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Robust Stability Analysis for Uncertain Genetic Regulatory Networks with Time-varying Delays

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Abstract: This study focuses on robust stability analysis for uncertain genetic regulatory networks (GRNs) with time-varying delays. Firstly, robust stability criteria for uncertain GRNs with time-varying delays are presented by combining Lyapunov functional approach, reciprocally convex approach and linear matrix inequality technique. Since triple-integral terms and cross products of double-integral terms are introduced into our Lyapunov-Krasovskii functional and a new method is used to estimate its derivatives, the obtained delay-range-dependent robust asymptotical stability criteria for uncertain GRNs with time-varying delays may be less conservative. Secondly, stability criteria for GRNs with the time-varying delays are investigated. Finally, numerical examples are provided to show the applicability of the proposed approach.

Key words: Genetic Regulatory Networks (GRNs), time-varying delay, robust asymptotic stability

INTRODUCTION

Recently, Genetic Regulatory Networks (GRNs) have attracted considerable attention because they have been extensively used to explain the mechanisms that genes encode proteins and some of proteins in turn regulate gene expression. Mathematical modeling of GRNs, such as boolean models, differential equation models, stochastic master equation models, etc., as dynamical system models provides a powerful tool for studying gene regulation processes in living organisms. Especially, the Functional Differential Equation Models (FDEMs) have been widely used in describing gene regulation process. The variables describe the concentrations of mRNAs and proteins as continuous values in FDEMs, which can provide detailed understanding of the nonlinear dynamical behavior exhibited by GRNs (Chen and Aihara, 2002; Wang *et al.*, 2013).

In real GRNs, time delay can not be avoided, due to the slow processes of transcription, translation and translocation, or the finite switching speed of amplifiers. On the other hand, since modeling GRNs is an approximate process, it is necessary to introduce uncertainties into FDEMs of GRNs. It has been well recognized that time delays and uncertainties are the main sources leading to instability and poor performance of a system.

It is worth pointing out that, Lyapunov functional method h as been widely used to analyze stability of GRNs described by FDEMs in literature. Wang *et al.* (2012) investigated a delay-range-dependent and delay-derivative-dependent srobust stability criterion for GRNs with time-varying delays and linear fractional uncertainties by constructing an augmented Lyapunov–Krasovskii functional with some triple integral terms and employing reciprocally convex combination technique, integral inequality technique and free-weighted matrix technique. Wang and Zhong (2012a), Koo *et al.* (2011) and Liu and Yue (2012) studied stability criteria for GRNs by employing the special cases of the Lyapunov-Krasovskii functional in Wang *et al.* (2012). By choosing an appropriate.

Lyapunov functional and employing stochastic analysis methods, Wang and Zhong (2012b) presented a robust analysis approach to establish stochastic asymptotic stability criteria for uncertain GRNs with both mixed time-varying delays and stochastic noise. Koo *et al.* (2011) proposed a delay-range-dependent robust stability criterion for GRNs with interval time-vary delays by employing a Lyapunov-Krasovskii functional method and convex combination technique. Liu and Yue (2012) chosen a Lyapunov-Krasovskii functional, that is similar to one in Koo *et al.* (2011), to analysis stability of a class of delayed GRNs described by the Takagi-Sugeno fuzzy model.

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Wang and Zhong (2012a) proposed robust stability criteria for GRNs with time-varying delays and nonlinear disturbance by introducing a Lyapunov-Krasovskii functional containing regulatory functions and further generalized the result to the case of stochastic GRNs (Wang and Zhong, 2012b).

Motivated by the current works, this study focuses on analyzing robust stability of GRN (9). By constructing a novel Lyapunov-Krasovskii functional with the triple-integral terms and cross products of double-integral terms, a delay-range-dependent robust asymptotic stability criterion for GRN (9) is derived. The obtained stability criteria may be less conservative, since (1) the use of cross product terms can bring a higher degree of freedoms and (2) the derivative of the Lyapunov-Krasovskii functional is scaled by employing reciprocally convex combination technique. Furthermore, a pair of examples are provided to illustrate the effectiveness and less conservativeness of our approach.

PROBLEM FORMULATION AND PRELIMINARIES

Recently, the following functional differential equations have been used to describe GRNs:

$$\dot{m}_i(t) = -a_i m_i(t) + b_i(p_1(t-\sigma(t)), p_2(t-\sigma(t)), \ldots, p_n(t-\sigma(t))) \quad (1a)$$

$$\dot{p}_i(t) = -c_i p_i(t) + d_i m_i(t-\tau(t)), i = 1, 2, \cdots, n, \quad (1b)$$

where, m_i (t) and p_i (t) are the concentrations of the ith mRNA and protein at time t, respectively $a_i>0$, $c_i>0$ and $d_i>0$ are constants, representing the degradation rate of the ith mRNA, the degradation rate of the ith protein and the translation rate from the ith mRNA to ith protein, respectively; both σ(t) and τ(t) are transcriptional and translational delays such that:

$$0 \le \tau_1 \le \tau(t) \le \tau_2, 0 \le \sigma_1 \le \sigma(t) \le \sigma_2 \quad (2a)$$

$$\dot{\tau}(t) \le \tau_d < \infty, \dot{\sigma}(t) \le \sigma_d < \infty \quad (2b)$$

with constants τ_1, τ_2, σ_1, σ_2, τ_d and σ_d:

$$b_i(p_1(t), p_2(t), \ldots, p_n(t)) = \sum_{j=1}^{n} b_{ij}(p_j(t))$$

$$b_{ij}(x) = \begin{cases} \alpha_{ij}\dfrac{(x/\beta_j)^{H_j}}{1+(x/\beta_j)^{H_j}} & \text{if transcription factor j is an activator of gene i,} \\ \alpha_{ij}\dfrac{1}{1+(x/\beta_j)^{H_j}} & \text{if transcription factor j is a represssor of gene i,} \end{cases} \quad (3)$$

here H_j is the Hill coefficient, β_j is a scalar and α_{ij} is a bounded constant which denotes the dimensionless transcriptional rate of transcription factor j to gene i.

