

A New Regulatory Interactions Suggested by Simulations for Circadian Genetic Control Mechanism in Mammals

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1 Introduction

Knowledge on molecular biological systems is increasing at an amazing pace. It is becoming harder to intuitively evaluate the significance of each interaction between molecules of the complex biological systems. Hence we need to develop an efficient mathematical method to explore the biological mechanism.

In this research, we employed hybrid functional Petri net (HFPPN) [2] to analyze the circadian genetic control mechanism, which is feedback loops of clock genes and generates endogenous near 24 hour rhythms in mammals [4]. Based on the available biological data, we constructed a model and, by using Genomic Object Net (GON) [3, 6], computer simulations were performed for time courses of clock gene transcription and translation. Although the original model successfully reproduced most of the circadian genetic control mechanism, two discrepancies remained despite wide selection of the parameters. We found that addition of an hypothetical path into the original model successfully simulated time courses and phase relations among clock genes. This also demonstrates usefulness of hybrid functional Petri net approach to biological systems.

2 HFPPN Model of Mammalian Circadian Gene Regulatory Mechanism

Molecular clocks reside within the suprachiasmatic nucleus cells. Each molecular circadian clock is a negative feedback loop of the gene transcription and its translation into protein. The loop includes several genes and their protein products. In case of mammals, three *Period* genes (*Per1*, *Per2* and *Per3*) and two *Cryptochrome* genes (*Cry1* and *Cry2*) comprise the negative limb, while *Clock* and *Bmal1* (*Bmal*) genes constitute positive limb of the feedback loop in the molecular circadian clock.

Fig. 1 is the constructed HFPPN model of a circadian genetic control system in mammal. Through simulations by GON on the constructed HFPPN model, we evaluated the mammalian circadian genetic control system, finding the following two inconsistencies in oscillations of mRNAs with the known biological facts: (a) The *Bmal* mRNA peaked at the almost same time as the peaks of *Cry* and *Per* mRNAs. However, it is biologically known that the peak of *Bmal* mRNA is located in the almost

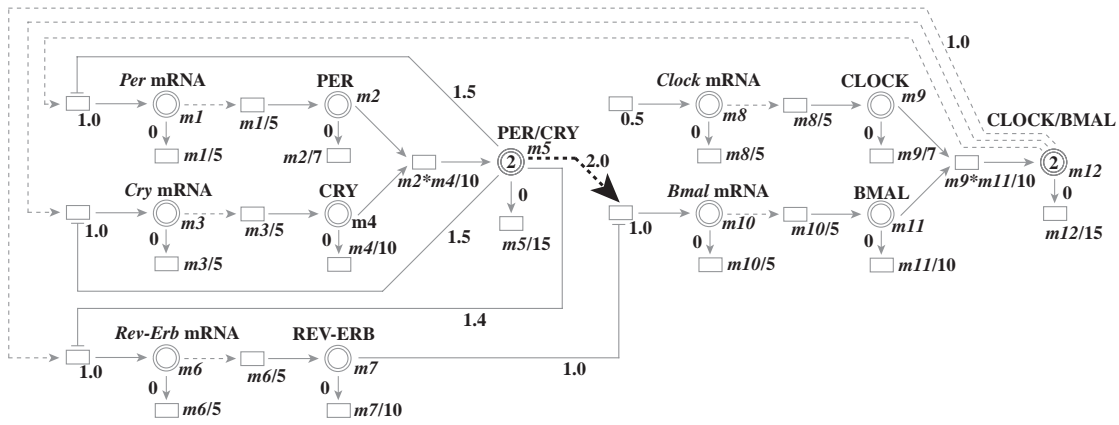


Figure 1: HFPN model of mammalian circadian gene regulatory system

center of two peaks of *Cry* or *Per* mRNA. (b) The *Bmal* mRNA was oscillated periodically in *Cry* knockout mouse. However, it contradicts the biological fact that *Bmal* gene stops oscillating in *Cry* knockout mouse [5].

In order to resolve these two inconsistencies, we compared the circadian genetic control systems of mammals and fruit flies. Then, we found the path of molecular interaction,

- PER/TIM complex activates the gene *dClock*, [1]

which exists in the circadian mechanism of fruit flies but not in that of mammals. Simulations by GON with introducing this path to the constructed HFPN model showed mRNA concentration behaviors consistent with biological observations.

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