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Periodic oscillation in delayed gene networks with SUM regulatory logic and small perturbations ☆

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ABSTRACT

In this paper, we derive new criteria for evaluating the global stability of periodic oscillation in delayed gene networks with SUM regulatory logic and small perturbation, which appear in many biological systems at biomolecular or cellular levels due to the weak coupling and signal diffusion (or transport) process. Our results rely on the Lipschtiz conditions of Hill function, topology of gene networks and delay kernels. 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.

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].

With the rapid advances in theoretical study and biological 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 GNs due to long time durations of transcription, translation, diffusion, and active transport process. Until now, most theoretical works on the study of coupling of gene oscillators [5–8]. There have been some studies devoted to the stability and oscillations of GNs with fixed time-delay [9–11]. It is shown that oscillations can be induced by delay in both nonstochastic and stochastic GNs. If we considered the process of macromolecular transport, the distributed delay is biologically plausible owing to delay time is drastic. Generally a distributed time-delay can be represented by an integral of a function of one or more variables over a specified range of previous time. In this paper, one of main targets is to analyze the global stability of GNs with the considerations of the distributed delays. The proposed approach is general and can model any macromolecular transport process. For example, if movement of mRNA from a transcription site to translation sites is an active process with a significant range of transportation times for individual molecules, a distributed delay is a proper modeling framework [12]. In addition, all cellular components exhibit intracellular noises owing to random births and deaths of individual molecules, and extracellular noises owing to environment fluctuations, which also contribute to distributed delay.

On the other hand, 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). Up to now, many theoretical models have been successfully developed to understand rhythmic generators or inherent oscillations, but few studies consider the biological

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oscillation driving by small perturbations (or synchronization), which are ubiquitous in the living cells, e.g. many cells or organs in mammals exhibit periodic oscillations with the same phase as rhythmic generators. Besides regular perturbations, there always exist many irregular oscillations in the GNs, such as the stochastic regulation, production and decay processes which are due to temporary chemical or physical changes in the environment. Gene regulation is an intrinsically noisy process, which is subject intracellular and extracellular noise perturbations and environment fluctuations [13–18]. Such perturbations and environment fluctuations will undoubtedly affect the dynamics of networks both quantitatively and qualitatively. Unfortunately, previous works mainly focused on the perturbations of the linear systems, and there is little result on the perturbations of nonlinear biological systems due to the mathematical difficulties.

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 perturbation 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 some 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. In appendix, we derive the theoretical results for a general GN with perturbation and distributed delay.

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]:

$$\begin{aligned} \dot{m}_i(t) &= -a_i m_i(t) + b_i(p_1(t),\ldots,p_n(t)),\\ \dot{p}_i(t) &= -c_i p_i(t) + d_i m_i(t),\ \ i = 1,\ldots,n. \end{aligned} \tag{2.1}$$

where $m_i(t), p_i(t) \in \mathbf{R}$ are the concentrations of mRNA and protein of the ith node, respectively. In (2.1), 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 (2.1) 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 $b_i(p_1(t),\ldots,p_n(t)) = \Sigma_{j=1}^{n} b_{ij}(p_j(t))$, 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

$$b_{ij}(p_j(t)) = \begin{cases} e_{ij}\frac{(p_j(t)/k)^H}{1+(p_j(t)/k)^H}, \\ \text{if transcription factor } j \text{ is an activator of gene } i; \\ e_{ij}\frac{1}{1+(p_j(t)/k)^H}, \\ \text{if transcription factor } j \text{ is a repressor of gene } i. \end{cases} \tag{2.2}$$

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.

In the following paper, the active transports which can be modeled with a time delay are introduced into system (2.1) to represent biological processes. The time delays can be assumed to be distributed delays which means that each macromolecule takes a different time to translocate from its place of synthesis to the location. Here, the derivative of a variable, which can be the concentration of a macromolecule, depends on an integral of a function of one or more variables over a specified range of previous time. For example, a general distributed delay for one variable takes the form

$$\frac{dx(t)}{dt} = F\left(x, \int_0^{\omega} f(\tau)x(t-\tau)d\tau\right), \text{ with } \int_0^{\omega} f(\tau)d\tau = 1.$$

The equation expresses a normalization condition imposed for biological realism [12,22].

Hence, (2.1) can be rewritten into the following equations with the distributed time-delay:

$$\begin{aligned} \dot{m}_i(t) &= -a_i m_i(t) + \sum_{j=1}^{n} e_{ij}h_{ij}\left(\int_0^{t_{ij}} f_{ij}(s)p_j(t-s)ds\right) + \alpha_i(t),\\ \dot{p}_i(t) &= -c_i p_i(t) + d_i \int_0^{\tau_{ji}} g_i(s)m_i(t-s)ds + \beta_i(t), \end{aligned} \tag{2.3}$$

where $\alpha_i(t) = \alpha_i(t+T)$ and $\beta_i(t) = \beta_i(t+T)(i = 1,\ldots,n)$ are small periodic perturbation which is considered as coupled periodic fluctuations from external environment or other rhythmic generators. Such a process include mechanisms may be relate to the cell division cycle or cellular motility [23].

For the sake of simplicity, we first consider the following equations with the fixed time-delay which assumes that each macromolecule takes the same length of time to translocate from its place of synthesis to the location and the general model with distributed delay will be analyzed in the Appendix. That is

$$\begin{aligned} \dot{m}_i(t) &= -a_i m_i(t) + \sum_{j=1}^{n} e_{ij}h_{ij}(p_j(t-\tau_j)) + \alpha_i(t),\\ \dot{p}_i(t) &= -c_i p_i(t) + d_i m_i(t-\sigma_i) + \beta_i(t), \end{aligned} \tag{2.4}$$

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 $|\, h_{ij}(u) - h_{ij}(v)\,| \leqslant M_{ij}|u-v|$ for each $u, v \in \mathbf{R}(i,j = 1,\ldots,n)$.

Assumption **A1** is generally satisfied in GNs due to the saturation effects of transcription and translation processes.

The following assumption is reasonable for the system (2.3) which is sure $sf_{ij}(s)$ and $sg_i(s)$ are integrable:

A2. The delay kernels $f_{ij}(s),\ g_i(s) : [0,+\infty) \to [0,+\infty)$ $(i.j = 1,2,\ldots,n)$ are continuous and integrable, and satisfy