Clearly, GRN (1) can be rewritten as

$$\dot{m}_i(t) = -a_i m_i(t) + \sum_{j=1}^{n} w_{ij} h_j(p_j(t-\sigma(t))) + l_i \quad (4a)$$

$$\dot{p}_i(t) = -c_i p_i(t) + d_i m_i(t-\tau(t)), i = 1, 2, \cdots, n \quad (4b)$$

Where:

$$h_j(x) = \frac{(x/\beta_j)^{H_j}}{1+(x/\beta_j)^{H_j}}$$

$$l_i = \sum_{j \in V_i} \alpha_{ij}$$

with V_i being the set of all the transcription factor j which is a repressor of gene i and:

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

Rewriting GRN (4) into compact matrix form, we obtain:

$$\dot{m}(t) = -Am(t) + Wh(p(t-\sigma(t))) + l \quad (5a)$$

$$\dot{p}(t) = -Cp(t) + Dm(t-\tau(t)) \quad (5b)$$

where, $A = \text{diag}(a_1, a_2, \cdots, a_n)$, $W = [w_{ij}]_{n\times n}$

$$C = \text{diag}(c_1, c_2, \ldots, c_n), D = \text{diag}(d_1, d_2, \ldots, d_n)$$

$$m(t) = \text{col}(m_1(t), m_2(t), \ldots, m_n(t)), l = \text{col}(l_1, l_2, \ldots, l_n)$$

$$p(t) = \text{col}(p_1(t), p_2(t), \ldots, p_n(t))$$

$$h(p(t)) = \text{col}(h_1(p_1(t)), h_2(p_2(t)), \ldots, h_n(p_n(t)))$$

Let (m*, p*) be an equilibrium point (steady state) of (5), that is, it is a solution of the following equations:

$$-Am^* + Wh(p^*) + l = 0, -Cp^* + Dm^* = 0 \quad (6)$$

For convenience, we always shift the equilibrium point (m*, p*) to the origin by using the transformatio x (t) = m (t)-m* and y (t) = p (t)-p*, then we have:

$$\dot{x}(t) = -Ax(t) + Wf(y(t-\sigma(t))) \tag{7a}$$

$$\dot{y}(t) = -Cy(t) + Dx(t-\tau(t)) \tag{7b}$$

where, $f(y(t)) = h(y(t)+p^*) - h(p^*)$.

From the relationship between h and f, one can easily find that:

$$f_j(0) = 0, l_j^- \le \frac{f_j(s)}{s} \le l_j^+, j = 1,2,\cdots,n, \forall s \in R \tag{8}$$

where, l_j^- and l_j^+ are a pair of nonnegative scalars and f_i (s) is the jth entry of f (s). Let $L^- = \mathrm{diag}(l_1^-, l_2^-, \cdots, l_n^-)$ and $L^+ = \mathrm{diag}(l_1^+, l_2^+, \cdots, l_n^+)$.

Next we consider the following GRN with time-varying delays and linear fractional uncertainties:

$$\dot{x}(t) = -A(t)x(t) + W(t)f(y(t-\sigma(t))) \tag{9a}$$

$$\dot{y}(t) = -C(t)y(t) + D(t)x(t-\tau(t)) \tag{9b}$$

$$x(\theta) = \varphi(\theta), y(\theta) = \phi(\theta), \forall\theta \in [-\omega, 0] \tag{9c}$$

where, $\omega = \max\{\tau_2, \sigma_2\}$, $\varphi(\theta)$ and $\phi(\theta)$ are initial functions:

$$\begin{aligned} A(t) &= A + \Delta A(t) = A + E_1\Delta(t)H_a, \\ W(t) &= W + \Delta W(t) = W + E_1\Delta(t)H_w, \\ C(t) &= C + \Delta C(t) = C + E_2\Delta(t)H_c, \\ D(t) &= D + \Delta D(t) = D + E_2\Delta(t)H_d, \end{aligned}$$

matrices E_1, E_2, H_a, H_w, H_c and H_d are known real constant matrices of appropriate sizes, the parametric matrix $\Delta(t)$ represents linear fractional uncertainties of the following form:

$$\Delta(t) = [I - F(t)J]^{-1}F(t)$$

where, J is a known real constant matrix of appropriate size satisfying $I-JJ^T>0$ and F (t) is an uncertain matrix satisfyin $F(t)F^T(t) \le I$ g.

The aim of this study is to investigate robust asymptotic stability criteria of GRN (9).

STABILITY CRITERIA

In this section, we will establish a delay-range-dependent and delay-rate-dependent robust asymptotic stability criterion for GRN (9).

