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Stability of gene regulatory networks with Lévy noise

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Abstract The stability of gene regulatory networks has attracted substantial research efforts in the field of systematic biology. Actual gene regulatory networks are always subject to noise interference and disruption to the organism either internally or externally. Specifically, the special case of instantaneous mutation may exist in gene regulatory networks at the mRNA or protein level. Compared with other existing models, a Lévy noise-driven gene regulatory network model has been proved to be more realistic, since it is a powerful tool to describe the above special case. On the basis of previous studies, we developed a theoretical proof of the Lévy noise-driven gene regulatory network, and carried out a large number of numerical simulations for validation. Based on adequate analysis of the simulation examples, the sufficient conditions were investigated and are presented herein to obtain the global asymptotic stability of gene regulatory networks with time-varying delays and Lévy noise.

Keywords Lévy noise, gene regulatory networks, time-varying delays, stability analysis, instantaneous mutation

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1 Introduction

Gene regulatory networks are composed of DNA, RNA, proteins, and other small molecules as well as the interactions among them [1]. For example, when a gene is transcribed, a group of transcription factors in the gene promoter system regulate the transcription process. These transcription factors can be the product of other gene transcription processes, which in turn shape a complex network system [2]. Maintenance of the stability of the network system is essential to sustain the life of the organism. Accordingly, the stability of gene regulatory networks is one of the primary core issues of biological research. To study a gene expression regulatory network, it is first necessary to establish a model of regulation network, and then analyze the relationships between genes in the model. Several models on gene regulation are well-documented, such as the Boolean model [3, 4], Bayesian networks model [5], Petri net model [6, 7], and differential equation model [8]. Among them, the differential equation model is widely adopted since it can describe the concentration changes of proteins and mRNA, and also accurately reflects the nonlinear dynamic behavior of a biological system.

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In recent years, stability analysis of gene regulatory networks with time delays has attracted the attention of many scholars worldwide. Chen & Aihara [9] first proposed a gene regulatory network model with constant time delays, and obtained the necessary and sufficient conditions for the stability of the model. Wu [10] studied the stability of the ring topology of gene regulatory networks with constant time delays, and presented the necessary and sufficient conditions for the local stability of gene regulatory networks with independent time delays. The multiple stability criteria for gene regulatory networks with a class of multiple differentiable time-varying delays are presented in Pan et al. [11]. Moreover, many studies have contributed to the analysis of the Lévy process [12–15]. Zhu [13] provided the sufficient conditions for the asymptotic stability of the p-order moments of the stochastic differential equation with Lévy noise and the detailed proof. Li [14] presented a complete proof of the asymptotic stability of the exponential function of the Lévy process, and divided the exponential functions of the Lévy process into five different types according to their convergence speeds. Curry et al. [15] defined a numerical integration scheme of stochastic differential equations with the Lévy process, which outperformed the random Taylor series with smaller error coefficients.

For practical problems, investigations are usually carried out for gene regulatory networks with stability, thus highlighting the primary importance of stability analysis for investigations of gene regulatory networks [16, 17]. On the one hand, a cell is first transformed into RNA under the action of the transcription enzymes, and then the RNA is transformed into a new DNA in the organism. This two-step process inevitably leads to time delays. Mouse and zebra-fish experiments [18] have shown that there is a 10–20-min time delay in the cytoplasm from transcription to mRNA maturation, and an approximately 1–3-min delay from translation initiation to protein maturation with complete function. Therefore, there is a very urgent and necessary need to establish a gene regulatory network model with time delays. On the other hand, gene expression is often affected by the internal and external noise caused by the random birth and death of individual molecules [19–25]. Because it is difficult to precisely determine how such noise affects the performance of the networks, the simplest way is to add random effects to the model by assuming that the random fluctuations occur within the gene regulatory networks [26]. To this end, researchers have adopted specific properties such as the strong Markov property of Wiener noise. For example, Wu [27] investigated the problem of the robust stability of a gene regulatory network model with parameter uncertainty and random disturbance. In addition, the stability of gene regulatory networks with interval time delays and stochastic noise was studied by Wu [28]. Wiener noise was used to represent the random disturbance in gene networks, and the Wiener noise-driven networks model could accurately describe the random disturbance of gene regulation networks as well as most of the dynamic behaviors. Note that in [29], long-chain non-coding RNA (lncRNA) regulated many important biological processes. In the steady state, lnc13 (a type of lncRNA) inhibited the expression of some inflammatory genes by binding to hnRNPD, a heterogeneous nuclear ribosomal protein. The lnc13 concentration was reduced when simulated, which led to the increase of the expression ability of the inhibited gene. Lnc13 levels in small bowel biopsy specimens from patients with celiac disease were found to be significantly decreased, indicating a concentration mutation, which can be described by the Wiener noise-driven networks model, although with low accuracy. The jump part of Lévy noise can be used to express the mutation concentration in some areas of the body; thus, a network model can be established to describe gene regulation to more accurately reflect real biological processes.

On the one hand, gene regulatory networks analysis is not only helpful to understand the formation and regulation of the organization of genes and transcription products, but can also provide a benefit of gaining an overall understanding of gene function, which can be applied to the search and identification of human pathogenic factors. For example, in most cancer studies, almost all of the experimental tools focus on the dominant oncogene, leading to neglect of the potential synergistic effects of the non-dominant oncogenes. In fact, in most cases, it is the interaction of several genes other than the target gene that leads to tumor formation. Substantial information is required to identify the synergistic effect of the non-dominant oncogene through experiments, and then the complex gene networks and their relationships to gene regulation must be analyzed with a powerful computer. Indeed, a gene regulatory networks model has been proposed to identify drug targets for cancer treatment. On the other hand, gene networks

analysis is also an effective approach for life information mining. Gene regulatory networks are analyzed with various methods, which is helpful for information mining and the determination of gene function based on collaborative information of the interactions and transmission processes in the gene networks. Accordingly, the information obtained can be used for practical applications with several potential benefits for improving mankind human quality of life.

In view of the above background, in this paper, we present a differential equation model of gene regulatory networks with time-varying delays and Lévy noise, and analyze its stability. Furthermore, the sufficient conditions for obtaining global asymptotic stability of the gene regulatory networks with time-varying delays and Lévy noise are obtained, and the conditions for the stochastic stabilization of gene regulatory networks with time-varying delays and Lévy noise are evaluated. Finally, a numerical example is presented to demonstrate that the proposed gene regulatory networks can achieve stochastic stability.

2 Preliminaries

A gene regulatory network consists of a large number of genes, which regulate the expression of other genes through protein-to-protein interactions. Gene expression is modified through the processes of transcription, translation, and post-translation via protein activation and inhibition. Here, we take the Hill function as an example to discuss gene regulatory networks. If the transcription factor is an activator of a gene, then this system is a positive feedback loop, which tends toward one of the two steady states. If the transcription factor is a suppressor of a gene, then this system is a negative feedback loop, which can be close to a steady state or around a steady state. Combined with [30], the following gene regulatory networks model is considered:

$$\begin{cases} \dot{m}(t) = -Am(t) + Wf(p(t-\tau_1(t))) + \Gamma, \\ \dot{p}(t) = -Cp(t) + Dm(t-\tau_2(t)). \end{cases} \tag{1}$$

$m(t) = [m_1(t), m_2(t), \ldots, m_n(t)]^{\mathrm{T}}$, $p(t) = [p_1(t), p_2(t), \ldots, p_n(t)]^{\mathrm{T}}$, where $m_i(t)$ and $p_i(t)$ denote the mRNA concentration and protein concentration in a node i at time t, respectively. $A = \mathrm{diag}\{a_1, a_2, \ldots, a_n\}$ and $C = \mathrm{diag}\{c_1, c_2, \ldots, c_n\}$ denote the mRNA and protein degradation rate, respectively. $D = \mathrm{diag}\{d_1, d_2, \ldots, d_n\}$ denotes the translation rate, and $W = (w_{ij}) \in \mathbb{R}^{n\times n}$ is defined as follows:

$$(w_{ij}) \begin{cases} > 0, & \text{if the transcription factor } j \text{ is an activator of the gene } i, \\ = 0, & \text{if the gene } j \text{ is not connected to the gene } i, \\ < 0, & \text{if the transcription of } j \text{ is a suppressor of the gene } i. \end{cases}$$

Remark 1. mRNA is a class of single-stranded RNA that is the product of DNA transcription with genetic information, and functions as a template for protein synthesis on the ribosome, which determines the amino acid sequence of the peptide chain. A protein is composed of α amino acids in a certain order that are combined to form a polypeptide chain, and then one or more of the polypeptide chains form a combination of high-molecular-weight compounds in accordance with the specific encoded conformation. Proteins are the scaffold and main substance of human tissues and organs that play an important role in sustaining human life.

