Simulation of Circadian Rhythms Using Grid Computing

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Keywords: simulator, circadian rhythms, random search, genetic algorithms, grid computing, sensitivity analysis

1 Introduction

The *Drosophila* circadian oscillator shows a robust property to environmental changes, internal variations, and fluctuations, where two interlocked negative feedback loops play a major role for oscillation [1, 2]. The PER-TIM loop is activated by dCLK-CYC and repressed by PER-TIM, whereas the dCLK loop is repressed by dCLK-CYC and activated by PER-TIM. Not only the molecular architecture, but also the parameters provide a robust property to the oscillator. To routinely construct the dynamic model of a biological system, we propose a novel and powerful strategy that consists of forward and reverse engineering. Forward engineering produces a mathematical model with kinetics-related parameters directly from biochemical networks. However, since it is hard to obtain all the real kinetic values *in vivo* experimentally, the use of reverse engineering explores the kinetic parameters of the dynamic model.

In order to estimate the values of the kinetic parameters that reproduce the dynamic features of the oscillator, we employed a random search (RS) and genetic algorithms (GAs). However, since there are many candidates of the kinetic parameter vectors that reproduce the similar dynamic behaviors, it is hard to obtain a unique solution. In order to select a unique solution out of many candidates, we carried out the sensitivity analysis by calculating the changes in the period or in the amplitudes with respect to the variations in each parameter. Since we needed extensive calculations for performing RS and GA, we used grid computing.

2 Method

Mathematical simulation

Using the CADLIVE (Computer-Aided Design of LIVing systEms) [3, 4] automatically converted the biochemical oscillator network with the regulator-reaction equations into a dynamic model with kinetic parameters. The proposed dynamic model is simple, but has still many kinetic parameters. In terms of computational complexity, it is not practical to explore all possible parameters to fit the model to biological reality. Thus, we selected the critical N-dimensional parameter vectors that involve generating a stable oscillator. The values of the remaining parameters are provided as biologically meaningful values. In order to explore the N-dimensional parameter vectors that reproduce the oscillation of PER with the 24 h-period and a large amplitude, we carried out a RS, and GAs for the parameter search. First, we randomly altered the values of the N-dimensional parameter vectors within a limited logarithmic space to explore all possible parameter vectors that generate some oscillations, which are set as the initial populations for the search by GAs. Second, we performed GAs to search the parameter vectors that show stable oscillations with a 24 h-period and a large amplitude.

Grid computing

In order to search the parameter vectors that show stable oscillations with a 24 h-period and a large amplitude, we needed extensive calculations for performing RS and GAs. Thus, we used grid computing to perform efficient calculation.

Sensitivity analysis

The sensitivity analysis contributes not only to finding a unique solution of the kinetic parameter vectors, but also finding the system-determining step of the circadian oscillator. The kinetic parameters that indicate a high sensitivity are critical factors for generating a stable oscillator.

3 Results and Discussion

First, we randomly altered the *N*-dimensional parameter vectors within limited logarithmic spaces to explore all parameter vectors that generate some oscillations of PER, which are set as the initial populations for the search by GAs. Parameter vectors with some attenuated oscillations are useful initial populations. In the oscillatory systems, the initial populations are critical, because genetic algorithms cannot grow up non-oscillatory populations to stable oscillators.

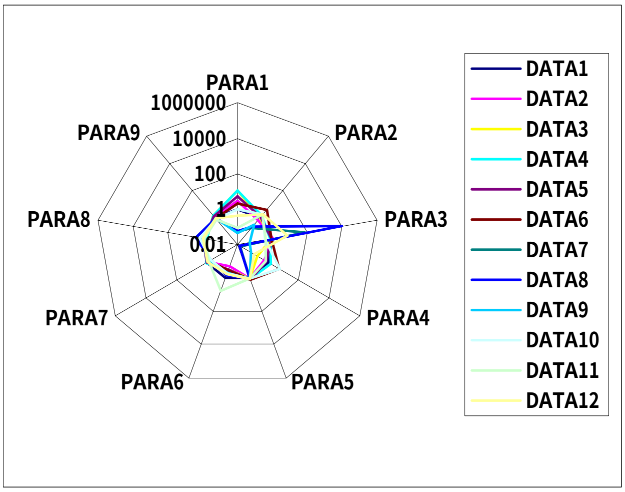

Figure 1: Variation of the parameter vectors providing oscillations

The use of GAs generated a considerable number of the parameter vectors that produce the oscillator with an approximately 24 h period and a large amplitude. And various combinations of the parameters provided the same time courses in the period and the amplitude. Figure 1 shows the relative values of kinetic parameter vectors that provide the same time courses in the period and the amplitude. In the Figure 1, we regard the DATA1 as the control vector. In order to further select the parameter vectors that fit the biological reality, we carried out the sensitivity analysis regarding the critical parameters, where the changes in the period and amplitudes are simulated with respect to the variation in gene expression. The sensitivity analysis has the capability to determine a unique parameter vector out of the multiple candidates. Since it is hard to measure the exact values of the kinetic parameters *in vivo*, the experimental analysis of the sensitivity by down-regulating a specific gene can be a useful method to select a unique solution out of many candidates. Figure 2 and Figure 3 show the sensitivity of the period and amplitude with respect to the transcription rate constant in the mutated circadian oscillator that is calculated by increasing the 0.5-fold constant. The results of the sensitivity analysis depended on the parameter vectors. A high sensitivity shows that the parameter is a critical factor to determine oscillator systems.

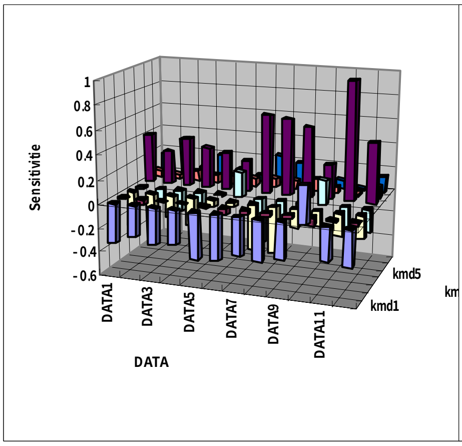

Figure 2:Sensitivity of the period

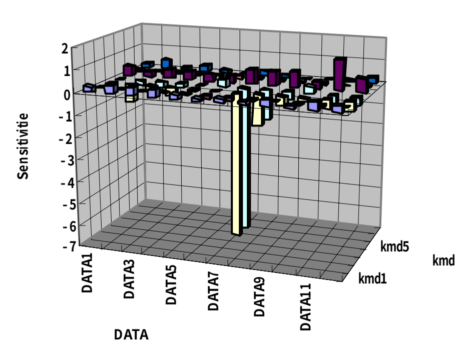

Figure 3:Sensitivity of the amplitude

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