

A method for estimation of enzyme kinetics in metabolic pathways using GMA

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Keywords: Modeling Method, Metabolic Model, Optimization, GMA

1 Introduction

In attempting to develop large-scaled metabolic models using general dynamic modeling methods, a large set of data, such as kinetics mechanisms and parameters, is required. It is difficult to obtain a complete set of rate equations and kinetic parameters. To solve the problem, we have proposed an algorithm which simulates a pathway model including dynamic kinetic parts and flux-based static parts together. The flux-based static part requires only stoichiometric coefficients and exchange flux rates at the system boundary to develop a model, and neither rate equations nor kinetic parameters are necessary in the static part. However, dynamic properties of bottle neck reactions are still needed for the dynamic part. To obtain their kinetic information without biochemical experiments, we developed a novel method for the estimation of parameters whose kinetics were unknown using GMA (general mass action) from time-course data of metabolites.

2 Method

2.1 GMA

GMA is one of the most powerful and uniform approaches to express enzyme reactions[1]. GMA adopts the following form:

$$\frac{dv}{dt} = \sum_{i=1}^P \gamma_i \prod_{j=1}^n X_j^{f_{ij}} \quad (1)$$

Where γ and f are coefficients, X_j is a concentration of the variable. Although GMA consists of the previous fixed form, it has an extremely wide expression space. This significant feature enables to express enzyme reactions systemically and automatically.

2.2 A method for estimation of enzyme kinetics in metabolic pathways using GMA

This method adopted the following three Steps:

Step 1. Information Collecting. Data of unknown kinetics of enzymes were collected from enzyme database, BRENDA and ExpASY, and pathway database KEGG with the focus on the following three points.

- List of stoichiometric relationship of the pathway
- Reversibility of enzyme activity
- List of effectors

Step 2. Model Building. GMA equations of the enzyme were built considering the previous points.

Step 3. Parameters Optimization. These parameters cannot be determined by the presence of kinetic equations transformed by GMA itself. They were optimised using real coded GA from time-course data of metabolite[2,3]. An evaluation function of this optimization method has the following form:

$$\sum_{i=1}^n \sum_{t=1}^m \left(\frac{X'_i(t) - X_i(t)}{X_i(t)} \right)^2 \rightarrow \text{Minimum} \quad (2)$$

Where n is the number of substrates and products of target enzymes, m is the number of sampling points of a time-course, $X'_i(t)$ is a time-course, calculated by the model previously obtained, of a state variable X'_i , $X_i(t)$ is a time-course obtained by experiments of a state variable X_i .

3 Results and Discussions

Verifications of this method using simple toy models were carried out. Firstly the toy models were constructed with pure dynamic kinetics. Some kinetic equations were selected and replaced with GMA following the previous method. These models showed high accuracies compared with the simulation results of the original kinetic models. The maximum error was 1.7%, which seemed to be sufficient to complement the kinetic dynamic equations.

In applying this method for constructing a metabolic model, we will obtain time-course data of metabolites from a high throughput metabolic technique using capillary electrophoresis mass spectrometry developed by our laboratory[4]. This method may enable the constructing and analysis of large-scaled dynamic metabolic models from metabolome data.

4 Acknowledgements

This research was supported by the Ministry of Education, Culture, Sports, Science and Technology, Grant-in-Aid for the 21st Century Center of Excellence (COE) Program entitled "Understanding and Control of Life's via Systems Biology(Keio University)" and for the Leading Project for Biosimulation.

References

- [1] Voit, E.O., *Computational Analysis of Biochemical Systems: A Practical Guide for Biochemists and Molecular Biologists*, Cambridge Univ Pr, 2000.
- [2] Hernandez-Bermejo, B., Fairen, V., Sorribas, A., Power-law modeling based on least-squares criteria: consequences for system analysis and simulation, *Math Biosci*, Oct;167(2):87-107, 2000.
- [3] Kikuchi, S., Tominaga, D., Arita, M., Takahashi, K., Tomita, M.. Dynamic modeling of genetic networks using genetic algorithm and S-system, *Bioinformatics*, Mar 22;19(5):643-50, 2003.
- [4] Soga, T., Ohashi, Y., Ueno, Y., Naraoka, H., Tomita, M., Nishioka, T., Quantitative metabolome analysis using capillary electrophoresis mass spectrometry, *J Proteome Res*, Sep-Oct;2(5):488-94, 2003.