Asymptotic stability of Markovian switching genetic regulatory networks with leakage and mode-dependent time delays

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Abstract

The problem of stability analysis of Markovian switching genetic regulatory networks (GRNs) with leakage and mode-dependent time-varying delays along Brownian motions is reported here. The GRNs are composed of \( N \) modes which switches from one mode to another according to a Markov chain with known transition probabilities. The regulatory functions of GRNs are assumed to be sector-like nonlinear functions. By applying delay-fractioning approach, the sufficient conditions are derived to guarantee the stability of Markovian switching GRNs with leakage and mode-dependent time-varying delays in the mean-square sense. Also, the corresponding results are obtained for the GRNs without leakage delays. To illustrate the effectiveness of the proposed theoretical results, repressilator model of \textit{Escherichia coli} is analyzed in the end.

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1. Introduction

Gene regulatory networks (GRNs) have an important role in every process of life, including cell differentiation, metabolism, the cell cycle and signal transduction [1–6]. A GRN is a dynamic system to describe interactions among genes (mRNA) and its products (proteins). Genes can be viewed as nodes in the network, with input being proteins such as transcription factors, and outputs being the level of

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gene expression. Schematic representation of a gene regulatory process is illustrated in Fig. 1, see [7]. In modeling genetic networks (or other systems), it is well known that there are no unique, exact mathematical descriptions of processes in nature. Only, approximations that capture all aspects of interest have been availed as accurately as feasible to gain insight from the analysis [8]. Mathematical models of GRNs have been developed to capture the behavior of the system being modeled, and in some cases generate predictions corresponding with experimental observations [9]. The most common modeling technique involves the use of coupled ordinary differential equations [10]. Other modeling techniques such as Boolean networks [11], Petri nets, Bayesian networks [12], graphical Gaussian models, Stochastic, and Process Calculi have also been utilized.

The study of stability is essential for designing or controlling GRNs [13–15]. The binding of regulators, transcription, translation, and diffusion in gene expression is subject to significant biochemical process delays (that is, time delays), intrinsic fluctuations and extrinsic fluctuations see [16]. Recently, a new type of time delay known as leakage delay was studied in [17]. Such a term may exist in the negative feedback terms of networks. The existence of the leakage delay may lead to instability or poor performance in dynamical systems. However, very few reports have been analyzed on the dynamical behavior of GRNs with leakage delay for example, the problem of global asymptotic stability criteria for GRNs with time delays in the leakage term have been investigated in [18]. So, it is significant to give more attention to the behaviors of GRNs with leakage delay.

On the other hand, systems with Markovian switching are powerful and appropriate to construct varieties of systems with abrupt changes in their structure (see, [19]), for instance, in solar thermal central receivers, robotic manipulator systems, aircraft control systems and large flexible structures for space stations, etc. Very recently, stability analysis of the differential GRNs model with time-varying delays and Markovian jumping parameters (MJPs) have been
studied in [20]. Further, authors in [21] have analyzed the problem of state estimation for Markovian jumping GRNs with random delays.

The noise fluctuations of gene expression data are an important issue to be considered, while modeling GRNs [22]. The gene regulation process is always subject to intrinsic noises and extrinsic noises. The intrinsic noises are due to the random births and deaths of individual components, and extrinsic noises, supposed to be Brownian motion for synthesis design, are derived from environment fluctuations [23,24].

Due to small numbers of transcriptional factors and other key signaling proteins, intracellular and extracellular noise perturbations are unavoidable during the modeling of genetic network models [25–30]. A system with MJP is a hybrid system with a state vector having two components \( m(t) \) and \( \eta_t \), where \( m(t) \) denotes the state and \( \eta_t \) is a continuous time Markov chain with a finite state space \( S = \{1, 2, \ldots, N\} \), which is usually regarded as the mode. In its operation, this class of systems will switch from one mode to another in a random way, which is determined by a continuous-time Markov chain \( \eta_t \) [31]. Moreover, the existence of the leakage delay in biological networks has the tendency to destabilize the system. Hence, it is of significance to study the stability problem of GRNs with MJP, mode-dependent time-varying delays, noise perturbations along with leakage delay. However, to the best of authors’ knowledge, the problem of stability analysis of stochastic GRNs with leakage and mode-dependent time-varying delays based on MJP has never been investigated yet.

Motivated by the above discussions, this paper concerns with the problem of stability analysis of stochastic Markovian switching GRNs with leakage and mode-dependent time-varying delays. By applying ‘delay-fractioning’ approach in the Lyapunov–Krasovskii functional (LKF), we attain the delay-dependent sufficient conditions in terms of linear matrix inequalities (LMIs). Finally, numerical examples are provided to show the effectiveness of the proposed method.

**Notations:** \( \mathbb{R}^n \) denotes the n-dimensional Euclidean space; for any matrix \( A = [a_{ij}]_{n \times n} \), let \( A^T \) and \( A^{-1} \) denote the transpose and the inverse of \( A \), respectively; \( |A| = [a_{ij}]_{n \times n} \); let \( A > 0 \) (\( A < 0 \)) denotes the positive-definite (negative-definite) symmetric matrix, respectively; \( I \) denotes the identity matrix of appropriate dimension and \( \Lambda = \{1, 2, \ldots, n\} \); \( \lambda_{\text{min}}(\cdot) \) and \( \lambda_{\text{max}}(\cdot) \) denote the minimal and maximal eigenvalues of matrix, respectively; \( (\Omega, \mathcal{F}, \mathcal{P}) \) is a probability space, \( \Omega \) is the sample space, \( \mathcal{F} \) is the \( \sigma \)-algebra of the sample space, and \( \mathcal{P} \) is the probability measure on \( \mathcal{F} \). \( \mathbb{E}\{\cdot\} \) refers to the expectation operator with respect to some probability measure \( \mathcal{P} \).

### 2. System formulation and some preliminaries

The activity of a gene is regulated by other genes through the interactions between them, that is, the transcription and translation factors. Here, the regulation can be regarded as the feedback, that is, the level of gene expressions as a function of the concentration of transcription factors. Taking the time delay into account, the GRNs with time-varying delays existing in both the translation process and feedback regulation process [32] can be described by the following differential equation:

\[
\begin{align*}
\dot{x}_m(t) &= -A x_m(t) + B g(x_p(t - \tau_1(t))) + J, \\
\dot{x}_p(t) &= -C x_p(t) + D x_m(t - \tau_2(t)),
\end{align*}
\]

where \( x_m(t) = [x_{m1}(t), x_{m2}(t), \ldots, x_{mn}(t)]^T \), \( x_p(t) = [x_{p1}(t), x_{p2}(t), \ldots, x_{pn}(t)]^T \), \( g(x_p(t - \tau_1(t))) = [g_1(x_{p1}(t - \tau_1(t))), g_2(x_{p2}(t - \tau_1(t))), \ldots, g_n(x_{pn}(t - \tau_1(t)))]^T \), \( A = \text{diag}[a_1, a_2, \ldots, a_n] \), \( C = \text{diag}[c_1, c_2, \ldots, c_n] \), \( J = [J_1, J_2, \ldots, J_n]^T \), \( D = \text{diag}[d_1, d_2, \ldots, d_n] \), in which \( x_{mi}\)’s and \( x_{pi}\)’s are the
concentrations of mRNA and protein of the \(i\)th node; \(a_i\)'s and \(c_i\)'s are the decay rates of mRNA and protein, respectively; \(g_j(x) = \frac{(\hat{x})^{\beta_j}}{(1+(\hat{x})^{\beta_j})}\) is a monotonically increasing function, in which \(H_j\)'s is the Hill coefficients and \(\beta_j\) is a positive constant; \(J_i\)'s and \(d_i\)'s represent the basal rates of degradation and translation rates, respectively; \(B = (b_{ij}) \in \mathbb{R}^{n \times n}\) is defined as follows:

\[
\begin{align*}
    b_{ij} = 
    \begin{cases} 
        \frac{\tilde{b}_{ij}}{2} & \text{if transcription factor } j \text{ is an activator of gene } i, \\
        0 & \text{if there is no link from node } j \text{ to } i, \\
        -\frac{\tilde{b}_{ij}}{2} & \text{if transcription factor } j \text{ is a repressor of gene } i.
    \end{cases}
\end{align*}
\]

Let \((x_m^*, x_p^*)^T\) be an equilibrium point of system (1), that is, it is the solution of equation

\[
\begin{align*}
    -A x_m^* + B g(x_p^*) + J &= 0, \\
    -C x_p^* + D x_m^* &= 0.
\end{align*}
\]

In the following, we will shift an intended equilibrium point \((x_m^*, x_p^*)^T\) of system (1) to the origin.

