Mathematical Analysis of Metabolic Networks Using the E-Cell Simulation Environment

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1 Introduction

We applied two mathematical analysis methods to a metabolic model constructed on E-Cell simulation environment, a generic simulation software suite for modeling cellular processes at the level of chemical reaction. The first is multivariate time series analysis. The second is sensitivity analysis, which is known as Metabolic Control Analysis in biological terms. In order to prove their effectiveness, we adopted the erythrocyte model (Nakayama *et al.* [1]) as a test case.

These analysis tools are packed into the integrated simulation management software named E-Cell Manager, which is equipped with sophisticated graphical user interface.

2 Time series analysis

An *impulse* is a sudden shock given to a system. An *impulse response* is the system's response to an impulse. From an impulse response, information about (a) difference in time between reactions in a metabolic pathway, (b) dependencies among reactions and (c) other characteristics of transfer function between reactions, can be obtained.

We applied the multivariate auto regressive (AR) model, which assumes that (a) the value of the series at time t depends only on its previous values and random disturbance, and (b) the dependency can be expressed as a linear combination of the values.

Oscillating time series are analyzed in frequency domain using power contribution ratio, an index of how fluctuation of one variable depends on the other variables at each frequency.

Systems where the substance concentrations fluctuate should also be analyzed in frequency domain. Although the fluctuations are often irregular, various rhythmic patterns are found in many fluctuations. As a result, the fluctuations are not periodic functions as a whole but periodic functions in part. Regulations found in such time series can be decomposed into spectrum with respect to frequency.

Operations, such as analyzing and plotting data, are integrated by E-Cell Manager, so that the users can execute each procedure conveniently and effectively.

3 Sensitivity analysis

Among many approaches to Metabolic Control Theory, the linear algebra approach based on Structural Approach [2] has been chosen because of its convenience in obtaining elasticity, control coefficient and some other characteristic properties.

The goal of this analysis is to describe the inter-dependency among simulation objects as a matrix, such as control coefficient matrix and Jacobian.

All reactions have their own rates v_j that can be represented as a vector ($\vec{v} = \{v_1, v_2, \cdots, v_n\}$). With this representation, differential values of all substances can be shown as one equation: $\frac{d\vec{x}}{dt} = Nv$.

This equation can also be represented as : $Nv = L \cdot N_R v$, where N_R is reduced matrix which has independent vectors of N, and L is link space which maps N_R onto N.

Elasticities can be derived from simulation results through a method following a certain experiment [3]. In the E-Cell system, data flow which appears in the figure 1 is processed by several software modules. Users are going to be able to use these modules through E-Cell Manager.

From elasticities and control coefficients, the connectivity structure of the system and condition of the certain steady state can be obtained.

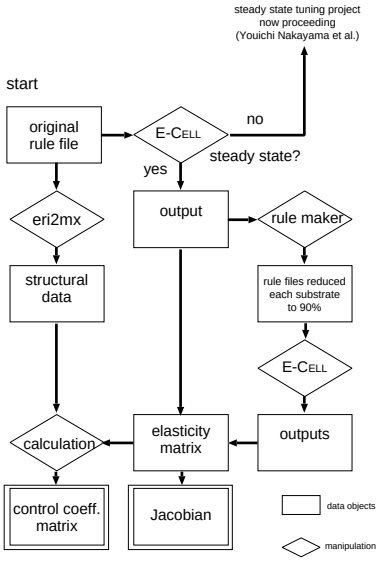

Figure1: Sensitivity Analysis Framework of E-Cell Simulation Environment

4 Concluding Remarks

This multivariate time series analysis is effective in analyzing metabolic network, particularly when feedback loops are present. Sensitivity analysis can help us better understand the dynamic structure of the cell.

It is nearly impossible for laboratory experiments to obtain a large collection of sample values sufficient to employ these analytical methods. Since computer simulation can produce ample data for mathematical analyses, we believe that the E-Cell system will be a promising means for investigating dynamic behavior of metabolic networks.

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