The organism has automatical ability: it can resist external interference, and at the same time, has mechanisms to maintain its structure and function in stable state. This automatic adjustment capability is realized through an internal feedback mechanism of the organism. $f(\cdot)$ denotes the feedback regulation of proteins to transcription factors, where f is a monotone saturated function of the Hill form. $\tau_1(t)$ and $\tau_2(t)$ denote the unknown time-varying delays, where $0 \leqslant \tau_1(t) \leqslant h_1$, $0 \leqslant \tau_2(t) \leqslant h_2$, $0 \leqslant \dot{\tau}_1(t) \leqslant d_1$, and $0 \leqslant \dot{\tau}_2(t) \leqslant d_2$, in which h_1, h_2, d_1, and d_2 are constants. In addition, $\Gamma = [\Gamma_1, \Gamma_2, \ldots, \Gamma_n]^{\mathrm{T}}$, where Γ_i is the basic transcription rate of the suppressor genes. According to [31], the system model (1) can be

transformed into the following form:

$$\begin{cases} \dot{m}(t) = -Am(t) + Wg(p(t-\tau_1(t))), \\ \dot{p}(t) = -Cp(t) + Dm(t-\tau_2(t)), \end{cases} \tag{2}$$

where $g(\cdot)$ satisfies the condition $g(x)(g(x)-Vx) \leqslant 0$, and V is a constant.

From a biological point of view, mRNA and protein can result from the synthesis of different parts, and therefore their transport or diffusion will lead to time delays. In addition, gene regulation is a process full of noise. In this paper, such stochastic perturbation and time-varying delays are introduced into the gene regulatory networks as follows:

$$\begin{cases} \mathrm{d}m(t) = [-Am(t) + Wg(p(t-\tau_1(t)))]\mathrm{d}t + \sigma_1(t, p(t), p(t-\tau_1(t)))\mathrm{d}L_1(t), \\ \mathrm{d}p(t) = [-Cp(t) + Dm(t-\tau_2(t))]\mathrm{d}t + \sigma_2(t, m(t), m(t-\tau_2(t)))\mathrm{d}L_2(t), \end{cases} \tag{3}$$

where $\sigma_1(t, p(t), p(t-\tau_1(t)))$, $\sigma_2(t, m(t), m(t-\tau_2(t)))$ are local Lipschitz continuous parameters and satisfy linear growth conditions, and there exist four proper dimensional constant matrices X_0, X_1, X_2, and X_3 satisfying:

$$\begin{aligned} &\mathrm{trace}[\sigma_1^{\mathrm{T}}(t, p(t), p(t-\tau_1(t)))\sigma_1(t, p(t), p(t-\tau_1(t)))] \\ &\quad \leqslant p^{\mathrm{T}}(t)X_0^{\mathrm{T}}X_0p(t) + p^{\mathrm{T}}(t-\tau_1(t))X_1^{\mathrm{T}}X_1p(t-\tau_1(t)), \end{aligned} \tag{4}$$

$$\begin{aligned} &\mathrm{trace}[\sigma_2^{\mathrm{T}}(t, m(t), m(t-\tau_2(t)))\sigma_2(t, m(t), m(t-\tau_2(t)))] \\ &\quad \leqslant m^{\mathrm{T}}(t)X_2^{\mathrm{T}}X_2m(t) + m^{\mathrm{T}}(t-\tau_2(t))X_3^{\mathrm{T}}X_3m(t-\tau_2(t)). \end{aligned} \tag{5}$$

$L_1(t)$, $L_2(t)$ denote Lévy processes so that:

$$L_1(t) = B_1(t) + \int_{|y|<c} H_1(m(u-), p(u-), y)\tilde{N}(\mathrm{d}u, \mathrm{d}y),$$

$$L_2(t) = B_2(t) + \int_{|y|<c} H_2(m(u-), p(u-), y)\tilde{N}(\mathrm{d}u, \mathrm{d}y),$$

where $B_1(t) = (b_1, b_2, \ldots, b_m)^{\mathrm{T}}$ and $B_2(t) = (b_1', b_2', \ldots, b_m')^{\mathrm{T}}$ capture the Brown motion of the independent m dimension, defined on the complete probability space (Ω, F, P). N is a Poisson random measure defined on $\mathbb{R}_+ \times (\mathbb{R}^d - \{0\})$ with compensator $\tilde{N}$ and intensity ν. We assume that N is independent of B, and ν is a Lévy measure such that $\tilde{N}(\mathrm{d}t, \mathrm{d}y) := N(\mathrm{d}t, \mathrm{d}y) - \nu(\mathrm{d}y)\mathrm{d}t$ and $\int_{\mathbb{R}^n - \{0\}}(|y|^2 \wedge 1)\nu(\mathrm{d}y) < \infty$, and $H : \mathbb{R}^d \times \mathbb{R}^d \times \mathbb{R}^d \to \mathbb{R}^d$ and the constant $c \in (0, \infty]$.

Remark 2. Generally speaking, the Wiener noise only considers the part of the Brown motion, whereas the Lévy noise increases the jump part on the basis of the Wiener noise. This paper mainly focuses on the effect of the jump part of the Lévy noise for the gene regulatory networks.

To analyze the network stability, we refer to the following assumptions and lemmas:

Lemma 1 ([32])**.** For any matrices $X, Y \in \mathbb{R}^n$, matrix $Q > 0$, the following inequality is established:

$$2X^{\mathrm{T}}Y \leqslant X^{\mathrm{T}}QX + Y^{\mathrm{T}}Q^{-1}Y. \tag{6}$$

.

Lemma 2 ([33])**.** For any constant matrix $M \in \mathbb{R}^{n\times n}, M = M^{\mathrm{T}} > 0$ and constant $\gamma > 0$, vector function $\omega : [0, \gamma] \to \mathbb{R}^n$, so the integral satisfies the following inequality:

$$\left[\int_0^\gamma \omega(s)\mathrm{d}s\right]^{\mathrm{T}} M \left[\int_0^\gamma \omega(s)\mathrm{d}s\right] \leqslant \gamma \int_0^\gamma \omega^{\mathrm{T}}(s)M\omega(s)\mathrm{d}s. \tag{7}$$

Lemma 3 (Schur Complement [34]). Given constant matrices $X = X^{\mathrm{T}}$, $Y = Y^{\mathrm{T}}$. If $\left[\begin{smallmatrix} X & Z \\ Z^{\mathrm{T}} & Y \end{smallmatrix}\right] > 0$, it leads to the condition that

$$X > 0,\ Y - Z^{\mathrm{T}}X^{-1}Z > 0,$$

or

$$Y > 0,\ X - Z^{\mathrm{T}}Y^{-1}Z > 0. \tag{8}$$

Assumption 1 ([35]). There exists a positive constant K, for any $x \in \mathbb{R}^n$, $q > 0$, such that

$$\int_{|y|<c} |H(x,y)|^q \nu(\mathrm{d}y) \leqslant K|x|^q. \tag{9}$$

3 Results

In this section, we analyze the stability of the stochastic gene regulatory networks with time-varying delays driven by Lévy noise. When the time-varying delays satisfy the above-mentioned conditions, a new criterion for the expected stability criterion is obtained.

