H_∞ Sampled-Data Controller Design for Stochastic Genetic Regulatory Networks

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Abstract: Artificially regulating gene expression is an important step in developing new treatment for system-level disease such as cancer. In this paper, we propose a method to regulate gene expression based on sampled-data measurements of gene products concentrations. Inherent noisy behaviour of Gene regulatory networks are modeled with stochastic nonlinear differential equation. To synthesize feedback controller, we formulate sampling process as an impulsive system. By using a new Lyapunov function with discontinuities at sampling times, state feedback gain that guarantees exponential mean-square stability and H_∞ performance is derived from LMIs. These LMIs also determine the maximum allowable time between sampling points. A numerical example and a practical application are presented to justify the applicability of the theoretical results.

Keywords: Gene Regulatory Networks, Impulsive Systems, Linear Matrix Inequality, Sampled-Data Control.

1 Introduction

Gene Regulatory Networks (GRNs) are complex networks of numerous genes and proteins with mutual interactions. These networks control various cell functions such as cell growth, differentiation, proliferation and apoptosis by regulating gene expression. Recent advances in cellular scale measurement techniques such as DNA microarray technology provide an incentive to probe underlying mechanisms of coherent behavior of living organisms. Since cellular networks are dynamic systems and full of feedbacks, it seems that studying GRNs in the context of systems theory will provide valuable insight into the functionality of these systems.

To analyze biochemical networks quantitatively, various mathematical models have been used. In many cases, differential equations are efficient tools for investigating dynamical behavior of GRNs [1] and [2]. In [3], GRNs are modeled by nonlinear differential equation in the form of Lur'e systems. Based on this model, stability of GRNs in the presence of noise and delay has been investigated [3-5]. In [6-10], less conservative conditions have been obtained which are dependent on delay's interval. In Refs. [11] and [12], by considering random delays, delay-probability-distribution-dependent stability conditions have been derived. Filter design for stochastic systems such as gene regulatory networks have been studied in [13] and [14].

Regulating gene products concentration in an appropriate range is essential for cells to continue their normal life so that dramatic changes in concentrations may lead to life-threatening disease. For example, it is believed that high level concentration of anti-apoptotic proteins leads to cancer [15]. Recently, discovery of RNAi mechanism enables researchers to silence target gene expression [16]. RNA interference is a post-transcriptional mechanism in which small interfering RNA (SiRNA) degrades encoded RNA and prevents further protein translation. This ability motivates scientists to synthesize new bio-drugs. Due to inherent feedback mechanism in gene networks, simply administration of SiRNA in order to change protein concentration is not sufficient [17]. Therefore, to reorganize abnormal gene expression level, we should consider system level analysis in designing therapeutic inputs.

Recently, artificial control of gene expression has received considerable attention from various researchers [18-20]. In [18] and [19], H_∞ state feedback controller has been designed for stochastic GRNs with constant delay. In [20], memory state feedback design for stochastic GRNs with time varying delay has been considered. In all of [18-20], however, the controller is

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designed in continuous time and it is assumed that system states are always available. This assumption is not possible in real world applications. Where control inputs are only implementable as sampled signals. In [21], finite time H_∞ controller problem has been investigated for discrete time GRNs. Discrete time models are not equal to nonlinear continuous time GRNs even at sampling points. In addition, this approach ignores the phenomena within the sampling intervals such as ripples. In [22], by using input delay approach, sampled data controller has been designed for gene regulatory networks. However, in [22] stochastic noise and disturbance hasn't been considered. Due to small number of molecules in cellular environment, stochastic noises and disturbances has a major role in cellular behavior. To solve such problems, we employ impulsive approach to design H_∞ sampled-data controller for stochastic GRNs.

Sampled-data systems have been investigated thoroughly during past decades. In classic method, the continuous time system is transformed into a discrete time system. It should be noted that these two systems are equivalent only at sampling times. Since GRNs are nonlinear, the transformed system is not equivalent to the initial continuous system even at sampling times. Also, classic methods disregard inter-sample behavior of the system. To deal with such an issue, lifting technique has been presented in [23] and [24]. This approach is although too conservative in dealing with parametric uncertainty. In addition, this method cannot be used in non-periodic sampling cases. Recently, input delay approach has been proposed to deal with uncertain sampling times [25] and [26]. In this approach, sampled input is modeled by continuous input with corresponding delay. By using this approach, H_∞ sampled data filter has been design for Gene regulatory networks [27]. In [28], by introducing new discontinuous Lyapunov function for impulsive systems, stability of uncertain sampled-data systems with non-identical sampling intervals has been studied.

In this paper, we aim to design a state feedback controller which guarantees H_∞ performance based on sampled data measurements. It should be noted that due to random nature of biochemical reactions in cellular environment, gene expression is a noisy process leading to considerable fluctuations in gene products level. So, it is necessary to consider these fluctuations in designing treatment protocols. To model these noisy effects, multiplicative Gaussian noises are added to translation and transcription dynamics. Sampling process is modeled by defining new variables which jump impulsively at sampling times. We propose new Lyapunov function with jump at sampling times to take into account the stochastic disturbances and sampling process. Then, by using appropriate slack matrices, applying congruence transformation and change of variables, we derive sufficient conditions ensuring mean-square exponential stability and H_∞ performance. Since these conditions are presented in the form of LMIs, the feedback gain can easily be obtained by using numerical solvers.

In contrast to the methods in [18-20], the presented method can be used when sampled data information are available. By considering inter-sample behavior, this method provide better disturbance attenuation than discrete time approach presented in [21] Input delay approach which is used in [22] leads to more conservative results. In addition, presence of noise and disturbance reduce controller performance seriously. While MPC approach provided in [29] is fragile in the presence of model's uncertainties and disturbances, our approach is robust against exogenous disturbances.

This paper is organized as follows: In section 2 we present the model of stochastic Genetic regulatory networks and give some definitions and preliminaries. In section 3 we provide the main results on controller design. Section 4 involves a simulation example to verify the effectiveness of the results. In section 5, we give the conclusion of the paper.

2 System Description and Preliminaries

In this paper, the following genetic regulatory networks are considered [3]:

$$\begin{aligned}\frac{dm}{dt} &= -Am(t) + Bg(p(t)) + l \\ \frac{dp}{dt} &= -Cp(t) + Dm(t)\end{aligned} \tag{1}$$

in which

$$\begin{aligned} m(t) &= \left[m_1(t), m_2(t), \ldots, m_n(t)\right]^T \\ P(t) &= \left[p_1(t), p_2(t), \ldots, p_n(t)\right]^T\end{aligned} \tag{2}$$

$m_i(t), p_i(t) \in \mathbb{R}$ represent concentrations of mRNA and protein of i'th gene. The parameters in Eq. (1) are as folllows:

$$\begin{aligned} &A = \mathrm{diag}\left(a_1, a_2, \ldots, a_n\right), \\ &C = \mathrm{diag}\left(c_1, c_2, \ldots, c_n\right), \\ &D = \mathrm{diag}\left(d_1, d_2, \ldots, d_n\right), \\ &l = \left[l_1 \quad l_2 \quad \ldots \quad l_n\right]^T, \\ &g(p(t)) = \left[g_1(p_1(t)) \quad g_2(p_2(t)) \quad \ldots \quad g_n(p_n(t))\right]^T, \end{aligned} \tag{3}$$

These parameters contain information about chemical reaction rates and interaction between nodes. a_i and c_i determine the degradation rates of the corresponding mRNA and protein and d_i represents the translation rate. $B \in \mathbb{R}^{n\times n}$ shows the structure of feedback influences of proteins on mRNA production. Nonlinear function Eq. (4) describe this influence quantitatively, in which β_i is positive constant and H_i is Hill coefficient. l_i is basal rates of mRNA production in transcription process.

$$g_i(x) = (x/\beta_i)^{H_i} / \left(1 + (x/\beta_i)^{H_i}\right) \tag{4}$$

For convenience, we shift an equilibrium point (m^*, p^*) to origin by letting $\bar{m}(t) = m(t) - m^*$, $\bar{p}(t) = p(t) - p^*$. Thus we have:

$$\begin{aligned} \frac{d\bar{m}}{dt} &= -A\bar{m}(t) + Bf(\bar{p}(t)), \\ \frac{d\bar{p}}{dt} &= -C\bar{p}(t) + D\bar{m}(t), \end{aligned} \tag{5}$$

where $f(\bar{p}(t)) = g(p(t)) - g(p^*)$. g_i is monotonically increasing function with bounded derivative, therefore for all a, $b \in \mathbb{R}$ with $a \neq b$

$$0 \le \frac{g_i(a) - g_i(b)}{a - b} \le k_i. \tag{6}$$

Since $f(.)$ is derived by subtracting a constant from $g(.)$, we conclude

$$f(\bar{p})(f(\bar{p}) - K_g\bar{p}) \le 0 \tag{7}$$

where $K_g = \mathrm{diag}(k_1, k_2, \ldots, k_n)$.

