The Second International Symposium on Optimization and Systems Biology (OSB'08)
Lijiang, China, October 31– November 3, 2008

Stability of stochastic genetic regulatory networks*

Yonghui Sun† Gang Feng

Department of Manufacturing Engineering and Engineering Management,
City University of Hong Kong, Hong Kong, China

Abstract This paper studies the stochastic stability of genetic regulatory networks with intrinsic and extrinsic noises. A delay dependent stability condition with disturbance attenuation is derived for the stochastic genetic networks with time-varying delays. The developed criteria can be tested efficiently by Matlab LMI Control Toolbox. A numerical example with simulations is given to illustrate the effectiveness and validity of the derived theoretical results.

Keywords Gene Networks; Noise Disturbance; Stability

1 Introduction

In the past decades, genetic regulatory networks have attracted considerable attention from researchers in various fields [1]-[2]. Basically, there are two types of gene network models, the Boolean model [1], where the activity of each gene has two states, and the differential equation model [3], where the variables describe the concentrations of gene products, such as mRNAs and proteins.

On the other hand, time delays are inevitable due to the transcription, translation, diffusion, and translocation processes of genes [5]. Hence, time delays should be taken into account. In [6], the authors presented a functional differential equation model for genetic networks with time delays. In [8], some stability conditions in the form of LMIs were derived for the genetic networks with time-varying delays. In [9], the authors studied the robust stability of genetic networks with time-varying delays.

It is worth noting that molecular events in cells are subject to significant thermal fluctuations and noisy process, thus gene expression is best viewed as a stochastic process [4]. In [7], the authors investigated cooperative behaviors in a general coupled noisy system with time delays. In [8], the authors studied the mean square stability for the gene networks with time-varying delays. In [10], the authors studied the stochastic stability with disturbance attenuation for stochastic gene networks.

To the authors' knowledge, when intrinsic and extrinsic noises appear simultaneously in stochastic gene networks, the problem of delay dependent stochastic stability of genetic regulatory networks with disturbance attenuation have not been fully investigated.

*The work was supported by a grant from the Research Grants Council of the Hong Kong Special Administrative Region of China [Project no.: CityU 113205]

†Corresponding author: sunyonghui168@gmail.com

Therefore, we will investigate stochastic stability of genetic networks with intrinsic and extrinsic noises, discuss how to find the optimal attenuation level of extrinsic noises for genetic networks.

The rest of this paper is organized as follows. In Section II, the stochastic gene networks model with extrinsic noises is introduced. In Section III, a delay dependent stability condition is derived. In Section IV, a numerical example is employed to illustrate effectiveness of the obtained results. At last, this paper is completed with a conclusion.

2 Genetic network model and preliminaries

In this study, we consider a stochastic genetic regulatory networks with intrinsic and extrinsic noises as follows [7]:

$$\begin{cases} dm(t) &= [-Am(t)+Bf(p(t-\sigma(t)))+Ev(t)+L]dt \\ & \quad +H(m(t),p(t),m(t-\tau(t)),p(t-\sigma(t)))d\omega(t), \\ dp(t) &= [-Cp(t)+Dm(t-\tau(t))]dt, \end{cases} \tag{1}$$

where $m(t), p(t) \in R^n$ are the concentrations of mRNA and protein, respectively. $A = \text{diag}(a_1, a_2, \cdots, a_n), C = \text{diag}(c_1, c_2, \cdots, c_n), D = \text{diag}(d_1, d_2, \cdots, d_n)$ and $L = [l_1, l_2, \cdots, l_n]^{\mathrm{T}}$, where A and C are the degradation rates of mRNA and protein, D is the translation rate. $\tau(t)$ and $\sigma(t)$ are time-varying delays satisfying $0 \le \tau(t) \le \tau$ and $0 \le \sigma(t) \le \sigma$, respectively. The Hill functions $f_j(x) = \frac{(\frac{x}{\alpha_j})^{H_j}}{1+(\frac{x}{\alpha_j})^{H_j}}$, α_j is a positive constant, H_j is the Hill coefficient; $l_i = \sum_{j \in I_i} \beta_{ij}$ and I_i is the set of all j node which are repressors of gene i. $B = (b_{ij}) \in R^{n \times n}$ is defined as follows:

$$b_{ij} = \begin{cases} \beta_{ij} \text{ if transcription factor } j \text{ is an activator of gene } i, \\ 0 \quad \text{if there is no link from node } j \text{ to } i, \\ -\beta_{ij} \text{if transcription factor } j \text{ is an repressor of gene } i. \end{cases}$$

Furthermore, $\omega(t)$ is an one-dimensional Brownian motion and $v(t)$ is the extrinsic noise belonging to $L_2[0,\infty]$.

