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Decentralized Controller Design for Stochastic Gene Regulatory Networks

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Abstract

Background and Objectives: Regulation of protein expression in cellular level are so challenging. In cellular scale, biochemical processes are intrinsically noisy and many convenient controllers aren't physically implementable.
Methods: In this paper, we consider standard Lyapunov function and by using Ito formula and stochastic analysis, we derive sufficient conditions for noise to state stability presented in the form of matrix inequalities. In the next step, by defining appropriate change of variables, matrix inequalities are transformed to Linear matrix inequalities which can be used to synthesize controller with the desired structure.
Results: This paper deals with the design of implementable controller for stochastic gene regulatory networks with multiplicative and additive noises. In particular, we consider structural limitations that are present in real cellular systems and design the decentralized feedback that guarantees noise to state stability. Since the proposed conditions for controller design are in the form of linear matrix inequalities, controller gains can be derived efficiently through solving presented LMIs numerically. It is noteworthy that Because of its simple structure, the proposed controller can be implemented universally in many cells. Moreover, we consider a synthetic gene regulatory networks and investigate the effectiveness of the proposed controller by simulations.
Conclusion: Our results provide a new method for designing Decentralized controller in gene regulatory networks with intrinsic and extrinsic noises. the proposed controller can be easily implemented in cellular environment.

Introduction

Proteins provide vital functions in cells, such as controlling the metabolism of a cell, regulating transcription and translation process and directing signal transduction. Therefore, adjusting expression levels of proteins is essential for cells to perform their biological functions. To this end, a collection of genes interacts with each other through specific proteins which are called transcription factors. This complex network of interactions which regulates gene expression is called gene regulatory network.

Mathematical methods have been used widely for analysis of physiological systems [1]-[4]. Recently, understanding the mechanism responsible for regulating gene expression has attracted considerable attention. Accordingly, different methods have been proposed to model these networks. In many applications, differential equations are successfully used to describe the dynamical behavior of GRNs [5]. Due to biological importance of homeostasis, stable behavior of GRNs has been investigated in [6]. In living organisms, parameters are highly uncertain and different from cell to cell or in a

cell in different times. In addition, nonlinear terms are ubiquitous in these networks. Generally, such nonlinearities are not precisely known. Therefore, various methods have been proposed to deal with these uncertainties in biochemical networks [7]-[9]. In some cells, transcription and translation are considerably time consuming. These time delays may influence on GRNs stability [10]-[13]. Recent progress in biotechnology has led to dramatic advances for controlling gene products at cellular scale [14]. Controlling protein concentrations may enable us to treat systematic disease such as cancer [15]. It also may help us to produce valuable biomaterials efficiently or reprogram cell's fate [16]. There are two main approaches for controlling cellular networks. In first approach, in silico feedback control has been designed to steer protein level to the desired value [17], [18]. In second approach, synthetic genetic circuits are employed to regulate gene expressions [19], [20]. Some synthetic architecture has been proposed to implement negative feedback controller in cells. In [21], [22], a universal synthetic feedback controller is introduced which can be easily portable to the broad range of processes. This synthetic circuit which is based on siRNA technology enables us to realize negative feedback control in gene regulatory networks [21]. The proposed feedback mechanism is such that the concentration of each mRNA only affect the expression of the corresponding gene. This feedback architecture poses limitations on controller structure that should be considered in designing feedback gain. Decentralized controllers are special case of these structured feedback controllers [23]. In cellular scale, random nature of molecular reactions affects the behavior of GRNs considerably [24]. Since the synthetic controller is implemented through low copy number of molecules, it seems necessary that the performance of the proposed controller should be guaranteed in presence of intrinsic and extrinsic noises [22]. To model these stochastic fluctuations, we consider both additive and multiplicative noises. Recently, some theoretical studies aimed to design controller for gene networks. In [25], observer based H_∞ controller has been designed for Gene regulatory networks. Controller design for GRNs with switching mechanism has been investigated in [26]. Fuzzy controller has also been proposed for controlling gene networks [27]. however, in previous studies practical aspects such as structural limitations in feedback architecture haven't been considered yet. In this article, we proposed new method for designing decentralized and structured synthetic controller which can be implemented in broad range of applications. Furthermore, the proposed controller guarantees stability and performance in presence of intrinsic and extrinsic noises. This paper is organized as follows: Section 2 describes the model of stochastic Genetic regulatory networks and the controller structure and gives some definitions and preliminaries on stochastic stability of GRNs. Section 3 presents the main results on decentralized controller design and gives simulation examples and finally Section 4 concludes the paper.