Theorem 1: For given constants τ_1, τ_2, σ_1, σ_2, τ_d and σ_d with $0<\tau_1<\tau_2$ and $0<\sigma_1<\sigma_2$, uncertain GRN (9) subject to (2) and (8) is robustly asymptotically stable if there exist matrice $P^T = P>0$, $Q_i^T = Q_i > 0$, $R_i^T = R_i > 0$ $(i = 1,2,\cdots,7)$, $\Lambda_j := \mathrm{diag}(\lambda_{1j}, \lambda_{2j}, \cdots, \lambda_{nj}) > 0, T_j := \mathrm{diag}(t_{1j}, t_{2j}, \cdots, t_{nj}) > 0$ $(j = 1,2)$, $\tilde{Q}_5$, $\tilde{R}_5$, of appropriate sizes and scalars $\rho_k>0$ (k = 1, 2) such that the following LMIs:

$$\begin{bmatrix} Q_5 & \tilde{Q}_5 \\ \tilde{Q}_5^T & Q_5 \end{bmatrix} \ge 0, \begin{bmatrix} R_5 & \tilde{R}_5 \\ \tilde{R}_5^T & R_5 \end{bmatrix} \ge 0 \tag{10}$$

$$\Upsilon := \begin{bmatrix} \Psi & \gamma_1^T & \rho_1\gamma_2^T & \gamma_3^T & \rho_2\gamma_4^T \\ \gamma_1 & -\rho_1 I & \rho_1 J^T & 0 & 0 \\ \rho_1\gamma_2 & \rho_1 J & -\rho_1 I & 0 & 0 \\ \gamma_3 & 0 & 0 & -\rho_2 I & \rho_2 \hat{J}^T \\ \rho_2\gamma_4 & 0 & 0 & \rho_2\hat{J} & -\rho_2 I \end{bmatrix} < 0, \tag{11}$$

Where:

$$\Psi := \begin{bmatrix} \Psi_{11} & \Psi_{12} & \Psi_{13} \\ \Psi_{12}^T & \Psi_{22} & 0 \\ \Psi_{13}^T & 0 & \Psi_{33} \end{bmatrix}$$

$$\Psi_{11} = \Psi_1 + \Psi_1^T + \sum_{i=2}^{6}\Psi_i + \Psi_7 + \Psi_7^T$$

$$\Psi_{12} = \begin{bmatrix} e_1 \\ -Ae_1 + We_{10} \end{bmatrix}^T \Psi_Q + \begin{bmatrix} e_2 \\ -Ce_2 + De_4 \end{bmatrix}^T \Psi_R$$

$$\Psi_{13} = (-Ae_1 + We_{10})^T\Phi_Q + (-Ce_2 + De_4)^T\Phi_R$$

$$\Psi_{22} = -\mathrm{diag}(Q_4, Q_5, R_4, R_5)$$

$$\Psi_{33} = -\mathrm{diag}(Q_6, Q_7, R_6, R_7)$$

$$\Psi_Q = \begin{bmatrix} \tau_1 Q_4 & \tau_{12}Q_5 & 0 & 0 \end{bmatrix}$$

$$\Psi_R = \begin{bmatrix} 0 & 0 & \sigma_1 R_4 & \sigma_{12}R_5 \end{bmatrix}$$

$$\Phi_Q = \begin{bmatrix} \frac{\tau_1^2}{2}Q_6 & \tau_s Q_7 & 0 & 0 \end{bmatrix}$$

$$\Phi_R = \begin{bmatrix} 0 & 0 & \frac{\sigma_1^2}{2}R_6 & \sigma_s R_7 \end{bmatrix}$$

$$\Psi_1 = \Gamma^T P\Gamma_d + \begin{bmatrix} e_9 - L^- e_2 \\ L^+ e_2 - e_9 \end{bmatrix}^T \begin{bmatrix} \Lambda_1 \\ \Lambda_2 \end{bmatrix} (-Ce_2 + De_4)$$

$$\Psi_2 = e_1^T(Q_1+Q_3)e_1 + e_3^T(Q_2-Q_1)e_3 - e_5^T Q_2 e_5 - (1-\tau_d)e_4^T Q_3 e_4$$

$$\Psi_3 = e_2^T R_1 e_2 + e_6^T(R_2-R_1)e_6 - e_8^T R_2 e_8 + \begin{bmatrix} e_2 \\ e_9 \end{bmatrix}^T R_3 \begin{bmatrix} e_2 \\ e_9 \end{bmatrix} - (1-\sigma_d)\begin{bmatrix} e_7 \\ e_{10} \end{bmatrix}^T R_3 \begin{bmatrix} e_7 \\ e_{10} \end{bmatrix}$$

$$\Psi_4 = -\begin{bmatrix} e_{11} \\ e_1-e_3 \end{bmatrix}^T Q_4 \begin{bmatrix} e_{11} \\ e_1-e_3 \end{bmatrix} - \begin{bmatrix} e_{13} \\ e_3-e_4 \\ e_{12} \\ e_4-e_5 \end{bmatrix}^T \begin{bmatrix} Q_5 & \tilde{Q}_5 \\ \tilde{Q}_5^T & Q_5 \end{bmatrix} \begin{bmatrix} e_{13} \\ e_3-e_4 \\ e_{12} \\ e_4-e_5 \end{bmatrix}$$

$$\Psi_5 = -\begin{bmatrix} e_{14} \\ e_2-e_6 \end{bmatrix}^T R_4 \begin{bmatrix} e_{14} \\ e_2-e_6 \end{bmatrix} - \begin{bmatrix} e_{16} \\ e_6-e_7 \\ e_{15} \\ e_7-e_8 \end{bmatrix}^T \begin{bmatrix} R_5 & \tilde{R}_5 \\ \tilde{R}_5^T & R_5 \end{bmatrix} \begin{bmatrix} e_{16} \\ e_6-e_7 \\ e_{15} \\ e_7-e_8 \end{bmatrix}$$

$$\begin{aligned}\Psi_6 = &-(\tau_1 e_1 - e_{11})^T Q_6 (\tau_1 e_1 - e_{11}) \\ &-\frac{2\tau_s}{\tau_{12}^2}(\tau_{12}e_3 - e_{12} - e_{13})^T Q_7 (\tau_{12}e_3 - e_{12} - e_{13}) \\ &-\frac{\tau_s\tau_{12}}{\tau_1}(e_1-e_3)^T Q_7 (e_1-e_3) \\ &-(\sigma_1 e_2 - e_{14})^T R_6 (\sigma_1 e_2 - e_{14}) \\ &-\frac{2\sigma_s}{\sigma_{12}^2}(\sigma_{12}e_6 - e_{15} - e_{16})^T R_7 (\sigma_{12}e_6 - e_{15} - e_{16}) \\ &-\frac{\sigma_s\sigma_{12}}{\sigma_1}(e_2-e_6)^T R_7 (e_2-e_6)\end{aligned}$$