Real biological networks are subjected to intrinsic noises and external disturbances. Therefore, we consider gene regulation network as follows:

$$\begin{aligned} \frac{d\bar{m}}{dt} &= \left[-A\bar{m}(t) + Bf(\bar{p}(t)) + E_m v(t)\right]dt \\ &\quad + g_m(\bar{m}(t), \bar{p}(t))d\omega_m(t), \\ \frac{d\bar{p}}{dt} &= \left[-C\bar{p}(t) + D\bar{m}(t) + E_p v(t)\right]dt \\ &\quad + g_p(\bar{m}(t), \bar{p}(t))d\omega_p(t), \end{aligned} \tag{8}$$

where

$$\begin{aligned} \omega_m(t) &= \left[\omega_{m1}(t) \quad \omega_{m2}(t) \quad \ldots \quad \omega_{mn}(t)\right]^T \\ \omega_p(t) &= \left[\omega_{p1}(t) \quad \omega_{p2}(t) \quad \ldots \quad \omega_{pn}(t)\right]^T \end{aligned} \tag{9}$$

are both n-dimensional independent Brownian motions defined on the probability space $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}, P)$. where Ω, $\mathcal{F}$, $\{\mathcal{F}_t\}$, and P are respectively sample space, σ-algebra, filter generated by Brownian motion and probability measure. Functions $g_m(.,.), g_p(.,.)$ satisfy

$$\begin{aligned} &\mathrm{Tr}\left(g_m^T(\bar{m}(t), \bar{p}(t))g_m(\bar{m}(t), \bar{p}(t))\right) \le \\ &\bar{m}^T(t)G_{m1}^T G_{m1}\bar{m}(t) + \bar{p}^T(t)G_{m2}^T G_{m2}\bar{p}(t) \\ &\mathrm{Tr}\left(g_p^T(\bar{m}(t), \bar{p}(t))g_p(\bar{m}(t), \bar{p}(t))\right) \le \\ &\bar{m}^T(t)G_{p1}^T G_{p1}\bar{m}(t) + \bar{p}^T(t)G_{p2}^T G_{p2}\bar{p}(t) \end{aligned} \tag{10}$$

and $G_{mi} \ge 0$ and $G_{pi} \ge 0, (i = 1, 2)$. We assume that disturbance signal belongs to $L_2([0, \infty], \mathbb{R})$.

We assume that we can sample protein and mRNA concentrations, and we are interested in designing sampled-data controller. We define $x(t) = \left[\bar{m}^T(t) \quad \bar{p}^T(t)\right]^T$. Therefore, we have:

$$\begin{aligned} dx(t) &= \left[\tilde{A}x(t) + B_f\tilde{f}(x(t)) + B_u u(t) + \tilde{E}v(t)\right]dt \\ &\quad + \tilde{g}(x(t))d\omega(t) \\ y &= \tilde{L}x(t) \end{aligned} \tag{11}$$

where:

$$\begin{aligned} &\tilde{A} = \begin{bmatrix} -A & 0 \\ D & -C \end{bmatrix}, B_f = \begin{bmatrix} B \\ 0 \end{bmatrix}, \tilde{E} = \begin{bmatrix} E_m \\ E_p \end{bmatrix}, \\ &\omega(t) = \begin{bmatrix} \omega_m(t) \\ \omega_p(t) \end{bmatrix}, \tilde{L} = \begin{bmatrix} L_m & L_p \end{bmatrix}, \\ &\tilde{f}(x(t)) = f(\bar{p}(t)), \tilde{g}(x(t)) = \\ &\mathrm{diag}\left(g_m(\bar{m}(t), \bar{p}(t)), g_p(\bar{m}(t), \bar{p}(t))\right), \end{aligned} \tag{12}$$

y(t) is control output, and $u(t) = Kx(t_k)$, $t_k \le t < t_{k+1}$ is sampled-data state feedback. t_k represents the sampling point. We assume that there exist $\tau_M > 0$ such that $t_{k+1} - t_k \le \tau_M$ for all $k \ge 0$. We define new variable $z(t) := x(t_k)$, $t \in [t_k, t_{k+1})$. Therefore, we have $u(t) = Kz(t)$, $t_k \le t < t_{k+1}$. The derivative of this variable is equal to zero between sampling times, but experience jump at sampling points.

From Eq. (7) and Eq. (10), we conclude:

$$\begin{aligned} &\tilde{f}^T(x(t))(\tilde{f}(x(t)) - \tilde{K}x(t)) \le 0, \tilde{K} = \begin{bmatrix} 0 & K_g \end{bmatrix} \\ &\mathrm{Tr}\left(\tilde{g}^T(x(t))\tilde{g}(x(t))\right) \le x^T(t)\tilde{G}^T\tilde{G}x(t), \\ &\tilde{G} = \mathrm{diag}\left(G_{m_1} + G_{p_1}, G_{m_2} + G_{p_2}\right) \end{aligned} \tag{13}$$

Definition 1 [27]: The system in Eq. (11) with $v(t) = 0$ is said to be exponentially mean-square stable if there exist two scalars ν > 0 and δ > 0 such that:

$$\mathbb{E}\left\{x(t)^2\right\} \le ve^{-\delta t}\mathbb{E}\left\{x(0)^2\right\} \tag{14}$$

Definition 2 [27]: The system in Eq. (11) is said to be exponentially mean-square stable with the γ disturbance attenuation if the dynamics are exponentially mean-square stable with definition 1 and under the zero initial condition, the following disturbance attenuation level is satisfied:

$$\mathbb{E}\left\{x(t)^2\right\} \le ve^{-\delta t}\mathbb{E}\left\{x(0)^2\right\} \tag{15}$$

3 Main Results

In this section, we synthesize sampled-data state feedback controller which provide exponential mean-square stability of GRN. Then the sufficient conditions that guarantee H_∞ performance of the controller are derived.

Theorem 1: There exists a state feedback gain K such that the GRN system in Eq. (11) with zero disturbance is exponentially mean-square stable if there exist symmetric and positive definite matrices Q, $\Gamma=\mathrm{diag}(\gamma_1, \gamma_2, \ldots, \gamma_n)$ matrices Y, $N=\begin{bmatrix} N_1^T & N_2^T & N_3^T \end{bmatrix}^T$ and positive constants ε_1, ε_2, ε_3 and c satisfying the following matrix inequalities:

$$\Psi_1=\begin{bmatrix} \Omega_1 & Y_1 & N & \tau_M Y_2 \\ * & -\left(1+\tau_M\epsilon_2+\tau_M\epsilon_3\right)^{-1}Q & 0 & 0 \\ * & * & -\epsilon_2\left(1-c\tau_M\right)Q & 0 \\ * & * & * & -\tau_M\epsilon_1^{-1}Q \end{bmatrix}<0$$

$$\Psi_2=\begin{bmatrix} \Omega_2 & Y_1 & N & \tau_M Y_2 & \tau_M N \\ * & -\left(1+\tau_M\epsilon_2+\tau_M\epsilon_3\right)^{-1}Q & 0 & 0 & 0 \\ * & * & -\epsilon_2\left(1-c\tau_M\right)Q & 0 & 0 \\ * & * & * & -\tau_M\epsilon_1^{-1}Q & 0 \\ * & * & * & * & -\epsilon_1\left(1-c\tau_M\right)Q \end{bmatrix}<0 \quad (16)$$

in which

$$\Omega_1=\begin{bmatrix} I \\ 0 \\ 0 \end{bmatrix}\begin{bmatrix} Q^T\tilde{A}^T \\ Y^TB_u^T \\ \Gamma B_f^T \end{bmatrix}^T+\begin{bmatrix} Q^T\tilde{A}^T \\ Y^TB_u^T \\ \Gamma B_f^T \end{bmatrix}\begin{bmatrix} I \\ 0 \\ 0 \end{bmatrix}^T+\begin{bmatrix} I \\ 0 \\ 0 \end{bmatrix}cQ\begin{bmatrix} I & 0 & 0 \end{bmatrix}$$
$$-N\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}^T-\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}N^T-\begin{bmatrix} 0 & 0 & -Q\tilde{K}^T \\ * & 0 & 0 \\ * & * & 2\Gamma \end{bmatrix}+\tau_M\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}\epsilon_3\times$$
$$\begin{bmatrix} Q^T\tilde{A}^T \\ Y^TB_u^T \\ \Gamma B_f^T \end{bmatrix}^T-\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}\epsilon_3\left(1-c\tau_M\right)Q\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}^T+\tau_M\begin{bmatrix} Q^T\tilde{A}^T \\ Y^TB_u^T \\ \Gamma B_f^T \end{bmatrix}\epsilon_3\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}^T$$

$$\Omega_2=\begin{bmatrix} I \\ 0 \\ 0 \end{bmatrix}\begin{bmatrix} Q^T\tilde{A}^T \\ Y^TB_u^T \\ \Gamma B_f^T \end{bmatrix}^T+\begin{bmatrix} Q^T\tilde{A}^T \\ Y^TB_u^T \\ \Gamma B_f^T \end{bmatrix}\begin{bmatrix} I \\ 0 \\ 0 \end{bmatrix}^T+\begin{bmatrix} I \\ 0 \\ 0 \end{bmatrix}cQ\begin{bmatrix} I & 0 & 0 \end{bmatrix} \quad (17)$$
$$-N\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}^T-\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}N^T-\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}\epsilon_3Q\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}^T-\begin{bmatrix} 0 & 0 & -Q\tilde{K}^T \\ * & 0 & 0 \\ * & * & 2\Gamma \end{bmatrix}$$

$$N=\mathrm{diag}\left(Q,Q,\Gamma\right)\tilde{N}Q,\ Y_1=\begin{bmatrix} Q\tilde{G}^T \\ 0 \\ 0 \end{bmatrix},Y_2=\begin{bmatrix} Q^T\tilde{A}^T \\ Y^TB_u^T \\ \Gamma B_f^T \end{bmatrix}$$

and State feedback gain is derived as $K=YQ^{-1}$.