Problem statement

In this paper, we consider following compact form of genetic regulatory networks [6]:

$$\begin{aligned} dx = &\left[-Ax(t) + Bf\big(y(t)\big) + B_x u_x(t)\right]dt \\ &+ \sigma_x\big(x(t)\big)d\omega_{x1}(t) \\ &+ \Sigma_x(t)d\omega_{x2}, \end{aligned} \tag{1}$$

$$\begin{aligned} &dy \\ &= \left[-Cy(t) + Dx(t) + B_y u_y(t)\right]dt \\ &+ \sigma_y\big(y(t)\big)d\omega_{x1}(t)d\omega_{y1}(t) + \Sigma_y(t)d\omega_{y2}, \end{aligned}$$

in which $x(t) = [x_1(t), x_2(t), \dots, x_n(t)]^T$, $y(t) = [y_1(t), y_2(t), \dots, y_n(t)]^T$ are states of the considered system. $x_i(t), y_i(t) \in \mathbb{R}$ represent the deviation of the mRNAs and proteins concentrations respect to equilibrium point. The parameters in (1) has a particular structure as follows:

$$\begin{aligned} &A = diag(a_1, a_2, \dots, a_n), \\ &C = diag(c_1, c_2, \dots, c_n), \\ &D = diag(d_1, d_2, \dots, d_n), \\ &l = [l_1 \quad l_2 \quad \dots \quad l_n]^T, \\ &f\big(x(t)\big) = \\ &\left[f_1\big(x_1(t)\big) \quad f\big(x_2(t)\big) \quad \dots \quad f_n\big(x_n(t)\big)\right]^T, \end{aligned} \tag{2}$$

$-a_i x_i(t)$ and $-c_i y(t)$ terms represent degradation process of mRNA and protein and $d_i m_i(t)$ term denote the translation. $B \in \mathbb{R}^{n\times n}$ shows the interaction graph of the genetic network. Nonlinear function $f_i\big(y(t)\big)$ quantifies the effect of protein on gene transcription. This function is defined as:

$$f_i\big(\mathrm{y_i}(t)\big) = g_i(y_i(t) + p_i^*) - g_i(p_i^*), \tag{3}$$

where $g_i(p(t)) = \big((t)/\beta_j\big)^{H_j} / \Big(1 + \big(p(t)/\beta_j\big)^{H_j}\Big)$ is in the form of Hill function and p_i^* is steady state value of the i'th protein concentration. Moreover, $\omega_{x1}(t) = [\omega_{x11}(t) \quad \omega_{x12}(t) \quad \dots \quad \omega_{x1n}(t)]^T$, $\omega_{x2}(t) = [\omega_{x21}(t) \quad \omega_{x22}(t) \quad \dots \quad \omega_{x2n}(t)]^T$, $\omega_{y1}(t) = \left[\omega_{y11}(t) \quad \omega_{y12}(t) \quad \dots \quad \omega_{y1n}(t)\right]^T$ and $\omega_{y2}(t) = \left[\omega_{y21}(t) \quad \omega_{y22}(t) \quad \dots \quad \omega_{y2n}(t)\right]^T$ are n-dimensional independent Brownian motions defined on the probability space$(\Omega, \mathcal{F}, \{\mathcal{F}_t\}, P)$. We consider functions $\sigma_x(.,.), \sigma_y(.,.)$ with the following properties:

$$\begin{aligned} &Tr\left(\sigma_x^T\big(x(t)\big)\sigma_x\big(x(t)\big)\right) \le x^T(t)G_x^T G_x x(t) \\ &Tr\left(\sigma_y^T\big(y(t)\big)\sigma_y\big(y(t)\big)\right) \le y^T(t)G_y^T G_y y(t) \end{aligned} \tag{4}$$

and $G_x \ge 0$ and $G_y \ge 0$.

Since g_i is increasing with rate limitation, its derivative lies in a bounded positive interval, and we have for all $a, b \in \mathbb{R}$ with $a \neq b$

$$0 \leq \frac{g_i(a) - g_i(b)}{a - b} \leq k_i. \tag{5}$$

By definition of $f_i(.)$, we can conclude that its derivative belongs to the interval $[0, k]$. Moreover, we have $f_i(0) = g_i(0 + p^*) - g_i(p^*) = 0$. Therefore, $f(.)$ lies in a sector or equivalently

$$f(y(t))\big(f(y(t)) - K_g y(t)\big) \leq 0 \tag{6}$$

where $K_g = diag(k_1, k_2, \dots, k_n)$.

In this article, we consider decentralized state feedback terms, $u_x(t) = K_{xD}x(t)$ and $u_y(t) = K_{yD}y(t)$ where K_{xD} and K_{yD} are diagonal. This kind of controllers can be implemented more easily than usual full state controller in cellular environment.