Using the transformations \(m(t) = x_m(t) - x_m^*, \ p(t) = x_p(t) - x_p^*\), system (1) can be rewritten as

\[
\begin{align*}
    \dot{m}(t) &= -A m(t) + B f(p(t - \tau_1(t))), \\
    \dot{p}(t) &= -C p(t) + D m(t - \tau_2(t)),
\end{align*}
\]

where \(f(p(t)) = [f_1(p_1(t)), f_2(p_2(t)), \ldots, f_n(p_n(t))]^T\), in which \(f_j(p_j(t)) = g_j(p_j(t) + x_p^*) - g_i(x_p^*)\).

For given positive scalars \(d_k, k = 1, 2, \ldots, 2\), we assume \(0 = d_0 < d_1 < d_2 < \cdots < d_n = 1\).

(A1) From the relationship between \(f_i(\cdot)\) and \(g_i(\cdot)\), the function \(f_i(\cdot)\) satisfies the sector condition,

\[
0 \leq \frac{f_i(x_i)}{x_i} \leq k_i, \quad \forall x_i \in \mathbb{R}, \ i = 1, 2, \ldots, n
\]

or equivalently \(f^T(x)(f(x) - Kx) \leq 0\), where \(K = \text{diag}(k_1, k_2, \ldots, k_n) \geq 0\).

However, Markovian jump systems (MJSs) can be defined as a special class of dynamical systems with finite mode operation due to random changes in their structure, such as component failures or repairs, sudden environmental disturbance, changing subsystem interconnections. The applications of the MJSs can be found in economic systems, modeling production system, network control systems, manufacturing systems, communication systems and so on.

Let \(\{\eta_i, \ i \geq 0\}\) be a right-continuous Markov chain on a probability space \((\Omega, \mathcal{F}, \mathbb{P})\) taking values in a finite state space \(S = \{1, 2, \ldots, N\}\) with generator \(\Pi = (\pi_{ij})_{n \times N}^{N \times N}\) given by

\[
\mathbb{P}(\eta_{t+\Delta} = j|\eta_t = i) = \begin{cases} 
    \pi_{ij}\Delta + o(\Delta), & \text{if } i \neq j, \\
    1 + \pi_{ij}\Delta + o(\Delta), & \text{if } i = j,
\end{cases}
\]

here \(\Delta > 0\), and \(\pi_{ij} \geq 0\) is the transition rate from \(i\) to \(j\) if \(j \neq i\) while

\[
\pi_{ii} = -\sum_{j \neq i} \pi_{ij}.
\]

Consider the following nonlinear Markovian GRNs with mode-dependent time-varying delays,
which is a modification of system (3)

\[
\begin{align*}
\dot{m}(t) &= -A_i m(t) + B_i f(p(t - \tau_1(t))), \\
\dot{p}(t) &= -C_i p(t) + D_i m(t - \tau_2(t)),
\end{align*}
\]

where \(\tau_1(\eta_i, t)\) and \(\tau_2(\eta_i, t)\) are mode-dependent time varying delays.

In the sequel, for simplicity, while \(\eta_i = i\), the matrices \(A(\eta_i), B(\eta_i), C(\eta_i), D(\eta_i)\), and time varying delays \(\tau_1(\eta_i, t), \tau_2(\eta_i, t)\) are represented by \(A_i, B_i, C_i, D_i\), and \(\tau_{1i}(t), \tau_{2i}(t)\), respectively:

\[
\begin{align*}
\dot{m}(t) &= -A_i m(t) + B_i f(p(t - \tau_{1i}(t))), \\
\dot{p}(t) &= -C_i p(t) + D_i m(t - \tau_{2i}(t)),
\end{align*}
\]

and the parameters associated with time delays are assumed to satisfy

\[
\begin{align*}
0 &\leq \tau_{1i}(t) \leq \tau_{1i}^*, \quad \dot{\tau}_{1i}(t) \leq \delta_i < 1, \\
0 &\leq \tau_{2i}(t) \leq \tau_{2i}^*, \quad \dot{\tau}_{2i}(t) \leq \nu_i < 1,
\end{align*}
\]

where \(\tau_1 = \max\{\tau_{1i}\}\) and \(\tau_2 = \max\{\tau_{2i}\}\). The initial conditions of the system (5) are assumed to be

\[
\begin{align*}
m(t) &= \phi_m(t), & t &\in [-\tau_2, 0], \\
p(t) &= \phi_p(t), & t &\in [-\tau_1, 0].
\end{align*}
\]

Meanwhile, in real systems stochastic effects are usually unavoidable due to the modeling error and the environmental noises. Transcription in eukaryotic cells reflects inherently the stochastic property of gene expression.

So, we consider the following nonlinear stochastic Markovian GRNs with mode-dependent time-varying delays:

\[
\begin{align*}
\dot{m}(t) &= -A_i m(t) + B_i f(p(t - \tau_{1i}(t))) dt + E_i m(t) d\omega_1(t), \\
\dot{p}(t) &= -C_i p(t) + D_i m(t - \tau_{2i}(t)) dt + F_i p(t) d\omega_2(t),
\end{align*}
\]

where \(E_i m(t) d\omega_1(t)\) and \(F_i p(t) d\omega_2(t)\) are the intrinsic fluctuations in which \(\omega_1(t)\) and \(\omega_2(t)\) are scalar Brownian motions defined on a probability space \((\Omega, \mathcal{F}, \mathbb{P})\).

If the leakage delays appear, that is \(\sigma_1 > 0, \sigma_2 > 0\), the GRNs system (6) becomes

\[
\begin{align*}
\dot{m}(t) &= -A_i m(t - \sigma_1) + B_i f(p(t - \tau_{1i}(t))) dt + E_i m(t) d\omega_1(t), \\
\dot{p}(t) &= -C_i p(t - \sigma_2) + D_i m(t - \tau_{2i}(t)) dt + F_i p(t) d\omega_2(t).
\end{align*}
\]

**Definition 1.** The dynamical delayed Markovian GRNs (6) is said to be globally stochastically stable in the mean-square sense, if the following condition holds:

\[
\lim_{t \to \infty} \mathbb{E}\{\|m(t)\|^2 + \|p(t)\|^2\} = 0,
\]

for all initial functions.
Lemma 1 (Gu [33]). Given any real matrix \( N = N^T > 0 \) of appropriate dimension, and a vector function \( \kappa(\cdot) : [a, b] \rightarrow \mathbb{R}^n \), such that the integrations concerned are well defined, then
\[
\left[ \int_a^b \kappa(s) \, ds \right]^T N \left[ \int_a^b \kappa(s) \, ds \right] \leq (b-a) \int_a^b \kappa^T(s)N\kappa(s) \, ds.
\]

Remark 1. It is well known that time delays which occur in the negative-feedback term (that is, leakage term or forgetting term) of the networks are known as leakage delay. The dynamic behavior of the system is also changes due to small amount of leakage delay.

3. Main results

In this section, we consider the globally stochastically stable of the GRNs with or without noise perturbations. By employing a new LKF based on the idea of ‘delay-fractioning’ approach, some delay dependent stability criteria for the GRNs with or without noise perturbations are derived in the form of LMI.