Proof: Consider the following Lyapunov function:

$$V\left(x(t),z(t),\tau(t)\right)=x^T(t)Px(t)+$$
$$\int_{t-\tau(t)}^{t}\left(\tau_M-t+s\right)r_o^T(s)Rr_o(s)ds+$$
$$\int_{t-\tau(t)}^{t}\left(\tau_M-t+s\right)\mathrm{Tr}\left(\tilde{g}^T\left(x(s)\right)S\tilde{g}\left(x(s)\right)\right)ds \quad (18)$$
$$+\left(\tau_M-\tau(t)\right)\left(x(t)-z(t)\right)^TX_1\left(x(t)-z(t)\right)$$

where

$$r_o(t)=\tilde{A}x(t)+B_f\tilde{f}\left(x(t)\right)+B_uKz(t) \quad (19)$$

Notice that if $V\left(x(t),z(t),\tau(t)\right)=0$ for $t\neq s_k$, we can conclude that $x^T(t)Px(t)=0$ and $\left(\tau_M-\tau(t)\right)\left(x(t)-z(t)\right)^TX_1\left(x(t)-z(t)\right)=0$. If P > 0 and $X_1>0$, we have $x(t)=0$ and $z(t)=x(t)=0$. Therefore, if $z(t)\neq 0$, $x(t)\neq 0$, then V > 0 for $t\neq s_k$. By using Itô formula, we have:

$$V\left(x(t),z(t),\tau(t)\right)=\mathcal{L}V\left(x(t),z(t),\tau(t)\right)dt$$
$$+2x^T(t)P\tilde{g}\left(x(t)\right)d\omega(t) \quad (20)$$
$$+2\left(x(t)-z(t)\right)^TX_1\tilde{g}\left(x(t)\right)d\omega(t),$$

Since:

$$V\left(x(t),z(t),\tau(t)\right)\leq x^T(t)Px(t)+$$
$$\int_{t-\tau(t)}^{t}\tau_Mr_o^T(s)Rr_o(s)ds+\int_{t-\tau(t)}^{t}\tau_M\mathrm{Tr}\left(\tilde{g}^T\left(x(s)\right)S\tilde{g}\left(x(s)\right)\right)ds$$
$$+\left(\tau_M-\tau(t)\right)\left(x(t)-z(t)\right)^TX_1\left(x(t)-z(t)\right) \quad (21)$$

In which $\mathcal{L}$ is infinitesimal generator. We can derive that:

$$\mathcal{L}V\left(x(t),z(t),\tau(t)\right)+cV\left(x(t),z(t),\tau(t)\right)\leq$$
$$2x^T(t)Pr_o(t)+cx^T(t)Px(t) \quad (22)$$
$$+\mathrm{Tr}\left(\tilde{g}^T\left(x(t)\right)P\tilde{g}\left(x(t)\right)\right)+\tau_Mr_o^T(t)Rr_o(t)$$
$$+\int_{t-\tau(t)}^{t}r_o^T(s)\varpi Rr_o(s)ds+\tau_M\mathrm{Tr}\left(\tilde{g}^T\left(x(t)\right)S\tilde{g}\left(x(t)\right)\right)$$
$$+\int_{t-\tau(t)}^{t}\mathrm{Tr}\left(\tilde{g}^T\left(x(s)\right)\varpi S\tilde{g}\left(x(s)\right)\right)ds$$
$$-\left(x(t)-z(t)\right)^T\left(1-c\left(\tau_M-\tau(t)\right)\right)X_1\left(x(t)-z(t)\right)$$
$$+2\left(\tau_M-\tau(t)\right)r_o^T(t)X_1\left(x(t)-z(t)\right)$$
$$+\left(\tau_M-\tau(t)\right)\mathrm{Tr}\left(\tilde{g}^T\left(x(t)\right)X_1\tilde{g}\left(x(t)\right)\right)$$

in which $\varpi = 1 - c\tau_M$. On the other hand, for any matrix N and an augmented vector $\xi^T(t) = \left[x^T(t) \quad z^T(t) \quad f^T(x(t))\right]$ with appropriate dimension, the following inequality could be written for any positive definite matrix ϖS and ϖR:

$$\begin{aligned}
&2\xi^T(t)N\left(x(t)-z(t)\right) = 2\xi^T(t)N\times \\
&\left(\int_{t-\tau(t)}^{t} r_o(s)ds + \int_{t-\tau(t)}^{t} \tilde{g}\left(x(s)\right)d\omega(s)\right)\le \\
&\xi^T(t)N\left(\tau(t)^{-1}\varpi R\right)^{-1}N^T\xi(t)+ \\
&\left(\int_{t-\tau(t)}^{t} r_o(s)ds\right)^T\left(\tau(t)^{-1}\varpi R\right)\left(\int_{t-\tau(t)}^{t} r_o(s)ds\right)+ \\
&\xi^T(t)N(\varpi S)^{-1}N^T\xi(t)+ \\
&\left(\int_{t-\tau(t)}^{t} g\left(x(s)\right)d\omega(s)\right)^T\varpi S\times\left(\int_{t-\tau(t)}^{t} g\left(x(s)\right)d\omega(s)\right)
\end{aligned} \tag{23}$$

Based on Jenson inequality and Itô isometry we have:

$$\begin{aligned}
&2\xi^T(t)N\left(x(t)-z(t)\right)\le \\
&\tau(t)\xi^T(t)N(\varpi R)^{-1}N^T\xi(t) \\
&+\int_{t-\tau(t)}^{t} r_o^T(s)\varpi R r_o(s)ds+ \\
&+\xi^T(t)N(\varpi S)^{-1}N^T\xi(t)+ \\
&+\int_{t-\tau(t)}^{t} \mathrm{Tr}\left\{g^T\left(x(s)\right)\varpi S g\left(x(s)\right)\right\}ds
\end{aligned} \tag{24}$$

Then from Eq. (24) and Eq. (13), we get

$$\begin{aligned}
&\mathcal{L}V\left(x(t),z(t),\tau(t)\right)+cV\left(x(t),z(t),\tau(t)\right)\le \\
&2x^T(t)Pr_o(t)+cx^T(t)Px(t) \\
&+x^T(t)\tilde{G}^T\left(P+\tau_M S+\tau_M X_1\right)\tilde{G}x(t) \\
&+\tau_M r_o^T(t)Rr_o(t)+\xi^T(t)N(\varpi S)^{-1}N^T\xi(t) \\
&+\tau(t)\xi^T(t)N(\varpi R)^{-1}N^T\xi(t)-2\xi^T(t)N\left(x(t)-z(t)\right) \\
&-\left(x(t)-z(t)\right)^T\left(1-c\left(\tau_M-\tau(t)\right)\right)X_1\left(x(t)-z(t)\right) \\
&+2\left(\tau_M-\tau(t)\right)r_o^T(t)X_1\left(x(t)-z(t)\right) \\
&-2\tilde{f}^T\left(x(t)\right)\Lambda\left(\tilde{f}\left(x(t)\right)-\tilde{K}x(t)\right)
\end{aligned} \tag{25}$$

Then, Eq. (25) can also be rewritten as follows:

$$\begin{aligned}
&\mathcal{L}V\left(x(t),z(t),\tau(t)\right)+cV\left(x(t),z(t),\tau(t)\right)\le \\
&\xi^T(t)\breve{\Omega}\xi(t)+\tau(t)\xi^T(t)N(\varpi R)^{-1}N^T\xi(t) \\
&-\xi^T(t)\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}\left(1-c\left(\tau_M-\tau(t)\right)\right)X_1\begin{bmatrix} I & -I & 0 \end{bmatrix}\xi(t) \\
&+2\left(\tau_M-\tau(t)\right)\xi^T(t)\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}X_1\begin{bmatrix} \tilde{A} & B_u K & B_f \end{bmatrix}\xi(t),
\end{aligned} \tag{26}$$

where

$$\begin{aligned}
\breve{\Omega} &= \begin{bmatrix} I \\ 0 \\ 0 \end{bmatrix}P\begin{bmatrix} \tilde{A} & B_u K & B_f \end{bmatrix}+\begin{bmatrix} \tilde{A} & B_u K & B_f \end{bmatrix}^T P\begin{bmatrix} I \\ 0 \\ 0 \end{bmatrix}^T \\
&+\begin{bmatrix} I \\ 0 \\ 0 \end{bmatrix}cP\begin{bmatrix} I & 0 & 0 \end{bmatrix}+\tau_M\begin{bmatrix} \tilde{A}^T \\ K^T B_u^T \\ B_f^T \end{bmatrix}R\begin{bmatrix} \tilde{A} & B_u K & B_f \end{bmatrix}+\begin{bmatrix} I \\ 0 \\ 0 \end{bmatrix}\times \\
&\tilde{G}^T\left(P+\tau_M S+\tau_M X_1\right)\tilde{G}\begin{bmatrix} I & 0 & 0 \end{bmatrix} \\
&+N(\varpi S)^{-1}N^T-N\begin{bmatrix} I & -I & 0 \end{bmatrix}-\begin{bmatrix} I & -I & 0 \end{bmatrix}^T N^T \\
&-\begin{bmatrix} 0 \\ 0 \\ I \end{bmatrix}\Lambda\begin{bmatrix} -\tilde{K} & 0 & I \end{bmatrix}-\begin{bmatrix} -\tilde{K} & 0 & I \end{bmatrix}^T\Lambda\begin{bmatrix} 0 \\ 0 \\ I \end{bmatrix}^T
\end{aligned} \tag{27}$$

