Deterministic and Stochastic Models Analyze the Robustness of Circadian Rhythms

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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 the robust property to the oscillator. However, the intrinsic mechanism of how the clock system acquires the robust oscillator remains to be elucidated. In this paper, we aim at understanding how critical the values of parameters is for producing the robust oscillator using a deterministic model, and how the probabilistic fluctuations involve the stable oscillation using a stochastic model [5]. In the deterministic model, we classified the various parameter combinations that produced the cycle of 24 hours. The robust properties depended on the values of the parameters. In the stochastic model, the proper use of fluctuation could make stable oscillations.

2 Method

2.1 Deterministic Model

The analysis for the deterministic model consists of mathematical modeling, numerical simulation, clustering the solutions, and sensitivity analysis. The CADLIVE system [3, 4] parsed the regulator-reaction equations for the *Drosophila* circadian clock into the mathematical model and simulated it numerically. The genetic algorithms with random searches were employed to explore the kinetic parameters that fit the simulated results to the experimental data. We classified the parameter combinations according to the similarity of the parameter values using the class average method in the statistic analysis software of SAS. The sensitivity analysis was carried out by calculating the changes in the period or in the amplitudes with respect to the variations in the parameters.

2.2 Stochastic Model

The deterministic model excludes the probabilistic features from all reactions that occur on an actual living system, and employs ordinary differential equations to describe the dynamic behaviors without any stochastic terms. In order to consider the effects of fluctuations, the stochastic model was built using the Gillespie algorithm.

3 Results and Discussion

The various combinations of the parameters provided the same dynamic features of the period and the amplitude, as shown in Fig. 1, but the results of the sensitivity analysis greatly depended on the parameter combinations. As has been expected, not only the molecular architectures, but also the parameters created the robust oscillator. It is important to determine which pathways or loops play a major role to make robust rhythms. The sensitivity analysis is a critical method to determine a unique parameter combination out of the multiple candidates. Since it is hard to measure the values of the kinetic parameters *in vivo*, the experimental analysis of the sensitivity by overexpressing or down-regulating a specific gene can be a useful method to estimate the kinetic parameters.

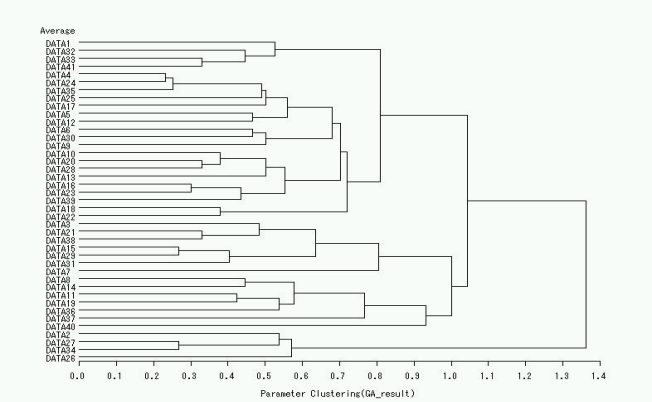

Figure 1: Clustering for the parameter sets.

The stochastic model showed that the use of fluctuations made a stable oscillator (Fig. 2), where the deterministic model indicated an attenuated oscillation (Fig. 3). Thus, the circadian clock system is suggested to utilize the noise properly to generate a robust feature of the cycles, which is different from the idea of artificial substances that always try to exclude noises or fluctuations.

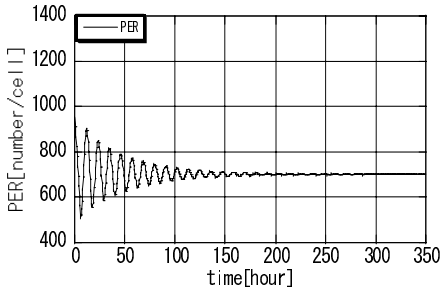

Figure 2: Time course of PER protein (stochastic model).

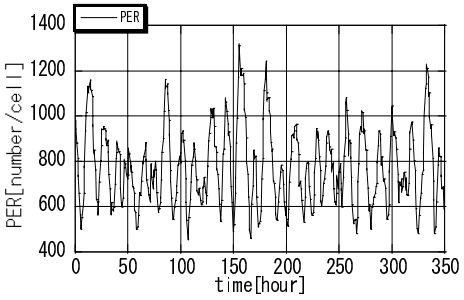

Figure 3: Time course of PER protein (deterministic model).

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