$$\Psi_7 = -(e_9 - L^+ e_2)^T T_1 (e_9 - L^- e_2) - (e_{10} - L^+ e_7)^T T_2 (e_{10} - L^- e_7)$$

$$\Gamma = \mathrm{col}(e_1, e_2, e_{11}, e_{12}+e_{13}, e_{14}, e_{15}+e_{16})$$

$$\Gamma_d = \mathrm{col}(-Ae_1 + We_{10}, -Ce_2 + De_4 e_1 - e_3, e_3 - e_5, e_2 - e_6, e_6 - e_8),$$

$$\tau_{12} = \tau_2 - \tau_1, \tau_s = \frac{1}{2}(\tau_2^2 - \tau_1^2), \sigma_{12} = \sigma_2 - \sigma_1$$

$$\sigma_s = \frac{1}{2}(\sigma_2^2 - \sigma_1^2), \gamma_1 = [\pi_1\ 0\ 0], \gamma_2 = [\pi_2\ 0\ 0]$$

$$\gamma_3 = [\pi_3\ \ \pi_4\ \ \pi_5], \gamma_4 = [\pi_6\ 0\ 0]$$

$$\pi_1 = E_2^T \begin{bmatrix} \Lambda_1 \\ \Lambda_2 \end{bmatrix}^T \begin{bmatrix} e_9 - L^- e_2 \\ L^+ e_2 - e_9 \end{bmatrix}, \pi_2 = -H_c e_2 + H_d e_4$$

$$\pi_3 = \begin{bmatrix} E_1^T & 0 & 0 & 0 & 0 & 0 \\ 0 & E_2^T & 0 & 0 & 0 & 0 \end{bmatrix} P\Gamma, \pi_4 = \begin{bmatrix} \hat{E}_1^T \Psi_Q \\ \hat{E}_2^T \Psi_R \end{bmatrix}$$

$$\pi_5 = \begin{bmatrix} E_1^T \Phi_Q \\ E_2^T \Phi_R \end{bmatrix}, \pi_6 = \begin{bmatrix} -H_a e_1 + H_w e_{10} \\ -H_c e_2 + H_d e_4 \end{bmatrix}, \hat{E}_1 = \begin{bmatrix} 0 \\ E_1 \end{bmatrix}$$

$$\hat{E}_2 = \begin{bmatrix} 0 \\ E_2 \end{bmatrix}, \hat{J} = \mathrm{diag}(J, J)$$

$$e_i = [\underbrace{0 \cdots 0}_{\text{number } i-1}\quad I_n \quad \underbrace{0 \cdots 0}_{\text{number } 16-i}], i = 1, 2, \cdots, 16$$

Proof set:

$$\begin{aligned}\eta(t) = \mathrm{col}(&x(t), y(t), x(t-\tau_1), x(t-\tau(t)), \\ &x(t-\tau_2), y(t-\sigma_1), y(t-\sigma(t)), y(t-\sigma_2), \\ &f(y(t)), f(y(t-\sigma(t))), \\ &\int_{t-\tau_1}^{t} x(s)ds, \int_{t-\tau_2}^{t-\tau(t)} x(s)ds, \int_{t-\tau(t)}^{t-\tau_1} x(s)ds, \\ &\int_{t-\sigma_1}^{t} y(s)ds, \int_{t-\sigma_2}^{t-\sigma(t)} y(s)ds, \int_{t-\sigma(t)}^{t-\sigma_1} y(s)ds)\end{aligned}$$

$$\begin{aligned}\eta_1(t) = \mathrm{col}(&x(t), y(t), \int_{t-\tau_1}^{t} x(s)ds, \int_{t-\tau_2}^{t-\tau_1} x(s)ds, \\ &\int_{t-\sigma_1}^{t} y(s)ds, \int_{t-\sigma_2}^{t-\sigma_1} y(s)ds)\end{aligned}$$

Then:

$$\dot{x}(t) = (-A(t)e_1 + W(t)e_{10})\eta(t)$$

$$\dot{y}(t) = (-C(t)e_2 + D(t)e_4)\eta(t)$$

$$\eta_1(t) = \Gamma\eta(t), \dot{\eta}_1(t) = \Gamma_d\eta(t)$$

Where:

$$\begin{aligned}\tilde{\Gamma}_d = \mathrm{col}(&-A(t)e_1 + W(t)e_{10}, -C(t)e_2 \\ &+D(t)e_4, e_1 - e_3, e_3 - e_5, e_2 - e_6, e_6 - e_8)\end{aligned}$$

Choose a Lyapunov-Krasovskii functional candidate as:

$$V(t, x_t, y_t) = \sum_{i=1}^{6} V_i(t, x_t, y_t) \tag{12}$$

Where:

$$V_1(t,x_t,y_t) = \eta_1^T(t)P\eta_1(t) + 2\sum_{i=1}^{n}\lambda_{1i}\int_0^{y_i(t)}(f_i(s) - l_i^- s)ds + 2\sum_{i=1}^{n}\lambda_{2i}\int_0^{y_i(t)}(l_i^+ s - f_i(s))ds$$

$$V_2(t,x_t,y_t) = \int_{t-\tau_1}^{t} x^T(s)Q_1x(s)ds + \int_{t-\tau_2}^{t-\tau_1} x^T(s)Q_2x(s)ds + \int_{t-\tau(t)}^{t} x^T(s)Q_3x(s)ds$$