Assume that vectors m^* and p^* are the equilibrium point of (1) with $v(t) \equiv 0$, shifting to the origin by letting $x(t) = m(t) - m^*, y(t) = p(t) - p^*$, one has

$$\begin{cases} dx(t) &= [-Ax(t)+Bg(y(t-\sigma(t)))+Ev(t)]dt \\ & \quad +H(x(t),y(t),x(t-\tau(t)),y(t-\sigma(t)))d\omega(t), \\ dy(t) &= [-Cy(t)+Dx(t-\tau(t))]dt, \end{cases} \tag{2}$$

with $H(m^*,p^*,m^*,p^*) = 0$, where $g(y(t))$ is defined as $g(y(t)) = f(y(t)+p^*) - f(p^*)$, it satisfies the sector condition $g(x)(g(x)-kx) \le 0$.

Assumption 1: Noise intensity $H(x(t),y(t),x(t-\tau(t)),y(t-\sigma(t)))$ in (2) satisfies the following conditions:

$$\text{trace}[H^{\mathrm{T}}(x_1,x_2,x_3,x_4)H(x_1,x_2,x_3,x_4)] \le \sum_{i=1}^{4} x_i^{\mathrm{T}} N_i x_i, \tag{3}$$

where $N_i, i = 1,2,3,4$ are the known matrices.

3 Main results

Theorem: Given a scalar $\gamma > 0$, genetic networks (2) is stochastically stable with disturbance attenuation γ, if there exist scalars $\rho_1 > 0, \rho_2 > 0$ matrices $P_1 > 0, P_2 > 0, R > 0, Q > 0, S > 0, \Lambda > 0, F$ and M such that the following LMIs hold

$$\Omega = \begin{bmatrix} \Pi_1 & 0 & F^{\mathrm{T}} & 0 & P_1B & P_1E & -\tau A^{\mathrm{T}}R & 0 & 0 & 0 & 0 \\ \star & \Pi_2 & P_2D & M^{\mathrm{T}} & 0 & 0 & 0 & 0 & 0 & -\sigma C^{\mathrm{T}}Q & 0 \\ \star & \star & \Pi_3 & 0 & 0 & 0 & 0 & F & \tau F & \sigma D^{\mathrm{T}}Q & 0 \\ \star & \star & \star & \Pi_4 & k\Lambda & 0 & 0 & 0 & 0 & 0 & \sigma MQ \\ \star & \star & \star & \star & -\Lambda-\Lambda^{\mathrm{T}} & 0 & \tau B^{\mathrm{T}}R & 0 & 0 & 0 & 0 \\ \star & \star & \star & \star & \star & -\gamma^2 I & \tau E^{\mathrm{T}}R & 0 & 0 & 0 & 0 \\ \star & \star & \star & \star & \star & \star & -\tau R & 0 & 0 & 0 & 0 \\ \star & \star & \star & \star & \star & \star & \star & -S & 0 & 0 & 0 \\ \star & \star & \star & \star & \star & \star & \star & \star & -\tau R & 0 & 0 \\ \star & \star & \star & \star & \star & \star & \star & \star & \star & -\sigma R & 0 \\ \star & \star & \star & \star & \star & \star & \star & \star & \star & \star & -\sigma Q \end{bmatrix} < 0, \quad (4)$$

$$P_1 \leq \rho_1 I, \quad (5)$$

$$S \leq \rho_2 I, \quad (6)$$

where $\Pi_1 = -P_1A - A^{\mathrm{T}}P_1 + \rho_1 N_1 + \tau\rho_2 N_1 + I$, $\Pi_2 = -P_2C - C^{\mathrm{T}}P_2 + \rho_1 N_2 + \tau\rho_2 N_2 + I$, $\Pi_3 = -F^{\mathrm{T}} - F + \rho_1 N_3 + \tau\rho_2 N_3$, $\Pi_4 = -M^{\mathrm{T}} - M + \rho_1 N_4 + \tau\rho_2 N_4$.