3.1. Stability analysis of GRNs with noise perturbations

Theorem 1. For given positive scalars \( \sigma_1, \sigma_2, \tau_{i1}, \tau_{2i}, \theta_i, \nu_i \), positive integer \( m \), scalars \( d_k \), and positive diagonal matrix \( K \), the system (7) is globally stochastically stable in the mean square, if there exist positive diagonal matrices \( P_{i1}, P_{2i} \), and some positive definite symmetric matrices \( H_1, H_2, Q_k, R_k, M_1, M_2, N_1, N_2, J_1, J_2 \) with appropriate dimensions, such that the following LMIs hold for all \( i \in S \), \( k = 1, 2, \ldots, m \) and \( l = 2, 3, \ldots, m \):
\[
Q_i - Q_{i-1} < 0,
\]
\[
R_i - R_{i-1} < 0,
\]
\[
\Xi^i = \left[ \Xi^i_{u,v} \right] < 0 \quad (u, v = 1, 2, \ldots, 2m + 10, \ i \in S),
\]

where
\[
\Xi^i_{1,1} = -2P_{i1}A_i + E_i^T P_{i1}E_i + \sum_{j=1}^N \pi_{ij}P_{1j} + H_1 + Q_1 + N_1 + \sigma_1J_1
\]
\[
+ \bar{\pi}_2 \sum_{k=1}^m ([d_k - d_{k-1}]Q_k) + \bar{\pi}_2N_1,
\]
\[
\Xi^i_{1,m+4} = A_i^T P_{1i}A_i - \sum_{j=1}^N \pi_{ij}P_{1j}A_i, \quad \Xi^i_{1,2m+8} = P_{1i}B_i, \quad \Xi_{2,2} = -H_1,
\]
\[
\Xi^i_{3,3} = (d_1\nu_i - 1)[Q_1 - Q_2], \quad \Xi^i_{4,4} = (d_2\nu_i - 1)[Q_2 - Q_3],
\]
\[
\Xi^i_{m+1,m+1} = (d_{m-1}\nu_i - 1)[Q_{m-1} - Q_m], \quad \Xi^i_{m+2,m+2} = -(1 - \nu_i)Q_m,
\]
\[
\Xi^i_{m+2,m+5} = D_i^T P_{2i}, \quad \Xi^i_{m+2,2m+10} = -D_i^T P_{2i}C_i, \quad \Xi^i_{m+3,m+3} = -N_1,
\]
\[ V(t, m(t), p(t), i) = \sum_{n=1}^{9} V_n(t, m(t), p(t), i), \]  

where

\[
\begin{align*}
V_1(t, m(t), p(t), i) &= \left[ m(t) - A_i \int_{\tau_{i-1}}^{t} m(s) \, ds \right]^T P_{1i} \left[ m(t) - A_i \int_{\tau_{i-1}}^{t} m(s) \, ds \right] \\
&\quad \left[ p(t) - C_i \int_{\tau_{i-2}}^{t} p(s) \, ds \right]^T P_{2i} \left[ p(t) - C_i \int_{\tau_{i-2}}^{t} p(s) \, ds \right],
\end{align*}
\]

\[
\begin{align*}
V_2(t, m(t), p(t), i) &= \int_{\tau_{i-1}}^{t} m^T(s) H_1 m(s) \, ds + \int_{\tau_{i-2}}^{t} p^T(s) H_2 p(s) \, ds, \\
V_3(t, m(t), p(t), i) &= \sum_{k=1}^{m} \int_{\tau_{k-1}}^{t-d_k-i\tau_{i-1}(t)} m^T(s) Q_k m(s) \, ds + \sum_{k=1}^{m} \int_{\tau_{k-1}}^{t-d_k-i\tau_{i-1}(t)} p^T(s) R_k p(s) \, ds, \\
V_4(t, m(t), p(t), i) &= \int_{\tau_{i-1}}^{t} m^T(s) N_1 m(s) \, ds + \int_{\tau_{i-1}}^{t} p^T(s) N_2 p(s) \, ds,
\end{align*}
\]

Proof. Consider the following LKFs:

\[
\begin{align*}
\Xi_{m+4,m+4}^i &= A_i^T \sum_{j=1}^{N} \pi_{ij} P_{1j} A_i - \frac{1}{\sigma_1} J_1, \quad \Xi_{m+4,2m+8}^i = -A_i^T P_{1i} B_i, \\
\Xi_{m+5,m+5}^i &= -2P_{2i} C_i + F_i^T P_{2j} F_i + \sum_{j=1}^{N} \pi_{ij} P_{2j} + H_2 + R_1 + N_2 + \sigma_2 J_2 \\
&\quad + \pi_{\tau_1} \sum_{k=1}^{m} (d_k - d_{k-1}) R_k + \pi_{\tau_1} N_2 + \sum_{j=1}^{2} K_i^T M_k K + \pi_{\tau_1} \sum_{j=1}^{2} K_i^T M_j K, \\
\Xi_{m+5,2m+10}^i &= C_i^T P_{2i} C_i - \sum_{j=1}^{N} \pi_{ij} P_{2j} C_i, \quad \Xi_{m+6,m+6} = -H_2, \\
\Xi_{m+7,m+7}^i &= (d_1^i - 1) [R_1 - R_2], \\
\Xi_{m+8,m+8}^i &= (d_2^i - 1) [R_2 - R_3], \quad \Xi_{2m+5,2m+5}^i = (d_{m-1}^i - 1) [R_{m-1} - R_m], \\
\Xi_{2m+6,2m+6}^i &= -(1 - \theta_i) R_m, \quad \Xi_{2m+7,2m+7} = -N_2, \\
\Xi_{2m+8,2m+8}^i &= -(1 - \theta_i) M_1, \\
\Xi_{2m+9,2m+9} &= -M_2, \quad \Xi_{2m+10,2m+10}^i = C_i^T \sum_{j=1}^{N} \pi_{ij} P_{2j} C_i - \frac{1}{\sigma_2} J_2, \\
\pi &= \max \{|\pi_{ij}|\}.
\end{align*}
\]
Differentiating Eq. (11) stochastically using Itô's formula, one can obtain

\[ V_5(t, m(t), p(t), i) = \int_{t - \tau_i(t)}^{t} f^T(p(s))M_1f(p(s)) \, ds + \int_{t - \tau_i(t)}^{t} f^T(p(s))M_2f(p(s)) \, ds, \]

\[ V_6(t, m(t), p(t), i) = \int_{-\sigma_1}^{0} \int_{t + \theta}^{t} m^T(s)J_1m(s) \, ds \, d\theta + \int_{-\sigma_2}^{0} \int_{t + \theta}^{t} p^T(s)J_2p(s) \, ds \, d\theta, \]

\[ V_7(t, m(t), p(t), i) = \pi \sum_{k=1}^{m} \int_{-d_k-1\tau_k}^{-d_k-1\tau_k} \int_{t + \theta}^{t} m^T(s)Q_km(s) \, ds \, d\theta + \pi \sum_{k=1}^{m} \int_{-d_k-1\tau_k}^{-d_k-1\tau_k} \int_{t + \theta}^{t} p^T(s)R_kp(s) \, ds \, d\theta, \]

\[ V_8(t, m(t), p(t), i) = \pi \int_{-\tau_2}^{0} \int_{t + \theta}^{t} m^T(s)N_1m(s) \, ds \, d\theta + \pi \int_{-\tau_1}^{0} \int_{t + \theta}^{t} p^T(s)N_2p(s) \, ds \, d\theta, \]

\[ V_9(t, m(t), p(t), i) = \sum_{j=1}^{2} \pi \int_{-\tau_1}^{0} \int_{t + \theta}^{t} f^T(p(s))[M_j]f(p(s)) \, ds \, d\theta. \]

Differentiating Eq. (11) stochastically using Itô's formula, one can obtain

\[ dV(t, m(t), p(t), i) = \sum_{n=1}^{9} \mathcal{L}V_n(t, m(t), p(t), i) \, dt \]

\[ + 2 \left[ m(t) - A_i \int_{t - \sigma_1}^{t} m(s) \, ds \right] P_{1i}E_i m(t) \, d\omega_1(t) \]

\[ + 2 \left[ p(t) - C_i \int_{t - \sigma_2}^{t} p(s) \, ds \right] P_{2i}F_i p(t) \, d\omega_2(t), \]  

(12)

where

\[ \mathcal{L}V_1(t, m(t), p(t), i) = 2 \left[ m(t) - A_i \int_{t - \sigma_1}^{t} m(s) \, ds \right] ^T P_{1i} \left[ -A_i m(t) + B_i f(p(t - \tau_i(t))) \right] \]

\[ + m^T(t)E_i^T P_{1i}E_i m(t) + \sum_{j=1}^{N} \pi_{ij} \left[ m(t) - A_i \int_{t - \sigma_1}^{t} m(s) \, ds \right] ^T P_{1j} \]

\[ \left[ m(t) - A_i \int_{t - \sigma_1}^{t} m(s) \, ds \right] + 2 \left[ p(t) - C_i \int_{t - \sigma_2}^{t} p(s) \, ds \right] ^T P_{2i} \]

\[ \left[ -C_i p(t) + D_i m(t - \tau_2(t)) \right] + p^T(t)F_i^T P_{2i} F_i p(t) \]

\[ + \sum_{j=1}^{N} \pi_{ij} \left[ p(t) - C_i \int_{t - \sigma_2}^{t} p(s) \, ds \right] ^T P_{2j} \left[ p(t) - C_i \int_{t - \sigma_2}^{t} p(s) \, ds \right], \]  

