Designing Periodic Oscillation of Biological Systems

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There are rhythmic phenomena Living organisms at all levels with periods ranging from less than a second to years. From both theoretical and experiment viewpoints, it is a great challenging problem in biological science to model, analyze and further predict the periodic behaviors of bio-systems. With the rapid advances in mathematics and experiments concerning the underlying regulatory mechanisms, more sophisticated theoretical models and general techniques are increasingly demanded to elucidate periodic behaviors, with the consideration of time delays that are particularly important for the eukaryotes due to time-consuming transportation or diffusion processes of molecules between the nucleus and cytoplasm in a cell. On the other hand, in addition to the natural systems, recent progress in genetic engineering has made the design and implementation of artificial or synthetic gene networks realistic from both theoretical and experimental viewpoints in particular for simple organisms, such as *E.coli* and *yeast*.

Mathematically, there are tremendous number of theoretical results providing the sufficient conditions of limit cycles in the framework of functional differential equations, but mainly with a few variables or with linear or certain special structures when time delays are considered. Generally, it is difficult to guarantee a system converge to a limit cycle or a sustained oscillation even for a simple-structured nonlinear system. Recently, based on monotone dynamical systems, Mallet-Paret and Sell introduced a discrete Lyapunov functional and successfully developed a general theory to show the existence of the omega-limit set by obtaining a Morse decomposition of the global attractor for a cyclic feedback-loop network with time delays, which opened the door to a general inquiry into not only the topological structure but also the sufficient conditions of the existence for a specific attractor, in particular periodic attractor. However rather than a general network structure, a cyclic network is a single cyclic loop which considerably limits its application, although the original cyclic network has been extend to a general cyclic feedback-loop system by us for which the sufficient conditions to ensure the periodic orbit are also derived.

We review our recent work for developing a new methodology to analyze and design a biological oscillating network with time delays, by using a multiple time-scale network which is composed of a cyclic network and multiple fast networks. A fast network is mainly constituted by fast reactions or a protein network, whereas a cyclic network consists of slow reactions or a gene network. It has been shown that a general monotone system with only positive loops has no dynamical attractors but stable equilibria. In contrast, a cyclic network has omega-limit sets composed of only periodic orbits and equilibria. We prove that such general network with certain conditions has no stable equilibria but stable periodic oscillations, depending on the total time delay, although it has a complicated network structure including both positive and negative feedback loops. Such a property is clearly ideal for designing or modeling biological oscillators. Since there is less restriction on the network structure, it can be expected to apply to a wide variety of areas on modelling, analyzing and designing of biological systems, such as circadian rhythms.

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