Necessary and sufficient conditions to derive negative definiteness of the right hand side of Eq. (26) are

$$\begin{aligned}
&\breve{\Omega}-\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}\left(1-c\tau_M\right)X_1\begin{bmatrix} I & -I & 0 \end{bmatrix}+\tau_M\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}\times \\
&X_1\begin{bmatrix} \tilde{A} & B_u K & B_f \end{bmatrix}+\tau_M\begin{bmatrix} \tilde{A} & B_u K & B_f \end{bmatrix}^T X_1\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}^T<0, \\
&\breve{\Omega}-\begin{bmatrix} I \\ -I \\ 0 \end{bmatrix}X_1\begin{bmatrix} I & -I & 0 \end{bmatrix}+\tau_M N(\varpi R)^{-1}N^T<0
\end{aligned} \tag{28}$$

By using schur complement Eq. (28) can be written as

$$\begin{aligned}
&\begin{bmatrix} \hat{\Omega}_1 & Y_1 & N & \tau_M Y_2 \\ * & -\left(P+\tau_M S+\tau_M X_1\right)^{-1} & 0 & 0 \\ * & * & -\varpi S & 0 \\ * & * & * & -\tau_M R^{-1} \end{bmatrix}<0 \\
&\begin{bmatrix} \hat{\Omega}_2 & Y_1 & N & \tau_m Y_2 & \tau_M N \\ * & -\left(P+\tau_M S+\tau_M X_1\right)^{-1} & 0 & 0 & 0 \\ * & * & -\varpi S & 0 & 0 \\ * & * & * & -\tau_M R^{-1} & 0 \\ * & * & * & * & -\tau_M \varpi R \end{bmatrix}
\end{aligned} \tag{29}$$

where

$$\hat{\Omega}_1=\begin{bmatrix}I\\0\\0\end{bmatrix}P\begin{bmatrix}\tilde{A} & B_uK & B_f\end{bmatrix}+\begin{bmatrix}\tilde{A} & B_uK & B_f\end{bmatrix}^T P\begin{bmatrix}I\\0\\0\end{bmatrix}^T$$
$$+\begin{bmatrix}I\\0\\0\end{bmatrix}cP\begin{bmatrix}I & 0 & 0\end{bmatrix}-N\begin{bmatrix}I & -I & 0\end{bmatrix}-\begin{bmatrix}I & -I & 0\end{bmatrix}^T N^T$$
$$-\begin{bmatrix}I\\-I\\0\end{bmatrix}\left(1-c\tau_M\right)X_1\begin{bmatrix}I & -I & 0\end{bmatrix}$$
$$-\begin{bmatrix}0\\0\\I\end{bmatrix}\Lambda\begin{bmatrix}-\tilde{K} & 0 & I\end{bmatrix}-\begin{bmatrix}-\tilde{K} & 0 & I\end{bmatrix}^T\Lambda\begin{bmatrix}0\\0\\I\end{bmatrix}^T$$
$$+\tau_M\begin{bmatrix}I\\-I\\0\end{bmatrix}X_1\begin{bmatrix}\tilde{A}^T\\K^TB_u^T\\B_f^T\end{bmatrix}^T+\tau_M\begin{bmatrix}\tilde{A}^T\\K^TB_u^T\\B_f^T\end{bmatrix}X_1\begin{bmatrix}I\\-I\\0\end{bmatrix}^T, \quad (30)$$

$$\hat{\Omega}_2=\begin{bmatrix}I\\0\\0\end{bmatrix}P\begin{bmatrix}\tilde{A} & B_uK & B_f\end{bmatrix}+\begin{bmatrix}\tilde{A} & B_uK & B_f\end{bmatrix}^T P\begin{bmatrix}I\\0\\0\end{bmatrix}^T$$
$$-N\begin{bmatrix}I & -I & 0\end{bmatrix}-\begin{bmatrix}I & -I & 0\end{bmatrix}^T N^T,$$
$$Y_1=\begin{bmatrix}\tilde{G}^T\\0\\0\end{bmatrix},Y_2=\begin{bmatrix}\tilde{A}^T\\K^TB_u^T\\B_f^T\end{bmatrix},$$

Pre and post multiplying Eq. (29) by diag(P^{-1}, P^{-1}, Λ^{-1}, I, P^{-1}, I) and diag(P^{-1}, P^{-1}, Λ^{-1}, I, P^{-1}, I, P^{-1}), and defining $R=\varepsilon_1P$, $S=\varepsilon_2P$, $X_1=\varepsilon_3P$ and $Q=P^{-1}$, we have:

$$\begin{bmatrix}\tilde{\Omega}_1 & \tilde{Y}_1 & \tilde{N} & \tau_M\tilde{Y}_2\\ * & -\left(1+\tau_M\epsilon_2+\tau_M\epsilon_3\right)^{-1}Q & 0 & 0\\ * & * & -\epsilon_2\varpi Q & 0\\ * & * & * & -\tau_M\epsilon_1^{-1}Q\end{bmatrix}<0$$
$$\begin{bmatrix}\tilde{\Omega}_2 & \tilde{Y}_1 & \tilde{N} & \\ * & -\left(1+\tau_M\epsilon_2+\tau_M\epsilon_3\right)^{-1}Q & 0 & \\ * & * & -\epsilon_2\varpi Q & \\ * & * & * & \\ * & * & * & \end{bmatrix}$$
$$\begin{matrix}\tau_m\tilde{Y}_2 & \tau_M\tilde{N}\\ 0 & 0\\ 0 & 0\\ -\tau_m\epsilon_1^{-1}Q & 0\\ * & -\epsilon_1\varpi Q\end{matrix}\Bigg]<0 \quad (31)$$

where

$$\tilde{\Omega}_1=\begin{bmatrix}I\\0\\0\end{bmatrix}\begin{bmatrix}\tilde{A}Q & B_uKQ & B_f\Lambda^{-1}\end{bmatrix}$$
$$+\begin{bmatrix}\tilde{A}Q & B_uKQ & B_f\Lambda^{-1}\end{bmatrix}^T\begin{bmatrix}I\\0\\0\end{bmatrix}^T+\begin{bmatrix}I\\0\\0\end{bmatrix}cQ\begin{bmatrix}I & 0 & 0\end{bmatrix}$$
$$-\tilde{N}\begin{bmatrix}I & -I & 0\end{bmatrix}-\begin{bmatrix}I & -I & 0\end{bmatrix}^T\tilde{N}^T$$
$$-\begin{bmatrix}I\\-I\\0\end{bmatrix}\epsilon_3\left(1-c\tau_M\right)Q\begin{bmatrix}I & -I & 0\end{bmatrix}-\begin{bmatrix}0 & 0 & -Q\tilde{K}^T\\0 & 0 & 0\\-\tilde{K}Q & 0 & 2\Lambda^{-1}\end{bmatrix}$$
$$+\tau_M\begin{bmatrix}I\\-I\\0\end{bmatrix}\epsilon_3\begin{bmatrix}Q^T\tilde{A}^T\\Q^TK^TB_u^T\\\Lambda^{-1}B_f^T\end{bmatrix}^T+\tau_M\begin{bmatrix}Q^T\tilde{A}^T\\Q^TK^TB_u^T\\\Lambda^{-1}B_f^T\end{bmatrix}\epsilon_3\begin{bmatrix}I\\-I\\0\end{bmatrix}^T \quad (32)$$

$$\tilde{\Omega}_2=\begin{bmatrix}I\\0\\0\end{bmatrix}\begin{bmatrix}\tilde{A}Q & B_uKQ & B_f\Lambda^{-1}\end{bmatrix}$$
$$+\begin{bmatrix}\tilde{A}Q & B_uKQ & B_f\Lambda^{-1}\end{bmatrix}^T\begin{bmatrix}I\\0\\0\end{bmatrix}^T+\begin{bmatrix}I\\0\\0\end{bmatrix}cQ\begin{bmatrix}I & 0 & 0\end{bmatrix}$$
$$-\tilde{N}\begin{bmatrix}I & -I & 0\end{bmatrix}-\begin{bmatrix}I & -I & 0\end{bmatrix}^T\tilde{N}^T-\begin{bmatrix}I\\-I\\0\end{bmatrix}\epsilon_3Q\begin{bmatrix}I & -I & 0\end{bmatrix}$$
$$-\begin{bmatrix}0 & 0 & -Q\tilde{K}^T\\0 & 0 & 0\\-\tilde{K}Q & 0 & 2\Lambda^{-1}\end{bmatrix},\ \tilde{Y}_1=\begin{bmatrix}Q\tilde{G}^T\\0\\0\end{bmatrix},\tilde{Y}_2=\begin{bmatrix}Q\tilde{A}^T\\QK^TB_u^T\\\Lambda^{-1}B_f^T\end{bmatrix}$$
$$\tilde{N}=\operatorname{diag}\left(Q,Q,\Lambda^{-1}\right)NQ$$