To derive the main result in the next section, we use the theorem that guarantees noise to state stability. To state the theorem, we define the following variables:

$$\begin{aligned} &z = [x, y]^T, \\ &\Upsilon(z,t) \\ &= \begin{bmatrix} -Ax(t) + Bf\big(y(t)\big) + B_x u_x(t) \\ -Cy(t) + Dx(t) + B_y u_y(t) \end{bmatrix} \\ &\Psi(z,t,\Sigma(t)) = \begin{bmatrix} \sigma_x\big(x(t)\big) & \Sigma_x(t) \\ \sigma_y\big(y(t)\big) & \Sigma_y(t) \end{bmatrix} \\ &\omega = [\omega_x \quad \omega_y]^T \\ &\Sigma(t) = \begin{bmatrix} \Sigma_x(t) \\ \Sigma_y(t) \end{bmatrix} \end{aligned} \tag{7}$$

Now, (1) can be written as follows:

$$dz = \Upsilon(z,t)dt + \Psi(z,t,\Sigma(t))d\omega \tag{8}$$

Theorem 1 [28]: Consider the system presented in (8). Suppose there exist a C^2 function $V: \mathbb{R}^{2\times n} \to \mathbb{R}_+$, a constant $c > 0$, class $\mathcal{K}_\infty$ function α_1, α_2 and a Borel measurable, increasing function $\gamma: \mathbb{R}_+ \to \mathbb{R}_+$, such that:

$$\begin{aligned} &\alpha_1(|z|) \leq V(z) \leq \alpha_2(|z|) \\ &\mathcal{L}V(z,t,\Sigma(t)) \\ &\triangleq \frac{\partial V}{\partial z}\Upsilon(z,t) \\ &+ \frac{1}{2}Tr\left\{\Psi(z,t,\Sigma(t))^T \frac{\partial^2 V}{\partial z^2} b(z,t)\right\} \\ &\leq -cV(z) + \gamma(|\Sigma\Sigma^T|) \end{aligned} \tag{9}$$

for all $z \in \mathbb{R}^{2n}$, $t > 0$, and all nonnegative definite matrices $\Sigma \in \mathbb{R}^{2n\times 2n}$. Then, there is a unique strong solution of (8) and it satisfies

$$\begin{aligned} \mathbb{E}[V(z)] \leq e^{-ct}V(z_0) \\ + c^{-1}\gamma\left(\sup_{0\leq s\leq t}|\Sigma(s)\Sigma(s)^T|\right) \end{aligned} \tag{10}$$

The system with the above property is said to be noise to state stable (NSS).

Results and Discussion

In this section we present the main theorem and provide LMI conditions that help us to design decentralized controller.

Theorem 2: There exists a decentralized state feedback gain $K_D = [K_{xD}, K_{yD}]$ such that the GRN system (1) is noise to state stable if there exist diagonal and positive definite matrices X_D,Y_D and $\Gamma = diag(\gamma_1, \gamma_2, \dots, \gamma_n)$, and diagonal matrices W_D and Z_D satisfying the following linear matrix inequalities:

$$\begin{bmatrix} \Phi & X_D D^T & B\Gamma & X_D G_x^T & 0 \\ DX_D & \Theta & -Y_D K_g^T & 0 & Y_D G_y^T \\ \Gamma B & -K_g Y_D & -2\Gamma & 0 & 0 \\ G_x X_D & 0 & 0 & -X_D & 0 \\ 0 & G_y Y_D & 0 & 0 & -Y_D \end{bmatrix} < 0 \tag{11}$$

In which, $\Phi = -X_D A^T - A^T X_D + W_D^T B_x^T + B_x W_D + cX_D$ and $\Theta = -Y_D C^T - CY_D + Z_D^T B_y^T + B_y Z_D$. decentralized State feedback gain is derived as $K_{xD} = W_D X_D^{-1}$ and $K_{yD} = Z_D Y_D^{-1}$.

Proof: First, consider following Lyapunov function:

$$V\big(x(t), y(t)\big) = x^T(t)Px(t) + y^T(t)Qy(t) \tag{12}$$

By using Ito formula, we have

$$\begin{aligned} &dV\big(x(t), y(t)\big) \\ &= \mathcal{L}V\big(x(t), y(t)\big)dt \\ &+ 2x^T(t)P\big(\sigma_x\big(x(t)\big)d\omega_{x1}(t) + \Sigma_x(t)d\omega_{x2}\big) \\ &+ 2y^T(t)Q\big(\sigma_y\big(y(t)\big)d\omega_{x1}(t)d\omega_{y1}(t) \\ &+ \Sigma_y(t)d\omega_{y2}\big) \end{aligned} \tag{13}$$

where

$$\begin{aligned} &\mathcal{L}V(x(t), y(t)) \\ &= \begin{pmatrix} -Ax(t) + Bf\big(y(t)\big) \\ +B_x K_{xD}x(t) \end{pmatrix}^T Px(t) \\ &+ x^T(t)P\begin{pmatrix} -Ax(t) + Bf\big(y(t)\big) \\ +B_x K_{xD}x(t) \end{pmatrix} \\ &+ \begin{pmatrix} -Cy(t) + Dx(t) \\ +B_y K_{yD}y(t) \end{pmatrix}^T Qy(t) \\ &+ y^T(t)Q\big(-Cy(t) + Dx(t) + B_y K_{yD}y(t)\big) \\ &+ Tr\left\{\sigma_x\big(x(t)\big)^T P\sigma_x\big(x(t)\big) + \Sigma_x^T(t)P\Sigma_x(t)\right\} \\ &+ Tr\left\{\sigma_y\big(y(t)\big)^T Q\sigma_y\big(y(t)\big) + \Sigma_y^T(t)Q\Sigma_y(t)\right\} \end{aligned} \tag{14}$$