Proof: Firstly, we show the stochastic stability of gene network (2) with $v(t) \equiv 0$. Consider the following Lyapunov-Krasovskii functional

$$V(t,x(t),y(t)) = V_1(t,x(t),y(t)) + V_2(t,x(t),y(t)) + V_3(t,x(t),y(t)) + V_4(t,x(t),y(t)), \quad (7)$$

where

$$\begin{aligned} V_1(t,x(t),y(t)) &= x^{\mathrm{T}}(t)P_1x(t) + y^{\mathrm{T}}(t)P_2y(t), \\ V_2(t,x(t),y(t)) &= \int_{-\tau}^{0}\int_{t+\theta}^{t} f_1^{\mathrm{T}}(s)Rf_1(s)dsd\theta, \\ V_3(t,x(t),y(t)) &= \int_{-\sigma}^{0}\int_{t+\theta}^{t} f_2^{\mathrm{T}}(s)Qf_2(s)dsd\theta, \\ V_4(t,x(t),y(t)) &= \int_{-\tau}^{0}\int_{t+\theta}^{t} H_1^{\mathrm{T}}(s)SH_1(s)dsd\theta, \end{aligned}$$

with $f_1(t), f_2(t)$ and $H_1(t)$ defined by $f_1(t) = -Ax(t) + Bg(y(t-\sigma(t)))$, $f_2(t) = -Cy(t) + Dx(t-\tau(t))$ and $H_1(t) = H(x(t),y(t),x(t-\tau(t)),y(t-\sigma(t)))$.

Then by the Itô-differential rule [11] and the condition (5), one has

$$\begin{aligned} \mathscr{L}V_1 \leq\ & 2\Big[-x^{\mathrm{T}}(t)P_1Ax(t) + x^{\mathrm{T}}(t)P_1Bg(y(t-\sigma(t))) - y^{\mathrm{T}}(t)P_2Cy(t) \\ & + y^{\mathrm{T}}(t)P_2Dx(t-\tau(t))\Big] + \rho_1\big[x^{\mathrm{T}}(t)N_1x(t) + y^{\mathrm{T}}(t)N_2y(t) \\ & + x^{\mathrm{T}}(t-\tau(t))N_3x(t-\tau(t)) + y^{\mathrm{T}}(t-\sigma(t))N_4y(t-\sigma(t))\big]. \end{aligned} \quad (8)$$

By introducing a free matrix F of appropriate dimensions, we have

$$\begin{aligned}\mathscr{L}V_2 &\leq \tau[-Ax(t)+Bg(y(t-\sigma(t)))]^{\mathrm{T}}R\cdot[-Ax(t)+Bg(y(t-\sigma(t)))]\\ &\quad-\int_{t-\tau(t)}^{t}f_1^{\mathrm{T}}(s)Rf_1(s)ds+2x^{\mathrm{T}}(t-\tau(t))F\cdot\Bigg[x(t)-x(t-\tau(t))\\ &\quad-\int_{t-\tau(t)}^{t}f_1(s)ds-\int_{t-\tau(t)}^{t}H_1(s)d\omega(s)\Bigg]\\ &\leq \tau[-Ax(t)+Bg(y(t-\sigma(t)))]^{\mathrm{T}}R\cdot[-Ax(t)+Bg(y(t-\sigma(t)))]\\ &\quad+2x^{\mathrm{T}}(t-\tau(t))Fx(t)-2x^{\mathrm{T}}(t-\tau(t))Fx(t-\tau(t))\\ &\quad+\tau x^{\mathrm{T}}(t-\tau(t))FR^{-1}F^{\mathrm{T}}x(t-\tau(t)+x^{\mathrm{T}}(t-\tau(t))FS^{-1}F^{\mathrm{T}}x(t-\tau(t)))\\ &\quad+\Bigg(\int_{t-\tau(t)}^{t}H_1(s)d\omega(s)\Bigg)^{\mathrm{T}}S\Bigg(\int_{t-\tau(t)}^{t}H_1(s)d\omega(s)\Bigg).\end{aligned}\tag{9}$$

