Neurocomputing 79 (2012) 39–49

Contents lists available at SciVerse ScienceDirect

Neurocomputing

journal homepage: www.elsevier.com/locate/neucom

Robust stochastic stability analysis of genetic regulatory networks with disturbance attenuation

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ARTICLE INFO

Article history:
Received 25 October 2009
Received in revised form
10 September 2011
Accepted 19 September 2011
Communicated by S. Hu
Available online 11 November 2011

Keywords:
Robust stochastic stability
Genetic regulatory networks
Disturbance attenuation
Extrinsic noises

ABSTRACT

This paper studies the robust stochastic stability of uncertain stochastic genetic regulatory networks with disturbance attenuation. A novel delay-dependent robust stability condition with disturbance attenuation, in the form of linear matrix inequalities (LMIs) is derived for the uncertain stochastic genetic networks with time-varying delays and intrinsic and extrinsic noises. These stability conditions can be tested efficiently by the available commercial software packages such as Matlab LMI Control Toolbox. Two numerical examples with simulations are given to illustrate the effectiveness and validity of the derived theoretical results.

1. Introduction

In the post-genomic era, one of the main challenges is to understand and study the gene functions, for example, how genes and proteins interact to form a complex network that performs complicated biological functions in living organisms. Genetic regulatory networks (GRNs) have thus attracted considerable attention from researchers in various fields recently. Scientists have tried to employ variety of methods to find, understand and predict the gene regulations. One of the popular methods is to study modeling and simulation of the genetic regulatory networks, see [1–5].

Some of genetic regulatory network models have been successfully constructed recently, and it is shown that the dynamical model can be an effective method to predict the regulations of genes and proteins. Basically, there are two types of genetic network models, the Boolean model [1,2], where the activity of each gene has two states, and the differential equation model, where the variables describe the concentrations of gene products, such as mRNAs and proteins [6–9]. In this paper, we will focus on the differential equation model of genetic regulatory networks with special regulation logics.

From many experiment results, it is understood that time delays are inevitable due to the transcription, translation, diffusion, and translocation processes of genes, which will affect the entire dynamics of the biochemical systems [10,11]. Hence, time delays should be taken into account when modeling the biochemical systems. In [10], the authors employed a reduced model to show the role of feedback loops and time delays in the Drosophila circadian oscillator. Chen and Aihara [12] presented a functional differential equation model for genetic regulatory networks with time delays, then analyzed its local stability and bifurcation. Genetic regulatory networks model with the SUM logic was presented in [13], some stability conditions in the form of LMIs were derived for the genetic regulatory networks with time-varying delays. In [14], Ren and Cao studied the robust stability of genetic networks with time-varying delays.

It is worth noting that molecular events in cells are subject to significant thermal fluctuations and noisy process with transcriptional control, alternative splicing, translation, diffusion and chemical modification reaction, thus gene expression is best viewed as a stochastic process [15–19]. Stochastic dynamic models are the ideal tools for the investigations of gene networks [20–22]. Chen et al. [23] revealed cooperative behaviors in a general coupled noisy system with time delays. Robust stability of stochastic interval genetic networks was studied by Wang et al. [24]. In [25], the authors studied the stochastic stability with disturbance attenuation for stochastic genetic regulatory networks. Chen and Wang [26] investigated the attenuation of molecular noises in genetic regulatory networks. By using the fuzzy interpolation approach, the stabilization problem for stochastic gene networks was considered in [27], where the time delay and specific regulation function have been ignored.

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doi:10.1016/j.neucom.2011.09.023

Furthermore, it is generally believed that robustness is a fundamental property of biological systems [31,32], cellular functioning is robust to a broad range of perturbations [33]. As pointed in [33], systemic diseases such as cancer and diabetes can be classified as failures in the robustness mechanisms of biological systems, which has also been named as genetic uncertainties consisting of mutations [34–36]. Thus, when modeling and analyzing genetic regulatory networks, it is desirable to take into account these uncertainties and extrinsic disturbances from system viewpoint [37–39], which is an important and promising way to quantify the robustness of the genetic regulatory networks. To the best of our knowledge, when the parameter uncertainties as well as extrinsic noises appear simultaneously in stochastic genetic regulatory networks, the problem of the robust stochastic stability of the uncertain genetic regulatory networks with disturbance attenuation have not been fully investigated.

Motivated by the above discussions, we will investigate robust stochastic stability of uncertain genetic regulatory networks with intrinsic and extrinsic noises. A novel delay-dependent robust stability condition will be derived, and how to find the optimal attenuation level of extrinsic noises for genetic regulatory networks is also discussed. These results and observations will help understand the process of gene regulations.

The rest of this paper is organized as follows. In Section 2, the uncertain stochastic genetic regulatory networks model with extrinsic noises and parameter perturbations is introduced, some necessary assumptions and a lemma which will be used in the proof of the main results are also given. In Section 3, delay-dependent robust stochastic stability conditions are derived, and some comparisons with the existing results are presented as well. In Section 4, two numerical examples with simulations are given to illustrate the effectiveness of the obtained results. At last, this paper is completed with a conclusion and some discussions.

In this study the following notations stand. For any matrix A, $A>0$ means that A is symmetric positive definite. $\mathcal{E}\{\cdot\}$ stands for the mathematical expectation operator. The superscript 'T' represents the transpose of the matrix. $\|x\|$ is used to denote a vector norm defined by $\|x\|=(\sum_{i=1}^{n}|x_i|^2)^{1/2}$. I is the identity matrix and $\omega(t)$ is an one-dimensional Brownian motion defined on the probability space.