Theorem 1. System (3) is globally asymptotically stable. If there exist matrices P_{11}, P_{12}, P_{22}, $S_1 \geqslant 0$, $S_2 \geqslant 0$, $S_3 \geqslant 0$, R_1, R_2, $Q_1 \geqslant 0$, $Q_2 \geqslant 0$, $Q_3 \geqslant 0$, $Q_4 \geqslant 0$, $U_1 > 0$, $U_2 > 0$, $M_1^{\mathrm{T}} = [M_{11}^{\mathrm{T}}, M_{12}^{\mathrm{T}}, M_{13}^{\mathrm{T}}, M_{14}^{\mathrm{T}}, M_{15}^{\mathrm{T}}, M_{16}^{\mathrm{T}}, M_{17}^{\mathrm{T}}, M_{18}^{\mathrm{T}}]$, $M_2^{\mathrm{T}} = [M_{21}^{\mathrm{T}}, M_{22}^{\mathrm{T}}, M_{23}^{\mathrm{T}}, M_{24}^{\mathrm{T}}, M_{25}^{\mathrm{T}}, M_{26}^{\mathrm{T}}, M_{27}^{\mathrm{T}}, M_{28}^{\mathrm{T}}]$, diagonal matrices $K_1 > 0$, $K_2 > 0$, $K_3 > 0$, $K_4 > 0$, positive constants α, β, ρ_1, ρ_2, ρ_3, ρ_4, c_1, c_2, and satisfies the following LMIs:

$$\begin{aligned}
&\Pi = \begin{bmatrix}
\Omega & \sqrt{h_1}\Phi_1^{\mathrm{T}} & \sqrt{h_2}\Phi_2^{\mathrm{T}} & \sqrt{h_1}M_1 & \sqrt{h_2}M_2 & M_1 & M_2 & M_1 & M_2 \\
\sqrt{h_1}\Phi_1 & -Q_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\sqrt{h_2}\Phi_2 & 0 & -Q_4 & 0 & 0 & 0 & 0 & 0 & 0 \\
\sqrt{h_1}M_1^{\mathrm{T}} & 0 & 0 & -Q_3 & 0 & 0 & 0 & 0 & 0 \\
\sqrt{h_2}M_2^{\mathrm{T}} & 0 & 0 & 0 & -Q_4 & 0 & 0 & 0 & 0 \\
M_1^{\mathrm{T}} & 0 & 0 & 0 & 0 & -R_1 & 0 & 0 & 0 \\
M_2^{\mathrm{T}} & 0 & 0 & 0 & 0 & 0 & -R_2 & 0 & 0 \\
M_1^{\mathrm{T}} & 0 & 0 & 0 & 0 & 0 & 0 & -U_1 & 0 \\
M_2^{\mathrm{T}} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -U_2
\end{bmatrix} < 0, \\
&P = \begin{bmatrix} P_{11} & P_{12} \\ P_{12}^{\mathrm{T}} & P_{22} \end{bmatrix} > 0, \\
&P_{11} \leqslant \rho_1 I,\ P_{22} \leqslant \rho_3 I, \\
&U_1 \leqslant \rho_2 I,\ U_2 \leqslant \rho_4 I, \\
&2c_1K_3U_1 - Q_1 < 0,\ 2c_2K_4U_2 - Q_2 < 0,
\end{aligned} \tag{10}$$

where $\Phi_1 = \begin{bmatrix} -A & 0 & 0 & 0 & 0 & W & 0 & 0 \end{bmatrix}$, $\Phi_2 = \begin{bmatrix} 0 & -C & 0 & D & 0 & 0 & 0 & 0 \end{bmatrix}$,

$$\Omega = \begin{bmatrix}
\gamma_{11} & \gamma_{12} & -M_{13}^{\mathrm{T}} & \Psi_1 & -M_{15}^{\mathrm{T}} & \Psi_2 & -M_{17}^{\mathrm{T}} & -M_{18}^{\mathrm{T}} \\
* & \gamma_{22} & -M_{23}^{\mathrm{T}} & \Psi_3 & -M_{25}^{\mathrm{T}} & \Psi_4 & -M_{27}^{\mathrm{T}} & -M_{28}^{\mathrm{T}} \\
* & * & \gamma_{33} & 0 & 0 & 0 & 0 & 0 \\
* & * & * & \gamma_{44} & 0 & 0 & 0 & 0 \\
* & * & * & * & \gamma_{55} & 0 & 0 & 0 \\
* & * & * & * & * & \gamma_{66} & 0 & 0 \\
* & * & * & * & * & * & \Xi_1 & 0 \\
* & * & * & * & * & * & * & \Xi_2
\end{bmatrix},$$

$\gamma_{11} = -P_{11}A - A^{\mathrm{T}}P_{11} + S_3 + R_1 + h_2Q_2 + K_1 + (\rho_3 + 2h_2\rho_4)X_2^{\mathrm{T}}X_2 - M_{11}^{\mathrm{T}} - M_{11}$,
$\gamma_{12} = -P_{12}C - A^{\mathrm{T}}P_{12} - M_{12}^{\mathrm{T}} - M_{21}^{\mathrm{T}}$,
$\gamma_{22} = -P_{22}C - C^{\mathrm{T}}P_{22} + S_1 + R_2 + h_1Q_1 + K_2 + \alpha V^{\mathrm{T}}V + (\rho_1 + 2h_1\rho_2)X_0^{\mathrm{T}}X_0 - M_{22}^{\mathrm{T}} - M_{22}$,
$\gamma_{33} = (\rho_1 + 2h_1\rho_2)X_1^{\mathrm{T}}X_1 - (1-d_1)S_1 + \beta V^{\mathrm{T}}V$,
$\gamma_{44} = (\rho_3 + 2h_2\rho_4)X_3^{\mathrm{T}}X_3 - (1-d_2)S_3$, $\gamma_{55} = S_2 - \alpha I$, $\gamma_{66} = -\beta I - (1-d_1)S_2$,
$\Xi_1 = -h_1^{-1}(Q_1 - 2c_1K_3U_1)$, $\Xi_2 = -h_2^{-1}(Q_2 - 2c_2K_4U_2)$, $\Psi_1 = P_{12}D - M_{14}^{\mathrm{T}}$, $\Psi_2 = P_{11}W - M_{16}^{\mathrm{T}}$,
$\Psi_3 = P_{22}D - M_{24}^{\mathrm{T}}$, $\Psi_4 = P_{12}^{\mathrm{T}}W - M_{26}^{\mathrm{T}}$.

Proof. Given the gene regulatory networks:

$$\begin{cases} \mathrm{d}m(t) = [-Am(t) + Wg(p(t-\tau_1(t)))]\mathrm{d}t + \sigma_1(t, p(t), p(t-\tau_1(t)))\mathrm{d}L_1(t), \\ \mathrm{d}p(t) = [-Cp(t) + Dm(t-\tau_2(t))]\mathrm{d}t + \sigma_2(t, m(t), m(t-\tau_2(t)))\mathrm{d}L_2(t). \end{cases}$$

Using the Lyapunov-Krasovskii functions, we get

$$V(m(t), p(t), t) = \sum_{i=1}^{5} V_i(m(t), p(t), t),$$

where

$$\begin{aligned}
V_1(m(t), p(t), t) &= \begin{bmatrix} m(t) \\ p(t) \end{bmatrix}^{\mathrm{T}} P \begin{bmatrix} m(t) \\ p(t) \end{bmatrix}, \\
V_2(m(t), p(t), t) &= \int_{t-\tau_1(t)}^{t} (p^{\mathrm{T}}(\theta)S_1p(\theta) + g^{\mathrm{T}}(p(\theta))S_2g(p(\theta)))\mathrm{d}\theta + \int_{t-\tau_2(t)}^{t} m^{\mathrm{T}}(\theta)S_3m(\theta)\mathrm{d}\theta, \\
V_3(m(t), p(t), t) &= \int_{t-h}^{t} m^{\mathrm{T}}(\theta)R_1m(\theta)\mathrm{d}\theta + \int_{t-h}^{t} p^{\mathrm{T}}(\theta)R_2p(\theta)\mathrm{d}\theta, \\
V_4(m(t), p(t), t) &= \int_{-h_1}^{0}\int_{t+\theta}^{t} \{p^{\mathrm{T}}(\eta)Q_1p(\eta) + [-Am(\eta) + Wg(p(\eta-\tau_1(\eta)))]^{\mathrm{T}}Q_3[-Am(\eta) \\
&\quad + Wg(p(\eta-\tau_1(\eta)))]\}\mathrm{d}\eta\mathrm{d}\theta + \int_{-h_2}^{0}\int_{t+\theta}^{t} \{m^{\mathrm{T}}(\eta)Q_2m(\eta) \\
&\quad + [-Cp(\eta) + Wm(\eta-\tau_2(\eta))]^{\mathrm{T}}Q_3[-Cp(\eta) + Wm(\eta-\tau_2(\eta))]\}\mathrm{d}\eta\mathrm{d}\theta, \\
V_5(m(t), p(t), t) &= 2\int_{-h_1}^{0}\int_{t+\theta}^{t} \mathrm{trace}[\sigma_1^{\mathrm{T}}(\eta, p(\eta), p(\eta-\tau_1(\eta)))U_1\sigma_1(\eta, p(\eta), p(\eta-\tau_1(\eta)))]\mathrm{d}\eta\mathrm{d}\theta \\
&\quad + 2\int_{-h_2}^{0}\int_{t+\theta}^{t} \mathrm{trace}[\sigma_2^{\mathrm{T}}(\eta, m(\eta), m(\eta-\tau_2(\eta)))U_2\sigma_2(\eta, m(\eta), m(\eta-\tau_2(\eta)))]\mathrm{d}\eta\mathrm{d}\theta.
\end{aligned}$$

