Simulation of Light-Induced Phase Response in Mammals with Hybrid Functional Petri Net

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1 Introduction

Circadian rhythmicity, which consists of endogenously generated near 24 h rhythms, is observed in virtually all mammalian physiological functions and behavior. These rhythms are centrally regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus. Most neurons in the SCN become active during the day and are believed to comprise the biological clock. It is known that the circadian rhythmicity is affected by various stimuli from environments. The most strong stimulus among them is light which makes the phase of circadian rhythm advance or delay depending on the hour.

On the other hand, we have simulated circadian genetic control mechanisms with hybrid functional Petri net (HFPN) and found a hypothetical path which can resolve the discrepancies in the existing circadian model [1]. In this study, we will report the result of computational experiment that examines the effect of light plus stimuli on phase shifts of circadian rhythms with varying the hours of stimuli.

2 Hybrid Functional Petri Net Model

Figure 1 shows the HFPN model that we have constructed for the simulation. The main difference between this HFPN model and the HFPN model in [1] is the number of transitions for transcriptions. In the former model of [1], the transcription speed of each gene was modeled with one transition that can fire while the content(s) of source place(s) attached to it exceed the threshold(s) assigned at the arc(s) incoming to the transition from the place(s). However, this model is not natural, since, in general, transcriptions of genes do not begin immediately after excesses of the content(s) of place(s) over threshold(s). Then, we used three transitions for the transcription, at which different parameters of speeds are assigned. This control of transcription speed in three steps enables the smooth mRNA concentration behavior of the corresponding gene. Without this modification of multiple transitions, we could not obtain the simulation result of phase response curve that is similar to the experimental result of it.

3 Simulation Result

Figure 2 is the phase response curve of mammals described in the biological literature [2]. The periods from CT0 (circadian time zero) to CT12 and from CT12 to CT24 are called subjective day
and subjective night, respectively. This phase response curve tells us that the activities of mammals delays at evening twilight, but advances at break of day.

Figure 3 is the phase response curve of Per mRNA obtained from simulations on HFPN model of Figure 1. We can see that this curve of simulation result is similar to the curve of Figure 2 from the biological literature. This result shows that the light induced phase response curve of mammals can be simulated by HFPN model of Figure 1. This implies that the principle of phase response induced by light can be explained with the existing molecular interaction model participating five genes of Per, Cry, Rev-Erb, Bmal, and Clock [1].

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References
