Neurocomputing 82 (2012) 143–156

Contents lists available at SciVerse ScienceDirect

Neurocomputing

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

Stochastic stability analysis of uncertain genetic regulatory networks with mixed time-varying delays ☆

Wenqin Wang [a,*], Shouming Zhong [a,b]

[a] School of Mathematical Sciences, University of Electronic Science and Technology of China, Chengdu, Sichuan 611731, PR China
[b] Key Laboratory for NeuroInformation of Ministry of Education, University of Electronic Science and Technology of China, Chengdu, Sichuan 611731, PR China

ARTICLE INFO

Article history:
Received 30 October 2010
Received in revised form
19 June 2011
Accepted 16 October 2011
Communicated by S. Arik
Available online 28 December 2011

Keywords:
Genetic regulatory networks
Stochastic disturbance
Time-varying delays
Uncertain systems
Lyapunov–Krasovskii functional

ABSTRACT

Genetic regulatory networks have become an important new area of research in the biological and biomedical sciences. This paper presents a robust analysis approach to stochastic asymptotic stability of the uncertain genetic regulatory networks with both mixed time-varying delays and stochastic noise. By choosing an appropriate new Lyapunov functional and employing stochastic analysis methods, some less conservative delay-range-dependent and delay-derivative-dependent stability criteria have been derived in terms of linear matrix inequalities. The important feature is that the obtained stability criteria are applicable to both fast and slow time-varying delays due to the ranges for the time-varying delays have been carefully considered. Finally, three numerical examples are presented to illustrate the effectiveness of the theoretical results.

1. Introduction

Genetic networks are biochemically dynamical systems, which are attracting more and more attention from biology, engineering and other research fields. Real genetic systems are made up of a large number of reactions and reacting species. We just consider the concentrations of mRNAs and proteins. During the past few years, a variety of models have been proposed, such as Boolean network model (see [1–4]), and linear differential equation model (see [5–7]). In Boolean models, the activity of each gene is expressed in one of two states: ON or OFF, and the state of a gene is described by a Boolean function of states of other related genes. While in the differential equation models, the concentration of gene products are determined by variables, such as mRNAs, proteins and continuous values of the gene regulation systems. In practical biological model, gene expression rates are usually continuous variables rather than ideal ON–OFF switches. Several typical GRNs have been modeled and studied, both in theories and in experiments (see [8–10]).

Due to the completion of the transcription and translation of DNA, mRNA and the diffusion to a certain place of a protein need time, time delay is an inevitable occurrence in modeling gene regulation processes. Considerable attention has been contributed to the theoretical analysis and experimental GRNs, and many results have been reported on dynamical behaviors of GRNs. For instance, it has been proved in an important experiment on mice that there exists a time lag of about 15 min in the peaks between the mRNA molecules and the proteins of the gene hes1 [11].

What is more, if we only assume that the time delays are discrete, it is too simple to express the movement of macromolecule. The distributed delays can be the proper modeling framework [23,24]. From [23], we can see that the concentration of macromolecule depends on an integral of the regulatory function over a specified range of past time. Indeed, this approach is general enough to model any mechanism of macromolecular transport. However, there are little work about the stability with distributed delays. In this paper, we will consider GRNs model with both discrete and distributed delays.

Furthermore, when modeling the GRNs, it should be noted that molecular noise play important roles in GRNs. Generally, the stochastic noise arising in gene expression can be described in the following two ways: intracelluar noise and extracelluar noise. The gene regulation process is always subject to intrinsic noise which is due to the random births and deaths of individual molecules, and

☆This research was supported by the National Basic Research Program of China (2010CB732501).
* Corresponding author.
E-mail addresses: wenqinwang123@163.com (W. Wang), zhongsm@uestc.edu.cn (S. Zhong).

0925-2312/$ - see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.neucom.2011.10.023

extrinsic noise which is derived from environment fluctuations. Thus the gene expression is best viewed as a stochastic process [12,13]. Therefore, the study of stochastic genetic regulatory networks has attracted increasing research interests (see [14–16]).

It should be noticed that the intrinsic noise and the extrinsic noise not only bring stochastic fluctuations to the gene regulation process, but also bring parameter uncertainties during the constructing of genetic models. Meanwhile, because of the use of an approximate system model for the purpose of simplifying models, the uncertainties such as external perturbations, parameter fluctuations, data errors are inevitable. This means that one has to investigate the robust stability of uncertain systems [17,18]. However, as far as we know, in most existing literature, the above analysis have been treated separately. Up to now, the stochastic stability analysis for genetic networks with both mixed time-varying delays and parametric uncertainties has not been fully studied, which is still open.