Using the generalized Itô formula [13], the Lyapunov-Krasovskii functions along the system (3) to the trajectory of the differential can be obtained as follows:

$$\begin{aligned}
&LV_1(m(t), p(t), t) = -2m^{\mathrm{T}}(t)P_{11}Am(t) + 2m^{\mathrm{T}}(t)P_{11}Wg(p(t-\tau_1(t))) + \mathrm{trace}[\sigma_1^{\mathrm{T}}(t, p(t), p(t-\tau_1(t))) \\
&\quad P_{11}\sigma_1(t, p(t), p(t-\tau_1(t)))] + \int_{|y|<c} [V_1(m(t), p(t) + H_1(m(t), p(t), y), t) - V_1(m(t), p(t), t) \\
&\quad -H_1(m(t), p(t), y), t)V_{1p}(m(t), p(t), t)]\nu(\mathrm{d}y) - 2p^{\mathrm{T}}(t)P_{12}^{\mathrm{T}}Am(t) + 2p^{\mathrm{T}}(t)P_{12}^{\mathrm{T}}Wg(p(t-\tau_1(t))) \\
&\quad -2m^{\mathrm{T}}(t)P_{12}Cp(t) + 2m^{\mathrm{T}}(t)P_{12}Dm(t-\tau_2(t)) - 2p^{\mathrm{T}}(t)P_{22}Cp(t) + 2p^{\mathrm{T}}(t)P_{22}Dm(t-\tau_2(t)) \\
&\quad \mathrm{trace}[\sigma_2^{\mathrm{T}}(t, m(t), m(t-\tau_2(t)))P_{22}\sigma_2(t, m(t), m(t-\tau_2(t)))] + \int_{|y|<c} [V_1(m(t) + H_2(m(t), p(t), y), \\
&\quad p(t), t) - V_1(m(t), p(t), t) - H_2(m(t), p(t), y), t)V_{1m}(m(t), p(t), t)]\nu(\mathrm{d}y), \\
&LV_2(m(t), p(t), t) \leqslant p^{\mathrm{T}}(t)S_1p(t) + g^{\mathrm{T}}(p(t))S_2g(p(t)) - (1-d_1)p^{\mathrm{T}}(t-\tau_1(t))S_1p(t-\tau_1(t)) \\
&\quad -(1-d_1)g^{\mathrm{T}}(p(t-\tau_1(t)))S_2g(p(t-\tau_1(t))) + m^{\mathrm{T}}(t)S_3m(t) - (1-d_2)m^{\mathrm{T}}(t-\tau_2(t))S_3m(t-\tau_2(t)), \\
&LV_3(m(t), p(t), t) = m^{\mathrm{T}}(t)R_1m(t) - m^{\mathrm{T}}(t-h)R_1m(t-h) + p^{\mathrm{T}}(t)R_2p(t) - p^{\mathrm{T}}(t-h)R_2p(t-h),
\end{aligned}$$

$$LV_4(m(t),p(t),t) \leqslant h_1 p^{\mathrm{T}}(t)Q_1 p(t) - \int_{t-\tau_1(t)}^{t} p^{\mathrm{T}}(\theta)Q_1 p(\theta)\mathrm{d}\theta + h_1[-Am(t)+Wg(p(t-\tau_1(t)))]^{\mathrm{T}}$$
$$Q_3[-Am(t)+Wg(p(t-\tau_1(t)))] - \int_{t-\tau_1(t)}^{t}[-Am(\theta)+Wg(p(\theta-\tau_1(\theta)))]^{\mathrm{T}}Q_3[-Am(\theta)$$
$$+Wg(p(\theta-\tau_1(\theta)))]\mathrm{d}\theta + h_2 m^{\mathrm{T}}(t)Q_2 m(t) - \int_{t-\tau_2(t)}^{t} m^{\mathrm{T}}(\theta)Q_2 m(\theta)\mathrm{d}\theta + h_2[-Cp(t)$$
$$+Dm(t-\tau_2(t))]^{\mathrm{T}}Q_4[-Cp(t)+Dm(t-\tau_2(t))] - \int_{t-\tau_2(t)}^{t}[-Cp(\theta)+Dm(\theta-\tau_2(\theta))]^{\mathrm{T}}$$
$$Q_4[-Cp(\theta)+Dm(\theta-\tau_2(\theta))]\mathrm{d}\theta,$$
$$LV_5(m(t),p(t),t) \leqslant 2h_1\mathrm{trace}[\sigma_1^{\mathrm{T}}(t,p(t),p(t-\tau_1(t)))U_1\sigma_1(t,p(t),p(t-\tau_1(t)))]$$
$$-2\int_{t-\tau_1(t)}^{t}\mathrm{trace}[\sigma_1^{\mathrm{T}}(\theta,p(\theta),p(\theta-\tau_1(\theta)))U_1\sigma_1(\theta,p(\theta),p(\theta-\tau_1(\theta)))]\mathrm{d}\theta$$
$$+2h_2\mathrm{trace}[\sigma_2^{\mathrm{T}}(t,m(t),m(t-\tau_2(t)))U_2\sigma_2(t,m(t),m(t-\tau_2(t)))]$$
$$-2\int_{t-\tau_2(t)}^{t}\mathrm{trace}[\sigma_2^{\mathrm{T}}(\theta,m(\theta),m(\theta-\tau_2(\theta)))U_2\sigma_2(\theta,m(\theta),m(\theta-\tau_2(\theta)))]\mathrm{d}\theta.$$

By the Leibniz-Newton formula, for the appropriate dimension of the matrices M_1, M_2 such that

$$-2\xi^{\mathrm{T}}(t)M_1\{m(t)-m(t-h)-\int_{t-h}^{t}[-Am(\theta)+Wg(p(\theta-\tau_1(\theta)))]\mathrm{d}\theta$$
$$-\int_{t-h}^{t}\sigma_1(\theta,p(\theta),p(\theta-\tau_1(\theta)))\mathrm{d}L_1(\theta)\}=0,$$
$$-2\xi^{\mathrm{T}}(t)M_2\{p(t)-p(t-h)-\int_{t-h}^{t}[-Cp(\theta)+Dm(\theta-\tau_2(\theta))]\mathrm{d}\theta$$
$$-\int_{t-h}^{t}\sigma_2(\theta,m(\theta),m(\theta-\tau_2(\theta)))\mathrm{d}L_2(\theta)\}=0,$$

where $h=\max\{h_1,h_2\}$ and $\xi^{\mathrm{T}}(t)=[m^{\mathrm{T}}(t),p^{\mathrm{T}}(t),p^{\mathrm{T}}(t-\tau_1(t)),m^{\mathrm{T}}(t-\tau_2(t)),g^{\mathrm{T}}(p(t)),g^{\mathrm{T}}(p(t-\tau_1(t))),(\int_{t-\tau_1}^{t}p(\theta)\mathrm{d}\theta)^{\mathrm{T}},(\int_{t-\tau_2}^{t}m(\theta)\mathrm{d}\theta)^{\mathrm{T}}]$.

From Lemmas 1 and 2, noting that $\tau_1\leqslant h_1\leqslant h$, we obtain

$$2\xi^{\mathrm{T}}(t)M_1 m(t-h)\leqslant\xi^{\mathrm{T}}(t)M_1R_1^{-1}M_1^{\mathrm{T}}\xi(t)+m^{\mathrm{T}}(t-h)R_1m(t-h), \tag{11}$$
$$2\xi^{\mathrm{T}}(t)M_1\int_{t-h}^{t}[-Am(\theta)+Wg(p(\theta-\tau_1(\theta)))]\mathrm{d}\theta\leqslant h_1\xi^{\mathrm{T}}(t)M_1Q_3^{-1}M_1^{\mathrm{T}}\xi(t)$$
$$+\int_{t-\tau_1(t)}^{t}[-Am(\theta)+Wg(p(\theta-\tau_1(\theta)))]^{\mathrm{T}}Q_3[-Am(\theta)+Wg(p(\theta-\tau_1(\theta)))]\mathrm{d}\theta, \tag{12}$$
$$2\xi^{\mathrm{T}}(t)M_1\int_{t-h}^{t}\sigma_1(\theta,p(\theta),p(\theta-\tau_1(\theta)))\mathrm{d}L_1(\theta)\leqslant\xi^{\mathrm{T}}(t)M_1U_1^{-1}M_1^{\mathrm{T}}\xi(t)+\Big(\int_{t-\tau_1(t)}^{t}\sigma_1(\theta,p(\theta),$$
$$p(\theta-\tau_1(\theta)))\mathrm{d}L_1(\theta)\Big)^{\mathrm{T}}U_1\Big(\int_{t-\tau_1(t)}^{t}\sigma_1(\theta,p(\theta),p(\theta-\tau_1(\theta)))\mathrm{d}L_1(\theta)\Big). \tag{13}$$

