The Second International Symposium on Optimization and Systems Biology (OSB'08)
Lijiang, China, October 31– November 3, 2008

Periodic Oscillation of Gene Networks with Forcing and Delay

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Abstract In this paper, we derive new criteria for evaluating the global stability of periodic oscillation for gene networks with small forcing and delay. Our results rely on the Lipschtiz conditions of Hill function, topology of gene networks. In particular, Our method based on the proposed model transforms the original network into matrix analysis problem, thereby not only significantly reducing the computational complexity but also making analysis of periodic oscillation tractable for even large-scale nonlinear networks.

Keywords gene network; periodic oscillation

1 Introduction

It is well known that the gene networks (GNs) plays a key role in regulating dynamics of processes transducing genetic signals into phenotypic variation and integrating genomic information, environmental cues, and physiological or developmental stimuli. Thus, understanding the architectures and their design principles of GNs will fundamentally advance the study of core biological problems[1, 2]. In particular, since genetic regulatory networks are high-dimensional and nonlinear, it is indispensable to consider the network dynamics from the viewpoint of nonlinear system theory. However, how to appropriately represent real gene regulatory systems mathematically in terms of gene function, expression mechanisms, and signal-transduction pathways remains unclear. Mathematical models are useful for discovering higher order structure of an organism and for gaining deep insights into both static and dynamic behaviors of gene networks by extracting functional information from observation data [9].

A cellular system is generally characterized with significant time delays in gene regulation, in particular, for the transcription, translation, diffusion, and translocation processes. Moreover, periodic perturbations are widespread in the external environment(e.g. daily light-dark cycle and Moon's gravitational)and internal circumstance (e.g. cell division cycle or cellular motility). Such time delays and perturbation may affect the dynamics of the entire biological system, both qualitatively and quantitatively. Until now, most theoretical works on the study of coupling of gene oscillators[5, 6, 7, 8]. There have been some studies devoted to the stability and oscillations of GNs with fixed time-delay

[9, 10, 11]. It is shown that oscillations can be induced by delay in both nonstochastic and stochastic GNs.

Motivated by the above discussions, rather than rhythmic generators, the purpose of this paper are to study the periodic oscillation of GNs with small periodic forcing and time-delays. In particular, in this paper we derive new criteria for checking the global stability of periodic oscillation of GNs with SUM regulatory logic by using the continuation theorem of Mawhin's coincidence degree theory and Lyapunov functional. The proposed approach is general and can be applied to analyze many biological oscillations in an accurate manner. In other words, the theoretical results are able to cover a large range of nonlinear GNs even under uncertain environments. The paper is organized as follows. In Section 2, a framework of the general gene networks is given. In Section 3, we derive the main results and new criteria about stability of periodic oscillations with fixed time-delay. Section 4 provides an example to illustrate the application of these criteria. Several summary remarks are given in Section 5.

2 Model of gene network

The activity of a gene is regulated by other genes through the concentrations of their gene products, i.e. the transcription factors. Regulation can be quantified by the response characteristics, i.e. the level of gene expression as a function of the concentrations of transcription factors. In this paper, based on the structure of the gene network (GN) or the genetic regulatory network presented in [9], we consider a differential equation model described as follows [3, 9]:

$$\begin{array}{rcll} \dot{m}_i(t) & = & -a_i m_i(t) + b_i(p_1(t),\ldots,p_n(t)), & \\ \dot{p}_i(t) & = & -c_i p_i(t) + d_i m_i(t), & i = 1,\ldots,n. \end{array} \tag{1}$$

where $m_i(t)$, $p_i(t) \in \mathbb{R}$ are the concentrations of mRNA and protein of the ith node, respectively. In (1), a_i and c_i are the degradation rates of the mRNA and protein, d_i is synthesize rate of the protein, and $b_i(t)$ is the regulatory function of the ith gene, which is a nonlinear function of the variables $(p_1(t),\ldots,p_n(t))$ but generally has a form of monotonicity with each variable [1, 4]. In this network, there is one output but multiple inputs for a single node or gene. A directed edge is linked from node j to i if the transcriptional factor or protein j regulates gene i.