In this paper, we construct a stochastic differential equation model for the uncertain gene regulation networks with both mixed time-varying delays and stochastic noise. By choosing an appropriate new Lyapunov functional and employing stochastic analysis methods, some less conservative delay-range-dependent and delay-derivative-dependent stability criteria have been derived. Because we have carefully considered the ranges for the time-varying delays, our criteria are applicable to both fast and slow time-varying delays. Our stability criteria are in LMI forms and can be easily checked in practice. Finally, three examples are also given to demonstrate the effectiveness and advantages of our analysis.

Notations: The notations used throughout the paper are fairly standard. The superscript 'T' stands for matrix transposition; R^n denotes the n-dimensional Euclidean space; $R^{n\times m}$ is the set of all $n\times m$ real matrices; the notation $P>0$ means that P is real symmetric and positive definite; I and 0 represent identity matrix and zero matrix, respectively. In symmetric block matrices, we use an asterisk ($*$) to represent a term that is induced by symmetry. Matrices, if their dimensions are not explicitly stated, are assumed to be compatible for algebraic operations.

2. Problem formulation and some preliminaries

Generally, a GRN consists of a group of genes which interact and regulate the expression of other genes by proteins. The change in expression of a gene is controlled by the stimulation and inhibition of proteins in transcriptional, translational, and post-translational processes. In [19], a single gene auto-regulatory genetic network with time delays containing n mRNAs and n proteins can be described by the following equations:

$$\begin{cases} \dot m_i(t) = -a_i m_i(t) + b_i(p_1(t-\sigma(t)),\quad p_2(t-\sigma(t)),\ldots,p_n(t-\sigma(t))),\\ \dot p_i(t) = -c_i p_i(t) + d_i m_i(t-\tau(t)),\quad i=1,2,\ldots,n. \end{cases} \tag{1}$$

where $\dot m_i(t),\dot p_i(t)$ are concentrations of mRNA and protein of the ith node at time t, respectively. In this network, there is one output but multiple inputs for a single node or gene. In model (1), a_i and c_i are the degradation rates of the mRNA and protein, d_i is the translation rate, and $b_i(\cdot)$ is the regulatory function of the ith gene, which is generally a nonlinear function of variables $(p_1(t),p_2(t),\ldots,p_n(t))$, but has a form of monotonicity with each variable. $\tau(t)$ and $\sigma(t)$ are the time-varying delays. The gene activity is tightly controlled in a cell, and gene regulation function $b_i(\cdot)$ plays an important role in the dynamics. Some genes can be activated by one of a few different possible transcription factors ("OR" logic). Other genes require that two or more transcription factors must all be bounded for activation ("AND" logic). Here, we focus on a model of genetic networks where each transcription factor acts additively to regulate the ith gene. The regulatory function is of the form $b_i(p_1(t),p_2(t),\ldots,p_n(t)) = \sum_{j=1}^{n} b_{ij}(p_j(t))$, which is called SUM logic [20]. The function $b_{ij}(p_j(t))$ is a monotonic function of the Hill form. If transcription factor j is an activator of gene i, then

$$b_{ij}(p_j(t)) = \begin{cases} \alpha_{ij}\dfrac{(p_j(t)/\beta_j)^{H_j}}{1+(p_j(t)/\beta_j)^{H_j}} & \text{if transcription factor } j \text{ is an activator of gene } i,\\ \alpha_{ij}\dfrac{1}{1+(p_j(t)/\beta_j)^{H_j}} & \text{if transcription factor } j \text{ is a repressor of gene } i, \end{cases}$$

where H is the Hill coefficient, β_j is a positive constant, and α_{ij} is the dimensionless transcriptional rate of transcription factor j to gene i, which is a bounded constant. Therefore, (1) can be rewritten into the following form:

$$\begin{cases} \dot m_i(t) = -a_i m_i(t) + \sum_{j=1}^{n} w_{ij} h_j(p_j(t-\sigma(t))) + u_i,\\ \dot p_i(t) = -c_i p_i(t) + d_i m_i(t-\tau(t)),\quad i=1,2,\ldots,n. \end{cases} \tag{2}$$

where $h_j(x) = (x/\beta_j)^{H_j}/(1+x/\beta_j)^{H_j}$, $u_i = \sum_{j\in I_i}\alpha_{ij}$ is defined as a basal rate, and I_i is the set of all the j which is a repressor of gene i. The matrix $W=(w_{ij})\in R^{n\times n}$ of the genetic network is defined as follows:

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

Rewriting system (2) into compact matrix form, we obtain

$$\begin{cases} \dot m(t) = -Am(t) + Wh(p(t-\sigma(t))) + u,\\ \dot p(t) = -Cp(t) + Dm(t-\tau(t)), \end{cases} \tag{3}$$

where

$$A = \mathrm{diag}(a_1,a_2,\ldots,a_n),\quad u=(u_1,u_2,\ldots,u_n)^T,$$