$$V_3(t,x_t,y_t) = \int_{t-\sigma_1}^{t} y^T(s)R_1y(s)ds + \int_{t-\sigma_2}^{t-\sigma_1} y^T(s)R_2y(s)ds + \int_{t-\sigma(t)}^{t}\begin{bmatrix} y(s) \\ f(y(s)) \end{bmatrix}^T R_3 \begin{bmatrix} y(s) \\ f(y(s)) \end{bmatrix}ds$$

$$V_4(t,x_t,y_t) = \tau_1\int_{-\tau_1}^{0}\int_{t+\theta}^{t}\begin{bmatrix} x(s) \\ \dot{x}(s) \end{bmatrix}^T Q_4 \begin{bmatrix} x(s) \\ \dot{x}(s) \end{bmatrix}dsd\theta + \tau_{12}\int_{-\tau_2}^{-\tau_1}\int_{t+\theta}^{t}\begin{bmatrix} x(s) \\ \dot{x}(s) \end{bmatrix}^T Q_5 \begin{bmatrix} x(s) \\ \dot{x}(s) \end{bmatrix}dsd\theta$$

$$V_5(t,x_t,y_t) = \sigma_1\int_{-\sigma_1}^{0}\int_{t+\theta}^{t}\begin{bmatrix} y(s) \\ \dot{y}(s) \end{bmatrix}^T R_4 \begin{bmatrix} y(s) \\ \dot{y}(s) \end{bmatrix}dsd\theta + \sigma_{12}\int_{-\sigma_2}^{-\sigma_1}\int_{t+\theta}^{t}\begin{bmatrix} y(s) \\ \dot{y}(s) \end{bmatrix}^T R_5 \begin{bmatrix} y(s) \\ \dot{y}(s) \end{bmatrix}dsd\theta$$

$$\begin{aligned} V_6(t,x_t,y_t) = {} & \frac{\tau_1^2}{2}\int_{-\tau_1}^{0}\int_{\theta}^{0}\int_{t+\lambda}^{t}\dot{x}^T(s)Q_6\dot{x}(s)dsd\lambda d\theta \\ & + \tau_s\int_{-\tau_2}^{-\tau_1}\int_{\theta}^{0}\int_{t+\lambda}^{t}\dot{x}^T(s)Q_7\dot{x}(s)dsd\lambda d\theta \\ & + \frac{\sigma_1^2}{2}\int_{-\sigma_1}^{0}\int_{\theta}^{0}\int_{t+\lambda}^{t}\dot{y}^T(s)R_6\dot{y}(s)dsd\lambda d\theta \\ & + \sigma_s\int_{-\sigma_2}^{-\sigma_1}\int_{\theta}^{0}\int_{t+\lambda}^{t}\dot{y}^T(s)R_7\dot{y}(s)dsd\lambda d\theta \end{aligned}$$

Taking the time derivative of $V(t,x_t,y_t)$ along the trajectories of GRN (9) can be easily obtained as follows:

$$\dot{V}(t,x_t,y_t) = \sum_{i=1}^{6}\dot{V}_i(t,x_t,y_t) \tag{13}$$

Where:

$$\begin{aligned} \dot{V}_1(t,x_t,y_t) = {} & 2\eta_1^T(t)P\dot{\eta}_1(t) \\ & + 2[f(y(t)) - L^- y(t)]^T\Lambda_1\dot{y}(t) \\ & + 2[L^+ y(t) - f(y(t))]^T\Lambda_2\dot{y}(t) \\ = {} & \eta^T(t)(\Psi_1 + \Psi_1^T + \pi_3^T\tilde{\Delta}(t)\pi_6 \\ & + \pi_6^T\tilde{\Delta}^T(t)\pi_3 + \pi_1^T\Delta(t)\pi_2 \\ & + \pi_2^T\Delta^T(t)\pi_1)\eta(t) \end{aligned} \tag{14}$$

$$\tilde{\Delta}(t) = \mathrm{diag}(\Delta(t), \Delta(t))$$

$$\dot{V}_2(t,x_t,y_t) \le \eta^T(t)\Psi_2\eta(t) \tag{15}$$

$$\dot{V}_3(t,x_t,y_t) \le \eta^T(t)\Psi_3\eta(t) \tag{16}$$

$$\begin{aligned} \dot{V}_4(t,x_t,y_t) = {} & \begin{bmatrix} x(t) \\ \dot{x}(t) \end{bmatrix}^T(\tau_1^2Q_4 + \tau_{12}^2Q_5)\begin{bmatrix} x(t) \\ \dot{x}(t) \end{bmatrix} \\ & - \tau_1\int_{t-\tau_1}^{t}\begin{bmatrix} x(s) \\ \dot{x}(s) \end{bmatrix}^T Q_4 \begin{bmatrix} x(s) \\ \dot{x}(s) \end{bmatrix}ds \\ & - \tau_{12}\int_{t-\tau_2}^{t-\tau_1}\begin{bmatrix} x(s) \\ \dot{x}(s) \end{bmatrix}^T Q_5 \begin{bmatrix} x(s) \\ \dot{x}(s) \end{bmatrix}ds \end{aligned} \tag{17}$$

$$\begin{aligned} \dot{V}_5(t,x_t,y_t) = {} & \begin{bmatrix} y(t) \\ \dot{y}(t) \end{bmatrix}^T(\sigma_1^2R_4 + \sigma_{12}^2R_5)\begin{bmatrix} y(t) \\ \dot{y}(t) \end{bmatrix} \\ & - \sigma_1\int_{t-\sigma_1}^{t}\begin{bmatrix} y(s) \\ \dot{y}(s) \end{bmatrix}^T R_4 \begin{bmatrix} y(s) \\ \dot{y}(s) \end{bmatrix}ds \\ & - \sigma_{12}\int_{t-\sigma_2}^{t-\sigma_1}\begin{bmatrix} y(s) \\ \dot{y}(s) \end{bmatrix}^T R_5 \begin{bmatrix} y(s) \\ \dot{y}(s) \end{bmatrix}ds \end{aligned} \tag{18}$$