In the same way:

$$2\xi^{\mathrm{T}}(t)M_2p(t-h)\leqslant\xi^{\mathrm{T}}(t)M_2R_2^{-1}M_2^{\mathrm{T}}\xi(t)+p^{\mathrm{T}}(t-h)R_2p(t-h), \tag{14}$$

$$2\xi^{\mathrm{T}}(t)M_2\int_{t-h}^{t}[-Cp(\theta)+Dm(\theta-\tau_2(\theta))]\mathrm{d}\theta\leqslant h_2\xi^{\mathrm{T}}(t)M_2Q_4^{-1}M_2^{\mathrm{T}}\xi(t)+\int_{t-\tau_2(t)}^{t}[-Cp(\theta)+$$
$$Dm(\theta-\tau_2(\theta))]^{\mathrm{T}}Q_4[-Cp(\theta)+Dm(\theta-\tau_2(\theta))]\mathrm{d}\theta, \tag{15}$$
$$2\xi^{\mathrm{T}}(t)M_2\int_{t-h}^{t}\sigma_2(\theta,m(\theta),m(\theta-\tau_2(\theta)))\mathrm{d}L_2(\theta)\leqslant\xi^{\mathrm{T}}(t)M_2U_2^{-1}M_2^{\mathrm{T}}\xi(t)+\Big(\int_{t-\tau_2(t)}^{t}\sigma_2(\theta,m(\theta),$$

$$m(\theta-\tau_2(\theta)))\mathrm{d}L_2(\theta)\Big)^{\mathrm{T}}U_2\Big(\int_{t-\tau_2(t)}^{t}\sigma_2(\theta,m(\theta),m(\theta-\tau_2(\theta)))\mathrm{d}L_2(\theta)\Big). \tag{16}$$

Noting that $g(\cdot)$ satisfies the condition $g(x)(g(x)-Vx)\leqslant 0$, it follows that

$$g^{\mathrm{T}}(p(t))g(p(t))-p^{\mathrm{T}}(t)V^{\mathrm{T}}Vp(t)\leqslant 0,$$

$$g^{\mathrm{T}}(p(t-\tau_1(t)))g(p(t-\tau_1(t)))-p^{\mathrm{T}}(t-\tau_1(t))V^{\mathrm{T}}Vp(t-\tau_1(t))\leqslant 0,$$

where $V=\mathrm{diag}\{v_1,v_2,\ldots,v_n\}$.

Therefore, for any constants $\alpha>0$, $\beta>0$, we obtain

$$-\alpha[g^{\mathrm{T}}(p(t))g(p(t))-p^{\mathrm{T}}(t)V^{\mathrm{T}}Vp(t)]\geqslant 0, \tag{17}$$

$$-\beta[g^{\mathrm{T}}(p(t-\tau_1(t)))g(p(t-\tau_1(t)))-p^{\mathrm{T}}(t-\tau_1(t))V^{\mathrm{T}}Vp(t-\tau_1(t))]\geqslant 0, \tag{18}$$

From conditions (4), (5) and the LMIs (10), we get

$$\begin{aligned}&\mathrm{trace}[\sigma_1^{\mathrm{T}}(t,p(t),p(t-\tau_1(t)))P_{11}\sigma_1(t,p(t),p(t-\tau_1(t)))]\\&\quad\leqslant\lambda(P_{11})[p^{\mathrm{T}}(t)X_0^{\mathrm{T}}X_0p(t)+p^{\mathrm{T}}(t-\tau_1(t))X_1^{\mathrm{T}}X_1p(t-\tau_1(t))]\\&\quad\leqslant\rho_1[p^{\mathrm{T}}(t)X_0^{\mathrm{T}}X_0p(t)+p^{\mathrm{T}}(t-\tau_1(t))X_1^{\mathrm{T}}X_1p(t-\tau_1(t))],\end{aligned} \tag{19}$$

$$\begin{aligned}&\mathrm{trace}[\sigma_1^{\mathrm{T}}(t,p(t),p(t-\tau_1(t)))U_1\sigma_1(t,p(t),p(t-\tau_1(t)))]\\&\quad\leqslant\lambda(U_1)[p^{\mathrm{T}}(t)X_0^{\mathrm{T}}X_0p(t)+p^{\mathrm{T}}(t-\tau_1(t))X_1^{\mathrm{T}}X_1p(t-\tau_1(t))]\\&\quad\leqslant\rho_2[p^{\mathrm{T}}(t)X_0^{\mathrm{T}}X_0p(t)+p^{\mathrm{T}}(t-\tau_1(t))X_1^{\mathrm{T}}X_1p(t-\tau_1(t))],\end{aligned} \tag{20}$$

$$\begin{aligned}&\mathrm{trace}[\sigma_2^{\mathrm{T}}(t,m(t),m(t-\tau_2(t)))P_{22}\sigma_2(t,m(t),m(t-\tau_2(t)))]\\&\quad\leqslant\lambda(P_{22})[m^{\mathrm{T}}(t)X_2^{\mathrm{T}}X_2m(t)+m^{\mathrm{T}}(t-\tau_2(t))X_3^{\mathrm{T}}X_3m(t-\tau_2(t))]\\&\quad\leqslant\rho_3[m^{\mathrm{T}}(t)X_2^{\mathrm{T}}X_2m(t)+m^{\mathrm{T}}(t-\tau_2(t))X_3^{\mathrm{T}}X_3m(t-\tau_2(t))],\end{aligned} \tag{21}$$

$$\begin{aligned}&\mathrm{trace}[\sigma_2^{\mathrm{T}}(t,m(t),m(t-\tau_2(t)))U_2\sigma_2(t,m(t),m(t-\tau_2(t)))]\\&\quad\leqslant\lambda(U_2)[m^{\mathrm{T}}(t)X_2^{\mathrm{T}}X_2m(t)+m^{\mathrm{T}}(t-\tau_2(t))X_3^{\mathrm{T}}X_3m(t-\tau_2(t))]\\&\quad\leqslant\rho_4[m^{\mathrm{T}}(t)X_2^{\mathrm{T}}X_2m(t)+m^{\mathrm{T}}(t-\tau_2(t))X_3^{\mathrm{T}}X_3m(t-\tau_2(t))].\end{aligned} \tag{22}$$

According to Kunita's estimate [35], we obtain

$$\begin{aligned}&\int_{|y|<c}[V_1(m(t)+H_2(m(t),p(t),y),p(t),t)-V_1(m(t),p(t),t)\\&\quad-H_2(m(t),p(t),y),t)V_{1m}(m(t),p(t),t)]\nu(\mathrm{d}y)\leqslant m^{\mathrm{T}}(t)K_1m(t),\end{aligned} \tag{23}$$

$$\begin{aligned}&\int_{|y|<c}[V_1(m(t),p(t)+H_1(m(t),p(t),y),t)-V_1(m(t),p(t),t)\\&\quad-H_1(m(t),p(t),y),t)V_{1p}(m(t),p(t),t)]\nu(\mathrm{d}y)\leqslant p^{\mathrm{T}}(t)K_2p(t).\end{aligned} \tag{24}$$

By the basic inequality, it follows that

$$\begin{aligned}&E\Big(\int_{t-\tau_1(t)}^{t}\sigma_1(\theta,p(\theta),p(\theta-\tau_1(\theta)))\mathrm{d}L_1(\theta)\Big)^{\mathrm{T}}U_1\Big(\int_{t-\tau_1(t)}^{t}\sigma_1(\theta,p(\theta),p(\theta-\tau_1(\theta)))\mathrm{d}L_1(\theta)\Big)\\&=E\Big[\int_{t-\tau_1(t)}^{t}\sigma_1^{\mathrm{T}}(\theta,p(\theta),p(\theta-\tau_1(\theta)))\mathrm{d}\omega_1(\theta)U_1\int_{t-\tau_1(t)}^{t}\sigma_1(\theta,p(\theta),p(\theta-\tau_1(\theta)))\mathrm{d}\omega_1(\theta)\\&\quad+2\int_{t-\tau_1(t)}^{t}\sigma_1^{\mathrm{T}}(\theta,p(\theta),p(\theta-\tau_1(\theta)))\mathrm{d}\omega_1(\theta)U_1\int_{t-\tau_1(t)}^{t}\int_{|y|<c}H_1(m(u-),p(u-),y)\tilde{N}(\mathrm{d}u,\mathrm{d}y)\\&\quad+\int_{t-\tau_1(t)}^{t}\int_{|y|<c}H_1(m(u-),p(u-),y)\tilde{N}(\mathrm{d}u,\mathrm{d}y)U_1\int_{t-\tau_1(t)}^{t}\int_{|y|<c}H_1(m(u-),p(u-),y)\tilde{N}(\mathrm{d}u,\mathrm{d}y)\Big],\end{aligned}$$