Generally, the form of (1) may be very complicated, depending on all biochemical reactions involved in this regulation. Typical regulatory logics include AND-like gates and OR-like gates [19, 20] for b_i. In this paper, we focus on a model of gene networks where each transcription factor acts additively to regulate a gene. That is, the regulatory function is of the form $b_i(p_1(t),...,p_n(t)) = \Sigma_{j=1}^{n} b_{ij}(p_j(t))$, which is also called SUM logic [9, 21], i.e. the regulatory function sums over all the inputs. Such a SUM logic does exist in many natural genetic networks[19]. In synthetic gene networks, one of the simplest ways to implement such an additive input function is to provide a gene with multiple promoters, each responding to one of the inputs[10, 21]. Such a regulation by multiple promoters is indeed found in many gene systems.

The function $b_{ij}(p_j(t))$ is generally expressed by a monotonic function of the Hill

form

$$b_{ij}(p_j(t)) = \begin{cases} e_{ij}\dfrac{(p_j(t)/k)^H}{1+(p_j(t)/k)^H}, & \text{if transcription factor } j \text{ is an activator of gene } i; \\ e_{ij}\dfrac{1}{1+(p_j(t)/k)^H}, & \text{if transcription factor } j \text{ is a repressor of gene } i. \end{cases} \tag{2}$$

where H is the Hill coefficient, k is a positive constant, and $e_{ij} \geqslant 0$ is the dimensionless transcriptional rate of transcription factor j to gene i, which is a bounded constant.

If the time delay are introduced into system (1), (1) can be rewritten into the following equations:

$$\begin{array}{rcl} \dot{m}_i(t) & = & -a_i m_i(t) + \sum_{j=1}^{n} e_{ij} h_{ij}(p_j(t-\tau_j)) + \alpha_i(t), \\ \dot{p}_i(t) & = & -c_i p_i(t) + d_i m_i(t-\sigma_i) + \beta_i(t), \end{array} \tag{3}$$

where $\alpha_i(t) = \alpha_i(t+T)$ and $\beta_i(t) = \beta_i(t+T)$ $(i = 1, \ldots, n)$.

Throughout this paper, we always make the following assumption:

A1. There exists $M_{ij} > 0$ such that $\mid h_{ij}(u) - h_{ij}(v) \mid \leqslant M_{ij}|u-v|$ for each $u, v \in \mathbb{R}$ $(i, j = 1, \ldots, n)$.

Assumption **A1** is generally satisfied in GNs due to the saturation effects of transcription and translation processes. In order to obtain our main results, we need the following Lemma 1.

Assume that $\mathbb{T}^{n\times n} = \{\mathbf{A} = (a_{ij})_{n\times n} : a_{ij} \leqslant 0, i \neq j\}$.

Lemma1. ([24]): Let $\mathbf{A} \in \mathbb{T}^{n\times n}$. Then, each of the following conditions is equivalent to the statement '**A** is a non-singular M-matrix':

(1) All of the principal minors of **A** are positive.

(2) **A** has all positive diagonal elements and there exists a positive diagonal matrix **D** such that **AD** is strictly diagonally dominant, that is:

$$a_{ii}d_i > \sum_{i\neq j} |a_{ij}|d_i, \qquad i = 1, 2, \ldots, n.$$

(3) **A** is inverse-positive, that is, $\mathbf{A^{-1}}$ exists and $\mathbf{A^{-1}} \geqslant 0$.

The above Lemma 1 is widely used in the theoretical analysis of optimization design, finance mathematics, and neural networks. In this paper, we adopt Lemma 1 to estimate the norm of $m_i(t)$ and $p_i(t)$ in the main results, i.e. Theorem I of next section.