Due to (6), we can write

$$\begin{aligned} &\mathcal{L}V\big(x(t), y(t)\big) + cV\big(x(t), y(t)\big) \\ &\leq x^T(t)cPx(t) + y^T(t)cQy(t) \\ &+ \begin{pmatrix} -Ax(t) + Bf\big(y(t)\big) \\ +B_x K_{xD}x(t) \end{pmatrix}^T Px(t) \\ &+ x^T(t)P\begin{pmatrix} -Ax(t) + Bf\big(y(t)\big) \\ +B_x K_{xD}x(t) \end{pmatrix} \\ &+ \big(-Cy(t) + Dx(t) + B_y K_{yD}y(t)\big)^T Qy(t) \\ &+ y^T(t)Q\big(-Cy(t) + Dx(t) + B_y K_{yD}y(t)\big) \\ &+ x^T(t)G_x^T PG_x x(t) + y^T(t)G_y^T QG_y y(t) \\ &- 2f^T\big(y(t)\big)\Lambda\big(f\big(y(t)\big) - K_g y(t)\big) \\ &+ Tr\{\Sigma_x^T(t)P\Sigma_x(t)\} + Tr\{\Sigma_y^T(t)Q\Sigma_y(t)\} \end{aligned} \tag{15}$$

where $\Lambda = diag(\lambda_1, \lambda_2, \dots, \lambda_n), \lambda_i > 0$. By defining

$\xi^T(t) = [x^T(t) \quad y^T(t) \quad f^T(t)]$, we can write

$$\begin{aligned}&\mathcal{L}V\big(x(t),y(t)\big) + cV\big(x(t),y(t)\big)\\ &\le \xi^T(t)\begin{bmatrix}\widehat{\Phi} & D^TQ & PB\\ QD & \widehat{\Theta} & -K_g^T\Lambda\\ BP & -\Lambda K_g & -2\Lambda\end{bmatrix}\xi(t)\\ &+ Tr\{\Sigma_x^T(t)P\Sigma_x(t)\} + Tr\{\Sigma_y^T(t)P\Sigma_y(t)\}\end{aligned} \tag{16}$$

and $\widehat{\Phi} = -A^TP - PA^T + K_{xD}^TB_x^TP + PB_xK_{xD} + G_x^TPG_x$ and $\hat{\theta} = -C^TQ - QC + +QB_yK_{yD} + K_{yD}^TB_y^TQ + G_y^TQG_y$.

If

$$\xi^T(t)\begin{bmatrix}\widehat{\Phi} & D^TQ & PB\\ QD & \widehat{\Theta} & -K_g^T\Lambda\\ BP & -\Lambda K_g & -2\Lambda\end{bmatrix}\xi(t) < 0 \tag{17}$$

we can conclude that $\mathcal{L}V\big(x(t),y(t)\big) \le -cV\big(x(t),y(t)\big) + \gamma(|\Sigma\Sigma^T|)$, where $\gamma(|\Sigma\Sigma^T|) = Tr\{\Sigma_x^T(t)P\Sigma_x(t)\} + Tr\{\Sigma_y^T(t)Q\Sigma_y(t)\}$ and $\Sigma = \text{diag}\{\Sigma_x, \Sigma_y\}$. Therefore, we should design K_{xD} and K_{yD} such that (17) is satisfied. First, by using Schur complement, (17) is equal to

$$\begin{bmatrix}\widehat{\Phi} & D^TQ & PB & G_x^T & 0\\ QD & \widehat{\Theta} & -K_g^T\Lambda & 0 & G_y^T\\ BP & -\Lambda K_g & -2\Lambda & 0 & 0\\ G_x & 0 & 0 & P^{-1} & 0\\ 0 & G_y & 0 & 0 & Q^{-1}\end{bmatrix} < 0 \tag{18}$$

we multiply both side of (18) with the following matrix

$$\begin{bmatrix}P^{-1} & 0 & 0 & 0 & 0\\ * & Q^{-1} & 0 & 0 & 0\\ * & * & \Lambda^{-1} & 0 & 0\\ * & * & * & I & 0\\ * & * & * & * & I\end{bmatrix} \tag{19}$$