Similarly, after introducing a free matrix M, one further has

$$\begin{aligned}\mathscr{L}V_3 &\leq \sigma[-Cy(t)+Dx(t-\tau(t))]^{\mathrm{T}}Q\cdot[-Cy(t)+Dx(t-\tau(t))]+2y^{\mathrm{T}}(t-\sigma(t))My(t)\\ &\quad-2y^{\mathrm{T}}(t-\sigma(t))My(t-\sigma(t))+\sigma y^{\mathrm{T}}(t-\sigma(t))MQ^{-1}M^{\mathrm{T}}y(t-\sigma(t)).\end{aligned}\tag{10}$$

Moreover, from Assumption 1 and the condition (6), it is easy to derive

$$\begin{aligned}\mathscr{L}V_4 &\leq \tau\rho_2\Big[x^{\mathrm{T}}(t)N_1x(t)+y^{\mathrm{T}}(t)N_2y(t)+x^{\mathrm{T}}(t-\tau(t))N_3x(t-\tau(t)))\\ &\quad+y^{\mathrm{T}}(t-\sigma(t))N_4y(t-\sigma(t))\Big]-\int_{t-\tau(t)}^{t}H_1^{\mathrm{T}}(s)SH_1(s)ds.\end{aligned}\tag{11}$$

By combining Eqs. (8)-(11), one can get

$$\begin{aligned}\mathscr{L}V &\leq \hat{\xi}^{\mathrm{T}}(t)\Big[\hat{\Gamma}_1+\tau\hat{\Gamma}_2^{\mathrm{T}}R\hat{\Gamma}_2+\hat{\Gamma}_3^{\mathrm{T}}S^{-1}\hat{\Gamma}_3+\tau\hat{\Gamma}_3^{\mathrm{T}}R^{-1}\hat{\Gamma}_3+\sigma\hat{\Gamma}_4^{\mathrm{T}}Q\hat{\Gamma}_4+\sigma\hat{\Gamma}_5^{\mathrm{T}}Q^{-1}\hat{\Gamma}_5\Big]\hat{\xi}(t)\\ &\quad+\Bigg(\int_{t-\tau(t)}^{t}H_1d\omega(s)\Bigg)^{\mathrm{T}}S\Bigg(\int_{t-\tau(t)}^{t}H_1d\omega(s)\Bigg)-\int_{t-\tau(t)}^{t}H_1^{\mathrm{T}}(s)SH_1(s)ds,\end{aligned}\tag{12}$$

where $\hat{\xi}=\left[x^{\mathrm{T}}(t),y^{\mathrm{T}}(t),x^{\mathrm{T}}(t-\tau(t)),y^{\mathrm{T}}(t-\sigma(t)),g^{\mathrm{T}}(y(t-\sigma(t)))\right]^{\mathrm{T}}$, $\hat{\Pi}_1=-P_1A-A^{\mathrm{T}}P_1+\rho_1N_1+\tau\rho_2N_1$, $\hat{\Pi}_2=-P_2C-C^{\mathrm{T}}P_2+\rho_1N_2+\tau\rho_2N_2$, $\hat{\Pi}_3=-F^{\mathrm{T}}-F+\rho_1N_3+\tau\rho_2N_3$, $\hat{\Pi}_4=-M^{\mathrm{T}}-M+\rho_1N_4+\tau\rho_2N_4$, $\hat{\Gamma}_1=\begin{bmatrix}\hat{\Pi}_1 & 0 & F^{\mathrm{T}} & 0 & P_1B\\ \star & \hat{\Pi}_2 & P_2D & M^{\mathrm{T}} & 0\\ \star & \star & \hat{\Pi}_3 & 0 & 0\\ \star & \star & \star & \hat{\Pi}_4 & k\Lambda\\ \star & \star & \star & \star & -\Lambda-\Lambda^{\mathrm{T}}\end{bmatrix}$, $\hat{\Gamma}_2=[-A,0,0,0,B]$, $\hat{\Gamma}_3=[0,0,F^{\mathrm{T}},0,0]$, $\hat{\Gamma}_4=[0,-C,D,0,0]$, $\hat{\Gamma}_5=[0,0,0,M^{\mathrm{T}},0]$.