3 Some results of stability in Gene Networks with fixed delay

In this section, we derive the main results which ensure the existence and stability of periodic oscillators in GNs with forcings and delay, where forcing $\alpha_i(t)$ and $\beta_i(t)$ are assumed to be small and periodic. Letting $\alpha_i^+ = \sup_{t\geqslant o} |\alpha_i(t)|$ and $\beta_i^+ = \sup_{t\geqslant o} |\beta_i(t)|$, we have the following sufficient conditions on the existence of periodic solutions:

Theorem I. Assume that α_i^+ and β_i^+ are bounded number, (**A**1) hold. Then, the system (3) has at least one T-periodic solution corresponding to the same periodic of forcing, if

$$\Gamma = \begin{pmatrix} I_n & \Gamma_{12} \\ \Gamma_{21} & I_n \end{pmatrix}$$

is a non-singular M-matrix, where I_n is a unit matrix and $\Gamma_{12} = (u_{ij})_{n\times n}$, $u_{ij} = -e_{ij}M_{ij}/a_i$; Γ_{21} = diag$\{-d_1/c_1, -d_2/c_2, \ldots, -d_n/c_n)$.

The detail proof of this result is given in [30]. To ensure non-singular M-matrix, all of the elements Γ_{12} and Γ_{21} should be relatively small, comparing with the diagonal elements. In other words, a_i and c_i are required to be relatively large, comparing with the synthetic rates. With those conditions, (3) is ensured to have one T-periodic solution.

In following theorem, we show that under certain conditions system (3) has at least one T-periodic solution which is globally attractive. It means that all the trajectories of (3) eventually converge to the unique periodic solution.

Theorem II. Assume that all conditions of Theorem I hold. The system (3) has a unique T- periodic solution, which is globally attractive, if

$$\mathbb{O} = \begin{pmatrix} \mathbb{O}_{11} & \mathbb{O}_{12} \\ \mathbb{O}_{21} & \mathbb{O}_{22} \end{pmatrix}$$

is a non-singular M-matrix, where $\mathbb{O}_{11}$ = diag $(2a_1 - \sum_{j=1}^{n} e_{1j}M_{1j}, 2a_2$ - $\sum_{j=1}^{n} e_{2j}M_{2j}$, …, $2a_n - \sum_{j=1}^{n} e_{nj}M_{nj})$; $\mathbb{O}_{12} = (v_{ij})_{n\times n}$, $v_{ij} = -e_{ij}M_{ij}$; $\mathbb{O}_{21} = \text{diag}(-d_1, -d_2, \ldots, -d_n)$; $\mathbb{O}_{22} = \text{diag}(2c_1 - d_1, 2c_2 - d_2, \ldots, 2c_n - d_n)$.

The proof is given in [30]. The conditions for Theorem II are similar to those of Theorem I, i.e. the degradation rates are required to be larger than those of the synthesis rates so that $\mathbb{O}$ is a non-singular M-matrix. Next, we further give the conditions for the asymptotical stability of the T-periodic solution.

Theorem III. Assume that all conditions of Theorem I hold. The system (3) has a unique T- periodic solution, which is globally and asymptotically stable if $\mathbb{O} \in \mathbb{T}$ and is a weakly column diagonally dominant matrices.

The detail proof is given in [30]. The conditions of Theorem III also require large degradation rates, comparing with the synthesis rates. As indicated by the theoretical results, a network with forcing (even with sufficiently small forcing) has globally stable oscillation under certain conditions. It means that all the trajectories of (3) will eventually reach the unique periodic solution. It's worth noting that, even if the parameters and regulatory functions are uncertain, we may design a robust GN, which can be driven by any periodic signals and thereby is able to be synchronized with the driven forces even under uncertain environment, as long as the parameter intervals are finite.

In this section, we present an example of a gene network to show the effectiveness and correctness of our theoretical results.