And reach to the sufficient condition as follows:

$$\begin{bmatrix}\widetilde{\Phi} & P^{-1}D^T & B\Lambda^{-1} & P^{-1}G_x^T & 0\\ DP^{-1} & \widetilde{\Theta} & -Q^{-1}K_g^T & 0 & Q^{-1}G_y^T\\ \Lambda^{-1}B & -K_gQ^{-1} & -2\Lambda^{-1} & 0 & 0\\ G_xP^{-1} & 0 & 0 & -P^{-1} & 0\\ 0 & G_yQ^{-1} & 0 & 0 & -Q^{-1}\end{bmatrix} < 0 \tag{20}$$

In which $\widetilde{\Phi} = -P^{-1}A^T - A^TP^{-1} + P^{-1}K_{xD}^TB_x^T + B_xK_{xD}P^{-1}$ and $\widetilde{\Theta} = -Q^{-1}C^T - CQ^{-1} + Q^{-1}K_{yD}^TB_y^T + B_yK_{yD}Q^{-1}$. Now, by defining diagonal matrixes $X_D = P^{-1}$, $Y_D = Q^{-1}$, $W_D = K_{xD}X_D$ and $Z_D = K_{yD}Y_D$ sufficient condition in the form of LMI in (11) can be derived. To derive decentralized feedback gain, we use diagonal matrices X_D, W_D, Y_D and Z_D. □

Remark 1: if any feedback term is not implementable we can change the structure of matrices X_D, W_D, Y_D and Z_D to derive the appropriate controller gain. For example, if it is not possible to implement feedback controller in proteins dynamic, we should consider $K_{yD} = 0$. In this case, we consider $Z_D = 0_n$ to derive appropriate K_{xD}.

Remark 2: if the following LMIs are satisfied

$$\begin{bmatrix}-\kappa_W I & W_D\\ W_D & -I\end{bmatrix} < 0$$
$$\begin{bmatrix}X_D & I\\ I & \kappa_X I\end{bmatrix} < 0$$
$$\begin{bmatrix}-\kappa_Z I & Z_D\\ Z_D & -I\end{bmatrix} < 0$$
$$\begin{bmatrix}Y_D & I\\ I & \kappa_Y I\end{bmatrix} < 0 \tag{21}$$

we can conclude that $\|W_D\|_2 < \sqrt{\kappa_W}$, $\|X_D^{-1}\|_2 < \kappa_X$ $\|Z_D\|_2 < \sqrt{\kappa_Z}$ and $\|Y_D^{-1}\|_2 < \kappa_Y$. Therefore, we have

$$\begin{aligned}&\|K_{xD}\|_2 < \|W_D\|_2\|X_D^{-1}\|_2 < \sqrt{\kappa_W}\kappa_X\\ &\|K_{yD}\|_2 < \|Z_D\|_2\|Y_D^{-1}\|_2 < \sqrt{\kappa_Z}\kappa_Y\end{aligned} \tag{22}$$

So, if the LMIs presented in (21) is also considered for designing the decentralized controller, the magnitude of the controller's gains will not be greater than bounds obtained in (22). Now, we examine our results to show the effectiveness of our method.

Example1: The Repressilator is an artificial genetic network which consists of three genes [29]. These genes are connected in one loop such that each gene represses the production of the next gene. Following model has been suggested for this gene network [29]:

$$\begin{aligned}&\frac{d}{dt}m_1(t) = \alpha_0 + \frac{\alpha}{1+p_3^2(t)} - m_1(t)\\ &\frac{d}{dt}m_2(t) = \alpha_0 + \frac{\alpha}{1+p_1^2(t)} - m_2(t)\\ &\frac{d}{dt}m_3(t) = \alpha_0 + \frac{\alpha}{1+p_2^2(t)} - m_3(t)\\ &\frac{d}{dt}p_1(t) = \beta m_1(t) - \beta p_1(t)\\ &\frac{d}{dt}p_2(t) = \beta m_2(t) - \beta p_2(t)\\ &\frac{d}{dt}p_3(t) = \beta m_3(t) - \beta p_3(t)\end{aligned} \tag{23}$$

In which $\alpha_0 = 5 \times 10^{-4}\ moleculle\ per\ cell.\min^{-1}$, $\beta = 5\ min^{-1}$ and $n = 2$. By considering $\alpha = 5$, the equilibrium point will be $[m^* \quad p^*] = [60.65 \quad 60.65 \quad 60.65 \quad 60.65 \quad 60.65 \quad 60.65]^T$. In presence of noise with intensity $\sigma_x\big(x(t)\big) = 0.1x(t)$, $\Sigma_x(t) = 0.05I$, $\sigma_y\big(y(t)\big) = 0.1y(t)$ and $\Sigma_y(t) = 0.05I$, the behavior of repressilator is shown in Fig. 1 and Fig. 2.

