Designing Oscillators in Synthetic Gene Networks Based on Multi-Scale Dynamics

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Abstract

Multistability, oscillations, and switching exist at various levels of biological processes and organizations and have been investigated on the basis of many theoretical models, such as circadian oscillations with the period protein (PER) and the timeless protein (TIM) in *Drosophila*, and multistable dynamics regulated by transcriptional factors. Considerable experimental evidence suggests that cellular processes are intrinsically rhythmic or periodic. Various periodic oscillations with different time scales ranging from less than a second to more than a year, which may allow for living organisms to adapt their behaviors to a periodically varying environment, have also been observed experimentally.

On the other hand, in synthetic gene networks, both toggle switch and repressilator have been theoretically proposed and further confirmed by experiments. All of these works stress the importance of feedback regulation of transcriptional factors, which is a key in giving rise to oscillatory or multistable dynamical behaviors exhibited by biological genetic systems. In addition, it should be noted that many periodic behaviors do not simply oscillate smoothly; rather, they change rapidly or jump at certain states.

In gene expression systems, many different time scales characterize the gene regulatory processes. For instance, the transcription and translation processes generally evolve on a time scale that is much slower than that of phosphorylation, dimerization or binding reactions of transcription factors. In genetic networks, the time scale for expression of some genes is much slower than that of others, depending on the length of the genes.

We aim to design robust periodic oscillators in synthetic gene-protein systems by simple nonlinear models and to analyze the basic mechanism of limit cycles with jumping behaviors or relaxation oscillations by exploiting multiple time-scale properties [1, 2]. We show that periodic oscillations are mainly generated by nonlinear feedback loops in gene regulatory systems and the jumping dynamics caused by time scale differences among biochemical reactions. Moreover, effects of time delay are also examined. We show that time delay generally enlarges the stability region of oscillations, thereby making the oscillations more sustainable despite parameter changes or noise [1, 2]. The dynamics of the proposed models is robust in terms of stability and period length to the parameter perturbations or environment variations. Although we mainly analyze some specific models, the mechanisms identified in this work are likely to apply to a variety of genetic regulatory systems. These simple models may actually act as basic building block in synthetic gene-protein networks, such as genetic oscillators or switches because the dynamics is robust for parameter perturbations or environment variations. Several examples are also provided to demonstrate implementation of synthetic oscillators by using genes of the λ phage bacteria [1, 2].

References

[1] L.Chen, K.Aihara. Stability of Genetic Regulatory Networks with Time Delay. *IEEE Trans. on Circuits and Systems - I*, **49**, No.5, pp.602-608, 2002.

[2] L.Chen, K.Aihara. A Model of Periodic Oscillation for Genetic Regulatory System.*IEEE Trans. on Circuits and Systems - I*, **49**. 2002. (to appear)

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