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Synchronization of stochastic genetic oscillator networks with time delays and Markovian jumping parameters ☆

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ABSTRACT

Genetic oscillator networks (GONs) are inherently coupled complex systems where the nodes indicate the biochemicals and the couplings represent the biochemical interactions. This paper is concerned with the synchronization problem of a general class of stochastic GONs with time delays and Markovian jumping parameters, where the GONs are subject to both the stochastic disturbances and the Markovian parameter switching. The regulatory functions of the addressed GONs are described by the sector-like nonlinear functions. By applying up-to-date 'delay-fractioning' approach for achieving delay-dependent conditions, we construct novel matrix functional to derive the synchronization criteria for the GONs that are formulated in terms of linear matrix inequalities (LMIs). Note that LMIs are easily solvable by the Matlab toolbox. A simulation example is used to demonstrate the synchronization phenomena within biological organisms of a given GON and therefore shows the applicability of the obtained results.

1. Introduction

The oscillatory behavior of genetic networks, as a fundamental challenge in the research field of systems biology, has recently attracted an increasing attention, see e.g. [1,5,6,10–12,14,29]. Generally speaking, the genetic networks are a class of complex dynamical networks since the genetic oscillators can be expressed in terms of complicated biological functions [9,16,17,23]. In such kind of genetic oscillator networks (GONs), the nodes represent the genetic oscillators, while the inner or outer couplings denote the interactions. In order to research into the intrinsic biological organisms of GONs, it is of great importance to investigate the collective dynamics of coupled genetic oscillators with hope to understand the rhythmic behavior of living organisms. Synchronization, as a universal phenomenon, occurs typically in genetic networks. For example, in [19], a synthetic gene network in *Escherichia coli* has been shown to have two features: the system acts as a relaxation oscillator and uses an intercell signaling mechanism to couple the oscillators and induce synchronous oscillations. A coupling scheme has been proposed that leads to synchronous behavior across a population of cells, and an analytical treatment of the synchronization process has been conducted. Up to now, the synchronization motion analysis problem for genetic oscillator networks has attracted considerate research attention. In [11,14,16,17], the synchronization problem in genetic networks has been thoroughly investigated via experiments (e.g. synchronization of cellular clock in the suprachiasmatic nucleus in genetic networks), numerical simulation (e.g. biological networks of identical genetic oscillators) as well as theoretical analysis (i.e. synchronizability of coupled nonidentical genetic oscillators).

It has been demonstrated experimentally that the network states or oscillatory expressions are significantly affected by the inherent state delay due primarily to the slow processes of transcription, translation, and translocation or the finite switching speed of amplifiers. From the synthetic biology viewpoint, it is necessary to address the time-delay effects in the mathematical models, and then a more accurate state value of the biological oscillators could be obtained from oscillatory expression measurements [22,26,30]. Note that the stability analysis issue of genetic regulatory networks with either constant or time-varying delays has recently been a research focus, see [30] and references

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therein. It is worth mentioning that a novel approach named 'delay-fractioning' has been exploited in many reported results in order to achieve less conservative delay-dependence conditions, see e.g. [20,27,28,35].

Biological data promises to enhance the fundamental understanding of life at the molecular level, from regulation of gene expression and gene function to cellular mechanisms, and may prove useful in medical diagnosis, treatment, and drug design. Substantial effort is being made to build models to analyze microarray data. It is evident that genetic networks are always affected by the random fluctuations [1,3,13,21,25,26,29,31]. Therefore, to have an accurate prediction of the dynamical behaviors of genetic oscillators, it is important to consider the random effects including intrinsic and extrinsic noise perturbations [1,3,25,26,29]. Also, as shown in [7,8,13], in gene regulatory networks, the transition from one state to the next usually takes place in accordance with certain transition probabilities, which forms a homogeneous Markov chain with finite state space. Subsequently, the dynamics of the so-called Markovian genetic regulatory networks, which are subject to mode switching (or jumping), has been thoroughly investigated in [7,8]. It should be pointed out that, up to now, the control and filtering problems for Markovian jumping systems have already been widely studied [4,18,33,34]. Recently, the stochastic synchrony study has been carried out for genetic networks in [32], where an adaptive filtering approach is elegantly developed to estimate uncertain delayed genetic regulatory networks. However, the stochastic synchrony problem for *Markovian* delayed genetic networks of specific structures has not gained adequate research attention yet, and this constitutes the main focus of this paper.

