Robust stability of uncertain genetic regulatory networks with multivariable regulation functions

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Abstract. This paper investigates robust stability of uncertain genetic regulatory networks (GRNs). It is assumed that the uncertainties are in the form of a parameter vector that determines the coefficients of the model via given functions. And the novel multivariable regulation functions are introduced here to describe the underlying relationship between different biochemical substance. Firstly, it is shown that, by using Lyapunov functional method and linear matrix inequality technology (LMI), a criteria is established to ensure the robust asymptotical stability of GRNs. Moreover, it is also shown that by using the square matrix representation (SMR) of matrix polynomials and by adopting polynomially parameter-dependent Lyapunov functions, a condition in form of linear matrix inequalities (LMIs) for robust stability for all admissible uncertainties can be obtained. An example with real biological model is provided to illustrate the use of the proposed methodology.

Keywords: uncertain GRNs, multivariable regulation function, robust stability, SMR

1 Introduction

Recent years, researches in the study of GRNs are active, and both theoretical and experimental results are fruitful. So far, in the literature, GRNs are typically considered as biological dynamic systems [1, 2], the dynamical behaviors of genes, proteins and mRNAs can be modeled by series of nonlinear differential equations. Similar to other dynamic systems, stability is one of the key properties of GRNs with obvious biological significance [3]. Please see [4, 5], and references therein for the stability analysis of GRNs. Other than "stability", another important issue is to construct a precise structure of the networks' mathematical model, in which the "uncertain" property plays a key role in the dynamic analysis. In synthetic and real GRNs, the uncertainties arise from various sources, both internal and external. Since the mathematical model of GRNs is derived from real-world gene expression data, the modeling error is unavoidable. Besides the modeling error, the internal and external perturbations or fluctuations also bring the uncertainties to the network [6]. Furthermore, in order to better reflect the underlying regulation mechanism of GRNs, the multivariable regulation

functions are proposed here. In such functions, different variables are multiplying or coupling together which yield the combinatorial regulation mechanism, and the combined effects of several regulatory proteins on the control of gene expression or protein degradation can be captured [8]. In real biological networks, such combined properties are indeed exist, and regulation functions with such forms can be found in [9].

Motivated by the reasons discussed above, in this paper, we focus on the robust stability of uncertain GRNs with multivariable regulation functions. It is shown that a condition for robust stability of the uncertain GRNs can be established by using Lyapunov functional method and LMI. Moreover, it is shown that by solving a convex optimization problem with LMIs built by using SMR, and by introducing polynomially parameter dependent Lyapunov functions, a condition for robust stability for all admissible uncertainties can be obtained.

2 Preliminaries

2.1 Problem Formulation

Notation: I_n: $n \times n$ identity matrix; 0_n: origin of $\mathbb{R}^n$; A^T: transpose of matrix A; $A > 0 (A \geq 0)$: symmetric positive definite (semidefinite) matrix A; $A \otimes B$: Kronecker product of matrices A and B; $diag(...)$: block-diagonal matrix; $\#$: represents a matrix which can be inferred by symmetry.

In this section, we introduce a GRN model described by differential equations as follows:

$$\begin{cases} \dfrac{dz(t)}{dt} = -A(\theta)z(t) + B(\theta)f(z(t)) + D(\theta)\bar{g}(z(t)) + u(\theta) \\ \theta \in \Theta \end{cases} \tag{1}$$

where $z(t) \in \mathbb{R}^n$ represents the concentration vector, i.e., each component $z_i(t)$ is the concentration of the ith node of a GRN. $A(\theta) \in \mathbb{R}^{n\times n}$ is diagonal, which contains the production or degradation rates, $B(\theta)$, $D(\theta) \in \mathbb{R}^{n\times n}$ are two matrices that defines the regulation effects of the regulation functions $f(z(t))$ and $\bar{g}(z(t))$, respectively. $u(\theta)$ is a vector accounting for the basal production rates of the components of the networks.