(13)

\[ \mathcal{L}V_2(t, m(t), p(t), i) = m^T(t)H_1 m(t) - m^T(t - \sigma_1)H_1 m(t - \sigma_1) \]

\[ + p^T(t)H_2 p(t) - p^T(t - \sigma_2)H_2 p(t - \sigma_2), \]  

(14)
\[ \mathcal{L}V_3(t, m(t), p(t), i) \leq m^T(t)Q_1m(t) - m^T(t - \tau_{2i}(t))[(1 - \nu_i)Q_m]m(t - \tau_{2i}(t)) \\
- \sum_{k=1}^{m-1} \left\{ m^T(t - d_k \tau_{2i}(t)) \left[ (1 - d_k \nu_i)(Q_k - Q_{k+1}) \right] m(t - d_k \tau_{2i}(t)) \right\} \\
+ \sum_{j=1}^{N} \pi_{ij} \sum_{k=1}^{m} \int_{t-d_k \tau_{2i}(t)}^{t} m^T(s)Q_{ij}m(s) \, ds + p^T(t)R_1p(t) \\
- p^T(t - \tau_{1i}(t))[(1 - \theta_i)R_m]p(t - \tau_{1i}(t)) - \sum_{k=1}^{m-1} \left\{ p^T(t - d_k \tau_{1i}(t)) \right\} \\
[(1 - d_k \theta_i)(R_k - R_{k+1})]p(t - d_k \tau_{1i}(t)) \\
+ \sum_{j=1}^{N} \pi_{ij} \sum_{k=1}^{m} \int_{t-d_k \tau_{1i}(t)}^{t} p^T(s)R_{ij}p(s) \, ds, \tag{15} \]

\[ \mathcal{L}V_4(t, m(t), p(t), i) = m^T(t)N_1m(t) - m^T(t - \tau_{2i})N_1m(t - \tau_{2i}) \\
+ \sum_{j=1}^{N} \pi_{ij} \int_{t-\tau_{2i}}^{t} m^T(s)N_1m(s) \, ds + p^T(t)N_2p(t) \\
- p^T(t - \tau_{1i})N_2p(t - \tau_{1i}) + \sum_{j=1}^{N} \pi_{ij} \int_{t-\tau_{1i}}^{t} p^T(s)N_2p(s) \, ds, \tag{16} \]

\[ \mathcal{L}V_5(t, m(t), p(t), i) \leq p^T(t)K^TM_1Kp(t) - (1 - \theta_i)Jf(t)p(t - \tau_{1i}(t)))M_1f(p(t - \tau_{1i}(t)) \\
+ \sum_{j=1}^{N} \pi_{ij} \int_{t-\tau_{1i}(t)}^{t} f^T(p(s))M_1f(p(s)) \, ds + p^T(t)K^TM_2Kp(t) \\
- f^T(p(t - \tau_{1i}))M_2f(p(t - \tau_{1i})) + \sum_{j=1}^{N} \pi_{ij} \int_{t-\tau_{1i}}^{t} f^T(p(s))M_2f(p(s)) \, ds \\
\leq p^T(t)K^TM_1Kp(t) - (1 - \theta_i)Jf(t)p(t - \tau_{1i}(t)))M_1f(p(t - \tau_{1i}(t)) \\
+ p^T(t)K^TM_2Kp(t) - f^T(p(t - \tau_{1i}))M_2f(p(t - \tau_{1i})) \\
+ \bar{\pi} \sum_{j=1}^{N} \int_{t-\tau_{1}}^{t} f^T(p(s))M_2f(p(s)) \, ds, \tag{17} \]

\[ \mathcal{L}V_6(t, m(t), p(t), i) \leq m^T(t)(\sigma_1J_1)m(t) - \frac{1}{\sigma_1} \left[ \int_{t-\sigma_1}^{t} m^T(s) \, ds \right] J_1 \left[ \int_{t-\sigma_1}^{t} m(s) \, ds \right] \\
+ \frac{1}{\sigma_2} \left[ \int_{t-\sigma_2}^{t} p^T(s) \, ds \right] J_2 \left[ \int_{t-\sigma_2}^{t} p(s) \, ds \right], \tag{18} \]

\[ \mathcal{L}V_7(t, m(t), p(t), i) = m^T(t) \left\{ \pi \tau_2 \sum_{k=1}^{m} [d_k - d_{k-1}]Q_k \right\} m(t) \]
\[
-\pi \sum_{k=1}^{m} \int_{t-d_k\tau_2}^{t-d_k-1\tau_2} m^T(s)Q_k m(s) \, ds + p^T(t) \left\{ \pi \tau_1 \sum_{k=1}^{m} [d_k - d_{k-1}] R_k \right\} p(t) - \pi \sum_{k=1}^{m} \int_{t-d_k\tau_1}^{t-d_k-1\tau_1} p^T(s)R_k p(s) \, ds,
\] (19)

\[
\begin{align*}
\mathcal{L}V_8(t, m(t), p(t), i) &= \pi \tau_2 m^T(t)N_1 m(t) - \pi \int_{t-\tau_2}^{t} m^T(s)N_1 m(s) \, ds \\
&+ \pi \tau_1 p^T(t)N_2 p(t) - \pi \int_{t-\tau_1}^{t} p^T(s)N_2 p(s) \, ds,
\end{align*}
\] (20)

\[
\begin{align*}
\mathcal{L}V_9(t, m(t), p(t), i) &\leq p^T(t) \sum_{j=1}^{2} \left[ \pi \tau_1 K^T M_j K \right] p(t) - \pi \sum_{j=1}^{2} \int_{t-\tau_1}^{t} f^T(p(s))M_j f(p(s)) \, ds.
\end{align*}
\] (21)

By using upper and lower bound of time-varying delays and \( \pi_{ii} \leq 0 \), the following relationship holds:

\[
\begin{align*}
\sum_{j=1}^{N} \pi_{ij} \sum_{k=1}^{m} \int_{t-d_k\tau_2(t)}^{t-d_k-1\tau_2(t)} m^T(s)Q_k m(s) \, ds &= \sum_{j \neq i}^{m} \pi_{ij} \sum_{k=1}^{m} \int_{t-d_k\tau_2(t)}^{t-d_k-1\tau_2(t)} m^T(s)Q_k m(s) \, ds \\
&+ \pi_{ii} \sum_{k=1}^{m} \int_{t-d_k\tau_2(t)}^{t-d_k-1\tau_2(t)} m^T(s)Q_k m(s) \, ds \\
&\leq \sum_{k=1}^{m} \int_{t-d_k\tau_2(t)}^{t-d_k-1\tau_2(t)} m^T(s)Q_k m(s) \, ds \\
&+ \pi_{ii} \sum_{k=1}^{m} \int_{t-d_k\tau_2(t)}^{t-d_k-1\tau_2(t)} m^T(s)Q_k m(s) \, ds \\
&\leq \sum_{k=1}^{m} \int_{t-d_k\tau_2(t)}^{t-d_k-1\tau_2(t)} m^T(s)Q_k m(s) \, ds,
\end{align*}
\] (22)

\[
\begin{align*}
\sum_{j=1}^{N} \pi_{ij} \sum_{k=1}^{m} \int_{t-d_k\tau_1(t)}^{t-d_k-1\tau_1(t)} p^T(s)R_k p(s) \, ds &\leq \sum_{k=1}^{m} \int_{t-d_k\tau_1(t)}^{t-d_k-1\tau_1(t)} p^T(s)R_k p(s) \, ds,
\end{align*}
\] (23)