By defining Y=KQ, we reach LMIs in Eq. (16). Therefore, from Eq. (16) we can conclude that

$$\mathcal{L}V\left(x(t),z(t),\tau(t)\right)+cV\left(x(t),z(t),\tau(t)\right)\le 0,\qquad \text{for } t\ne s_k \quad (33)$$

Now, applying Ito inequality we have:

$$e^{ct}V\left(x(t),z(t),\tau(t)\right)=V\left(x(0),z(0),\tau(0)\right)$$
$$+\int_0^{s_1^-}e^{cs}2\begin{pmatrix}x^T(s)P\\+\left(x(s)-z(s)\right)^TX_1\end{pmatrix}\tilde{g}\left(x(s)\right)d\omega(s)$$
$$+\int_0^{S_1^-}e^{cs}\begin{pmatrix}\mathcal{L}V\left(x(s),z(s),\tau(s)\right)\\+cV\left(x(s),z(s),\tau(s)\right)\end{pmatrix}ds \quad (34)$$
$$+\begin{bmatrix}V\left(x(s_1^+),z(s_1^+),\tau(s_1^+)\right)\\-V\left(x(s_1^-),z(s_1^-),\tau(s_1^-)\right)\end{bmatrix}+\ldots$$
$$+\int_{S_k^-}^{t}e^{cs}\begin{pmatrix}\mathcal{L}V\left(x(s),z(s),\tau(s)\right)\\+cV\left(x(s),z(s),\tau(s)\right)\end{pmatrix}ds$$

From Eq. (33) and

$$V\left(x(t),z(t),\tau(t)\right)\le V\left(x(t^-),z(t^-),\tau(t^-)\right) \quad \text{for } t=s_i, 1\le i\le k \tag{35}$$

we can write,

$$e^{ct}\mathbb{E}\left[V\left(x(t),z(t),\tau(t)\right)\right]\le V\left(x(0),z(0),\tau(0)\right) \tag{36}$$

And finally, the following inequality is derived.

$$\lambda_{\min}(P)\mathbb{E}\left[|x(t)|^2\right]\le e^{-ct}\lambda_{\max}(P)\mathbb{E}\left[|x(0)|^2\right] \tag{37}$$

In the following theorem, controller gains which guarantees H_∞ performance is synthesized.

Theorem 2: Consider the disturbance attenuation level γ is given. There exists a state feedback gain K such that the GRN system in Eq. (11) with zero disturbance is exponentially mean-square stable and under zero initial condition provide guaranteed H_∞ performance, if there exist symmetric and positive definite matrices Q, $\Gamma=\mathrm{diag}(\gamma_1,\gamma_2,\ldots,\gamma_n)$, matrices Y, $M=\left[M_1^T\ M_2^T\ M_3^T\ M_4^T\ M_5^T\right]^T$ and positive constants ε_1, ε_2, ε_3 and c satisfying the following matrix inequalities:

$$\Xi_1=\begin{bmatrix}\Pi_1 & \Delta_1 & \tilde{M} & \tau_M\Delta_2 & \Delta_3\\ * & -(1+\tau_M\varepsilon_2+\tau_M\varepsilon_3)^{-1}Q & 0 & 0 & 0\\ * & * & -\varepsilon_2(1-c\tau_M)Q & 0 & 0\\ * & * & * & -\tau_M\varepsilon_1^{-1}Q & 0\\ * & * & * & * & -I\end{bmatrix}<0,$$

$$\Xi_2=\begin{bmatrix}\Pi_2 & \Delta_1 & \tilde{M} & \tau_M\Delta_2 & \tau_M\tilde{M} & \Delta_3\\ * & -(1+\tau_M\varepsilon_2+\tau_M\varepsilon_3)^{-1}Q & 0 & 0 & 0 & 0\\ * & * & -\int_2(1-c\tau_M)Q & 0 & 0 & 0\\ * & * & * & -\tau_M\varepsilon_1^{-1}Q & 0 & 0\\ * & * & * & * & -\tau_M\varepsilon_1(1-c\tau_M)Q & 0\\ * & * & * & * & * & -I\end{bmatrix}<0, \tag{38}$$

where

$$\Pi_1=\begin{bmatrix}I\\0\\0\\0\end{bmatrix}\begin{bmatrix}Q^T\tilde{A}^T\\Y^TB_u^T\\\Gamma B_f^T\\\tilde{E}\end{bmatrix}^T+\begin{bmatrix}Q^T\tilde{A}^T\\Y^TB_u^T\\\Gamma B_f^T\\\tilde{E}\end{bmatrix}\begin{bmatrix}I\\0\\0\\0\end{bmatrix}^T+\begin{bmatrix}I\\0\\0\\0\end{bmatrix}cQ\begin{bmatrix}I&0&0&0\end{bmatrix}$$

$$-\tilde{M}\begin{bmatrix}I\\-I\\0\\0\end{bmatrix}^T-\begin{bmatrix}I\\-I\\0\\0\end{bmatrix}\tilde{M}-\begin{bmatrix}I\\-I\\0\\0\end{bmatrix}\epsilon_3(1-\tau_M)Q\begin{bmatrix}I&-I&0&0\end{bmatrix}-$$

$$-\begin{bmatrix}0&0&-Q\tilde{K}^T&0\\*&0&0&0\\*&*&2\Gamma&0\\*&*&*&0\end{bmatrix}-\gamma^2\begin{bmatrix}0\\0\\0\\I\end{bmatrix}\begin{bmatrix}0&0&0&I\end{bmatrix}$$

$$+\tau_M\begin{bmatrix}I\\-I\\0\\0\end{bmatrix}\epsilon_3\begin{bmatrix}Q^T\tilde{A}^T\\Y^TB_u^T\\\Gamma B_f^T\\\tilde{E}\end{bmatrix}^T+\tau_M\begin{bmatrix}Q^T\tilde{A}^T\\Y^TB_u^T\\\Gamma B_f^T\\\tilde{E}\end{bmatrix}\epsilon_3\begin{bmatrix}I\\-I\\0\\0\end{bmatrix}^T$$

$$\Pi_2=\begin{bmatrix}I\\0\\0\\0\end{bmatrix}\begin{bmatrix}Q^T\tilde{A}^T\\Y^TB_u^T\\\Gamma B_f^T\\\tilde{E}\end{bmatrix}^T+\begin{bmatrix}Q^T\tilde{A}^T\\Y^TB_u^T\\\Gamma B_f^T\\\tilde{E}\end{bmatrix}\begin{bmatrix}I\\0\\0\\0\end{bmatrix}^T+\begin{bmatrix}I\\0\\0\\0\end{bmatrix}cQ\begin{bmatrix}I&0&0&0\end{bmatrix}$$

$$-\tilde{M}\begin{bmatrix}I\\-I\\0\\0\end{bmatrix}^T-\begin{bmatrix}I\\-I\\0\\0\end{bmatrix}\tilde{M}-\begin{bmatrix}I\\-I\\0\\0\end{bmatrix}\epsilon_3Q\begin{bmatrix}I&-I&0&0\end{bmatrix}-$$

$$\begin{bmatrix}0&0&-Q\tilde{K}^T&0\\*&0&0&0\\*&*&2\Gamma&0\\*&*&*&0\end{bmatrix}-\gamma^2\begin{bmatrix}0\\0\\0\\I\end{bmatrix}\begin{bmatrix}0&0&0&I\end{bmatrix}$$

$$\tilde{M}=\mathrm{diag}(Q,Q,\Gamma,I)MQ$$

$$\Delta_1=\begin{bmatrix}Q\tilde{G}^T\\0\\0\\0\end{bmatrix},\Delta_2=\begin{bmatrix}Q\tilde{A}^T\\Y^TB_u^T\\\Gamma B_f^T\\\tilde{E}^T\end{bmatrix},\Delta_3=\begin{bmatrix}Q\tilde{L}^T\\0\\0\\0\end{bmatrix} \tag{39}$$

controller gain is given by $K=YQ^{-1}$.