By Schur complement [12], follows from (4) that

$$\hat{\Gamma} = \hat{\Gamma}_1+\tau\hat{\Gamma}_2^{\mathrm{T}}R\hat{\Gamma}_2+\hat{\Gamma}_3^{\mathrm{T}}S^{-1}\hat{\Gamma}_3+\tau\hat{\Gamma}_3^{\mathrm{T}}R^{-1}\hat{\Gamma}_3+\sigma\hat{\Gamma}_4^{\mathrm{T}}Q\hat{\Gamma}_4+\sigma\hat{\Gamma}_5^{\mathrm{T}}Q^{-1}\hat{\Gamma}_5<0.\tag{13}$$

Then, by taking the mathematical expectation of both sides of (12), one has

$$\mathscr{E}\{\mathscr{L}V(t,x(t),y(t))\}\leq\mathscr{E}\{\hat{\xi}^{\mathrm{T}}(t)\hat{\Gamma}\hat{\xi}(t)\}<0.\tag{14}$$

This implies that the gene networks (2) is stochastically asymptotically stable in the mean square with $v(t) \equiv 0$.

Next, we will show the disturbance attenuation. Consider the same Lyapunov functional (16) with $v(t) \neq 0$.

For a given $\gamma > 0$, we define

$$J(t) = \mathscr{E}\left\{ \int_0^t \left[x^{\mathrm{T}}(s)x(s) + y^{\mathrm{T}}(s)y(s) - \gamma^2 v^{\mathrm{T}}(s)v(s) \right] ds \right\}. \tag{15}$$

It follows from (15) that

$$J(t) \leq \mathscr{E}\left\{ \int_0^t \left[x^{\mathrm{T}}(s)x(s) + y^{\mathrm{T}}(s)y(s) - \gamma^2 v^{\mathrm{T}}(s)v(s) + \mathscr{L}V(s,x(s),y(s)) \right] ds \right\}. \tag{16}$$

Hence,

$$\begin{aligned} S(t): &= x^{\mathrm{T}}(t)x(t) + y^{\mathrm{T}}(t)y(t) - \gamma^2 v^{\mathrm{T}}(t)v(t) + \mathscr{L}V(t,x(t),y(t)) \\ &\leq \xi^{\mathrm{T}}(t)\Gamma\xi(t) - \int_{t-\tau(t)}^{t} H_1^{\mathrm{T}}(s)SH_1(s)ds \\ &\quad + \left(\int_{t-\tau(t)}^{t} H_1 d\omega(s) \right)^{\mathrm{T}} S \left(\int_{t-\tau(t)}^{t} H_1 d\omega(s) \right), \end{aligned} \tag{17}$$

where $\xi(t) = \left[x^{\mathrm{T}}(t), y^{\mathrm{T}}(t), x^{\mathrm{T}}(t-\tau(t)), y^{\mathrm{T}}(t-\sigma(t)), g^{\mathrm{T}}(y(t-\sigma(t))), v^{\mathrm{T}}(t)\right]^{\mathrm{T}}$, $\Gamma = \Gamma_1 + \tau\Gamma_2^{\mathrm{T}} R\Gamma_2 + \Gamma_3^{\mathrm{T}} S^{-1}\Gamma_3 + \tau\Gamma_3^{\mathrm{T}} R^{-1}\Gamma_3 + \sigma\Gamma_4^{\mathrm{T}} Q\Gamma_4 + \sigma\Gamma_5^{\mathrm{T}} Q^{-1}\Gamma_5$, $\Pi_1 = -P_1A - A^{\mathrm{T}}P_1 + \rho_1 N_1 + \tau\rho_2 N_1 + I$, $\Pi_2 = -P_2C - C^{\mathrm{T}}P_2 + \rho_1 N_2 + \tau\rho_2 N_2 + I$, $\Pi_3 = -F^{\mathrm{T}} - F + \rho_1 N_3 + \tau\rho_2 N_3$, $\Pi_4 = -M^{\mathrm{T}} - M + \rho_1 N_4 + \tau\rho_2 N_4$, $\Gamma_1 = \begin{bmatrix} \Pi_1 & 0 & F^{\mathrm{T}} & 0 & P_1B & P_1E \\ \star & \Pi_2 & P_2D & M^{\mathrm{T}} & 0 & 0 \\ \star & \star & \Pi_3 & 0 & 0 & 0 \\ \star & \star & \star & \Pi_4 & k\Lambda & 0 \\ \star & \star & \star & \star & -\Lambda - \Lambda^{\mathrm{T}} & 0 \\ \star & \star & \star & \star & \star & -\gamma^2 I \end{bmatrix}$, $\Gamma_2 = [-A,0,0,0,B,E]$, $\Gamma_3 = [0,0,F^{\mathrm{T}},0,0,0]$, $\Gamma_4 = [0,-C,D,0,0,0]$, $\Gamma_5 = [0,0,0,M^{\mathrm{T}},0,0]$.

