Mathematical Biosciences 226 (2010) 97–108

Contents lists available at ScienceDirect

Mathematical Biosciences

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

Stochastic stability of Markovian jumping uncertain stochastic genetic regulatory networks with interval time-varying delays ☆

P. Balasubramaniam *, R. Rakkiyappan, R. Krishnasamy

Department of Mathematics, Gandhigram Rural University, Gandhigram 624 302, Tamilnadu, India

ARTICLE INFO

Article history:
Received 15 June 2009
Received in revised form 13 April 2010
Accepted 14 April 2010
Available online 27 April 2010

Keywords:
Asymptotic stability
Genetic regulatory networks
Linear matrix inequality
Lyapunov–Krasovskii functional
Markovian jumping parameters
Uncertain systems

ABSTRACT

This paper investigates the robust stability problem of stochastic genetic regulatory networks with interval time-varying delays and Markovian jumping parameters. The structure variations at discrete time instances during the process of gene regulations known as hybrid genetic regulatory networks based on Markov process is proposed. The jumping parameters considered here are generated from a continuous-time discrete-state homogeneous Markov process, which is governed by a Markov process with discrete and finite state space. The new type of Markovian jumping matrices P_i and Q_i are introduced in this paper. The parameter uncertainties are assumed to be norm bounded and the discrete delay is assumed to be time-varying and belong to a given interval, which means that the lower and upper bounds of interval time-varying delays are unavoidable. Based on the Lyapunov–Krasovskii functional and stochastic stability theory, delay-interval dependent stability criteria are obtained in terms of linear matrix inequalities. Some numerical examples are given to illustrate the effectiveness of our theoretical results.

1. Introduction

Regulatory networks have become an important new area of research in the biological and biomedical sciences [1–3]. Specifically, the DNA information controlling gene expression (regulation) is the key to understand the differences between species and evolution [4]. Gene expression is a process consisting of transcription and translation. During transcription process, messenger RNAs (mRNAs) are synthesized from genes by the regulation of transcription factors, which are proteins. During translational process, the sequence of nucleotides in the mRNA is used in the synthesis of a protein. Genetic regulatory networks (GRNs), structured by networks of regulatory interactions between DNA, RNA, proteins. GRNs are applied for gaining insight into the underlying processes of living systems at the molecular level. Considerable attention has been contributed to the theoretical analysis and experimental GRNs. A large amount of results have been reported on dynamical behaviors of GRNs for example [5–11].

Recently, by extracting functional information from observable data, significant advances on discovering the structure of the genetic network have been made. Further deeper insights have been gained on both the static and dynamic behaviors of genetic networks. Similar to other dynamic systems [12,13], stability is a natural requirement for GRNs with clear biological significance [14]. On the other hand, it is also observed that time delays are present during the slow reaction process, such as transcription, translation and translocation involving multistage reactions in genetic networks [15]. It has been shown in [16], by mathematical modelling observation data, that the oscillatory expression of three proteins is likely to be the consequence of transcriptional delays. In fact, delay is often the key factor to the instability of a given system and plays an important role in the analysis of gene regulation dynamics. The theoretical results obtained for gene networks with or without time delays are scattered in the literature. To mention a few, a simple gene circuit, a regulator and transcriptional repressor modules in *Escherichia coli* [5] has been designed and studied for testing the role of negative feedback in the stability analysis of gene networks. Considering the fact that a genetic network is composed of a number of molecules that interact and regulate the expression of other genes by proteins, the authors presented a GRN model. This was described by a delay differential equation to study the local stability, using the characteristic equation discussed in [6]. A non-linear model for GRNs with SUM regulatory functions was proposed in the form of the Lure system. Also sufficient conditions for ensuring the stability of the gene networks were derived in terms of linear matrix inequalities (LMIs) in [9]. Moreover, from the viewpoint of potential applications, the study of asymptotic stability is more important and meaningful since the dynamic process of a gene network provides a better

☆ The work of the first author was supported by CSIR Project, New Delhi, India under the sanctioned No. 25(0161)/08/EMR-II. The work of the second author was supported by CSIR-SRF under Grant No. 09/715(0013)/2009-EMR-I.

* Corresponding author. Tel.: +91 451 2452371; fax: +91 451 2453071.
E-mail addresses: pbalgri@rediffmail.com, balugru@gmail.com (P. Balasubramaniam).

0025-5564/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.mbs.2010.04.002

understanding of the mechanism of the interactions between biochemical molecules.