where

$$\begin{aligned}
&E\bigg[\int_{t-\tau_1(t)}^{t}\int_{|y|<c} H_1(m(u-),p(u-),y)\tilde{N}(\mathrm{d}u,\mathrm{d}y)\bigg]^2 U_1\\
&\leqslant c_1 E\bigg[\bigg(\int_{t-\tau_1(t)}^{t}\int_{|y|<c}(H_1(m(u-),p(u-),y))^2\nu(\mathrm{d}y)\mathrm{d}u\bigg)U_1\bigg]\\
&\leqslant c_1 E\bigg[\bigg(\int_{t-\tau_1(t)}^{t}(\int_{|y|<c}(H_1(m(u-),p(u-),y))^2\nu(\mathrm{d}y))\mathrm{d}u\bigg)U_1\bigg]\\
&\leqslant c_1 K_3 E\bigg[\bigg(\int_{t-\tau_1(t)}^{t}p^2(u-)\mathrm{d}u\bigg)U_1\bigg].
\end{aligned}$$

Since the following inequalities are established [36]:

$$\begin{aligned}
&E\int_{t-\tau_1(t)}^{t}\sigma_1^{\mathrm{T}}(\theta,p(\theta),p(\theta-\tau_1(\theta)))\mathrm{d}\omega_1(\theta)U_1\int_{t-\tau_1(t)}^{t}\sigma_1(\theta,p(\theta),p(\theta-\tau_1(\theta)))\mathrm{d}\omega_1(\theta)\\
&=E\int_{t-\tau_1(t)}^{t}\mathrm{trace}[\sigma_1^{\mathrm{T}}(\theta,p(\theta),p(\theta-\tau_1(\theta)))U_1\sigma_1(\theta,p(\theta),p(\theta-\tau_1(\theta)))]\mathrm{d}\omega_1(\theta),
\end{aligned}$$

we can obtain

$$\begin{aligned}
&E\left(\int_{t-\tau_1(t)}^{t}\sigma_1(\theta,p(\theta),p(\theta-\tau_1(\theta)))\mathrm{d}L_1(\theta)\right)^{\mathrm{T}}U_1\left(\int_{t-\tau_1(t)}^{t}\sigma_1(\theta,p(\theta),p(\theta-\tau_1(\theta)))\mathrm{d}L_1(\theta)\right)\\
&\leqslant 2E\int_{t-\tau_1(t)}^{t}\mathrm{trace}[\sigma_1^{\mathrm{T}}(\theta,p(\theta),p(\theta-\tau_1(\theta)))U_1\sigma_1(\theta,p(\theta),p(\theta-\tau_1(\theta)))]\mathrm{d}\omega_1(\theta)\\
&\quad+2c_1K_3E\left[\left(\int_{t-\tau_1(t)}^{t}p(u-)\mathrm{d}u\right)^{\mathrm{T}}U_1\left(\int_{t-\tau_1(t)}^{t}p(u-)\mathrm{d}u\right)\right].
\end{aligned}\tag{25}$$

In the same way, we obtain

$$\begin{aligned}
&E\left(\int_{t-\tau_2(t)}^{t}\sigma_2(\theta,m(\theta),m(\theta-\tau_2(\theta)))\mathrm{d}L_2(\theta)\right)^{\mathrm{T}}U_2\left(\int_{t-\tau_2(t)}^{t}\sigma_2(\theta,m(\theta),m(\theta-\tau_2(\theta)))\mathrm{d}L_2(\theta)\right)\\
&\leqslant 2E\int_{t-\tau_2(t)}^{t}\mathrm{trace}[\sigma_2^{\mathrm{T}}(\theta,m(\theta),m(\theta-\tau_2(\theta)))U_2\sigma_2(\theta,m(\theta),m(\theta-\tau_2(\theta)))]\mathrm{d}\omega_2(\theta)\\
&\quad+2c_2K_4E\left[\left(\int_{t-\tau_2(t)}^{t}m(u-)\mathrm{d}u\right)^{\mathrm{T}}U_2\left(\int_{t-\tau_2(t)}^{t}m(u-)\mathrm{d}u\right)\right].
\end{aligned}\tag{26}$$

Finally, we consider (11)–(26) together, and take the mathematical expectation to get

$$ELV(m(t),p(t),t)\leqslant E\xi^{\mathrm{T}}(t)\Pi\xi(t),$$

where

$$\begin{aligned}
\Pi=&\Omega+h_1\Phi_1^{\mathrm{T}}Q_3\Phi_1+h_2\Phi_2^{\mathrm{T}}Q_4\Phi_2+h_1M_1Q_3^{-1}M_1^{\mathrm{T}}+h_2M_2Q_4^{-1}M_2^{\mathrm{T}}\\
&+M_1R_1^{-1}M_1^{\mathrm{T}}+M_2R_2^{-1}M_2^{\mathrm{T}}+M_1U_1^{-1}M_1^{\mathrm{T}}+M_2U_2^{-1}M_2^{\mathrm{T}}.
\end{aligned}$$

4 Numerical examples

Example 1. As an example, we first consider a gene regulatory networks with three genes (*lacl*, *tetR*, *cl*):

$$\begin{cases}\mathrm{d}m(t)=-Am(t)+Wp(t),\\ \mathrm{d}p(t)=-Cp(t)+Dm(t),\end{cases}\tag{27}$$

where $A = \mathrm{diag}\{3.5, 3.5, 3.5\}$, $D = \mathrm{diag}\{2.5, 2.5, 2.5\}$, $C = \mathrm{diag}\{0.5, 2.5, 2.5\}$, $W = \{0, 2, 0; 2, 0, 0; 0, 2, 0\}$, and $f(x) = x^2/(1 + x^2)$. Using the MATLAB system, we get the general solution of the following form

$$\begin{cases} m(t) = c_1 * \exp((t * (17^{\frac{1}{2}} - 6))/2) * (17^{\frac{1}{2}}/4 - 1/4) - c_2 * \exp(-(t * (17^{\frac{1}{2}} + 6))/2) * (17^{\frac{1}{2}}/4 + 1/4), \\ p(t) = c_1 * \exp((t * (17^{\frac{1}{2}} - 6))/2) + c_2 * \exp(-(t * (17^{\frac{1}{2}} + 6))/2). \end{cases}$$

Therefore, over time, $m(t)$ and $p(t)$ deviate from the 0 point at an exponential rate, so that the system is not stable. The trajectories of the mRNA concentration $m(t)$ and protein concentration $p(t)$ are shown in Figure 1.

As demonstrated in Figure 1, the mRNA and protein concentrations in the three nodes increase with time from the 0 point, and are in divergent states. Thus, at this time, the system is not stable.

However, an actual gene regulatory network is affected by both internal factors and the external environment. Based on the gene regulatory network defined above (27), we consider delay factors and random factors, and obtain the following gene regulatory network model (28):

$$\begin{cases} \mathrm{d}m(t) = [-Am(t) + Wg(p(t - \tau_1(t)))]\mathrm{d}t + \sigma_1(t, p(t), p(t - \tau_1(t)))\mathrm{d}L_1(t), \\ \mathrm{d}p(t) = [-Cp(t) + Dm(t - \tau_2(t))]\mathrm{d}t + \sigma_2(t, m(t), m(t - \tau_2(t)))\mathrm{d}L_2(t), \end{cases} \tag{28}$$

where $A = \mathrm{diag}\{3.5, 3.5, 3.5\}$, $D = \mathrm{diag}\{2.5, 2.5, 2.5\}$, $C = \mathrm{diag}\{0.5, 2.5, 2.5\}$, $X_0 = X_2 = \mathrm{diag}\{0.2, 0.2, 0.2\}$, $X_1 = X_3 = \mathrm{diag}\{0.3, 0.3, 0.3\}$, $V = \mathrm{diag}\{0.65, 0.65, 0.65\}$, $K_1 = \mathrm{diag}\{1.5, 1.5, 1.5\}$, $K_2 = \mathrm{diag}\{2, 2, 2\}$, $W = \{0, 2, 0; 2, 0, 0; 0, 2, 0\}$, and $f(x) = x^2/(1 + x^2)$.