We consider the dynamics of the repressilator, which has been theoretically predicted and experimentally investigated in Escherichia coli [3]. The repressilator is a cyclic negative-feedback loop comprising three repressor genes (*lacI*, *tetR* and *cI*) and their promoters. The kinetics of the system are determined by six coupled first-order differential equations

$$\begin{array}{rcl} \dot{m}_i(t) & = & -a_i m_i(t) + \dfrac{e}{1 + p_j(t-\tau_i))^2} + \alpha_i(t), \\ \dot{p}_j(t) & = & -c_j p_j(t) + d_j m_j(t-\sigma_j) + \beta_j(t), \\ i & = & lacI, tetR, cI; j = cI, lacI, textR, \end{array} \tag{4}$$

where m_i and p_i are the concentrations of the three mRNAs and repressor-proteins, and e denotes the ratio of the protein decay rate to the mRNA decay rate. We select a set of

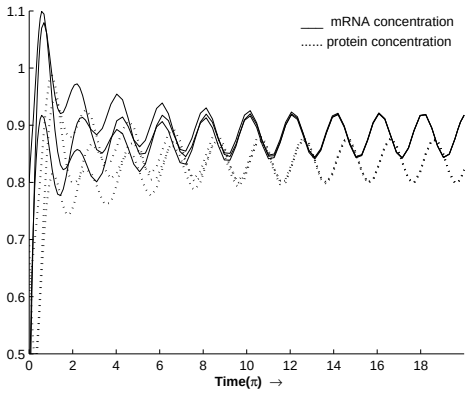

Figure 1: Time evolution of three mRNA and protein concentrations of GN (4)

biologically plausible parameters as $e = 1.5$, $a_i = c_i = 1$, $d_i = 0.95$, $\tau_i = 0.4$, $\sigma_j = 0.6$, and choose small periodic perturbations as $\alpha_i(t) = 0.025\cos t$, $\beta_i(t) = 0.025\sin t$ with $T = 2\pi$, which are assumed to be weakly coupled from external environment or other rhythmic generators.

By appropriate computation, we have $\max h' = \frac{3\sqrt{3}}{8} < 21/32$,

$$\Gamma = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & -\frac{63}{64} \\ 0 & 1 & 0 & -\frac{63}{64} & 0 & 0 \\ 0 & 0 & 1 & 0 & -\frac{63}{64} & 0 \\ -\frac{19}{20} & 0 & 0 & 1 & 0 & 0 \\ 0 & -\frac{19}{20} & 0 & 0 & 1 & 0 \\ 0 & 0 & -\frac{19}{20} & 0 & 0 & 1 \end{pmatrix}$$

and

$$\mathbb{O} = \begin{pmatrix} \frac{65}{64} & 0 & 0 & 0 & 0 & -\frac{63}{64} \\ 0 & \frac{65}{64} & 0 & -\frac{63}{64} & 0 & 0 \\ 0 & 0 & \frac{65}{64} & 0 & -\frac{63}{64} & 0 \\ -\frac{19}{20} & 0 & 0 & \frac{21}{20} & 0 & 0 \\ 0 & -\frac{19}{20} & 0 & 0 & \frac{21}{20} & 0 \\ 0 & 0 & -\frac{19}{20} & 0 & 0 & \frac{21}{20} \end{pmatrix}.$$

It is easy to check that Γ and $\mathbb{O}$ are non-singular M-matrices. From Theorem 3, the

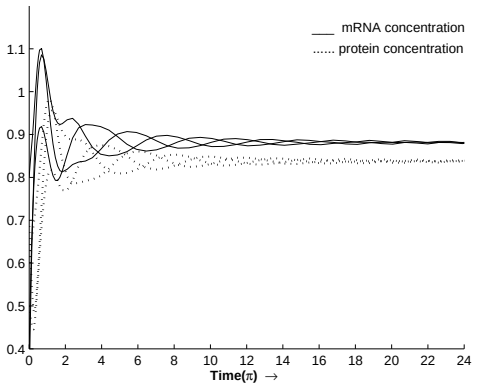

Figure 2: Time evolution of three mRNA and protein concentrations of GN(4) without forcing.

repressilator with this set of parameters has a T-Periodic oscillation, which is globally and asymptotically stable. In Fig.1 we plot the trajectories of mRNAs and proteins concentrations, which confirm the theoretical prediction.