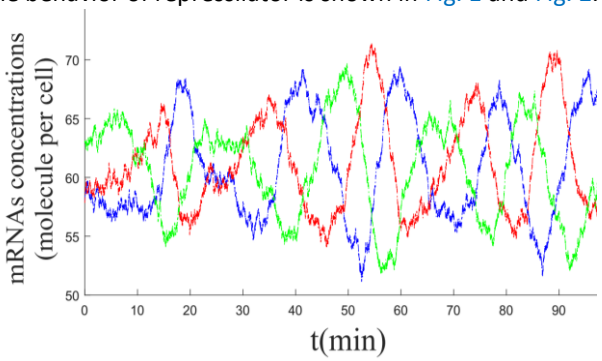

Fig. 1: mRNA concentrations of repressilator network without control.

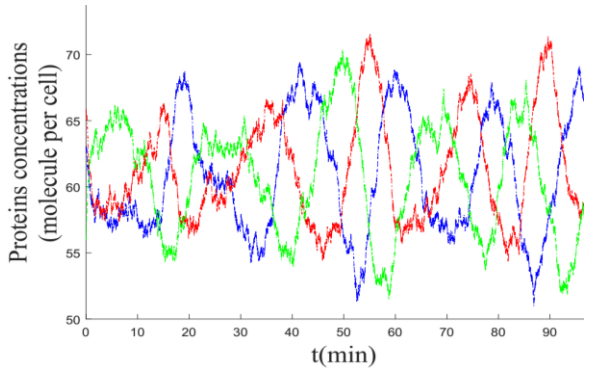

Fig. 2: protein concentrations of repressilator network without control.

As can be seen in these figures, the concentration of mRNAs and proteins varies largely over time which may lead to undesirable cellular behavior.

Parameters of the system will be:

$$A=\begin{bmatrix}1&0&0\\0&1&0\\0&0&1\end{bmatrix},\quad B=5\begin{bmatrix}0&0&-1\\-1&0&0\\0&-1&0\end{bmatrix}\quad B_f=\begin{bmatrix}1\\1\\1\end{bmatrix}$$

$$D=5*\begin{bmatrix}1&0&0\\0&1&0\\0&0&1\end{bmatrix},\qquad C=5*\begin{bmatrix}1&0&0\\0&1&0\\0&0&1\end{bmatrix},$$

$G_x=0.1I, \Sigma_x(t)=0.05I,$

$G_y=0.1I$ and $\Sigma_y(t)=0.05I,$

For $c=5$, Decentralized feedback gain based on LMI presented in (11) is derived as

$$K=\begin{bmatrix}K_m&0\\0&K_P\end{bmatrix},$$

$$K_m=\begin{bmatrix}-8.6458&0&0\\0&-8.6458&0\\0&0&-8.6458\end{bmatrix},$$

$$K_p=\begin{bmatrix}-0.6787&0&0\\0&-0.6787&0\\0&0&-0.6787\end{bmatrix}$$

Systems trajectories in presence of decentralized controller are shown in Fig 3 and Fig.4.

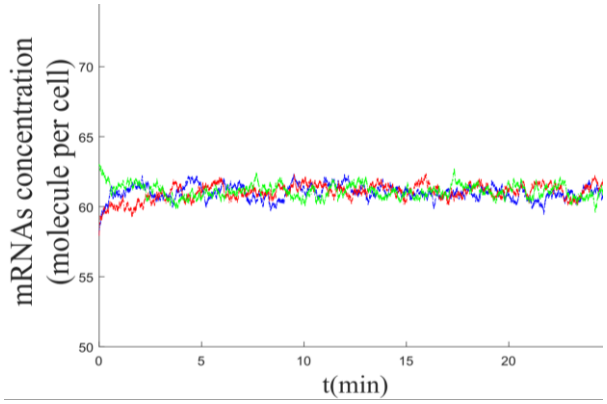

Fig. 3: mRNA concentrations of repressilator network with decentralized control.

The controllers' inputs are shown in Fig.5 and Fig.6.

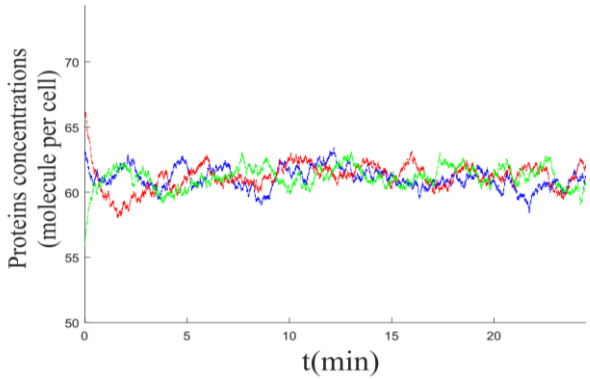

Fig. 4: protein concentrations of repressilator network with decentralized control.