2. Genetic network model and preliminaries

In a genetic network, lots of genes interact and regulate the expression of other genes by proteins and the gene derivatives. The change in expression of a gene is controlled by the stimulation and inhibition of proteins in the process of transcription, translation and post-translation. In this paper, we start from the following genetic networks model [12,43]:

$$\begin{cases}\dot{m}_i(t)=-a_i m_i(t)+\overline{b}_i(p_1(t),p_2(t),\ldots,p_n(t)),\\ \dot{p}_i(t)=-c_i p_i(t)+d_i m_i(t), \quad i=1,2,\ldots,n,\end{cases} \tag{1}$$

where $m_i(t),p_i(t)\in\mathbb{R}$ are the concentrations of mRNA and protein of the ith node, respectively. The parameters a_i and c_i are the degradation rates of mRNA and protein, respectively; d_i is the translation rate, and $\overline{b}_i$ represent the feedback regulation of the protein on the transcription, which is generally a nonlinear function but has a form of monotonicity with its variables [2,6].

Generally, the form of $\overline{b}_i$ may be very complicated, depending on all biochemical reactions involved in this regulation. Here for convenience, we only consider the SUM logic [4] representing the case that each transcription factor acts additively to regulate the ith gene, which is considered in [13,14,24]. That is

$$\overline{b}_i(p_1(t),p_2(t),\ldots,p_n(t))=\sum_{j=1}^{n}\overline{b}_{ij}(p_j(t)). \tag{2}$$

Without loss of generality, the function is expressed by the following Hill form

$$\overline{b}_{ij}(p_j(t))=\begin{cases}\beta_{ij}\dfrac{\left(\frac{p_j(t)}{\alpha_j}\right)^{h_j}}{1+\left(\frac{p_j(t)}{\alpha_j}\right)^{h_j}} & \text{if transcription factor } j\\ & \text{is an activator of gene } i,\\ \beta_{ij}\dfrac{1}{1+\left(\frac{p_j(t)}{\alpha_j}\right)^{h_j}} & \text{if transcription factor } j\\ & \text{is an repressor of gene } i,\end{cases}$$

where h_j is the Hill coefficient and α_j is a positive constant, and β_{ij} is a bounded constant, which is the dimensionless transcriptional rate of transcription factor j to i.

Note that

$$\frac{\left(\frac{p_j(t)}{\alpha_j}\right)^{h_j}}{1+\left(\frac{p_j(t)}{\alpha_j}\right)^{h_j}}=1-\frac{1}{1+\left(\frac{p_j(t)}{\alpha_j}\right)^{h_j}},$$

hence we can rewrite (1) as follows:

$$\begin{cases}\dot{m}_i(t)=-a_i m_i(t)+\sum_{j=1}^{n}b_{ij}f_j(p_j(t))+l_i,\\ \dot{p}_i(t)=-c_i p_i(t)+d_i m_i(t), \quad i=1,2,\ldots,n,\end{cases} \tag{3}$$

where

$$f_j(x)=\frac{\left(\frac{x}{\alpha_j}\right)^{h_j}}{1+\left(\frac{x}{\alpha_j}\right)^{h_j}}$$

is a monotonically increasing function. $l_i=\sum_{j\in I_i}\beta_{ij}$ and I_i is the set of all j nodes which are repressors of gene i. $B=(b_{ij})\in\mathbb{R}^{n\times n}$ is defined as follows:

$$b_{ij}=\begin{cases}\beta_{ij} & \text{if transcription factor } j\\ & \text{is an activator of gene } i,\\ 0 & \text{if there is no link from node } j \text{ to } i,\\ -\beta_{ij} & \text{if transcription factor } j\\ & \text{is an repressor of gene } i.\end{cases}$$

Taking into account the transcriptional time delay, we have the following genetic regulatory networks model with SUM regulatory logic [13,14,25]:

$$\begin{cases}\dot{m}_i(t)=-a_i m_i(t)+\sum_{j=1}^{n}b_{ij}f_j(p_j(t-\sigma(t)))+l_i,\\ \dot{p}_i(t)=-c_i p_i(t)+d_i m_i(t-\tau(t)), \quad i=1,2,\ldots,n,\end{cases} \tag{4}$$

where $\tau(t)$ and $\sigma(t)$ are time-varying delays satisfying $0\le\tau(t)\le\tau$ and $0\le\sigma(t)\le\sigma$, respectively.

Rewrite model (4) into the compact form

$$\begin{cases}\dot{m}(t)=-Am(t)+Bf(p(t-\sigma(t)))+L,\\ \dot{p}(t)=-Cp(t)+Dm(t-\tau(t)),\end{cases} \tag{5}$$

where $m(t)=[m_1(t),m_2(t),\ldots,m_n(t)]^{\mathrm{T}}$, $p(t)=[p_1(t),p_2(t),\ldots,p_n(t)]^{\mathrm{T}}$, $A=\mathrm{diag}(a_1,a_2,\ldots,a_n)$, $C=\mathrm{diag}(c_1,c_2,\ldots,c_n)$, $D=\mathrm{diag}(d_1,d_2,\ldots,d_n)$ and $L=[l_1,l_2,\ldots,l_n]^{\mathrm{T}}$.