

Periodic Oscillation in Gene Networks Modelled by Cyclic Feedback Systems

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1 Introduction

Periodic oscillations have been found in many different natural or physical systems, in particular biological organisms which have rhythmic phenomena 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 living organisms. Thereby study on topics, such as, how to model, analyze, predict and even create the periodic rhythms is essential and fundamental.

Generally, it is difficult to guarantee a system converging to a limit cycle or a sustained oscillation even for a simple-structured nonlinear system. Therefore, many important physiological factors such as time delays are simply ignored in order to reduce dimensionality and complexity of the systems [1, 4]. It is well known, however, that such factors may play important roles in dynamics of the biological systems. Recently, based on monotone dynamical systems, Mallet-Paret and Sell introduced successfully developed a general theory to show the existence of the omega-limit set, 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. In this paper, we further extend the results in to more general networks and provide the sufficient conditions of limit cycles for gene regulatory systems according to both local and global analysis.

Specifically, this paper aims to develop a new methodology to analyze and design biological oscillating networks with time delays, by using monotone cyclic feedback systems. We first give a local analysis of the oscillation network by local bifurcation theory. On the basis of the local result, we derive our main theorems, which ensure negative cyclic feedback systems to converge to periodic orbits globally. Furthermore, we extend our results to more general networks, which can have any types of interactions between nodes and are much easy to implement.

2 Main Results

Cyclic feedback network has the following form

$$\begin{aligned}\dot{x}_1(t) &= f_1(x_2(t - \tau_{1,2}), x_1(t), x_n(t - \tau_{1,n})), \\ \dot{x}_i(t) &= f_i(x_{i+1}(t - \tau_{i,i+1}), x_i(t), x_{i-1}(t - \tau_{i,i-1})), \\ &2 \leq i \leq n - 1, \\ \dot{x}_n(t) &= f_n(x_n(t), x_{n-1}(t - \tau_{n,n-1})),\end{aligned}\tag{1}$$

where $\tau_{i+1,i} = \tau_{i,i+1} = 0$ if reaction rates f_i and f_{i+1} depend on x_{i+1} and x_i respectively. Otherwise, if the interaction between them is one-direction, then $\tau_{i+1,i}$ can be any non-negative finite real number. Moreover, all self-feedbacks have no time delays, i.e. $\tau_{i,i} = 0$ for all $i \in N$. Moreover,

$$\frac{\partial f_i(x_{i+1}, x_i, x_{i-1})}{\partial x_{i+1}} \frac{\partial f_i(x_{i+1}, x_i, x_{i-1})}{\partial x_{i-1}} \geq 0, \quad (2)$$

where $\partial f_i(x_{i+1}, x_i, x_{i-1})/\partial x_{i-1} \neq 0$, for $1 \leq i \leq n$, which means for any two neighbor chemical components i and $i+1$, the interaction from the $(i+1)$ -th to the i -th chemical components has the same type as that from the i -th to the $(i+1)$ -th chemical components or is zero.

Theorem 2.1 (*Global convergence to nontrivial periodic orbits*). For eqn.(1), if the feedback for total one-direction interactions is negative and sufficiently strong, i.e. $\frac{\partial f_1}{\partial x_n} \prod_i \frac{\partial f_{i+1}}{\partial x_i}$ for those i with $\frac{\partial f_i}{\partial x_{i+1}} = 0$ at any equilibrium is sufficiently large, then there exists a $\bar{\tau}$,

$$\bar{\tau} = \frac{1}{\bar{v}} \left[\arccos \left(\frac{(-1)^n \sum_{i \in I_e} (-1)^{\frac{i}{2}} b_i v^i}{B} \right) \right], \quad (3)$$

where the range of arccos is $[0, \pi]$, and the system converges to a stable periodic orbit for almost all initial condition, when $\tau > \bar{\tau}$, where the total time delay $\tau = \sum_{i=1}^n \tau_{i+1,i}$, b_i is the coefficient of λ^i in characteristic equation, and $I_e = \{i \in N : \text{mod}(i, 2) = 0\} \cup \{0\}$.

Theorem 2.2 (*Global convergence to nontrivial periodic orbits*). For the negative cyclic network eqn.(1), if $\det(A(0)) < 0$ at all equilibria in X , then for almost all initial conditions converges to a stable periodic solution, where $A(\lambda) = (\frac{\partial f_i}{\partial x_j} e^{-\tau_{i,j}\lambda})$ is a $n \times n$ matrix.

3 Numerical Implementation

Finally, to demonstrate the theoretical results, we use two examples, one from a circadian network formed by a period protein (PER) and *per* mRNA, and the other from a synthetic gene regulatory network, i.e. Repressilator, for numerical simulations. All numerical results show good agreement with our theoretical results [2, 3]. There are also other important facts, which may play crucial roles in biological processes and should be further investigated in future works from both theoretical and experimental viewpoints, such as stochastic noise and discrete nature of biological models [5].

References

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