$$\begin{aligned} \dot{V}_6(t,x_t,y_t) = {} & \dot{x}^T(t)(\frac{\tau_1^4}{4}Q_6 + \tau_s^2Q_7)\dot{x}(t) \\ & + \dot{y}^T(t)(\frac{\sigma_1^4}{4}R_6 + \sigma_s^2R_7)\dot{y}(t) \\ & - \frac{\tau_1^2}{2}\int_{-\tau_1}^{0}\int_{t+\theta}^{t}\dot{x}^T(s)Q_6\dot{x}(s)dsd\theta \\ & - \tau_s\int_{t-\tau_2}^{t-\tau_1}\int_{t+\theta}^{t}\dot{x}^T(s)Q_7\dot{x}(s)dsd\theta \\ & - \frac{\sigma_1^2}{2}\int_{-\sigma_1}^{0}\int_{t+\theta}^{t}\dot{y}^T(s)R_6\dot{y}(s)dsd\theta \\ & - \sigma_s\int_{t-\sigma_2}^{t-\sigma_1}\int_{t+\theta}^{t}\dot{y}^T(s)R_7\dot{y}(s)dsd\theta \end{aligned} \tag{19}$$

From the Jensen inequality(Gu, 2001), we have:

$$\begin{aligned} & -\tau_1\int_{t-\tau_1}^{t}\begin{bmatrix} x(s) \\ \dot{x}(s) \end{bmatrix}^T Q_4 \begin{bmatrix} x(s) \\ \dot{x}(s) \end{bmatrix}ds \\ & \le -\eta^T(t)\begin{bmatrix} e_{11} \\ e_1 - e_3 \end{bmatrix}^T Q_4 \begin{bmatrix} e_{11} \\ e_1 - e_3 \end{bmatrix}\eta(t) \end{aligned} \tag{20}$$

$$\begin{aligned} & -\sigma_1\int_{t-\sigma_1}^{t}\begin{bmatrix} y(s) \\ \dot{y}(s) \end{bmatrix}^T R_4 \begin{bmatrix} y(s) \\ \dot{y}(s) \end{bmatrix}ds \\ & \le -\eta^T(t)\begin{bmatrix} e_{14} \\ e_2 - e_6 \end{bmatrix}^T R_4 \begin{bmatrix} e_{14} \\ e_2 - e_6 \end{bmatrix}\eta(t) \end{aligned} \tag{21}$$

And from the Lower bounds theorem (Park *et al.*, 2011), we can obtain:

$$-\tau_{12}\int_{t-\tau_2}^{t-\tau_1}\begin{bmatrix}x(s)\\ \dot{x}(s)\end{bmatrix}^T Q_5\begin{bmatrix}x(s)\\ \dot{x}(s)\end{bmatrix}ds \le \eta^T(t)\begin{bmatrix}e_{13}\\ e_3-e_4\\ e_{12}\\ e_4-e_5\end{bmatrix}^T\begin{bmatrix}Q_5 & \tilde{Q}_5\\ \tilde{Q}_5^T & Q_5\end{bmatrix}\begin{bmatrix}e_{13}\\ e_3-e_4\\ e_{12}\\ e_4-e_5\end{bmatrix}\eta(t) \quad (22)$$

Similarly, we have:

$$-\sigma_{12}\int_{t-\sigma_2}^{t-\sigma_1}\begin{bmatrix}y(s)\\ \dot{y}(s)\end{bmatrix}^T R_5\begin{bmatrix}y(s)\\ \dot{y}(s)\end{bmatrix}ds \le \eta^T(t)\begin{bmatrix}e_{16}\\ e_6-e_7\\ e_{15}\\ e_7-e_8\end{bmatrix}^T\begin{bmatrix}R_5 & \tilde{R}_5\\ \tilde{R}_5^T & R_5\end{bmatrix}\begin{bmatrix}e_{16}\\ e_6-e_7\\ e_{15}\\ e_7-e_8\end{bmatrix}\eta(t) \quad (23)$$

When $w: D \to R^n$ is a derivative vector function, one can easily obtain:

$$\int_{-b}^{-a}\int_{t+\theta}^{t-a}\dot{w}(s)dsd\theta = (b-a)w(t-a) - \int_{t-b}^{t-a}w(s)ds \quad (24)$$

Then it follows from Lemma in Sun *et al*. (2009) and (24), we have:

$$-\frac{\tau_1^2}{2}\int_{-\tau_1}^{0}\int_{t+\theta}^{t}\dot{x}^T(s)Q_6\dot{x}(s)dsd\theta \le -\eta^T(t)(\tau_1 e_1 - e_{11})^T Q_6(\tau_1 e_1 - e_{11})\eta(t) \quad (25)$$

$$-\frac{\sigma_1^2}{2}\int_{-\sigma_1}^{0}\int_{t+\theta}^{t}\dot{y}^T(s)R_6\dot{y}(s)dsd\theta \le -\eta^T(t)(\sigma_1 e_2 - e_{14})^T R_6(\sigma_1 e_2 - e_{14})\eta(t) \quad (26)$$