From other study[5, 9, 12], we knew delay always induce the periodic oscillation. Here, by numerical simulation, we find that GN have only stable stationary solution absent small forcing(i.e., $\alpha_i(t) = \beta_i(t) = 0$), see Fig.2. It is sufficiently demonstrate that the small extra forcing can produce periodic oscillation.

4 Numerical Example

In this section, we present an example of a gene network to show the effectiveness and correctness of our theoretical results.

We consider the dynamics of the repressilator, which has been theoretically predicted and experimentally investigated in Escherichia coli [3]. The repressilator is a cyclic negative-feedback loop comprising three repressor genes ($lacl$, $tetR$ and cl) and their promoters. The kinetics of the system are determined by six coupled first-order differential equations

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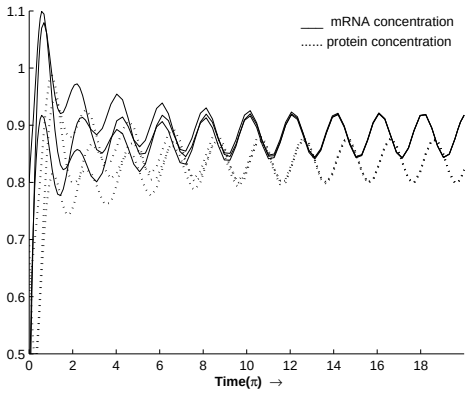
where m_i and p_i are the concentrations of the three mRNAs and repressor-proteins, and e denotes the ratio of the protein decay rate to the mRNA decay rate. We select a set of biologically plausible parameters as $e = 1.5$, $a_i = c_i = 1$, $d_i = 0.95$, $\tau_i = 0.4$, $\sigma_j = 0.6$, and choose small periodic perturbations as $\alpha_i(t) = 0.025\cos t$, $\beta_i(t) = 0.025\sin t$ with $T = 2\pi$, which are assumed to be weakly coupled from external environment or other rhythmic generators.



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By appropriate computation, we have $\max h' = \frac{3\sqrt{3}}{8} < 21/32$,

$$\Gamma = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & -\frac{63}{64} \\ 0 & 1 & 0 & -\frac{63}{64} & 0 & 0 \\ 0 & 0 & 1 & 0 & -\frac{63}{64} & 0 \\ -\frac{19}{20} & 0 & 0 & 1 & 0 & 0 \\ 0 & -\frac{19}{20} & 0 & 0 & 1 & 0 \\ 0 & 0 & -\frac{19}{20} & 0 & 0 & 1 \end{pmatrix}$$

and

$$\mathbb{O} = \begin{pmatrix} \frac{65}{64} & 0 & 0 & 0 & 0 & -\frac{63}{64} \\ 0 & \frac{65}{64} & 0 & -\frac{63}{64} & 0 & 0 \\ 0 & 0 & \frac{65}{64} & 0 & -\frac{63}{64} & 0 \\ -\frac{19}{20} & 0 & 0 & \frac{21}{20} & 0 & 0 \\ 0 & -\frac{19}{20} & 0 & 0 & \frac{21}{20} & 0 \\ 0 & 0 & -\frac{19}{20} & 0 & 0 & \frac{21}{20} \end{pmatrix}.$$

It is easy to check that Γ and $\mathbb{O}$ are non-singular M-matrices. From Theorem 3, the repressilator with this set of parameters has a T-Periodic oscillation, which is globally and asymptotically stable. In Fig.1 we plot the trajectories of mRNAs and proteins concentrations, which confirm the theoretical prediction.

