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New delay-dependent stability criteria of genetic regulatory networks subject to time-varying delays ☆

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ABSTRACT

In this paper, the stability analysis problem is investigated for a class of genetic regulatory networks (GRNs) with time-varying delays. Here, the addressed GRNs are modelled by the nonlinear differential equations. A new Lyapunov–Krasovkii functional is constructed by additionally introducing some triple integral terms. By employing the Jensen inequality, the free-weighting matrix and the convex combination idea, a semi-definite programme approach is developed to derive new sufficient condition guaranteeing the global asymptotic stability of the addressed GRNs subject to time-varying delays. Subsequently, a new stability criterion is proposed for GRNs with time-varying delays when the upper bounds of the derivative of the time delays are unknown. It is shown that the feasibility of presented results can be readily checked by using the standard numerical software. Finally, we provide two numerical examples to illustrate the effectiveness and less conservativeness of the proposed stability criteria.

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1. Introduction

Over the past few decades, the genetic regulatory network (GRN) has attracted considerable attention in the biological and biomedical sciences since it can effectively reflect the living organisms of molecular and cellular levels [1,2]. Accordingly, several types of models have been presented to describe the GRNs, such as the Bayesian network model [3], the Boolean model [4] and the differential equation model [5]. As discussed in [4], the expression of each gene in the network has been assumed to be either ON or OFF and the state of a gene has been described by a Boolean function of the states and other related genes. However, in practical biological model, the gene expression rates are usually continuous variables rather than the ideal switch between ON and OFF. As such, the differential equation model has been introduced, where the concentrations of gene products have been modelled by variables, such as mRNAs and proteins. Recently, it is realized that the GRNs described by differential equations can depict the gene regulatory process in living organisms more efficient.

It is well known that, due to the slow process of transcription, translation and shifting or the finite switching speed of amplifiers, the time-delays are inevitably encountered in the modelling process of GRNs [6,7]. The existence of the time-delays would degrade the whole system performance and even leads to instability [8–13]. In fact, the observed oscillatory expression and activity of proteins in GRNs are most likely to be driven by transcriptional delays, and delays can bring high effect on both the dynamical behavior of models and the numerical parameter prediction. Hence, it is of great significance to investigate the stability analysis problem of GRNs with time-varying delays. So far, a great deal of effort has been made concerning the analysis problem of GRNs with time-varying delays and a variety of important results have been published in the literature to examine the effect of the time-varying delays onto the system performance, see e.g. [14–20] and the references therein.

The main objective of the stability analysis problem of delayed GRNs is to propose new stability criteria and reduce the possible conservativeness caused by the time delays. In reality, the time delay varying in an interval is often encountered and the lower

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bound of the interval is not strictly restricted to be 0 [16–20]. By conducting the characteristic equation analysis, in [14], the stability analysis problem of GRNs with time delays modelled by differential equation has been studied. In [15], some stability criteria have been presented to guarantee the global asymptotic stability of the delayed GRNs by using the Lur'e system approach and constructing the Lyapunov functional. It should be pointed out that the time-varying delays in [15] are assumed to be differentiable and the upper bound of the derivative must be less than 1 [15], which constrain the application of the proposed results in [15]. Compared with [15], new sufficient condition with less conservativeness has been given in [16] by constructing an appropriate Lyapunov–Krasovkii functional involving the lower bounds of delays. Recently, several sufficient criteria have been established to further reduce the conservativeness. For example, in [17–20], the upper bound of the derivative is allowed to be more than 1. In this paper, we revisit the stability analysis problem of delayed GRNs and aim to propose new sufficient conditions with less conservatism by fully taking the matrix analysis techniques into account.

Motivated by the above discussions, in this paper, we aim to investigate the stability analysis problem of GRNs described by differential equations model with time-varying delays and propose new stability conditions with less conservativeness. A new Lyapunov–Krasovkii functional is constructed with hope to reduce the conservatism caused by the time delays, where some triple integral terms are introduced. By using the Jensen inequality, free-weighting matrix method and convex combination approach, new delay-range-dependent and delay-rate-dependent/independent stability criteria are presented by fully taking the ranges of time-varying delays into account. It is shown that the proposed results are in terms of the matrix inequalities which can be easily verified by using the standard numerical software. Finally, two numerical examples are used to demonstrate the usefulness and less conservativeness of the obtained theoretical results. The main contribution of this paper lies in (1) a new Lyapunov–Krasovskii functional is constructed which contains more information of time-varying delays; and (2) some new stability criteria are given, where the admissible upper bound of time-delay can be enlarged by adequately employing the Jensen inequality, free-weighting matrix and convex combination methods in a same framework.