\[
\begin{align*}
\sum_{j=1}^{N} \pi_{ij} \int_{t-\tau_2}^{t} m^T(s)N_1 m(s) \, ds &= \sum_{j \neq i} \pi_{ij} \int_{t-\tau_2}^{t} m^T(s)N_1 m(s) \, ds \\
&+ \pi_{ii} \int_{t-\tau_2}^{t} m^T(s)N_1 m(s) \, ds \\
&\leq \pi \int_{t-\tau_2}^{t} m^T(s)N_1 m(s) \, ds,
\end{align*}
\] (24)

\[
\begin{align*}
\sum_{j=1}^{N} \pi_{ij} \int_{t-\tau_1}^{t} p^T(s)N_2 p(s) \, ds &\leq \pi \int_{t-\tau_1}^{t} p^T(s)N_2 p(s) \, ds,
\end{align*}
\] (25)
\[
\sum_{j=1}^{N} \pi_{ij} \int_{t-\tau_j(t)}^{t} f^T(p(s))M_1 f(p(s)) \, ds \leq \pi \int_{t-\tau_1}^{t} f^T(p(s))M_1 f(p(s)) \, ds,
\]
\[
\sum_{j=1}^{N} \pi_{ij} \int_{t-\tau_j}^{t} f^T(p(s))M_2 f(p(s)) \, ds \leq \pi \int_{t-\tau_1}^{t} f^T(p(s))M_2 f(p(s)) \, ds.
\]
Hence, from Eqs. (12) to (27), one can obtain
\[
\mathbb{E}\{\mathcal{L} V(t, m(t), p(t), i)\} \leq \xi^T(t) \Xi \xi(t),
\]
where
\[
\xi^T(t) = [m^T(t), m^T(t - \sigma_1), m^T(t - d_1 \tau_2(t)), m^T(t - d_2 \tau_2(t)), \ldots, m^T(t - d_{m-1} \tau_2(t)), m^T(t - \tau_2), m^T(t - \tau_2), \ldots, m^T(s), p^T(t), p^T(t - \sigma_2), p^T(t - d_1 \tau_1(t)), p^T(t - d_2 \tau_1(t)), \ldots, p^T(t - d_{m-1} \tau_1(t)), p^T(t - \tau_1(t)), p^T(t - \tau_1(t)), \ldots, f^T(p(t - \tau_1)), f^T(p(t - \tau_1), f^T(p(t - \tau_1)), f^T(p(t - \tau_1)), f^T(p(t - \tau_1))]_1^T \Xi \xi(t).
\]
and \(\Xi\) is defined in Eq. (10).

Now, we show that the system (7) is globally stochastically stable in the mean-square sense. We can conclude from Eqs. (8) to (10) that \(\Xi^T < 0\), which implies that
\[
\mathbb{E}\{\mathcal{L} V(t, m(t), p(t), i)\} \leq \xi^T(t) \Xi \xi(t) < 0.
\]
Thus, from Eq. (29), we have
\[
\mathbb{E}\{\mathcal{L} V(t, m(t), p(t), i)\} \leq -q \\mathbb{E}\{\|m(t)\|^2 + \|p(t)\|^2\},
\]
where \(q = \min_{i \in S} \lambda_{\min} (-\Xi^T) > 0\). Integrating both sides of Eq. (30) from 0 to \(t\), one have by Dynkin’s formula that
\[
\mathbb{E}\{V(t, m(t), p(t), i)\} + q \int_{0}^{t} \mathbb{E}\{\|m(s)\|^2 + \|p(s)\|^2\} \, ds \leq \mathbb{E}\{V(0, m(0), p(0), i)\},
\]
where
\[
\mathbb{E}\{V(0, m(0), p(0), i)\} = \mathbb{E}\left\{ \begin{bmatrix} m(0) - A_i \int_{-\sigma_1}^{0} m(s) \, ds \\ p(0) - C_i \int_{-\sigma_2}^{0} p(s) \, ds \end{bmatrix}^T \begin{bmatrix} P_{1i} & m(0) - A_i \int_{-\sigma_1}^{0} m(s) \, ds \\ P_{2i} & p(0) - C_i \int_{-\sigma_2}^{0} p(s) \, ds \end{bmatrix} + \int_{-\sigma_1}^{0} m^T(s)H_1 m(s) \, ds + \int_{-\sigma_2}^{0} p^T(s)H_2 p(s) \, ds + \sum_{k=1}^{m} \int_{-d_{k-1} \tau_2(0)}^{-d_{k-1} \tau_2(0)} m^T(s)Q_k m(s) \, ds + \sum_{k=1}^{m} \int_{-d_{k-1} \tau_1(0)}^{-d_{k-1} \tau_1(0)} p^T(s)R_k p(s) \, ds + \int_{-\tau_2}^{0} m^T(s)N_1 m(s) \, ds \right\}
\]
+ \int_{-\sigma_1}^{0} \int_{\theta}^{0} p^T(s)J_2 p(s) d\theta d\theta \\
+ \pi \sum_{k=1}^{m} \int_{-\tau_2}^{0} \int_{-d_k \tau_2}^{0} m^T(s)Q_k m(s) d\theta d\theta \\
+ \pi \sum_{k=1}^{m} \int_{\theta}^{0} p^T(s)R_k p(s) d\theta d\theta \\
+ \pi \int_{-\tau_1}^{0} \int_{\theta}^{0} m^T(s)N_1 m(s) d\theta d\theta \\
+ \pi \int_{-\tau_1}^{0} \int_{\theta}^{0} p^T(s)N_2 p(s) d\theta d\theta \\
+ \pi \sum_{j=1}^{2} \int_{-\tau_1}^{0} \int_{\theta}^{0} f^T(p(s))M_j f(p(s)) d\theta d\theta \\
\leq \left\{ 2\lambda_{\text{max}}(P_{1i}) \left( 1 + \sigma_1^2 \max_{l \in A} a_{li} \right) + \sigma_1 \lambda_{\text{max}}(H_1) \right. \\
\left. + (\tau_{2j} + \pi \tau_2^2) \left[ \sum_{k=1}^{m} (d_k - d_{k-1}) \lambda_{\text{max}} Q_k \right] + \lambda_{\text{max}}(N_1) \right\} \mathbb{E}\{\|q_m\|^2\} \\
+ \left\{ 2\lambda_{\text{max}}(P_{2i}) \left( 1 + \sigma_2^2 \max_{l \in A} c_{li} \right) + \sigma_2 \lambda_{\text{max}}(H_2) \right. \\
\left. + (\tau_{1j} + \pi \tau_1^2) \left[ \sum_{k=1}^{m} (d_k - d_{k-1}) \lambda_{\text{max}} R_k \right] + \lambda_{\text{max}}(N_2) \right\} \\
+ \sigma_2^2 \lambda_{\text{max}}(J_2) + (\tau_{1j} + \pi \tau_1^2) \sum_{j=1}^{N} \left[ \lambda_{\text{max}}(M_j) \right] \mathbb{E}\{\|q_p\|^2\} < \infty.

This implies that the trivial solution of Eq. (7) is locally stable.

Considering the continuity of the function \( f(\cdot) \), the solutions \( m(t) \) and \( p(t) \) of system (7) are bounded on \([0, \infty)\). The uniform boundedness of solutions of Eq. (7) implies that the derivatives of the solutions of Eq. (7) are bounded on \([0, \infty)\), which lead to the uniform continuity of solutions \( m(t) \) and \( p(t) \) on \([0, \infty)\). By Barbalat’s lemma, we have

\[
\lim_{t \to \infty} \mathbb{E}\{\|m(t)\|^2 + \|p(t)\|^2\} = 0.
\]