In the model (28), time-varying delays are used to represent the influence of time delays, and $\tau_1(t) = 1 + 0.2\sin(t)$, $\tau_2(t) = 1 + 0.1\sin(t)$. Moreover, we use Lévy noise to represent random factors. In this case, the system is not stable because the parameters do not satisfy the conditions outlined in Theorem 1 and Ω is not a negative definite matrix. The trajectories of the mRNA concentration $m(t)$ and protein concentration $p(t)$ of the gene regulatory network with time-varying delays and Lévy noise are shown in Figure 2.

As shown in Figure 2, the mRNA and protein concentrations in the three nodes increase over time from the 0 point, which are in divergent states. At this time, the system is still not stable.

However, when we control the parameters to meet the conditions proposed in Theorem 1, let $A = \mathrm{diag}\{3.5, 3.5, 3.5\}$, $C = D = \mathrm{diag}\{2.5, 2.5, 2.5\}$, $X_0 = X_2 = \mathrm{diag}\{0.2, 0.2, 0.2\}$, $X_1 = X_3 = \mathrm{diag}\{0.3, 0.3, 0.3\}$, $V = \mathrm{diag}\{0.65, 0.65, 0.65\}$, $K_1 = \mathrm{diag}\{1.5, 1.5, 1.5\}$, $K_2 = \mathrm{diag}\{2, 2, 2\}$, $W = \{0, 0.2, 0; 0.2, 0, 0; 0, 0.2, 0\}$, and $f(x) = x^2/(1 + x^2)$, and then Ω becomes a negative definite matrix, and the system is stable. We can obtain the trajectories of the mRNA concentration $m(t)$ and protein concentration $p(t)$ of the gene regulatory network with time-varying delays and Lévy noise, as shown in Figure 3. From Figure 3, we can see that the gene regulatory network (3) is globally asymptotic stable. According to the above time-delay functions $\tau_1(t)$, $\tau_2(t)$, we choose $d_1 = 0.2$, $d_2 = 0.1$, $h_1 = 1.2$, $h_2 = 1.1$, and the feasible solution of the LMIs (10) can be obtained by using the LMI toolbox in MATLAB. The values of some of the matrix variables are listed below:

$$P_{11} = \begin{bmatrix} 1.3087 & 0 & -0.0010 \\ 0 & 1.3087 & 0 \\ -0.0010 & 0 & 1.3096 \end{bmatrix}, \quad P_{12} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \quad P_{22} = \begin{bmatrix} 0.3720 & 0 & -0.0000 \\ 0 & 0.3720 & 0 \\ -0.0000 & 0 & 0.3720 \end{bmatrix},$$

$$S_1 = \begin{bmatrix} 5.6668 & 0 & -0.0000 \\ 0 & 5.6668 & 0 \\ -0.0000 & 0 & 5.6668 \end{bmatrix}, \; S_2 = \begin{bmatrix} 1.4027 & 0 & -0.0000 \\ 0 & 1.4029 & 0 \\ -0.0000 & 0 & 1.4029 \end{bmatrix}, \; S_3 = \begin{bmatrix} 3.4081 & 0 & -0.0000 \\ 0 & 3.4081 & 0 \\ -0.0000 & 0 & 3.4081 \end{bmatrix}.$$

In this paper, we added Lévy noise control into model (28). Therefore, the system achieves a stable state. In addition, we added a reasonable and effective control method to meet the inequality group (10). By comparing Figure 2 and Figure 3, we find that in Figure 3, the protein concentration curve has three

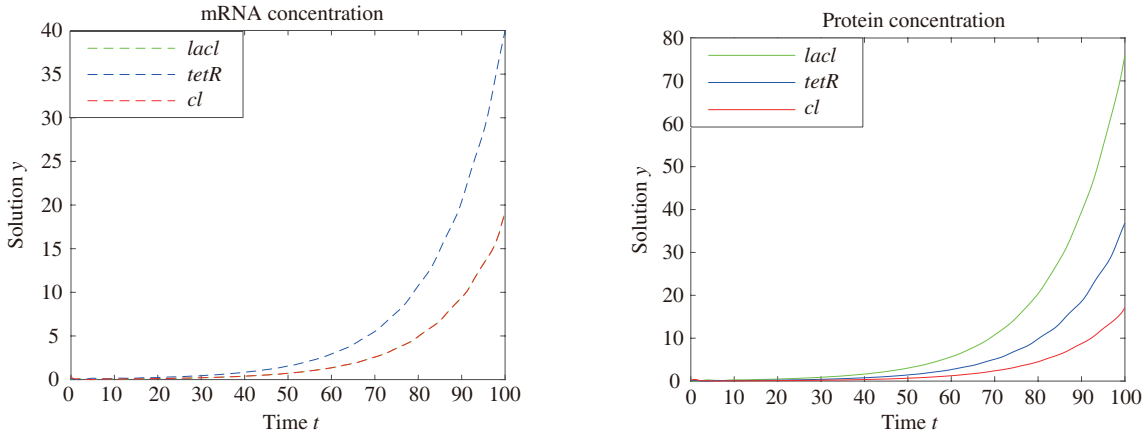

Figure 1 Trajectories of $m(t)$ and $p(t)$ of the gene regulatory network.

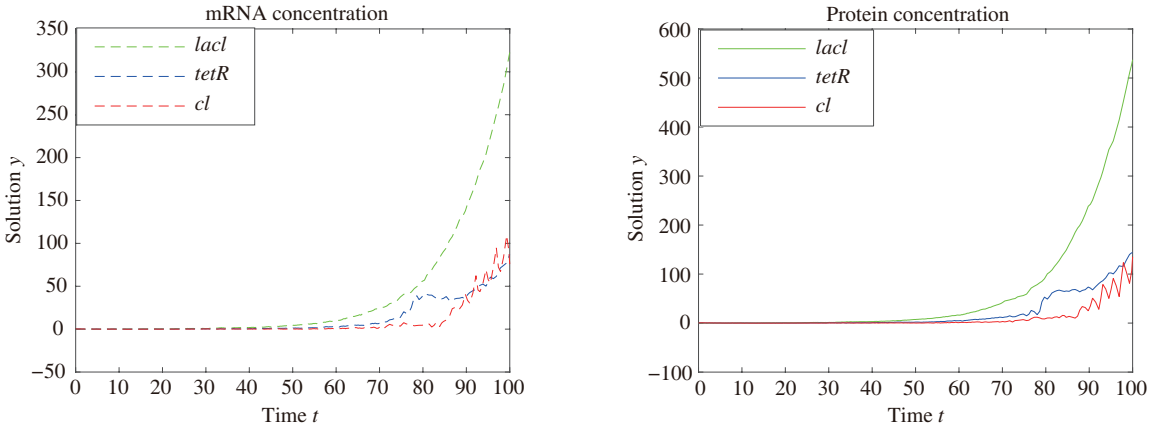

Figure 2 Trajectories of $m(t)$ and $p(t)$ of the gene regulatory network with time-varying delays and Lévy noise.

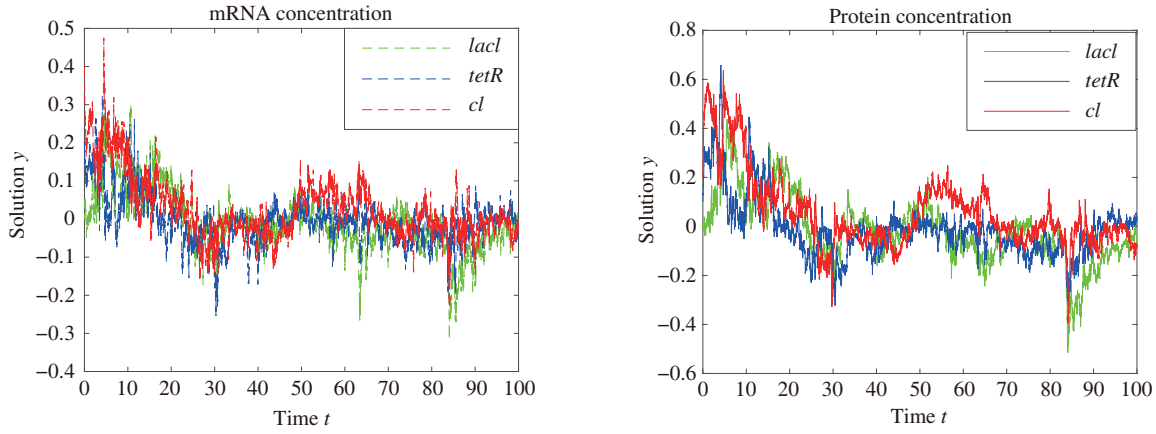

Figure 3 Trajectories of $m(t)$ and $p(t)$ of the gene regulatory network with time-varying delays and Lévy noise.

nodes at the mRNA levels and some moderate fluctuation around the 0 point, but finally converges to 0, suggesting that it is in a generally steady state. At this time, the gene regulatory network achieves the status of stochastic stabilization.