The rest of this paper is organized as follows. In Section 2, the GRNs with time-varying delays addressed are described and some Lemmas are briefly introduced. In Section 3, the sufficient criteria are given to guarantee the global asymptotic stability of the addressed GRNs. Two numerical examples are presented in Section 4 to show the feasibility and advantages of the main results. Conclusions are given in Section 5.

Notations: The notations used throughout the paper are fairly standard. The superscript T represents the matrix transposition; R^n denotes the n-dimensional Euclidean space; $R^{n\times m}$ is the set of all $n\times m$ real matrices; $P>0$ ($P\geq 0$) means that P is a real symmetric and positive definite (positive semi-definite) matrix; I and 0 represent identity matrix and zero matrix, respectively. diag{·} denotes the diagonal matrix; col{·} means a column vector. In symmetric block matrices or long matrix expressions, 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 formulations

As in [15], we consider the GRNs with time-varying delays containing n mRNAs and n proteins described by the following delay differential equations:

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

where $m_i(t)$ is the concentration of mRNA of the i-th node at time t, $p_i(t)$ is the concentration of protein of the i-th node at time t, a_i is the degradation rate of mRNA, c_i is the degradation rate of protein, d_i is the translation rate, $\sigma(t)$ is transcriptional delay and $\tau(t)$ is translational delay. $b_i(\cdot)$ is the regulatory function of the i-th gene, which is generally a nonlinear function of the variables $p_1(t)$, $p_2(t),\ldots,$ $p_n(t)$ and has a form of monotonicity with respect to each variable [21,22]. The regulatory function is taken as $b_i(p_1(t),p_2(t),\ldots,p_n(t)) = \sum_{j=1}^{n} b_{ij}(p_j(t))$, which is also called the sum input function (SUM) logic as in [23,24].

Following [25], the function $b_{ij}(p_j(t))$ is a monotonic function of the Hill form,

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

where H_j is the Hill coefficient, β_j is a positive scalar, and α_{ij} is a bounded constant denoting the dimensionless transcriptional rate of transcription factor j to gene i. Hence, GRNs (1) can be rewritten as

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

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

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

For time-delays $\tau(t)$ and $\sigma(t)$, we introduce the following assumption:

Assumption 1. The time-varying delays $\tau(t)$ and $\sigma(t)$ satisfy

$$0\leq\tau_1\leq\tau(t)\leq\tau_2,\quad 0\leq\sigma_1\leq\sigma(t)\leq\sigma_2,\quad \dot{\tau}(t)\leq\mu<\infty,\quad \dot{\sigma}(t)\leq d<\infty, \tag{3}$$

where $0\leq\tau_1\leq\tau_2$, $0\leq\sigma_1\leq\sigma_2$, $\mu>0$ and $d>0$.

Remark 1. In fact, Assumption 1 is used to characterize the time-varying delays in the GRNs due to the finite speed in the slow processes of transcription, translation, and diffusion to the place of action of a protein. In this assumption, the time-delays vary in an interval and the upper bound of the time-varying delays' derivative can be more than 1, which gives clearer practical insight from the modelling viewpoint and is used in many existing results, see e.g. [17–20].

By setting

$$A=\mathrm{diag}\{a_1,a_2,\ldots,a_n\},$$
$$u=\mathrm{col}\{u_1,u_2,\ldots,u_n\},$$
$$C=\mathrm{diag}\{c_1,c_2,\ldots,c_n\},$$
$$D=\mathrm{diag}\{d_1,d_2,\ldots,d_n\},$$
$$m(t)=\mathrm{col}\{m_1(t),m_2(t),\ldots,m_n(t)\},$$
$$p(t)=\mathrm{col}\{p_1(t),p_2(t),\ldots,p_n(t)\},$$
$$h(p(t))=\mathrm{col}\{h_1(p_1(t)),h_2(p_2(t)),\ldots,h_n(p_n(t))\},$$

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