Simulation and System Analysis of Gene Regulatory Networks Using the Two-phase Partition Method

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1 Introduction

Metabolic Control Analysis (MCA) and Biochemical Systems Theory (BST) have been demonstrated to be useful for simulating various metabolic circuits. In contrast, conventional mass action equations or the method for simplifying complicated networks into rate equations have been employed to simulate the protein and DNA networks. The problem in the conventional mass action equations is that the differential equations with the rate parameters whose values are quite different in the time-scale of reactions are so stiff that the calculation time becomes quite large. On the other hand, the simplified rate equation method strongly depends on the structures of the network and on the values of the system parameters, because it neglected some reactions to simplify a complicated network. To overcome these problems, the two-phase partition method was developed that automatically divided all the chemical reaction equations into two phases: the binding phase and the reaction phase [3]. This method simulated all the reactions involving protein and DNA signal transduction, and calculated them at an extremely high speed. Actually, the two-phase partition method accurately simulated the dynamic behavior of the heat shock response that contained the huge differences in the time-scale of reactions. The calculation speed was 4×10^4-fold higher than the conventional mass action method. The heat shock response was an excellent model showing the dynamic behavior with a quick and sharp transient response of a regulatory protein. However, there have been only a few gene regulatory networks that the two-phase partition method simulated. In order to demonstrate the high performance of the two-phase partition method, we applied this method to the nitrogen fixation system in *E. coli* and circadian clock in *Drosophila* cells.

In this study, we try another problem regarding parameter tuning. In simulation of a biological system, many parameters remain to be measured, because there is a huge amount of kinetic parameters and it is often hard to experimentally measure them. Actually, it is impossible to measure all the biochemical parameters. Practically, it is important to tune the values of kinetic parameters so as to adjust to dynamic behaviors of a biological system. To solve this problem, we compared genetic algorithms (GAs) to find the optimal method for the simulation using the two-phase partition method.

2 Genetic Algorithm for Parameter Tuning

There are few viewpoints for understanding features of genetic algorithms (GAs) for optimization of a gene regulatory network. Ono [4] introduced some guidelines for designing crossover operators for function optimization, such as Unimordal Normal Distribution Crossover (UNDX), UNDX-m, and Simplex Crossover (SPX). We employed these genetic algorithms for tuning many kinetic parameters to adjust to the typical time-course of σ^{32} and heat shock proteins, which were well simulated by the two-phase partition method. Figure 1 shows the comparison between the target time-course and the tuned one by the UNDX method. UNDX showed the high performance (data not shown).

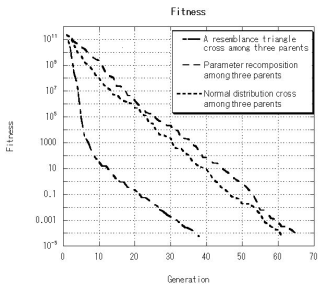

Figure 1: Parameter tuning by GAs in the heat shock response.

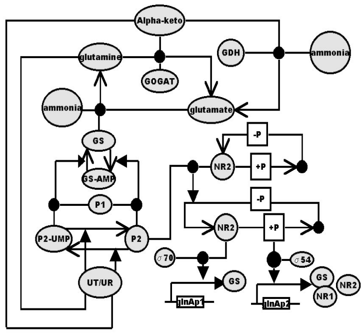

Figure 2: A schematic diagram of the nitrogen fixation system.

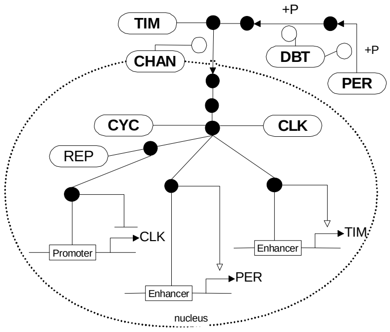

Figure 3: A schematic diagram of the circadian clock in *Drosophila*.

3 Biological Systems for Simulation with the Two-Phase Partition Method

Nitrogen fixation system: Since the nitrogen fixation system (Figure 2) consists of not only a gene regulatory network but also metabolic circuits, it is an example suitable for employing S-system for the metabolic reactions and the two-phase partition method for the gene regulatory network, respectively. The nitrogen fixation system in *E. coli* that controls the uptake rate of extracellular ammonia (nitrogen source) to adjust the balance between the nitrogen and carbon amounts within a cell [1]. This system consists of metabolisms of small molecules such as glutamine, a-ketoglutarate, glutamate, and signal transduction through regulatory proteins, UT/UR, PI, PII, NRI, and NRII. In order to adjust the main feature of the nitrogen fixation system, a genetic algorithm was used to tune the values of many biochemical parameters, which were crossed or mutated to obtain a high adaptability. The adaptability was defined as the fitness, i.e., the ratio of glutamine/a-ketoglutarate, because the aim of this process is to maintain the glutamine concentration at a high level by increasing the uptake rate of ammonia from ammonia-depleted medium.

Circadian clock system: In *Drosophila*, circadian oscillations in the level of two proteins, PER and TIM, result from the negative feedback exerted by a PER-TIM complex on the expression of the *per* and *tim* genes which code for these two proteins [2, 5] (Figure 3). The well-established mechanism of circadian clocks in *Drosophila* is a great example for extending the application area of the two-phase partition method from prokaryotes to eukaryotes. In addition, this system includes the nonlinearity of transcription. The two-phase partition method was able to solve those problems by giving some modifications to the reaction equations. The parameter set that gave the stable oscillation of the 24 h period was optimized by GAs. At present, we analyze how the simple feedback control system realizes the robustness of the time period.

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