During the past decades quantitative and qualitative network models such as boolean networks model [17,18], linear differential equation model [19–21] and a single negative feedback loop network [5] have been developed for gene regulatory networks. It has been shown in [22], by mathematically modelling recent data, that the observed oscillatory expression and activity of three proteins is most likely to be driven by transcriptional delays and time delay is often inevitable when analyzing the dynamical behaviors of GRNs [6,23,24]. Due to small numbers of transcriptional factors and other key signaling proteins, there is a considerable experimental evidence that noise plays a very important role in gene regulation [25]. Genetically identical cells and organisms exhibit remarkable diversity even when they have identical histories of environmental exposure. Noise, in the process of gene expression, may contribute to this phenotypic variability [28]. It is suggested that this noise has multiple sources including the stochastic disturbances of the biochemical reactions of gene expression that affects the kinetics of the networks [29,33]. We know very little about the noise in the genetic network which is different from the method discussed in [31] and [32]. The external noise is used to control a single gene autoregulatory network in the concentration of protein, we assume here that the noise perturbations are unknown and additively perturb the network. Authors in [26] proposed a stochastic model for gene expression in prokaryotes to study the origins of noise in gene expressions. Further stochastic differential equations have been applied in stochastic simulations based chemical master equation. In general, the stochastic noise arises in gene expression in one of two ways. The intrinsic noise is inherent in the biochemical reactions. Its magnitude is proportional to the inverse of the system size and its origin is often thermal. The external noise originates in the random variation of one or more of the externally set control parameters [27].

It is noted that the hybrid system modelling involves some kind of natural switching. Furthermore, Markov chains have also been widely used as a generic framework for modelling gene networks. A finite state homogeneous Markov chain model has been constructed from microarray data in [30]. Markov chain models incorporating rule-based transitions between states are capable of mimicking biological phenomena. All the existing Markovian models are based on the qualitative approaches and they can be used to characterize the state of a gene network in terms of discrete logical variables. However, this might not be enough to describe the dynamics of gene networks accurately. In [9], a non-linear model for GRNs with SUM regulatory functions and some stability criteria are presented. In [33], sufficient stability conditions for the stochastic GRNs with disturbance attenuation are obtained. Note that, in [9] and [33], parametric uncertainties are not taken into account while the ranges of time-varying delays ranged from 0 to an upper bound. However, in practice, a time-varying interval delay is often encountered. In [11], the stability analysis of GRNs with interval time-varying delays and parametric uncertainties is addressed. However, in [11] the information of the derivative of time-varying delays have not been included to study stability results. In [34–37], the authors studied stochastic stability analysis for GRNs with time-varying delays. Delay-range dependent stability results for GRNs have been studied in [34] with both time-varying and parameter uncertainties without Markovian jumping parameters. To the best of authors' knowledge, the problem of delay-range dependent stability results for Markovian jumping stochastic genetic regulatory networks with interval time-varying delays has not been fully investigated and it is very challenging.

In this paper, we are concerned with the stochastic robust stability analysis for GRNs with interval time-varying delays and Markovian jumping parameters. Based on a hybrid stochastic model for GRNs with Markovian uncertain switching probabilities discussed in [38], stochastic stability results have been derived at by constructing an appropriate new Lyapunov–Krasovskii functional, employing some free-weighting matrices and LMI technique. Less conservative delay-range dependent and rate-dependent stability criteria are derived based on the consideration of the ranges for time-varying delays. Finally, five numerical examples are given to illustrate the effectiveness and conservativeness of the proposed method.

1.1. Notations

Throughout this paper, $\mathbb{R}^n$ and $\mathbb{R}^{n\times m}$ denote, respectively, the n-dimensional Euclidean space and the set of all $n\times m$ real matrices. For symmetric matrices X and Y, the notation $X \geqslant Y$ ($X > Y$) means that $X - Y$ is positive-semidefinite (positive-definite); M^T denotes the transpose of the matrix M; I is the identity matrix with appropriate dimension; $|\cdot|$ is the Euclidean norm in $\mathbb{R}^n$. Moreover, let $(\Omega, \mathscr{F}, \{\mathscr{F}_t\}_{t\geqslant 0}, \mathscr{P})$ be a probability space with a filtration $\{\mathscr{F}_t\}_{t\geqslant 0}$ satisfying the usual conditions (that is, the filtration contains all $\mathscr{P}$-null sets and is right continuous). $L^2_{\mathscr{F}_0}((-\infty, 0]; \mathbb{R}^n)$ denotes the family of all $\mathscr{F}_0$-measurable. $\mathbb{E}(\cdot)$ stands for the expectation operator with respect to the given probability measure $\mathscr{P}$; and matrices, if not explicitly stated, are assumed to have compatible dimensions.

2. Problem description and preliminaries

Generally, a GRN consists of a group of genes that 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 [14]. From [6], GRNs with time delays containing of n mRNAs and n proteins can be described by the following equations:

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

where $\dot{m}_i(t)$ and $\dot{p}_i(t)$ are the 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 Eq. (1), a_i and c_i are the degradation rates of the mRNA and protein, respectively. d_i is the translation rate and $b_i(\cdot)$ is the regulatory function of the ith gene, which is generally a non-linear function of the variables $(p_1(t), p_2(t), \ldots, p_n(t))$, but has a form of monotonicity with each variable [9,39,40]. $\tau(t)$ and $\sigma(t)$ are the time-varying delays satisfying
$0 \leqslant \tau_1 \leqslant \tau(t) \leqslant \tau_2$, $\dot{\tau}(t) \leqslant \mu$ and $0 \leqslant \sigma_1 \leqslant \sigma(t) \leqslant \sigma_2$, $\dot{\sigma}(t) \leqslant \eta$. 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 bound 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 also called SUM logic [41,42]. The function $b_{ij}(p_j(t))$ is a monotonic function of the Hill form [8,43]. If transcription factor j is an activator of gene i, then

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