And from (24), the Jensen inequality (Gu, 2001) and Lemma 1 in Sun *et al.* (2009), we can obtain:

$$\begin{aligned}&-\tau_s\int_{-\tau_2}^{-\tau_1}\int_{t+\theta}^{t}\dot{x}^T(s)Q_7\dot{x}(s)dsd\theta\\ &\le -\frac{2\tau_s}{\tau_{12}^2}\eta^T(t)[\tau_{12}e_3 - e_{12} - e_{13}]^T\\ &\cdot Q_7[\tau_{12}e_3 - e_{12} - e_{13}]\eta(t)\\ &-\frac{\tau_s\tau_{12}}{\tau_1}\eta^T(t)(e_1-e_3)^T Q_7(e_1-e_3)\eta(t)\end{aligned} \quad (27)$$

Similarly, we have:

$$\begin{aligned}&-\sigma_s\int_{-\sigma_2}^{-\sigma_1}\int_{t+\theta}^{t}\dot{y}^T(s)R_7\dot{y}(s)dsd\theta\\ &\le -\frac{2\sigma_s}{\sigma_{12}^2}\eta^T(t)[\sigma_{12}e_6 - e_{15} - e_{16}]^T\\ &\cdot R_7[\sigma_{12}e_6 - e_{15} - e_{16}]\eta(t)\\ &-\frac{\sigma_s\sigma_{12}}{\sigma_1}\eta^T(t)(e_2-e_6)^T R_7(e_2-e_6)\eta(t)\end{aligned} \quad (28)$$

Next, from Assumption (8) we can obtain:

$$\begin{aligned}0 &\le -2[f(y(t)) - L^+y(t)]^T T_1[f(y(t)) - L^-y(t)]\\ &-2[f(y(t-\sigma(t))) - L^+y(t-\sigma(t))]^T\\ &T_2[f(y(t-\sigma(t))) - L^-y(t-\sigma(t))]\\ &= \eta^T(t)(\Psi_7 + \Psi_7^T)\eta(t)\end{aligned} \quad (29)$$

Then, the combination of (13)-(29) yields:

$$\dot{V}(t, x_t, y_t) \le \eta^T(t)\tilde{\Upsilon}\eta(t) \quad (30)$$

where, $\tilde{\Upsilon} = \Psi_{11} + \tilde{\Psi}_4 + \tilde{\Psi}_5 + \tilde{\Psi}_6$

$$\tilde{\Psi}_4 = \begin{bmatrix}e_1\\ -A(t)e_1 + W(t)e_{10}\end{bmatrix}^T(\tau_1^2 Q_4 + \tau_{12}^2 Q_5)\begin{bmatrix}e_1\\ -A(t)e_1 + W(t)e_{10}\end{bmatrix}$$

$$\tilde{\Psi}_5 = \begin{bmatrix}e_2\\ -C(t)e_2 + D(t)e_4\end{bmatrix}^T(\sigma_1^2 R_4 + \sigma_{12}^2 R_5)\begin{bmatrix}e_2\\ -C(t)e_2 + D(t)e_4\end{bmatrix}$$

$$\begin{aligned}\tilde{\Psi}_6 &= (-A(t)e_1 + W(t)e_{10})^T(\frac{\tau_1^4}{4}Q_6 + \tau_s^2 Q_7)\\ &(-A(t)e_1 + W(t)e_{10}) + (-C(t)e_2 + D(t)e_4)^T\\ &(\frac{\sigma_1^4}{4}R_6 + \sigma_s^2 R_7)(-C(t)e_2 + D(t)e_4)\end{aligned}$$

It follows from Xie (1996) that the LMI (11) can imply the following inequality holds:

$$\Psi + \gamma_1^T\Delta(t)\gamma_2 + \gamma_2^T\Delta^T(t)\gamma_1 + \gamma_3^T\tilde{\Delta}(t)\gamma_4 + \gamma_4^T\tilde{\Delta}^T(t)\gamma_3 < 0 \quad (43)$$

Then using Schur complement yields $\tilde{\Upsilon} < 0$. The proof is completed.

Remark 1: In the special case that $P = \text{diag}(P_1, P_2, 0)$, the item $V_1(t, x_t, y_t)$ simplifies to $x^T(t)P_1x(t) + y^T(t)P_2y(t)$, which has been used in Wu *et al*. (2010). Therefore the above theorem may be less conservative stability than one in Wu *et al.* (2010). This will be verified by a numerical example in next section.

Remark 2: In this study, we introduce a new term:

$$\int_{-\tau_1}^{0}\int_{t+\theta}^{t}\begin{bmatrix} x(s) \\ \dot{x}(s)\end{bmatrix}^T Q_4 \begin{bmatrix} x(s) \\ \dot{x}(s)\end{bmatrix} dsd\theta$$

into our Lyapunov functional. Set:

$$Q_4 = \begin{bmatrix} Q_{41} & Q_{42} \\ Q_{42}^T & Q_{43}\end{bmatrix}$$

Then the new term contains not only:

$$\int_{-\tau_1}^{0}\int_{t+\theta}^{t}[x^T(s)Q_{41}x(s)+\dot{x}^T(s)Q_{43}\dot{x}(s)]dsd\theta$$

used in Wang *et al*. (2012) but also a cross product term:

$$\int_{-\tau_1}^{0}\int_{t+\theta}^{t}x^T(s)Q_{42}\dot{x}(s)dsd\theta$$

Since the matrix Q_{42} brings a higher degree of freedoms, which leads to a less conservative stability criterion.

Remark 3: Although the same term $V_6(t, x_t, y_t)$ has been chosen in the Lyapunov-Krasovskii functionals of this study and Wang *et al*. (2012), we use a new method, different from the one in Wang *et al*. (2012), to scalar the derivative of $V_6(t, x_t, y_t)$. The above theorem maybe less conservative than one in Wang *et al*. (2012) and a numerical example will verify this in next section.

Remark 4: When the uncertainties in GRN (9) vanish, Theorem 1 is still valid if (11) is replaced by $\Psi < 0$.