In this paper, we aim to make one of the first attempts to investigate the synchronization problem for stochastic GONs with Markovian jumping parameters and time delays so as to exhibit more realistic characteristics of the GONs, where the regulation functions are assumed to be sector-like, and the intrinsically stochastic fluctuation is a scalar Brownian motion. The main results obtained are illustrated through a numerical simulation example. The rest of this paper is organized as follows. Section 2 introduces the model formulation and some preliminary works. In Section 3, by utilizing the approach of 'delay-fractioning' and a novel matrix functional method, stochastic analysis is conducted to obtain delay-dependent sufficient criteria described by linear matrix inequalities (LMIs) [2] that can be easily checked by using standard numerical software. Section 4 illustrates the obtained results and Section 5 concludes the paper.

Notations: Throughout this paper, $\Re^n$ and $\Re^{n\times m}$ denote, respectively, the n dimensional Euclidean space and the set of all $n\times m$ real matrices. $P>0$ means that matrix P is real, symmetric and positive definite. I and 0 denote the identity matrix and the zero matrix with compatible dimensions, respectively; and diag$\{\cdots\}$ stands for a block-diagonal matrix, col$\{\cdots\}$ denotes a matrix column with blocks given by the matrices in $\{\cdots\}$. If A is a matrix, the notation $\lambda_{\max}(A)$ means the largest eigenvalue of A. The superscript 'T' stands for matrix transposition and the asterisk '*' in a matrix is used to represent the term which is induced by symmetry. The Kronecker product of matrices $Q\in\Re^{m\times n}$ and $R\in\Re^{p\times q}$ is a matrix in $\Re^{mp\times nq}$ and denoted as $Q\otimes R$. We let $\mathcal{C}([-h,0];\Re^n)$ denote the family of all continuous functions φ from $[-h,\ 0]$ to $\Re^n$ with the norm $|\varphi|=\sup_{-h\le\theta\le 0}\|\varphi(\theta)\|$, where $\|\cdot\|$ is the Euclidean norm on $\Re^n$. Moreover, let $(\Omega,\mathcal{F},\{\mathcal{F}_t\}_{t\ge 0},\mathcal{P})$ be a complete probability space with a filtration $\{\mathcal{F}_t\}_{t\ge 0}$ satisfying the usual conditions (i.e. the filtration contains all $\mathcal{P}-$null sets and is right continuous). Denote by $L^p_{\mathcal{F}_0}([-h,0];\Re^n)$ the family of all $\mathcal{F}_0-$measurable $\mathcal{C}([-h,0];\Re^n)-$valued random variables $\xi=\{\xi(\theta):-h\le\theta\le 0\}$ such that $\sup_{-h\le\theta\le 0}\mathcal{E}\{|\xi(\theta)|^p\}<\infty$, where $\mathcal{E}\{\cdot\}$ stands for the mathematical expectation operator with respect to the given probability measure $\mathcal{P}$. Sometimes, the arguments of a function will be omitted in the analysis when no confusion arises.

2. Problem formulation and preliminaries

Let $r(t)$ $(t\ge 0)$ be a right-continuous Markovian chain on a probability space $(\Omega,\mathcal{F},\{\mathcal{F}_t\}_{t\ge 0},P)$ taking values in a finite state space $\mathbb{S}=\{1,2,\ldots,m\}$ with generator $\Pi=\{\pi_{ij}\}$ given by

$$P\{r(t+\Delta)=j|r(t)=i\}=\begin{cases}\pi_{ij}\Delta+o(\Delta) & \text{if } i\neq j,\\ 1+\pi_{ij}\Delta+o(\Delta) & \text{if } i=j.\end{cases}$$

Here $\Delta>0$, and $\pi_{ij}\ge 0$ is the transition rate from i to j if $j\neq i$ while $\pi_{ii}=-\sum_{j\neq i}\pi_{ij}$.