Thus, the system of stochastic Markovian GRNs with leakage and mode-dependent time-varying delays (7) is globally stochastically stable in the mean square by Definition 1. This completes the proof of Theorem 1. □
Corollary 1. For given positive scalars $\tau_{1i}$, $\tau_{2i}$, $\vartheta_i$, $\nu_i$, positive integer $m$, scalars $d_k$, and positive diagonal matrix $K$, the system (6) is globally stochastically stable in the mean square, if there exist positive diagonal matrices $P_{1i}$, $P_{2i}$, and some positive definite symmetric matrices $Q_k$, $R_k$, $N_1$, $N_2$, $M_1$, $M_2$, with appropriate dimensions, such that the following LMIs hold for all $i \in S$, $k = 1, 2, \ldots, m$ and $l = 2, 3, \ldots, m$:

$$Q_l - Q_{l-1} < 0,$$

$$R_l - R_{l-1} < 0,$$

$$\chi_i^{1} = \begin{bmatrix}
    \Psi_i^{j} & 0 & 0 & \ldots & 0 & 0 & 0 \\
    * & \Psi_i^{j} & 0 & \ldots & 0 & 0 & 0 \\
    * & * & \Psi_i^{j} & \ldots & 0 & 0 & 0 \\
    \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\
    * & * & * & \ldots & (d_{m-1}\nu_i - 1)[Q_{m-1} - Q_m] & 0 & 0 \\
    * & * & * & \ldots & * & -(1 - \nu_i)Q_m & 0 \\
    * & * & * & \ldots & * & * & -N_1
\end{bmatrix} < 0 \quad (i \in S),$$

where

$$\chi_i^{11} = \begin{bmatrix}
    \Psi_i^{j} & 0 & 0 & \ldots & 0 & 0 & 0 \\
    * & \Psi_i^{j} & 0 & \ldots & 0 & 0 & 0 \\
    * & * & \Psi_i^{j} & \ldots & 0 & 0 & 0 \\
    \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\
    * & * & * & \ldots & (d_{m-1}\nu_i - 1)[Q_{m-1} - Q_m] & 0 & 0 \\
    * & * & * & \ldots & * & -(1 - \nu_i)Q_m & 0 \\
    * & * & * & \ldots & * & * & -N_1
\end{bmatrix},$$

$$\chi_i^{12} = \begin{bmatrix}
    \Phi_i^{j} & 0 & 0 & \ldots & 0 & 0 & 0 & P_{1i}B_i \\
    0 & 0 & 0 & \ldots & 0 & 0 & 0 & 0 \\
    0 & 0 & 0 & \ldots & 0 & 0 & 0 & 0 \\
    \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots \\
    0 & 0 & 0 & \ldots & 0 & 0 & 0 & 0 \\
    0 & 0 & 0 & \ldots & 0 & 0 & 0 & 0 \\
    0 & 0 & 0 & \ldots & 0 & 0 & 0 & 0 \\
\end{bmatrix},$$

$$\chi_i^{13} = \begin{bmatrix}
    \Phi_i^{j} & 0 & 0 & \ldots & 0 & 0 & 0 & 0 \\
    * & \Phi_i^{j} & 0 & \ldots & 0 & 0 & 0 & 0 \\
    * & * & \Phi_i^{j} & \ldots & 0 & 0 & 0 & 0 \\
    \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots \\
    * & * & * & \ldots & \Phi_i^{j} & 0 & 0 & 0 \\
    * & * & * & \ldots & * & -(1 - \vartheta_i)R_m & 0 & 0 \\
    * & * & * & \ldots & * & * & -N_2 & 0 \\
    * & * & * & \ldots & * & * & * & -(1 - \vartheta_i)M_1 \\
    * & * & * & \ldots & * & * & * & -M_2
\end{bmatrix}.$$
\[
\Phi_i = -2P_2^T C_i + F_i^T P_2 F_i + \sum_{j=1}^{N} \pi_{ij} P_{2j} + R_1 + N_2 + \pi_1 \sum_{k=1}^{m} ((d_k - d_{k-1})R_k) \\
+ \sum_{j=1}^{2} K^T M_j K + \pi_1 \sum_{j=1}^{2} K^T M_j K + \pi_1 N_2, \quad \pi = \max(|\pi_{ii}|),
\]

\[
\Phi_2 = (d_1 \vartheta_1 - 1)[R_1 - R_2], \quad \Phi_3 = (d_2 \vartheta_1 - 1)[R_2 - R_3],
\]

\[
\Phi_m = (d_m \vartheta_1 - 1)[R_{m-1} - R_m].
\]

**Proof.** We have considered the following LKFs:

\[
V(t, m(t), p(t), i) = V_1(t, m(t), p(t), i) + \sum_{n=3}^{5} V_n(t, m(t), p(t), i) \\
+ \sum_{n=7}^{9} V_n(t, m(t), p(t), i),
\]

where

\[
V_1(t, m(t), p(t), i) = m^T(t)P_1 m(t) + p^T(t)P_2 p(t),
\]

\[
\sum_{n=3}^{5} V_n(t, m(t), p(t), i), \quad \sum_{n=7}^{9} V_n(t, m(t), p(t), i)
\]

are defined in Eq. (11), then the proof is followed from Theorem 1 directly and is omitted here. \(\Box\)

**Remark 2.** In this paper, we have considered the mode-dependent time-varying delays \(\tau_{1i}(t), \tau_{2i}(t), i \in S\), and leakage delays \(\sigma_1, \sigma_2\) in the negative-feedback terms of GRNs which lead to instability of system with small amount of leakage delay. However, few results are concerned with the dynamic behavior of GRNs with leakage delay \([17, 18]\). To the best of the authors' knowledge, no results have been established on stability criteria for Markovian switching GRNs with leakage delays and mode-dependent time-varying delays along with extrinsic noises.

### 3.2. Stability analysis of GRNs without noise perturbations

Let us consider the GRNs without noise perturbations described by the following model:

\[
\begin{align*}
\dot{m}(t) &= -Am(t) + Bf(p(t - \sigma(t))), \\
\dot{p}(t) &= -Cp(t) + Dm(t - \tau(t)),
\end{align*}
\]

where the time-varying delays \(\sigma(t)\) and \(\tau(t)\) are assumed to satisfy \(0 \leq \sigma(t) \leq \sigma_M, 0 \leq \tau(t) \leq \tau_M, \dot{\sigma}(t) \leq \sigma_d < 1, \dot{\tau}(t) \leq \tau_d < 1\).

**Corollary 2.** For given positive scalars \(\sigma_M, \tau_M, \sigma_d, \tau_d\), positive integer \(m\), scalars \(d_k\), and positive diagonal matrix \(K\), the system (36) is globally asymptotically stable, if there exist positive diagonal matrices \(P_1, P_2, V\), and some positive definite symmetric matrices \(Q_k, R_k, N, M\), with appropriate dimensions, such that the following LMIs hold for all \(k = 1, 2, \ldots, m\) and...
\(l = 2, 3, \ldots, m:\)

\[Q_l - Q_{l-1} < 0,\]  
\[R_l - R_{l-1} < 0,\]  
\[Y = \left[ Y_{uv} \right] < 0 \quad (u, v = 1, 2, \ldots, 2m + 5),\]  

where

\[Y_{1,1} = -2P_1A + Q_1 + \tau_M N, \quad Y_{1,2m+5} = P_1 B,\]  
\[Y_{2,2} = (d_1 \tau_d - 1)[Q_1 - Q_2],\]  
\[Y_{3,3} = (d_2 \tau_d - 1)[Q_2 - Q_3],\]  
\[Y_{m,m} = (d_{m-1} \tau_d - 1)[Q_{m-1} - Q_m],\]  
\[Y_{m+1,m+1} = -(1 - \tau_d)Q_m, \quad Y_{m+1,m+3} = D^T P_2^T,\]  
\[Y_{m+2,m+2} = -\tau_M N, \quad Y_{m+3,m+3} = -2P_2 C + R_1 + \sigma_M M, \quad Y_{m+4,m+4} = (d_1 \sigma_d - 1)[R_1 - R_2],\]  
\[Y_{m+5,m+5} = (d_2 \sigma_d - 1)[R_2 - R_3], \quad Y_{2m+2,2m+2} = (d_{m-1} \sigma_d - 1)[R_{m-1} - R_m],\]  
\[Y_{2m+3,2m+3} = -(1 - \sigma_d)R_m, \quad Y_{2m+3,2m+5} = K^T V^T,\]  
\[Y_{2m+4,2m+4} = -\sigma_M M, \quad Y_{2m+5,2m+5} = -2V.\]

**Proof.** We have consider the following LKFs:

\[V(t, m(t), p(t)) = \sum_{n=1}^{3} V_n(t, m(t), p(t)),\]  

![GRNs comprising three genes.](image)
where
\[ V_1(t, m(t), p(t)) = m^T(t)P_1m(t) + p^T(t)P_2p(t), \]
\[ V_2(t, m(t), p(t)) = \sum_{k=1}^{m} \int_{t-d_{k}}^{t} m^T(s)Q_km(s) \, ds + \sum_{k=1}^{m} \int_{t-d_{k}}^{t} p^T(s)R_kp(s) \, ds, \]
\[ V_3(t, m(t), p(t)) = \tau M \int_{t-\tau M}^{t} m^T(s)Nm(s) \, ds + \sigma_M \int_{t-\sigma M}^{t} p^T(s)Mp(s) \, ds. \]

The proof is similar as Theorem 1 and is omitted here. □

4. Numerical example

In this section, a mathematical model of the repressilator in Escherichia coli [34,35] is generalized by introducing leakage delays, mode-dependent time-varying delays, MJPs and Brownian motions for the three genes (Lacl, TetR, and Cl) as shown in Fig. 2.