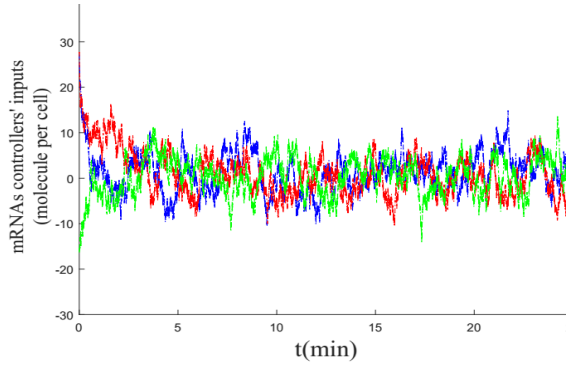

Fig. 5: mRNAs controllers' inputs with decentralized control.

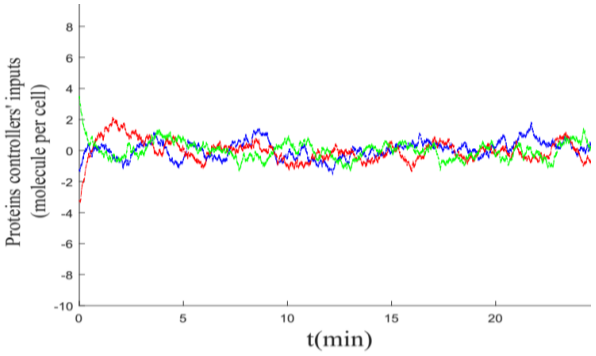

Fig. 6: Proteins controllers' inputs with decentralized control.

If we consider more restricted decentralized feedback mechanism which is implemented only in mRNA dynamics, the feedback gain for $c=5$ will be derived as follows:

$$K=\begin{bmatrix}K_m&0\\0&K_P\end{bmatrix},$$

$$K_p=\begin{bmatrix}0&0&0\\0&0&0\\0&0&0\end{bmatrix},$$

$$K_m=\begin{bmatrix}-10.3248&0&0\\0&-10.3248&0\\0&0&-10.3248\end{bmatrix},$$

This controller can be implemented by using synthetic feedback controller for "in vivo" regulation as shown in [21]. As can be seen in Fig. 7 and Fig. 8, performance of the controller is downgraded. However, this controller has simpler structure. To compare the proposed method with the traditional methods, structure of the controller is shown graphically in Fig.9.

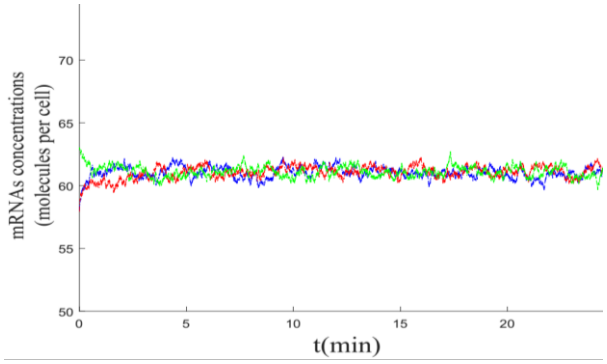

Fig. 7: mRNA concentrations of repressilator network with restricted decentralized control.

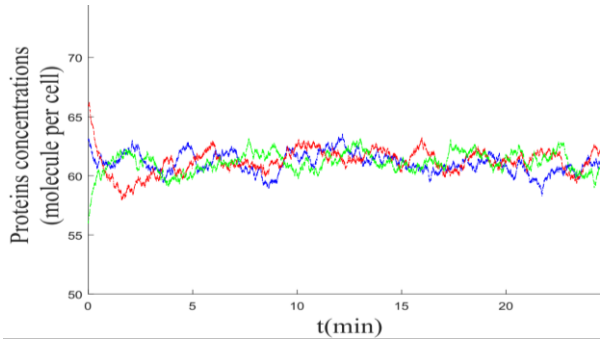

Fig. 8: protein concentrations of repressilator network with restricted decentralized control.

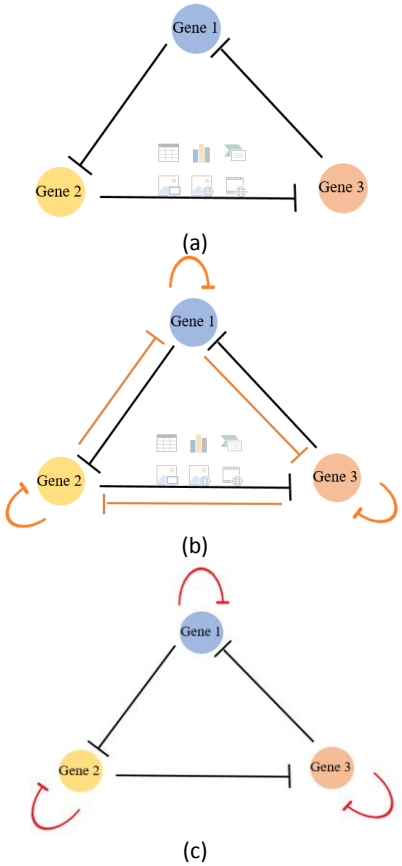

Fig. 9: (a) the repressilator structure. (b) traditional controller structure (c) decentralized controller structure.