Proof: since Eq. (38) implies Eq. (16), based on the theorem 1, exponential mean-square stability of dynamics is guaranteed when $v(t)=0$. We consider this new Lyapunov function,

$$\begin{aligned}V\left(x(t),z(t),\tau(t)\right)&=x^T(t)Px(t)\\&+\int_{t-\tau(t)}^{t}(\tau_M-t+s)r^T(s)Sr^T(s)\mathrm{d}\\&+\int_{t-\tau(t)}^{t}(\tau_M-t+s)Tr\left(\tilde{g}^T(x(t))S\tilde{g}(x(t))\right)\\&+(\tau_M-\tau(t))(x(t)-z(t))^TX_1(x(t)-z(t))\end{aligned} \tag{40}$$

where

$$r(t)=\tilde{A}x(t)+B_f\tilde{f}(x(t))+B_uKz(t)+\tilde{E}v(t) \tag{41}$$

By defining $\bar{\xi}(t)=\begin{bmatrix}\xi^T(t) & v^T(t)\end{bmatrix}^T$, and using the similar method in theorem 1, it is easy to show that,

$$\begin{aligned}&\mathbb{E}\left\{\begin{matrix}\mathcal{L}V(x(t),z(t),\tau(t))\\+cV(x(t),z(t),\tau(t))+y(t)^2-\gamma^2v(t)^2\end{matrix}\right\}\le\\&\bar{\xi}^T(t)\bar{\Pi}\,\bar{\xi}(t)\\&+\tau(t)\,\bar{\xi}^T(t)M\left((1-c\tau_M)R\right)^{-1}M^T\,\bar{\xi}(t)\\&+2\left(\tau_M-\tau(t)\right)\bar{\xi}^T(t)\begin{bmatrix}\tilde{A} & B_uK & B_f & \tilde{E}\end{bmatrix}^T\times\\&X_1\begin{bmatrix}I & -I & 0 & 0\end{bmatrix}\bar{\xi}(t)\\&-\begin{bmatrix}I\\-I\\0\\0\end{bmatrix}\left(1-c\left(\tau_M-\tau(t)\right)\right)X_1\begin{bmatrix}I & -I & 0 & 0\end{bmatrix}\end{aligned} \tag{42}$$

where

$$\begin{aligned}&\bar{\Pi}=\begin{bmatrix}I\\0\\0\\0\end{bmatrix}P\begin{bmatrix}\tilde{A} & B_uK & B_f & \tilde{E}\end{bmatrix}+\begin{bmatrix}\tilde{A} & B_uK & B_f & \tilde{E}\end{bmatrix}^TP\begin{bmatrix}I\\0\\0\\0\end{bmatrix}^T\\&+\begin{bmatrix}I\\0\\0\\0\end{bmatrix}cP\begin{bmatrix}I & 0 & 0 & 0\end{bmatrix}+\begin{bmatrix}\tilde{L}^T\\0\\0\\0\end{bmatrix}\begin{bmatrix}\tilde{L} & 0 & 0 & 0\end{bmatrix}\\&+\tau_M\begin{bmatrix}\tilde{A}^T\\K^TB_u^T\\B_f^T\\\tilde{E}^T\end{bmatrix}R\begin{bmatrix}\tilde{A} & B_uK & B_f & \tilde{E}\end{bmatrix}+\begin{bmatrix}I\\0\\0\\0\end{bmatrix}G^T\times\\&\left(P+\tau_MS+\tau_MX_1\right)G\begin{bmatrix}I & 0 & 0 & 0\end{bmatrix}+M\left((1-c\tau_M)S\right)^{-1}M^T\\&-M\begin{bmatrix}I & -I & 0 & 0\end{bmatrix}-\begin{bmatrix}I & -I & 0 & 0\end{bmatrix}^TM^T-\\&\begin{bmatrix}-\tilde{K} & 0 & I & 0\end{bmatrix}^T\Lambda\begin{bmatrix}0\\0\\I\\0\end{bmatrix}^T-\gamma^2\begin{bmatrix}0\\0\\0\\I\end{bmatrix}\begin{bmatrix}0 & 0 & 0 & I\end{bmatrix}-\begin{bmatrix}I\\-I\\0\\0\end{bmatrix}\times\\&\left(1-c\left(\tau_M-\tau(t)\right)\right)X_1\begin{bmatrix}I & -I & 0 & 0\end{bmatrix}\\&-\begin{bmatrix}0\\0\\I\\0\end{bmatrix}\Lambda\begin{bmatrix}-\tilde{K} & 0 & I & 0\end{bmatrix}\end{aligned} \tag{43}$$

If we have

$$\begin{aligned}&\bar{\Pi}+\tau(t)M\left((1-c\tau_M)R\right)^{-1}M^T\\&-\begin{bmatrix}I\\-I\\0\\0\end{bmatrix}\left(1-c\left(\tau_M-\tau(t)\right)\right)X_1\begin{bmatrix}I & -I & 0 & 0\end{bmatrix}\\&+2\left(\tau_M-\tau(t)\right)\times\begin{bmatrix}\tilde{A} & B_uK & B_f & \tilde{E}\end{bmatrix}^T\times\\&X_1\begin{bmatrix}I & -I & 0 & 0\end{bmatrix}<0\end{aligned} \tag{44}$$

then

$$\mathbb{E}\left\{\begin{matrix}\mathcal{L}V(x(t),z(t),\tau(t))\\+cV(x(t),z(t),\tau(t))+y(t)^2-\gamma^2v(t)^2\end{matrix}\right\}<0 \tag{45}$$

for all nonzero $v(t)$. Since $(x(t_k),e(t_k),z(t_k),0)\le\lim_{t\uparrow t_k}V(x(t),e(t),z(t),\tau(t))$, we have,

$$\begin{aligned}&\mathbb{E}\left\{\int_0^t\left(y(s)^2-\gamma^2v(s)^2\right)ds\right\}=\\&\mathbb{E}\left\{\begin{matrix}\int_0^t\left(\begin{matrix}y(s)^2-\gamma^2v(s)^2\\+\mathcal{L}V(x(s),z(s),\tau(s))\end{matrix}\right)ds\\-V(x(t),z(t),\tau(t))+V(x(0),z(0),\tau(0))\end{matrix}\right\}\end{aligned} \tag{46}$$

Under zero initial condition, we get

$$\begin{aligned}&\mathbb{E}\left\{\int_0^t\left(y(s)^2-\gamma^2v(s)^2\right)ds\right\}\le\\&\mathbb{E}\left\{\int_0^t\left(\begin{matrix}y(s)^2-\gamma^2v(s)^2\\+\mathcal{L}V(x(s),z(s),\tau(s))\end{matrix}\right)ds\right\}\le\\&\mathbb{E}\left\{\int_0^t\left(\begin{matrix}y(s)^2-\gamma^2v(s)^2\\+\mathcal{L}V(x(s),z(s),\tau(s))\\+cV(x(t),z(t),\tau(t))\end{matrix}\right)ds\right\}\le0\end{aligned} \tag{47}$$

Therefore, the H_∞ performance is satisfied. Sufficient and necessary condition to satisfy Eq. (44) is

$$\begin{aligned}&\bar{\Pi}+\tau_M\begin{bmatrix}I & -I & 0 & 0\end{bmatrix}^TX_1\begin{bmatrix}\tilde{A} & B_uK & B_f & \tilde{E}\end{bmatrix}\\&+\begin{bmatrix}\tilde{A} & B_uK & B_f & \tilde{E}\end{bmatrix}^TX_1\begin{bmatrix}I & -I & 0 & 0\end{bmatrix}\\&-\begin{bmatrix}I\\-I\\0\\0\end{bmatrix}\left(1-c\tau_M\right)X_1\begin{bmatrix}I & -I & 0 & 0\end{bmatrix}<0\end{aligned}$$

$$\bar{\Pi}+\tau_MM\left((1-c\tau_M)R\right)^{-1}M^T<0 \tag{48}$$

By using schur complement Eq. (48) can be written as,

$$\begin{bmatrix} \breve{\Pi}_1 & \breve{\Delta}_1 & \mathrm{M} & \mathrm{M} & \tau_m\breve{\Delta}_2 & \breve{\Delta}_3 \\ * & -\left(\mathrm{P}+\tau_M\mathrm{S}+\tau_M\mathrm{X}_1\right)^{-1} & 0 & 0 & 0 & 0 \\ * & * & -\left(1-c\tau_M\right)\mathrm{S} & -\left(1-c\tau_M\right)\mathrm{S} & 0 & 0 \\ * & * & * & * & -\tau_M\mathrm{R}^{-1} & 0 \\ * & * & * & * & * & -\mathrm{I} \end{bmatrix} < 0$$

$$\begin{bmatrix} \breve{\Pi}_2 & \breve{\Delta}_1 & \mathrm{M} & \tau_m\breve{\Delta}_2 & \tau_M\mathrm{M} & \breve{\Delta}_3 \\ * & -\left(\mathrm{P}+\tau_M\mathrm{S}+\tau_M\mathrm{X}_1\right)^{-1} & 0 & 0 & 0 & 0 \\ * & * & -\left(1-c\tau_M\right)\mathrm{S} & 0 & 0 & 0 \\ * & * & * & -\tau_M\mathrm{R}^{-1} & 0 & 0 \\ * & * & * & * & -\tau_M\left(1-c\tau_M\right)\mathrm{R} & 0 \\ * & * & * & * & * & -\mathrm{I} \end{bmatrix} < 0 \quad (49)$$