Example 1. Here, we experimentally investigate a synthetic oscillatory networks of transcriptional regulators as a mathematical model of the repressilator in Escherichia coli, consisting of three repressor genes (Lacl, TetR, and Cl) and time delays. The kinetics of the system are determined by six coupled first-order differential equations:

\[
\begin{align*}
\dot{m}_i(t) &= -\kappa_i m_i(t-\sigma_1) + \frac{\alpha_i}{1 + p_j^M(t-\tau_1(t))} + \alpha_0, \\
\dot{p}_i(t) &= -\beta_i p_i(t-\sigma_2) + \lambda_i m_i(t-\tau_2(t)),
\end{align*}
\]

(41)

Fig. 3. Original state trajectories of GRNs of each mode for Example 1 (Case 1).
where $\kappa_i$ and $\beta_i$ are positive real numbers that represent the degradation rates of mRNA and protein, respectively; $\lambda_i$ denotes the $i$th translation rate from mRNA to protein, $\sigma_1$ and $\sigma_2$ are leakage delays, $\tau_1(t)$ and $\tau_2(t)$ are time-varying delays, and $H$ represents the Hill coefficient.

Based on the SUM logic proposed in [10,36], if transcription factor $j$ is an repressor of gene $i$, then

$$\frac{\alpha_i}{1 + p_j^H(t - \tau_1(t))} = -\alpha_i \left(1 - \frac{p_j^H(t - \tau_1(t))}{1 + p_j^H(t - \tau_1(t))}\right).$$

Hence, system (41) can be rewritten as

$$\begin{cases}
\dot{m}_i(t) = -\kappa_i m_i(t - \sigma_1) + \frac{\alpha_i p_j^H(t - \tau_1(t))}{1 + p_j^H(t - \tau_1(t))} - \alpha_i + \alpha_0, \\
\dot{p}_i(t) = -\beta_i p_i(t - \sigma_2) + \lambda_i m_i(t - \tau_2(t)).
\end{cases} \tag{42}$$

Taking into account the leakage delays, mode-dependent time-varying delays, MJPs and stochastic disturbances, the system (42) can be modified with the system (7).

Fig. 4. State trajectories of system (7) with $\sigma_1 = \sigma_2 = 0.1$. 
Case 1: The parameters are selected as follows:

\[
\begin{align*}
\text{Mode}(\eta_t = 1) & : \kappa_i = 1, \alpha_i = 0.01, \beta_i = 3.5, \lambda_1 = \lambda_2 = 0.8, \lambda_3 = 0.1, \alpha_0 = 0. \\
\text{Mode}(\eta_t = 2) & : \kappa_i = 3, \alpha_i = 0.02, \beta_i = 3.2, \lambda_i = 1, \alpha_0 = 0, i = 1, 2, 3.
\end{align*}
\]

Then, the matrices for system (7) can be obtained as

\[
A_1 = I, \quad B_1 = \begin{bmatrix}
0 & 0 & -0.01 \\
-0.01 & 0 & 0 \\
0 & -0.01 & 0
\end{bmatrix},
\]

\[
C_1 = 3.5I, \quad D_1 = \begin{bmatrix}
0.8 & 0 & 0 \\
0 & 0.8 & 0 \\
0 & 0 & 0.1
\end{bmatrix},
\]

\[
A_2 = 3I, \quad B_2 = \begin{bmatrix}
0 & 0 & -0.02 \\
-0.02 & 0 & 0 \\
0 & -0.02 & 0
\end{bmatrix},
\]

\[
C_2 = 3.2I, \quad D_2 = I,
\]
and the rest of the parameters in Eq. (7) are assumed to be
\[
E_1 = \begin{bmatrix}
0.05 & 0 & 0 \\
0 & 0.04 & 0 \\
0 & 0 & 0.07
\end{bmatrix}, \quad E_2 = \begin{bmatrix}
0.04 & 0 & 0 \\
0 & 0.05 & 0 \\
0 & 0 & 0.2
\end{bmatrix},
\]
\[
F_1 = \begin{bmatrix}
0.03 & 0 & 0 \\
0 & 0.04 & 0 \\
0 & 0 & 0.04
\end{bmatrix}, \quad F_2 = \begin{bmatrix}
0.01 & 0 & 0 \\
0 & 0.09 & 0 \\
0 & 0 & 0.4
\end{bmatrix}.
\]

The transition probability matrix is considered as \( \Pi = \begin{bmatrix}
-3 & 3 \\
10 & -10
\end{bmatrix} \), \( \sigma_1 = \sigma_2 = 0.1 \), \( \tau_{11} = \tau_{12} = 30 \), \( \tau_{21} = \tau_{22} = 4 \), \( \theta_1 = 0.5 \), \( \theta_2 = 0.3 \), \( \nu_1 = \nu_2 = 0.5 \), \( m = 4 \), \( d_1 = 0.1 \), \( d_2 = 0.2 \), \( d_3 = 0.3 \), and the nonlinear regulatory functions can be taken as
\[
f(x) = \frac{x^2}{1 + x^2},
\]
and it can be verified that \( K = 0.65I \). By using Matlab LMI toolbox, the simulation results for Case 1 are shown in Figs. 3–6. The time-varying delays can be taken as \( \tau_{11}(t) = \tau_{12}(t) = 29.7 + 0.3 \sin(t) \), \( \tau_{21}(t) = \tau_{22}(t) = 3.5 + 0.5 \sin(t) \). Fig. 3 shows the original state trajectories of GRNs of each mode for the system (7). Therefore, it follows from Theorem 1 that GRNs (7) with

![Fig. 6. State trajectories of system (7) with \( \sigma_1 = 0.4, \sigma_2 = 0.2 \).](image-url)
given parameters for the genes (Lacl, TetR, and Cl) are globally stochastically stable in the mean square sense.

Case 2: Consider the GRNs (6) with the same parameters $A_1, B_1, C_1, D_1, E_1, F_1, A_2, B_2, C_2, D_2, E_2, F_2$ as provided in Case 1. The transition probability matrix is considered as $\Pi = \begin{bmatrix} -3 & 3 \\ 10 & -10 \end{bmatrix}$, $\sigma_1 = \sigma_2 = 0$, $\tau_{11} = \tau_{12} = 30$, $\tau_{21} = \tau_{22} = 4$, $\theta_1 = 0.5$, $\theta_2 = 0.3$, $\nu_1 = \nu_2 = 0.5$, $m = 4$, $d_1 = 0.1$, $d_2 = 0.2$, $d_3 = 0.3$, and the nonlinear regulatory functions can be taken as

$$f(x) = \frac{x^2}{1 + x^2},$$

and it can be verified that $K = 0.65I$. The time-varying delays can be taken as $\tau_{11}(t) = \tau_{12}(t) = 29.7 + 0.3 \sin(t)$, $\tau_{21}(t) = \tau_{22}(t) = 3.5 + 0.5 \sin(t)$. By using the Matlab LMI toolbox, we solve the LMIs (32)–(34) to obtain a feasible solution as follows:

$$P_{11} = \text{diag}(165.6856, 170.5183, 152.6058), \quad P_{12} = \text{diag}(132.3962, 136.2413, 155.9968),$$

$$P_{21} = \text{diag}(12.1205, 12.5701, 9.1915), \quad P_{22} = \text{diag}(13.9898, 14.5088, 13.2212),$$

$$Q_1 = \text{diag}(15.3054, 15.6312, 10.6808), \quad Q_2 = \text{diag}(11.6025, 11.9098, 7.9437),$$

$$Q_3 = \text{diag}(9.1779, 9.4734, 6.2148), \quad Q_4 = \text{diag}(7.3499, 7.6377, 4.9319),$$

$$R_1 = \text{diag}(0.3293, 0.3299, 0.3166), \quad R_2 = \text{diag}(0.1715, 0.1718, 0.1648),$$

$$R_3 = \text{diag}(0.0840, 0.0841, 0.0806), \quad R_4 = \text{diag}(0.0153, 0.0154, 0.0147),$$

Fig. 7. State trajectories of system (6) without leakage delay.
Therefore, it follows from Corollary 1 that GRNs (6) with given parameters for the genes (Lacl, TetR, and Cl) are globally stochastically stable in the mean square sense.

