Prediction of genes and metabolic pathways based on system-level analysis

System Estimation of Cell Dynamics using E-CELL Simulation Environment

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1 Introduction

This paper describes our attempts to adopt S-system [1] for estimating unknown pathways using the E-CELL simulation environment [2], a generic software we have developed for cell simulation.

S-system is one of the methodologies in power-low formalism. In S-system representation, cell dynamics is described as the following equation:

$$\frac{dX_i}{dt} = \alpha_i \prod_{j=1}^{n} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{n} X_j^{h_{ij}} \quad (i = 1, 2, \cdots, n)$$

where X_i is a state variable of the i-th component such as substance concentration, n is the number of state variables. The nonnegative parameters α_i and β_i are rate constants, g_{ij} and h_{ij} are the kinetic orders of the biochemical kinetics. α_i and g_{ij} are related to the aggregate rate law for synthesis of X_i, while β_i and h_{ij} are related to the aggregate rate law for degradation of X_i.

Virtually any ordinary differential equation can be described in this formalism. The only factor affecting cell dynamics is its parameters, that is α,β,h,g. Therefore the dynamics of a cell can be expressed in a single matrix, as follows:

$$\begin{pmatrix} \alpha_1 & g_{11} & g_{12} & \cdots & g_{1n} & \beta_1 & h_{11} & h_{12} & \cdots & h_{1n} \\ \alpha_2 & g_{21} & g_{22} & \cdots & g_{2n} & \beta_2 & h_{21} & h_{22} & \cdots & h_{2n} \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ \alpha_n & g_{n1} & g_{n2} & \cdots & g_{nn} & \beta_n & h_{n1} & h_{n2} & \cdots & h_{nn} \end{pmatrix}$$

2 Estimation of Cell Dynamics

Using S-system, system estimation can resolve itself to parameter estimation. Parameter estimation can be viewed as searching the minimum of a certain evaluation function, which we define as square sum of difference between simulation results and values obtained by laboratory experiments as the following formula:

$$F = \sum_{i=1}^{N} \sum_{j=1}^{n} \left(\frac{x_{cal,i,j} - x_{exp,i,j}}{x_{exp,i,j}} \right)^2$$

where N is the number of sampling points, n is the number of variables, X_{cal} is calculation value, and X_{exp} is experiment value.

Steadiness of the time series can be used as the evaluation function. In this way, a set of parameters which leads the cell model to a steady state can be obtained.

Four optimization methods (the Rosenbrock method, the Modified Powell method, Simulated Annealing and Genetic Algorithm) are provided as software modules of E-CELL simulation environment.

3 Estimation of Reaction Network

It is difficult to estimate the accurate values of h and g when the system contains numerous components. However, the estimation of reaction network is much easier since it is only necessary to estimate whether h(or g) equal 0 or not.

g_{ij} represents how much Xj is related to the synthesis of Xj, and h_{ij} represents how much Xj is related to the degradation of Xi. Therefore, $g_{ij} = 0$ or $h_{ij} = 0$ means that the network from X_j to X_i does not exist.

S-system representation and parameter estimation mechanism can be used as powerful tools of estimating reaction network.

4 Evaluation

As a sample case of cell dynamics and reaction network estimation, we adopted *lac* operon model and Mitochondria model, which are being constructed by the E-CELL Project.

5 Concluding Remarks

This work is the first step towards large-scale estimation of cell dynamics, which we believe is one of the most important key technologies for cell simulation.

Acknowledgments

We would like to thank Dr. Masahiro Okamoto at Kyushu Institute of Technology for useful suggestions.

This work was supported in part by Japan Science and Technology Corporation and a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science, Sports and Culture of Japan.

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