where

$$\breve{\Pi}_1 = \begin{bmatrix} I \\ 0 \\ 0 \\ 0 \end{bmatrix} P\begin{bmatrix} \tilde{A} & B_u K & B_f & \tilde{E} \end{bmatrix} + \begin{bmatrix} \tilde{A} & B_u K & B_f & \tilde{E} \end{bmatrix}^T P \begin{bmatrix} I \\ 0 \\ 0 \\ 0 \end{bmatrix}^T - M\begin{bmatrix} I & -I & 0 & 0 \end{bmatrix} - \begin{bmatrix} I & -I & 0 & 0 \end{bmatrix}^T M^T +$$

$$\begin{bmatrix} I \\ 0 \\ 0 \\ 0 \end{bmatrix} cP\begin{bmatrix} I & 0 & 0 & 0 \end{bmatrix} - \begin{bmatrix} 0 \\ 0 \\ I \\ 0 \end{bmatrix} \Lambda\begin{bmatrix} -\tilde{K} & 0 & I & 0 \end{bmatrix} - \begin{bmatrix} -\tilde{K} & 0 & I & 0 \end{bmatrix}^T \Lambda \begin{bmatrix} 0 \\ 0 \\ I \\ 0 \end{bmatrix}^T - \begin{bmatrix} I \\ -I \\ 0 \\ 0 \end{bmatrix} \left(1-c\tau_M\right) X_1 \begin{bmatrix} I & -I & 0 & 0 \end{bmatrix} -$$

$$\gamma^2 \begin{bmatrix} 0 \\ 0 \\ 0 \\ I \end{bmatrix} \begin{bmatrix} 0 & 0 & 0 & I \end{bmatrix} + \tau_M \begin{bmatrix} I \\ -I \\ 0 \\ 0 \end{bmatrix} X_1 \begin{bmatrix} \tilde{A}^T \\ K^T B_u^T \\ B_f^T \\ \tilde{E}^T \end{bmatrix}^T + \tau_M \begin{bmatrix} \tilde{A}^T \\ K^T B_u^T \\ B_f^T \\ \tilde{E}^T \end{bmatrix} X_1 \begin{bmatrix} I \\ -I \\ 0 \\ 0 \end{bmatrix}^T$$

$$\breve{\Pi}_2 = \begin{bmatrix} I \\ 0 \\ 0 \\ 0 \end{bmatrix} P\begin{bmatrix} \tilde{A} & B_u K & B_f & \tilde{E} \end{bmatrix} + \begin{bmatrix} \tilde{A} & B_u K & B_f & \tilde{E} \end{bmatrix}^T P \begin{bmatrix} I \\ 0 \\ 0 \\ 0 \end{bmatrix}^T + \begin{bmatrix} I \\ 0 \\ 0 \\ 0 \end{bmatrix} cP\begin{bmatrix} I & 0 & 0 & 0 \end{bmatrix} - M\begin{bmatrix} I & -I & 0 & 0 \end{bmatrix} -$$

$$\begin{bmatrix} I & -I & 0 & 0 \end{bmatrix}^T M^T - \begin{bmatrix} I \\ -I \\ 0 \\ 0 \end{bmatrix} X_1 \begin{bmatrix} I & -I & 0 & 0 \end{bmatrix} - \begin{bmatrix} 0 \\ 0 \\ I \\ 0 \end{bmatrix} \Lambda\begin{bmatrix} -\tilde{K} & 0 & I & 0 \end{bmatrix} - \begin{bmatrix} -\tilde{K} & 0 & I & 0 \end{bmatrix}^T \Lambda \begin{bmatrix} 0 \\ 0 \\ I \\ 0 \end{bmatrix}^T -$$

$$\gamma^2 \begin{bmatrix} 0 \\ 0 \\ 0 \\ I \end{bmatrix} \begin{bmatrix} 0 & 0 & 0 & I \end{bmatrix}, \quad \breve{\mathrm{Y}}_1 = \begin{bmatrix} \tilde{G}^T \\ 0 \\ 0 \\ 0 \end{bmatrix}, \breve{\mathrm{Y}}_2 = \begin{bmatrix} \tilde{A}^T \\ K^T B_u^T \\ B_f^T \\ \tilde{E}^T \end{bmatrix}, \breve{\Delta}_3 = \begin{bmatrix} \tilde{L}^T \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad (50)$$

Pre and post multiplying Eq. (50) by $\mathrm{diag}\left(\mathrm{P}^{-1},\mathrm{P}^{-1},\Lambda^{-1},\mathrm{I},\mathrm{I},\mathrm{P}^{-1},\mathrm{I}\right)$, $\mathrm{diag}\left(\mathrm{P}^{-1},\mathrm{P}^{-1},\Lambda^{-1},\mathrm{I},\mathrm{I},\mathrm{P}^{-1},\mathrm{I},\mathrm{P}^{-1}\right)$ and defining $\mathrm{R}=\varepsilon_1\mathrm{P}$, $\mathrm{S}=\varepsilon_2\mathrm{P}$, $\mathrm{X}_1=\varepsilon_3\mathrm{P}$, $\mathrm{Q}=\mathrm{P}^{-1}$ and Y=KQ LMIs in (38) are obtained.

4 Simulations

In this section, we examine our results to show the effectiveness of our method.

Example 1: Consider a GRN system with the following parameters:

$$A=\begin{bmatrix}0.4 & 0 & 0\\ 0 & 0.2 & 0\\ 0 & 0 & 0.1\end{bmatrix},\quad B=2.5\begin{bmatrix}0 & 0 & -1\\ -1 & 0 & 0\\ 0 & -1 & 0\end{bmatrix},$$

$$D=0.8\begin{bmatrix}1 & 0 & 0\\ 0 & 1 & 0\\ 0 & 0 & 1\end{bmatrix},\quad C=0.9\begin{bmatrix}1 & 0 & 0\\ 0 & 1 & 0\\ 0 & 0 & 1\end{bmatrix}, \tag{51}$$

$$E_m=\begin{bmatrix}0.2\\ 0.15\\ 0.1\end{bmatrix},\quad E_p=\begin{bmatrix}0.18\\ 0.21\\ 0.25\end{bmatrix},\quad l=\begin{bmatrix}2.5\\ 2.5\\ 2.5\end{bmatrix}.$$

The regulation function is assumed to be $g_i(p_i)=\frac{p_i^2}{(1+p_i^2)}$ $(i=1,2,3)$. It can be easily getting that $k=3\sqrt{3}/8$. We consider the intensity functions of intrinsic noises and the output matrices as follows:

$$\begin{aligned}&G_{m1}=0.25I, G_{m2}=0.25I,\\ &G_{p1}=0.25I, G_{p2}=0.25I,\\ &L_m=0.2\begin{bmatrix}1 & 1 & 1\end{bmatrix},\ L_p=0.2\begin{bmatrix}1 & 1 & 1\end{bmatrix}\end{aligned} \tag{52}$$

To synthesize controller gain, we choose $\gamma = 0.5$ and $\tau_M = 0.2$. The controller gain is derived as follows

$$K=\begin{bmatrix}-2.4611 & -0.1705 & -0.1265\\ -0.1151 & -2.5384 & -0.1686\\ -0.1606 & -0.1155 & -2.5725\\ -0.8222 & -0.1769 & 0.5920\\ 0.6100 & -0.8094 & -0.1717\\ -0.1610 & 0.6133 & -0.7925\end{bmatrix} \tag{53}$$

The simulation results are presented in Figs. 1 and Fig. 2. Initial values are coincide with equilibrium point:

$$\begin{bmatrix}m^* & p^*\end{bmatrix}=$$
$$\begin{bmatrix}7.634 & 8.32 & 0.8982 & 6.785 & 7.394 & 0.7984\end{bmatrix}^T \tag{54}$$

The disturbance signal is considered as v(t) = 5exp(-0.1t). The disturbance attenuation level is derived smaller than $\gamma = 0.5$.

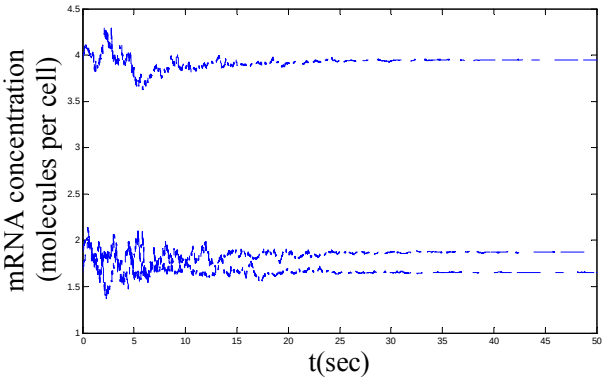

Fig. 1 mRNAs concentration in the presence of control.

Then, we consider nonzero initial states and show the results in Fig. 3. As can be seen, errors approach zero exponentially.

Next, we compare our method with the one proposed in [22] in presence of uncertainty and noise. We consider similar system presented in (51), and for $\tau_M = 0.1$ derive the feedback gain from LMIs presented in [22]. We simulate both systems with the noise intensity $G_{m1}=0, G_{m2}=0.5I, G_{p1}=0.5I, G_{p2}=0$ and disturbance $v(t)=5\exp(-0.1t)$. As can be seen in Figs. 4 and Fig. 5, our method show better results. It is noticeable that considering exponential stability in our method may lead to reduction in response speed.