Applying the Schur Complement [12], one obtains

$$J(t) \leq \mathscr{E}\left\{ \int_0^t \xi^{\mathrm{T}}(s)\Gamma\xi(s)ds \right\} < 0, \tag{18}$$

which implies that the condition (4) is satisfied. This completes the proof.

In fact, the optimal attenuation level γ^* can be obtained by solving the following constrained optimization problem:

$$\begin{aligned} &\delta_0 = \min_{\rho_1,\rho_2,P_1,P_2,R,Q,S,\Lambda,F,M} \delta \ \text{ with } \ \delta = \gamma^2 \\ &\text{subject to } \ \rho_1 > 0, \rho_2 > 0, P_1 > 0, P_2 > 0, R > 0, \\ &Q > 0, S > 0, \Lambda > 0, F, M \ \text{ and } \ (4)-(6), \end{aligned} \tag{19}$$

then the optimal performance level $\gamma^* = (\delta_0)^{1/2}$.

Remark 1: In [10], the authors investigated stochastic stability of gene networks with disturbance attenuation, where time delays $\tau(t)$ and $\sigma(t)$ are required to be differentiable and satisfy $\dot{\tau}(t) < 1$ and $\dot{\sigma}(t) < 1$. However, the result here has removed these restrictions and it is thus expected that our results are less conservative than the results in [10].

4 Illustrative example

Example: Consider a gene network model [13], which comprises three repressor genes ($i = lacl, tetR$ and cl) and their promoters ($j = cl, lacl$ and $tetR$):

$$\begin{cases} \frac{dx_i}{dt} &= -x_i + \frac{\alpha}{1+y_j^n} + \alpha_0, \\ \frac{dy_i}{dt} &= \beta(x_i - y_i). \end{cases} \tag{20}$$

where $A = \mathrm{diag}(1,1,1)$, $C = \mathrm{diag}(0.5,0.5,0.5)$, $D = \mathrm{diag}(0.5,0.5,0.5)$ and the coupling matrix $B = 0.4 \times \begin{bmatrix} 0 & 0 & 1 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix}$, with 0.4 being the coupling intensity. Time delays are set as $\tau(t) = 0.4 + 0.3|\cos(t)|$, $\sigma(t) = 0.4|\sin(t)|$, which are both not differentiable at some points, it is easy to check that $\tau = 0.7$ and $\sigma = 0.4$.

Without loss of generality, the noise intensity is set as

$$H(x(t), y(t), x(t-\tau(t)), y(t-\sigma(t))) = \Omega_2 x(t-\tau(t)) + \Omega_3 y(t), \tag{21}$$

where $\Omega_2 = \begin{bmatrix} 0.2 & 0.1 & 0 \\ 0 & -0.1 & 0 \\ 0 & 0 & 0.2 \end{bmatrix}, \Omega_3 = \begin{bmatrix} 0.1 & 0 & 0 \\ 0 & 0.2 & -0.1 \\ 0.1 & 0 & 0.1 \end{bmatrix}$. It is easy to verify that $N_1 = 0$, $N_2 = 2\Omega_2^{\mathrm{T}}\Omega_2$, $N_3 = 2\Omega_3^{\mathrm{T}}\Omega_3$ and $N_4 = 0$. Let extrinsic noises $v(t)$ be the Brownian Motion with the covariance 0.04 and $E = \mathrm{diag}(1,1,1)$.

By using the LMI control toolbox, we can get feasible solutions with the optimal attenuation level $\gamma = 0.2617$. Thus, it can be concluded that the system is stochastically stable with the disturbance attenuation level $\gamma = 0.2617$.

Given initial conditions $x(0) = [0.8, 1.2, 0.4]^{\mathrm{T}}$ and $y(0) = [0.3, 0.1, 0.6]^{\mathrm{T}}$ of the networks (20), the simulation results are presented as Fig 1 (a) and (b).