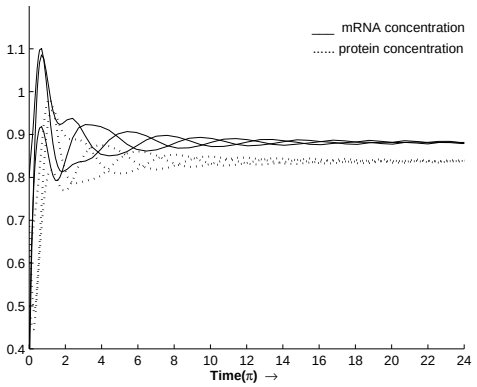

Figure 4: Time evolution of three mRNA and protein concentrations of GN(4) without forcing.

From other study[5, 9, 12], we knew delay always induce the periodic oscillation. Here, by numerical simulation, we find that GN have only stable stationary solution absent small forcing(i.e., $\alpha_i(t) = \beta_i(t) = 0$), see Fig.2. It is sufficiently demonstrate that the small extra forcing can produce periodic oscillation.

5 Discussion.

Generally speaking, a cellular system is not only affected by various external fluctuations but also characterized with significant time delays in gene regulation, in particular, for the transcription, translation, diffusion, and translocation processes. Such time delays may affect the dynamics of the entire biological system both qualitatively and quantitatively. In this paper, we derived new criteria for checking the global stability of periodic oscillation of GNs with delays and periodic forcings by using the continuation theorem of Mawhin's coincidence degree theory, the non-singular M-matrix and Lyapunov function. Theoretical results ensure that the GN has a stable periodic oscillation provided that there is a small periodic driving force, which can be used to analyze cellular oscillations, to understand synchronization phenomena, and even to design a robust synthetic oscillator.

5.1 Designing a large scale GN

As indicated in this paper, the networks with forcing have stable oscillation under certain conditions which relay on the Lyapunov constants of the regulatory functions, dimensionless transcriptional rate, and the degradation rates of mRNAs or proteins. When analyzing or designing a large scale GN, we need the following steps based on Theorems I-III.

1) Firstly, we select a set of biologically plausible parameters and compute the Lipschitz constants M_{ij} of the function b_i.

2) Check whether Γ and $\mathbb{O}$ are non-singular M-matrixes.

If all of the conditions are satisfied, there exists a stable periodic oscillation, which

coincides with the weak periodic signal in phase. Owing to the fact that our results are robust for genetic oscillator networks with forcing and distributed delay, we can design a robust oscillation in the GN within the defined parameter intervals or ranges.

5.2 Small perturbation can also induce oscillation

Since genetic regulatory networks are high-dimensional and nonlinear, it is indispensable to consider the network dynamics from the viewpoint of nonlinear systems theory. Up to now, several theoretical models have been successfully developed to understand circadian phenomena of GNs, but few studies consider the small perturbations. On the other hand, these perturbations always exist in the GNs, such as the stochastic regulation, production and decay processes which are due to temporary chemical or physical changes in the environment, or periodic perturbations from other cells. Unfortunately, previous results are mainly for the perturbations on linear systems, and there are few results on the perturbations of nonlinear systems due to the mathematical difficulties.

In [23], a model for a synthetic gene oscillator is present, and the coupling of the small oscillator to a periodic process that is intrinsic to the cell is considered. They studied the synchronization properties of the coupled system, and showed how the oscillator can be constructed to yield a significant amplification of cellular oscillations both numerically and experimentally.

In our paper, we consider a general nonlinear GN model and show that under certain conditions, the nonlinear system coupled with even small perturbation can always oscillate with the signals.

Acknowledges

This work is supported by the NNSF of China: No. 10672093. The authors thank Prof. Zengrong Liu and Prof. Luonan Chen for helpful discussions and suggestions.

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