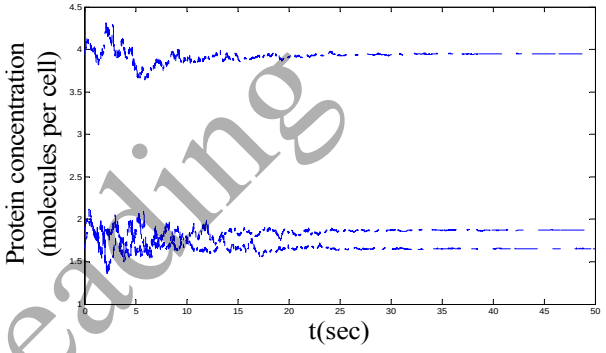

Fig. 2 proteins concentration in the presence of control.

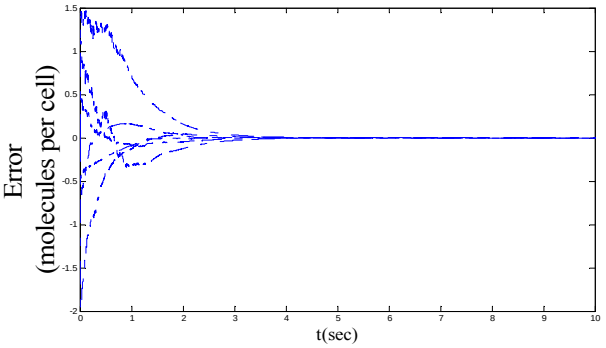

Fig. 3 exponential stability in the presence of initial state.

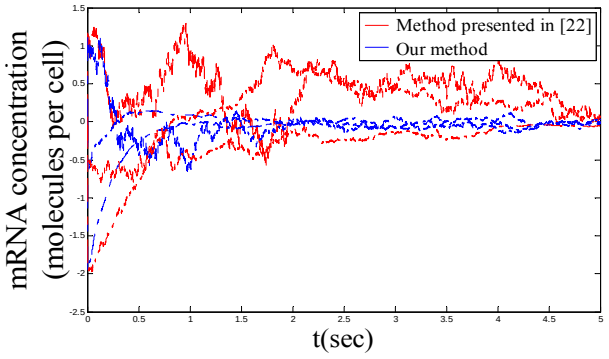

Fig. 4 mRNA concentration comparison.

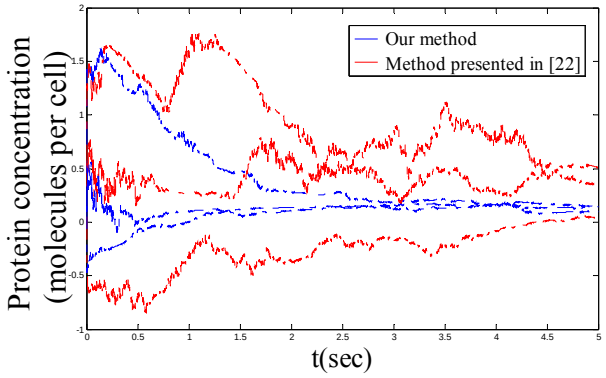

Fig. 5 protein concentrations comparison.

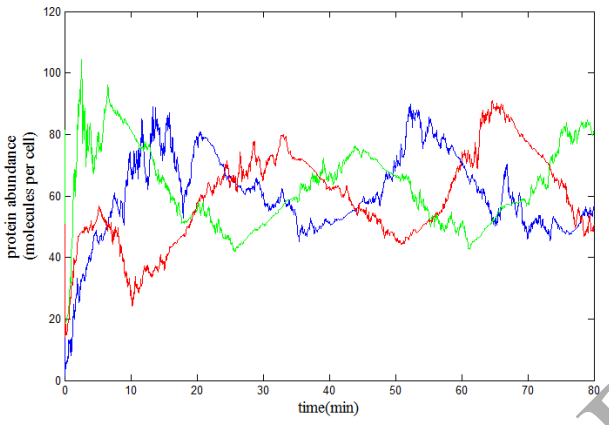

Fig. 6 protein concentrations of repressilator network without control.

Example 2: The repressilator is a synthetic genetic circuit which is proposed by Elowitz and Leibler [30]. It consists of three genes in a loop. Each gene has an inhibitory effect on the next gene production. Following model has been suggested for this gene network [30]:

$$\begin{aligned}
\frac{d}{dt}m_1(t) &= \alpha_0 + \frac{\alpha}{1+p_3^2(t)} - m_1(t)\\
\frac{d}{dt}m_2(t) &= \alpha_0 + \frac{\alpha}{1+p_1^2(t)} - m_2(t)\\
\frac{d}{dt}m_3(t) &= \alpha_0 + \frac{\alpha}{1+p_2^2(t)} - m_3(t)\\
\frac{d}{dt}p_1(t) &= \beta m_1(t) - \beta p_1(t)\\
\frac{d}{dt}p_2(t) &= \beta m_2(t) - \beta p_2(t)\\
\frac{d}{dt}p_3(t) &= \beta m_3(t) - \beta p_3(t)
\end{aligned} \tag{55}$$

In which $\alpha_0 = 0.03$ molecule per cell.min^{-1}, $\beta = 2$ min^{-1} and $n = 2$. By considering $\alpha = 5$, the equilibrium point will be:

$$\begin{bmatrix} m^* & p^* \end{bmatrix} = \begin{bmatrix} 61.25 & 61.25 & 61.25 & 61.25 & 61.25 & 61.25 \end{bmatrix}^T \tag{56}$$

Fig. 6 shows the behavior of the network in presence of noise with intensity $G_{m1} = 0$, $G_{m2} = 0.25I$, $G_{p1} = 0.25I$, $G_{p2} = 0$, disturbance $v(t) = 5\exp(-0.1t)$. Parameters of the system will be:

$$\begin{gathered}
A = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix},\ B = 5\begin{bmatrix} 0 & 0 & -1 \\ -1 & 0 & 0 \\ 0 & -1 & 0 \end{bmatrix},\ B_f = \begin{bmatrix} 1 \\ 1 \\ 1 \end{bmatrix}\\
D = 0.2*\begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix},\ C = 0.2*\begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}\\
E_m = \begin{bmatrix} 0.2 \\ 0.15 \\ 0.1 \end{bmatrix},\ E_p = \begin{bmatrix} 0.18 \\ 0.21 \\ 0.25 \end{bmatrix}\\
G_{m1} = 0, G_{m2} = 0.25I, G_{p1} = 0.25I, G_{p2} = 0\\
L_m = 0.33*\begin{bmatrix} 1 & 1 & 1 \end{bmatrix},\ L_p = 0.33*\begin{bmatrix} 1 & 1 & 1 \end{bmatrix}
\end{gathered} \tag{57}$$

For $\tau_M = 1.1478$ min, $L_m = 0.2[1\ 1\ 1]$, $L_p = 0.2[1\ 1\ 1]$ and $\gamma = 1$, feedback gain is derived as:

$$K = \begin{bmatrix} -1.3207 & -0.1564 & -0.2366 & -4.9342 & -0.4463 & -1.3277 \\ -0.2333 & -1.3214 & -0.1634 & -1.3282 & -4.9817 & -0.3437 \\ -0.1727 & -0.2502 & -1.3297 & 0.3322 & -1.4127 & -4.9815 \end{bmatrix} \tag{58}$$

This controller can be implemented by using silico feedback control for in vivo regulation as shown in [30]. Systems trajectories in presence of designed controller are shown in Fig. 7.

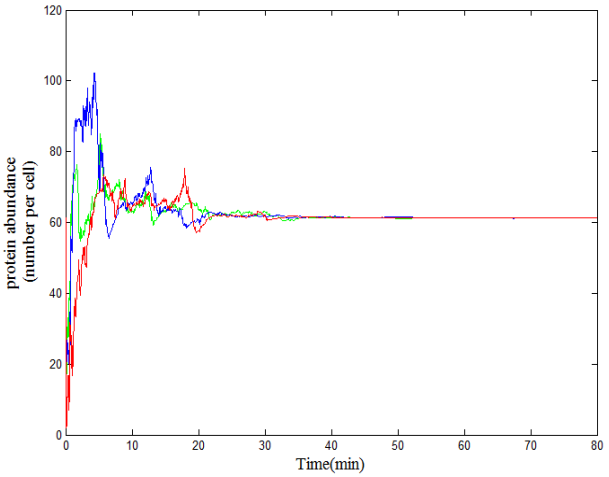

Fig. 7 protein concentrations of repressilator network with control.

10 Conclusion

In this paper, we have dealt with the problem of Sampled-data H_∞ control design for gene regulatory networks with stochastic perturbations. Based on impulsive approach and exploiting discontinuous Lyapunov functions, sampled data feedback control with prescribed H_∞ performance is designed for stochastic GRNs. By using stochastic analysis methods the existing results for sampled-data control of deterministic systems is developed for stochastic GRNs. Finally, the effectiveness of the proposed method for H_∞ control design has been shown by simulations.

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