Remark 3. By simulations, one may find that GRNs (7) with \( s_1 = s_2 = 0.1 \) converge to zero (see Fig. 4). However, by increasing the values of leakage delays \( s_1 = 0.4 \), \( s_2 = 0.2 \), respectively, it is easy to check that the LMIs (8)–(10) do not have any feasible solutions via the MATLAB LMI toolbox, which imply that the proposed results cannot assure the stability of GRNs (7). In this case, from simulations, it is interesting to find that GRNs (7) are unstable (see Figs. 5 and 6). This exhibits the effects of considering time delays in the leakage term which has the tendency to destabilize system or poor system performance. Hence, it is essential to consider leakage delays in GRNs.

Remark 4. Fig. 7 illustrates the simulation results of the true concentrations of mRNA and protein without leakage delays by solving the LMIs (32)–(34) in Corollary 1 using Matlab LMI toolbox.

Remark 5. The number of variables involved in LMIs (8)–(10) for Theorem 1 and Eqs. (32)–(34) for Corollary 1 are \( (m + 4)[n(n + 1)] + 2i(n) \) and \( (m + 2)[n(n + 1)] + 2i(n) \), respectively. Also, the advantage of delay-fractioning approach is to obtain more tighter upper bound of delays for guaranteeing the stochastically stable of the concerned network is shown from Tables 1–4.

Example 2. We consider delayed GRNs (36) with the parameters given as follows [37]:

\[
A = \text{diag}(3, 3, 3), \quad B = \begin{bmatrix} 0 & 0 & -2.5 \\ -2.5 & 0 & 0 \\ 0 & -2.5 & 0 \end{bmatrix}, \quad C = \text{diag}(2.5, 2.5, 2.5),
\]

<table>
<thead>
<tr>
<th>Cases</th>
<th>( d_1 = 0.3 )</th>
<th>( d_1 = 0.5 )</th>
<th>( d_1 = 0.7 )</th>
<th>( d_1 = 0.9 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \sigma_1 = \sigma_2 = 0.10 )</td>
<td>12.7312</td>
<td>12.6543</td>
<td>12.5314</td>
<td>12.4173</td>
</tr>
<tr>
<td>( \sigma_1 = \sigma_2 = 0.12 )</td>
<td>6.2199</td>
<td>6.1130</td>
<td>6.0157</td>
<td>5.9973</td>
</tr>
<tr>
<td>( \sigma_1 = \sigma_2 \geq 0.14 )</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th>( d_3 = 0.3 )</th>
<th>( d_3 = 0.5 )</th>
<th>( d_3 = 0.7 )</th>
<th>( d_3 = 0.9 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \sigma_1 = \sigma_2 = 0.10 )</td>
<td>13.5561</td>
<td>13.4378</td>
<td>13.3323</td>
<td>13.2189</td>
</tr>
<tr>
<td>( \sigma_1 = \sigma_2 = 0.12 )</td>
<td>7.1763</td>
<td>7.0314</td>
<td>6.9876</td>
<td>6.8873</td>
</tr>
<tr>
<td>( \sigma_1 = \sigma_2 \geq 0.14 )</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
Table 3
The allowable upper bound $\tau_2$ for Example 1 (Case 2) with different values of $d_1$.

<table>
<thead>
<tr>
<th>Cases</th>
<th>$d_1=0.3$</th>
<th>$d_1=0.5$</th>
<th>$d_1=0.7$</th>
<th>$d_1=0.9$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$m=2$</td>
<td>38.4997</td>
<td>38.3421</td>
<td>38.2763</td>
<td>38.1551</td>
</tr>
</tbody>
</table>

Table 4
The allowable upper bound $\tau_2$ for Example 1 (Case 2) with different values of $d_3$ ($d_1=0.1$, $d_2=0.2$).

<table>
<thead>
<tr>
<th>Cases</th>
<th>$d_3=0.3$</th>
<th>$d_3=0.5$</th>
<th>$d_3=0.7$</th>
<th>$d_3=0.9$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$m=4$</td>
<td>38.5047</td>
<td>38.4123</td>
<td>38.3789</td>
<td>38.2501</td>
</tr>
</tbody>
</table>

Table 5
The allowable upper bound for $\sigma_M$ with different values of $\tau_M$.

<table>
<thead>
<tr>
<th>$\tau_M$</th>
<th>$\tau_M=0.125$</th>
<th>$\tau_M=0.25$</th>
<th>$\tau_M=0.55$</th>
<th>$\tau_M=0.1$</th>
<th>$\tau_M=1.1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[37] ($r=N=2$)</td>
<td>2.8273</td>
<td>2.1661</td>
<td>1.5444</td>
<td>0.4904</td>
<td>0.3845</td>
</tr>
<tr>
<td>[38] ($N=M=2$)</td>
<td>5.2268</td>
<td>4.8848</td>
<td>3.7840</td>
<td>2.5066</td>
<td>2.3018</td>
</tr>
<tr>
<td>Corollary 2 ($m=2$)</td>
<td>17.8103</td>
<td>17.5124</td>
<td>17.1761</td>
<td>16.8792</td>
<td>16.2375</td>
</tr>
</tbody>
</table>

$$ D = \text{diag}(0.8, 0.8, 0.8), \quad f(x) = \frac{x^2}{1+x^2}, \quad K = \text{diag}(0.65, 0.65, 0.65). $$

The allowable upper bounds of $\sigma_M$ obtained from Corollary 2 are listed in Table 5 for different $\tau_M$. Clearly, the results obtained in this paper are less conservative than the existing ones.

Furthermore, for the parameters listed above, let $\tau_M=0.25$, $\sigma_M=17.5124$, $\sigma_d=\tau_d=0.7$, $m=2$, $d_1=0.1$, we can obtain the following feasible solutions by Corollary 2. Due to the limitation of the length of this paper, we only provide a part of the feasible solutions here

$$ P_1 = \text{diag}(41.4453, 41.4453, 41.4453), \quad P_2 = \text{diag}(74.4455, 74.4455, 74.4455). $$

Therefore, it follows from Corollary 2 that GRNs (36) with given parameters are globally asymptotically stable.

Remark 6. The number of variables involved in LMIs (37)–(39) for Corollary 2 is $(m+1)[n(n+1)]+3n$, while Corollary 1 in [37] needs to check the solvability of its LMI with respect to $(4+2r+3N)[\frac{m(n+1)}{2}+(N+2)n]$ variables. It can be easily seen that our method involves fewer variables when $m \geq 2$ than in [37] and also obtained less conservative results in Table 5.

5. Conclusion

In this paper, the stability criteria have been investigated for the stochastic GRNs with leakage and mode-dependent time-varying delays along MJPs. By choosing suitable LKFs, LMI technique and
delay-fractioning approach, sufficient conditions have been derived to propose the stability of Markovian switching GRNs with leakage and mode-dependent time-varying delays in the mean-square sense. Table 5 shows that, for \( m > 1 \), our criteria in Corollary 2 are much less conservative than existing methods available in the literature. Furthermore, it is verified from Tables 1–4 that the calculated upper bounds increase as the numbers of fractioning \( m \) increase. Finally, numerical examples and its simulations of Escherichia coli network model have been demonstrated to illustrate the practical importance and the effectiveness of the proposed method.

Recently, by utilizing Wirtinger-based integral inequality, the maximum delay bounds can be more enhanced than those of criteria with delay-decomposition approach. In future, the above results may be extended further with Wirtinger-based integral inequality to obtain less conservative results. Also, we will consider estimation problem for the above results in near future by referring this issue [39] and [40].

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**References**