As a practical example, the models presented in this paper were used to analyze genes and their regulatory mechanism related to idiopathic or isolated atrial fibrillation (AF) in AF patients [37–40]. The results showed that approximately 10 genes, including Connexin40, 10q22-q24, 6q14-q16, and 5p13, were related to AF. Connexin40 is the main structural basis for the synchronization of the electrical

activity of the myocardium and the impulse of the electrical activity in the heart. Abnormal contraction of Connexin40 will lead to imbalance in regional myocardial electrical activity, and thus increase action potential propagation anisotropy and conduction velocity heterogeneity. Connexin40 is associated with atrial electrical remodeling and structural remodeling in AF, and is thus involved in the occurrence and progress of AF. Therefore, mutation of the Connexin40 gene can induce idiopathic AF, which threatens the life of a patient with AF. Usually, polymorphisms in the Connexin40 gene may result in changes in connexin expression with respect to both quantity and distribution, leading to atrial electrical conduction disturbance, resulting in the occurrence and progression of AF. The antiarrhythmic peptides can enhance the conduction velocity of gap junctions, improve the electrical coupling between cells, and reduce atrial vulnerability. Therefore, the use of antiarrhythmic peptides for AF patients can restore the cardinal function and improve the patient's quality of life.

5 Concluding remarks

In this paper, the stability of gene regulatory networks with time-varying delays and with Lévy noise is investigated. In addition, the sufficient conditions for achieving stochastic stabilization are presented, and a simulation example is provided to illustrate that system (3) is globally asymptotically stable. However, in this paper, only time-varying delays of the gene regulatory networks are taken into consideration, and thus the stability of the gene regulatory networks with Lévy noise needs to be further investigated in future studies.

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Conflict of interest The authors declare that they have no conflict of interest.

References

1 Liu W W, He J. Applications of differential equation model in the construction of gene regulatory networks (in Chinese). Chin J Health Stat, 2008, 25: 91–96
2 Davidson E H, Erwin D H. Gene regulatory networks and the evolution of animal body plans. Science, 2006, 311: 796–800
3 Somogyi R, Sniegoski C A. Modeling the complexity of genetic networks: understanding multigenic and pleiotropic regulation. Complexity, 1996, 1: 45–63
4 Guo Y Q. Controllability of Boolean control networks with state-dependent constraints. Sci China Inf Sci, 2016, 59: 032202
5 Friedman N, Linial M, Nachman I, et al. Using bayesian networks to analyze expression data. J Comput Biol, 2000, 7: 601–620
6 Hardy S, Robillard P N. Modeling and simulation of molecular biology systems using Petri nets: modeling goals of various approaches. J Bioinf Comput Biol, 2004, 2: 595–613
7 Ding Z H, Jiang M Y, Chen H B, et al. Petri net based test case generation for evolved specification. Sci China Inf Sci, 2016, 59: 080105
8 Hu S G, Huang C M, Wu F K. Stochastic Differential Equations. Beijing: Science Press, 2008. 27–30
9 Chen L, Aihara K. Stability of genctic regulatory networks with time delay. IEEE Trans Circuits Syst I, 2002, 49: 602–608
10 Wu F X. Stability and bifurcation of ring-Structured genetic regulatory networks with time delays. IEEE Trans Circuits Syst I, 2012, 59: 1312–1320
11 Pan W, Wang Z D, Gao H J, et al. On multistability of delayed genetic regulatory networks with multivariable regulation functions. Math Biosci, 2010, 228: 100–109
12 Zhou G L. Stochastic partial differential equations with Lévy jump. Dissertation for the Doctoral Degree. Hunan: Central South University, 2010. 51–78
13 Zhu Q X. Asymptotic stability in the pth moment for stochastic differential equations with Lévy noise. J Math Anal Appl, 2014, 416: 126–142
14 Li Z H, Xu W. Asymptotic results for exponential functionals of Lévy processes. arXiv:1601.02363
15 Curry C, Ebrahimi-Fard K, Malham S J A, et al. Algebraic structures and stochastic differential equations driven by Lévy processes. arXiv: 1601.04880

16 Wu F X. Delay-independent stability of genetic regulatory networks. IEEE Trans Neural Netw, 2011, 22: 1685–1693
17 Feng W, Yang S X, Fu W, et al. Robust stability of stochastic genetic regulatory networks with disturbance attenuation. In: Proceedings of IEEE/ASME International Conference on Advanced Intelligent Mechatronics, Xi'an, 2008. 985–989
18 Hirata H, Yoshiura S, Ohtsuka T, et al. Oscillatory expression of the bHLH factor Hes1 regulated by a negative feed back loop. Science, 2002, 298: 840–843
19 Elowitz M B, Levine A J, Siggia E D, et al. Stochastic gene expression in a single cell. Science, 2002, 297: 1183–1186
20 Raser J M, O'Shea E K. Noise in gene expression: origins, consequences and control. Science, 2005, 309: 2010–2013
21 Wang Z X, Liu G D, Sun Y H, et al. Robust stability of stochastic delayed genetic regulatory networks. Cogn Neurodyn, 2009, 3: 271–280
22 Zhang W B, Fang J A, Tang Y. Stochastic stability of Markovian jumping genetic regulatory networks with mixed time delays. Appl Math Comput, 2011, 217: 7210–7225
23 Zhang W, Tang Y, Fang J A, et al. Exponential cluster synchronization of impulsive delayed genetic oscillators with external disturbances. Chaos, 2011, 21: 1187–1202
24 Wang Z D, Shu H S, Liu Y R, et al. Robust stability analysis of generalized neural networks with discrete and distributed time delays. Chaos Soliton Fract, 2006, 30: 886–896
25 Ma Q, Xu S Y, Zou Y, et al. Robust stability for discrete-time stochastic genetic regulatory networks. Nonlinear Anal-Real World Appl, 2011, 12: 2586–2595
26 Li C G, Chen L N, Aihara K. Stability of genetic networks with SUM regulatory logic: Lur'e system and LMI approach. IEEE Trans Circuits Syst I, 2006, 53: 2451–2458
27 Wu F X, Zhang W J, Kusalik A J. On robust stability of stochastic genetic regulatory networks with time delays: a delay fractioning approach. IEEE Trans Syst Man Cybern B, 2010, 40: 729–740
28 Wu H X, Liao X F, Guo S T, et al. Stochastic stability for uncertain genetic regulatory networks with interval time-varying delays. Neurocomputing, 2009, 72: 3263–3276
29 CastellanosRubio A, FernandezJimenez N, Kratchmarov R. A long noncoding RNA associated with susceptibility to celiac disease. Science, 2016, 352: 91–95
30 Sun Y H, Feng G, Cao J D. Stochastic stability of Markovian switching genetic regulatory networks. Phys Lett A, 2009, 373: 1646–1652
31 Zhang W B. Stochastic dynamics analysis of gene regulatory networks. Dissertation for the Doctoral Degree. Shanghai: Donghua University, 2012. 3–30
32 Ren F L, Cao J D. Asymptotic and robust stability of genetic regulatory networks with time-varying delays. Neurocomputing, 2008, 71: 834–842
33 Gu K. An integral inequality in the stability problem of time-delay systems. In: Proceedings of the 39th IEEE Conference on Decision and Control, Sydney, 2000. 2805–2810
34 Boyd S P. Linear Matrix Inequalities in System and Control Theory. Philadelphia: SIAM, 1994. 7–42
35 Zhu Q X. Stability of stochastic differential equations with Lévy noise. In: Proceedings of the 33rd Chinese Control Conference, Nanjing, 2014. 5211–5216
36 Oksendal B. Stochastic Differential Equations. 5th ed. New York: Springer-Verlag, 2000. 109–122
37 Yang Y Q, Zhang X L, Wang X H, et al. Connexin40 nonsense mutation in familial atrial fibrillation. Int J Mol Med, 2010, 26: 605–610
38 Lin X, Gemel J, Glass A, et al. Connexin40 and connexin43 determine gating properties of atrial gap junction channels. J Mol Cell Cardiol, 2010, 48: 238–245
39 Chaldoupi S, Loh P, Hauer R N W, et al. The role of connexin40 in atrial fibrillation. Cardiovasc Res, 2009, 84: 15–23
40 Alonso F, Domingospereira S, Le G L, et al. Targeting endothelial connexin40 inhibits tumor growth by reducing angiogenesis and improving vessel perfusion. Oncotarget, 2016, 7: 14015–14028