Among many models of genetic networks, the differential equation model is one of the mostly adopted ones. A general delayed genetic oscillator network could be described by the following vector form [16,17]:

$$\frac{dy(t)}{dt}=Ay(t)+\sum_{i=1}^{l}B_if_i(y(t))+\sum_{i=1}^{l}C_ig_i(y(t-\tau)), \tag{1}$$

where l is a positive integer and $y(t)=\text{col}\{y_1(t),y_2(t),\ldots,y_n(t)\}\in\Re^n$ represents the concentrations of proteins, mRNAs and chemical complexes; A, B_i, C_i (i=1,2,…, l) are matrices in $\Re^{n\times n}$; $f_i(y(t))=\text{col}\{f_{i1}(y_1(t)),f_{i2}(y_2(t)),\ldots f_{in}(y_n(t))\}\in\Re^n$ and $g_i(y(t-\tau))=\text{col}\{g_{i1}(y_1(t-\tau)),g_{i2}(y_2(t-\tau)),\ldots,g_{in}(y_n(t-\tau))\}\in\Re^n$ are monotonic genetic regulatory functions which are usually taken as the Hill form. The scalar $\tau>0$ denotes the translation time delay in the translation process.

As discussed in the Introduction, the genetic oscillators in biological networks are tightly coupled between each other, and both the stochastic perturbations [1,3,13,21,25,26,29] and Markovian jumping parameters [13] are playing important roles in generating the network dynamics. Therefore, we consider the following coupled GONs consisting of N genetic oscillators with Markovian jumping parameters and time delays:

$$\begin{aligned}dx_k(t)=&\left[A(r(t))x_k(t)+B(r(t))f(x_k(t))+C(r(t))g(x_k(t-\tau))+\sum_{l=1}^{N}w_{kl}\Gamma_{r(t)}x_l(t)\right]dt\\&+\sigma_k(x_k(t),x_k(t-\tau),t,r(t))\,d\omega(t),\end{aligned}$$

$$x_k(t)=\phi_k(t),\quad r(t)|_{t=0}=r_0\in\mathbb{S},\quad t\in[-\tau,0],\ k=1,2,\ldots,N, \tag{2}$$

where $x_k(t)=\text{col}\{x_{k1}(t),x_{k2}(t),\ldots,x_{kn}(t)\}\in\Re^n$ is the state vector of the kth genetic oscillator representing the concentrations of proteins, mRNAs and chemical complexes, which are of limited values; for $r(t)=i\in\mathbb{S}$, $A(i)$ includes the degradation terms and all the other linear terms of the kth genetic oscillator; $B(i)$, $C(i)$ are known matrices in $\Re^{n\times n}$; $f(x_k(t))=\text{col}\{f_1(x_{k1}(t)),f_2(x_{k2}(t)),\ldots,f_n(x_{kn}(t))\}\in\Re^n$ and $g(x_k(t-\tau))=\text{col}\{g_1(x_{k1}(t-\tau)),g_2(x_{k2}(t-\tau)),\ldots,g_n(x_{kn}(t-\tau))\}\in\Re^n$ are usually monotonic functions satisfying the sector-bounded conditions that will be given later; $\phi_k(t)\in L^p_{\mathcal{F}_0}([-h,0];\Re^n)$ is the initial condition of $x_k(t)$.

The matrix $\Gamma_{r(t)}=[\gamma_{kl,r(t)}]_{n\times n}$ is a matrix linking the state variable of the lth genetic oscillator in the genetic network mode $r(t)$ if $\gamma_{kl,r(t)}\neq 0$; and $W=[w_{kl}]_{N\times N}$ is the coupling matrix that represents the coupling topology, direction, as well as the coupling strength of the genetic network. The definition is given as follows: if there is a link from the kth oscillator to the lth oscillator ($k\neq l$), then w_{kl} equals to a positive constant denoting the coupling strength of this link; otherwise $w_{kl}=0$;