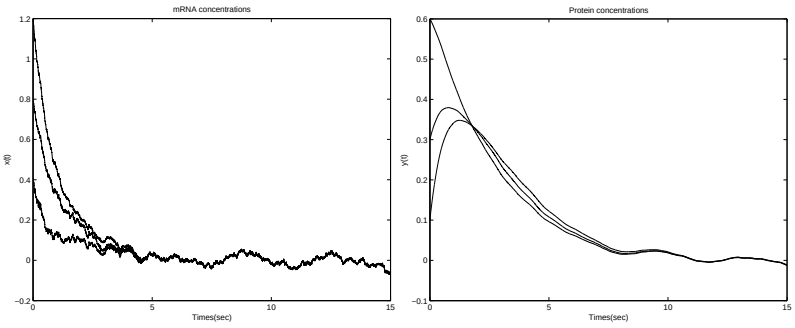

Fig. 1(a) mRNA concentrations x_i. Fig. 1(b) Protein concentrations y_i.

Remark 2: It is noted that time delays $\tau(t)$ and $\sigma(t)$ in this example are not differentiable, which do not satisfy the conditions required in [10], so the results in [10] fail to be used to study this example. Furthermore, in order to make fare comparison with results obtained in [10], we also consider the same time delays as in [10], that is, both of them are differentiable. In this case, after applying the constrained optimization algorithm proposed in this paper, one can get the optimal attenuation level $\gamma^* = 0.1522$, which is much smaller than the level $\gamma = 4.5$ given in [10].

5 Conclusions

In this paper, we have studied the stochastic stability of genetic regulatory networks with extrinsic noises. Based on the Lyapunov stability theory, a delay dependent stochastic stability condition is derived for the genetic networks with intrinsic and extrinsic noises. The derived results do not require the differentiability of the time-varying delays. A numerical example is presented to illustrate the effectiveness of the obtained results.

References

[1] P. Smolen, D. Baxter and J. Byrne, "Mathematical modeling of gene networks," *Neuron*, vol. 26, no. 3, pp. 567-580, Jun. 2000.

[2] A. Becskei and L. Serrano, "Engineering stability in gene networks by autoregulation," *Nature*, vol. 405, no. 6786, pp. 590-593, Jun. 2000.

[3] H. Jong, "Modelling and simulation of genetic regulatory systems: a literature review," *J. Comp. Biol.*, vol. 9, no. 1, pp. 67-103, Jan. 2002.

[4] J. Paulsson, "Summing up the noise in gene networks," *Nature*, vol. 427, no. 6973, pp. 415-418, Jan. 2004.

[5] P. Smolen, D. Baxter and J. Byrne, "A reduced model clarifies the role of feedback loops and time delays in the Drosophila circadian oscillator," *Biophy. J.*, vol. 83, no. 5, pp. 2349-2359, Nov. 2002.

[6] L. Chen and K. Aihara, "Stability of genetic regulatory networks with time delay," *IEEE Trans. Circuits Syst. I*, vol. 49, no. 5, pp. 602-608, May 2002.

[7] L. Chen, R.Wang, T. Zhou and K. Aihara, "Noise-induced cooperative behavior in a multicell system," *Bioinformatics*, vol. 21, no. 11, pp. 2722-2729, Jun. 2005.

[8] C. Li, L. Chen and K. Aihara, "Stability of genetic networks with SUM regulatory logic: Lur'e system and LMI approach," *IEEE Trans. Circuits Syst. I*, vol. 53, no. 11, pp. 2451-2458, Nov. 2006.

[9] F. Ren and J. Cao, "Asymptotic and robust stability of genetic regulatory networks with time-varying delays," *Neurocomputing*, doi:10.1016/j.neucom.2007.03.011, 2007.

[10] C. Li, L. Chen and K. Aihara, "Stochastic stability of genetic networks with disturbance attenuation," *IEEE Trans. Circuits Syst. II*, vol. 54, no. 10, pp. 892-896, Oct. 2007.

[11] X. Mao, "A note on the LaSalle-type theorems for stochastic differential delay equations," *J. Math. Anal. Appl.*, vol. 268, no. 1, pp. 125-142, Apr. 2002.

[12] S. Boyd, L. Ghaoui, E. Feron and V. Balakrishnan, *Linear Matrix Inequalities in Systems and Control Theory*, Philadelphia, PA: SIAM, 1994.

[13] M. Elowitz and S. Leible, "A synthetic oscillatory network of transcriptional regulators," *Nature*, vol. 403, no. 20, pp. 335-338, Jan. 2000.