In Fig. 9.a, repressilator genetic circuit is shown. The black color lines show the inhibitory effect of each gene on the production of the next gene. The traditional controller structure is depicted in Fig. 9.b. The controller interactions that are augmented to the system is drawn by colored arrows. In this approach, number of interactions becomes large. As can be seen in Fig 9.c, decentralized controller has a simpler form with lower number of interactions. Therefore, it can be implemented in practice more easily.

Example2: in this example, we consider genetic toggle switch [30]. Genetic toggle switch has two stable equilibrium points. Enforcing this system to transit from one equilibrium point to another is an important issue in biological systems. In [30], following model has been proposed for genetic toggle switch:

$$\begin{aligned}\frac{d}{dt}m_1(t) &= \frac{\alpha}{1+p_2^2(t)} - m_1(t)\\ \frac{d}{dt}m_2(t) &= \frac{\alpha}{1+p_1^2(t)} - m_2(t)\\ \frac{d}{dt}p_1(t) &= \beta m_1(t) - \beta p_1(t)\\ \frac{d}{dt}p_2(t) &= \beta m_2(t) - \beta p_2(t)\end{aligned} \tag{24}$$

This system has two stable steady-state $[m^*, p^*]^T = [156.2, 0.0006, 156.2, 0.006]$ and $[m^*, p^*]^T = [0.175, 15.14, 0.175, 15.14]$. for each initial state, system converges to one of these two equilibrium point. The set of all initial states that lead to one of the equilibrium point is called basin of attraction for that stable steady state. In this example, we design a state feedback controller that enable us to transit the system from basin of attraction of one equilibrium point to the another one. In Fig. 10, time response of the system without controller is shown for the initial state $[m^*, p^*]^T = [15, 17.5, 15, 17.5]$. As can be seen, system's states converge to $[m^*, p^*]^T = [156.2, 0.0006, 156.2, 0.006]$. Our object is to regulate the system to the other equilibrium point by appropriate state feedback. We use the presented LMI in (11) and derive the decentralized state feedback.

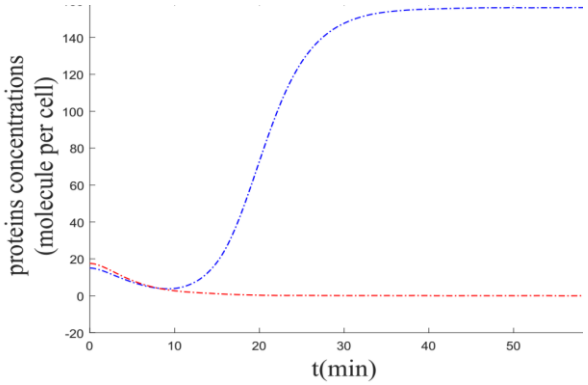

Fig. 10: protein concentrations of toggle switch without control.

It is shown in Fig. 11 that the decentralized controller regulates the system's states to the equilibrium point $[m^*, p^*]^T = [0.175, 15.14, 0.175, 15.14]$.

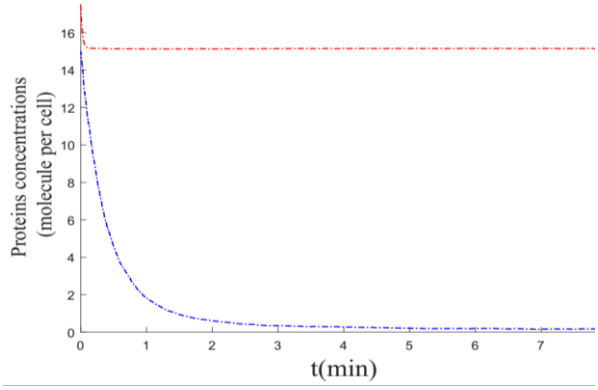

Fig. 11: protein concentrations of toggle switch with decentralized control.

Conclusion

Decentralized controller design for gene regulatory networks with intrinsic and extrinsic noises was considered. By using Lyapunov function, Ito formula and stochastic analysis, LMI conditions for designing decentralized controller that guarantees noise to state stability were developed. The proposed controller has simpler structure than ones proposed by the previous works and can be implemented in living cells. At the end, the effectiveness of the proposed method for structure decentralized controller design has been shown by simulations.

Author Contributions

M.Mohammadian proved the theoretical theorems, performed the simulations and wrote the manuscript.

Conflict of Interest

The author declares that there is no conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy have been completely observed by the authors.

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