic network of Sce

2.3 Results and Conclusions

According to the methods introduced in subsection 2.1, we compute the eigenvalues of the Jacobian matrix separately. The results are as follows:

For Sce, there are 12 nonzero eigenvalues, in which there are one pair eigenvalues whose real part are greater than zero, say: 3.9257+1.9579i and 3.9527-1.9579i.

For Dmgr, the number is 10 and there are 2 real eigenvalues which are greater than zero: 4.476 and 0.086336. Remember that there is one root which is greater than Sce's.

For Dsmi, the number is 12. Except one pair eigenvalues 3.476+2.62i and 3.476-2.62i, there are other 2 real eigenvalues which are greater than zero, say: 2.2326E-14 and 3.6887E-13. That is to say, it is the most instable networks comparatively.

Follow the conclusions in subsection 2.1, if the largest real part of the eigenvalues is positive, it implies the instability of the metabolic state. And only if all the eigenvalues have a negative real part, the metabolic state is stable.

Therefore, for the above 3 glycolytic networks, we think that it becomes more stable with more complex networks when their networks are similar in producing the same important product. The relative sequences are: Sce>Dmgr>Pic. No matter for considering the complexity or the stability. The results proved the assumption's correctness. Well, the networks of Pic is quite different from the others, our conclusion is that there is no comparative among them.

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