Remark 5: Theorem 1 is applicable to known τ_d and σ_d. However, when the information of the derivatives of delays is unknown, theorem 1 is still valid by setting $Q_3 = R_3 = 0$.

ILLUSTRATIVE EXAMPLE

In this section, two examples are given to illustrate the effectiveness of our theoretical results.

Eample 1: Consider the GRN (9) with the parameters described as:

$$A = 3I_3, C = 2.5I_3, D = 0.8I_3, E_1 = [H_a \;\; H_2]$$

$$W = \begin{bmatrix} 0 & 0 & -2.5 \\ -2.5 & 0 & 0 \\ 0 & -2.5 & 0 \end{bmatrix}, l = \begin{bmatrix} 2.5 \\ 2.5 \\ 2.5 \end{bmatrix}, E_2 = [H_c \;\; H_d]$$

Table 1: Maximum allowable upper bounds of τ_{12}

σ_{12}	0.1	0.3	0.5	1
Ren and Cao (2008)	0.274	0.104	0.023	Infeasible
Koo et al. (2011)	2.738	2.534	2.239	1.561
Wu et al. (2010)	3.100	3.000	2.700	2.000
Theorem 1	5.600	3.900	3.100	2.100

Table 2: Maximum allowable upper bounds of τ_2

Method	Wu *et al.* (2010)	Wang *et al.* (2012)	Theorem 1
τ_2	3.7	5.3	5.5

$$H_a = \begin{bmatrix} 0.04 & 0.01 & -0.02 \\ 0.01 & 0.04 & -0.01 \\ -0.02 & -0.01 & 0.03 \end{bmatrix},$$

$$H_2 = \begin{bmatrix} 0 & 0 & 0.2 \\ 0.2 & 0 & 0 \\ 0 & -0.2 & 0 \end{bmatrix}, H_c = \begin{bmatrix} 0.4 & 0.1 & -0.2 \\ 0.1 & 0.4 & -0.1 \\ -0.2 & -0.1 & 0.3 \end{bmatrix}$$

$$H_d = \begin{bmatrix} 0.04 & 0.02 & -0.04 \\ 0.02 & 0.03 & -0.02 \\ -0.04 & -0.02 & 0.06 \end{bmatrix},$$

$$H_w = \text{diag}(0.2, 0.2, 0.2), \Delta(t) = \text{col}(\Delta_1(t), \Delta_2(t))$$

$$\Delta_1(t) = \text{diag}(0.5\sin(t), 0.5\cos(2t), 0.5\cos(t)),$$
$$\Delta_2(t) = \text{diag}(-0.5\sin(t), -0.5\cos(2t), -0.5\cos(t))$$

Let $h_j(x) = x^2/(x^2+1)$, $j = 1, 2, \cdots, n$. Then:

$$L^- = 0, L^+ = \text{diag}(0.65, 0.65, 0.65)$$

For $\tau_1 = 0.25$, $\sigma_1 = 0.5$ and different σ_{12}, the corresponding admissible upper bounds of τ_{12} obtained by Theorem 1, Ren and Cao (2008), Koo *et al*. (2011) and Wu *et al*. (2010) are shown in Table 1.

Eample 2: For part of the parameters in Example 1, we consider the GRN (9). For $\tau_1 = \sigma_1 = 0.1$, $\sigma_2 = 0.3$, $\tau_d = 1.5$ and $\sigma_d = 0.7$, the maximum allowable upper bounds of τ_2 obtained by Theorem 1, Wu *et al*. (2010) and Wang *et al*. (2012) are listed in Table 2.

When:

$$\tau(t) = 5.4\sin^2(\frac{5}{18}t) + 0.1, \sigma(t) = 0.2\sin^2(3.5t) + 0.1$$

the trajectories of mRNAs and proteins are given in Fig. 1 with the initial condition $m(t) \equiv [0.6, 1, 1.5]^T, t \in [-5.5, 0]$, $p(t) \equiv [1, 2, 0.8]^T, t \in [-0.3, 0]$.

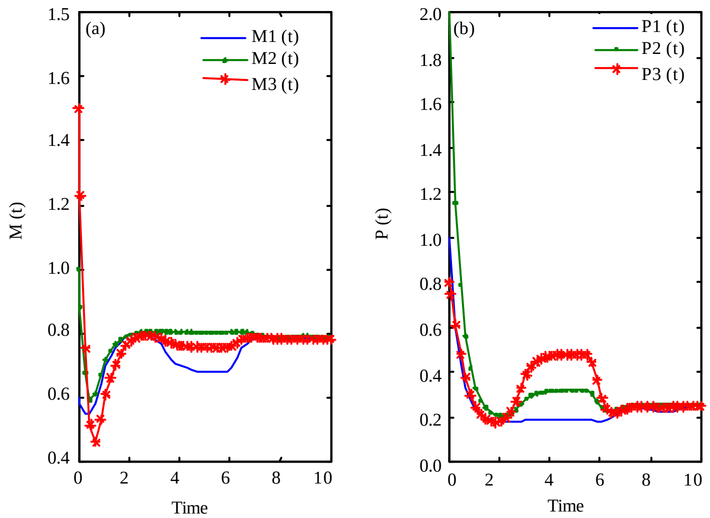

Fig. 1: Trajectories of mRNAs and proteins

CONCLUSION

This study studied the robust asymptotical stability for GRN (9). By constructing an appropriate Lyapunov-Krasovskii functional and combining Jensen inequality approach and reciprocally convex combination approach, a robust stability criterion for GRN (9) is firstly given in the form of LMIs, which can be easily tested by the LMI Toolbox of MATLAB. Finally, numerical examples and theirs simulation results show that the stability criteria proposed here are less conservative than ones in Wang *et al.* (2012), Ren and Cao (2008), Koo *et al.* (2011) and Wu *et al.* (2010).

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