In GRN (1), $\theta \in \mathbb{R}^r$ is the time-invariant uncertainty vector and Θ is the uncertainty set described by

$$\Theta = \{\theta \in \mathbb{R}^r : t_i(\theta) \geq 0 \quad \forall i = 1, 2, ..., r\} \tag{2}$$

where $t_i(\theta)$ are polynomials. One thing worth noting that, in GRNs, regulation functions are used to capture the combined effect of several regulatory proteins on the control of gene expression or protein degradation and describe the topology structure of these metabolites. Since in many GRNs, the monotone regulation functions are not just simply added together only, but may be coupled with another variable also. So, multivariable regulation function $\bar{g}(z(t))$ is introduced here. In (1), $\bar{g}(z(t))$ is defined as follows:

$$\bar{g}(z(t)) = diag(w(t))g(z(t)) \tag{3}$$

where $w_i(t) \in \{z_1(t), z_2(t), ..., z_n(t)\}$. Here, $f(z(t))$ and $g(z(t))$ are regulation functions, which are generally nonlinear or linear single-variable functions. One special case of the regulation function is with Hill form, i.e.

$$g_i(z(t)) = \frac{z_i(t)^H}{\beta^H + z_i(t)^H} \qquad \beta > 0,\ z_i(t) > 0 \quad \forall i \tag{4}$$

where H is the Hill coefficient. The function ranges from 0 to 1 and increases as $z_i \to \infty$.

Let $z^*(\theta)$ be an equilibrium point of (1), i.e., a solution of the following equation

$$0_n = -A(\theta)z^*(\theta) + B(\theta)f(z^*(\theta)) + D(\theta)w^*(\theta)g(z^*(\theta)) + u(\theta). \tag{5}$$

For convenience, let us shift the origin to the equilibrium point z^* by defining $x = z - z^*(\theta)$, $y = w - w^*(\theta)$, and letting $h(x(t)) = f(x(t) + z^*(\theta)) - f(z^*(\theta))$, $r(x(t)) = g(x(t) + z^*(\theta)) - g(z^*(\theta))$.

Then, for all $\theta \in \Theta$, system (1) becomes

$$\frac{dx(t)}{dt} = -[A(\theta) + E(\theta)]x(t) + B(\theta)h(x(t)) + C(\theta)r(x(t)) + D(\theta)\bar{r}(x(t)) \tag{6}$$

where

$$\begin{aligned} &x(t) = [x_1(t), x_2(t), ..., x_n(t)]^T, h(x(t)) = [h_1(x_1(t)), h_2(x_2(t)), ..., h_n(x_n(t))]^T, \\ &\bar{r}(x(t)) = [y_1(t)r_1(x_1(t)), y_2(t)r_2(x_2(t)), ..., y_n(t)r_n(x_n(t))]^T \end{aligned} \tag{7}$$

and $y_i(t) \in \{x_1(t), x_2(t), ..., x_n(t)\}$.

2.2 Representation of Polynomials

Before proceeding, let us introduce a key technique that will be exploited in the next section. Let $M(x) \in \mathbb{R}^{n \times n}$ be a matrix polynomial of degree 2m in x. Then, $M(x)$ can be written as

$$M(x) = \triangle(\bar{M} + U(\alpha), x^{\{m\}}, I_n) \tag{8}$$

where $\triangle(\bar{M} + U(\alpha), x^{\{m\}}, I_n)$ denotes the notation

$$\triangle(\bar{M} + U(\alpha), x^{\{m\}}, I_n) = (x^{\{m\}} \otimes I_n)^T(\bar{M} + U(\alpha))(x^{\{m\}} \otimes I_n) \tag{9}$$

where $\bar{M}$ is a symmetric matrix, and $U(\alpha)$ is a linear parametrization of the linear space

$$\mathcal{U} = \{U = U^T : \triangle(U, x^{\{m\}}, I_n) = 0\}. \tag{10}$$

The matrix polynomial $M(x)$ is said to be SOS if it can be written as

$$M(x) = \sum_i M_i(x)^T M_i(x) \tag{11}$$

for some matrix polynomials $M_i(x)$. Then, $M(x)$ is SOS if and only if there exists α such that the following LMI holds:

$$\exists \alpha : \bar{M} + U(\alpha) \geq 0. \tag{12}$$

See also [10] for further details on the SMR and on SOS polynomials.

3 Stability Analysis

Let us observe that, for all $i = 1, 2, ..., n$, the regulation functions $h_i(x(t))$ and $r_i(x(t))$ satisfy the following sector conditions

$$\begin{aligned} h_i(s)(h_i(s) - K_{1i}s) \leq 0 \\ r_i(s)(r_i(s) - K_{2i}s) \leq 0 \end{aligned} \tag{13}$$

for any $s \in \mathbb{R}$ and K_{1i}, K_{2i} are non-negative [6].

Now, let us consider the sector condition for $\bar{r}(x(t))$. In (6), each multivariable regulation function $\bar{r}_i(x(t))$ satisfies the following condition:

$$\bar{r}_i(x)(\bar{r}_i(x) - K_{3i}x_i - K_{4i}y_i) \leq 0 \tag{14}$$

where K_{3i}, K_{4i} are non-negative and $x_i, y_i \in \mathbb{R}$. Since $y_i \in \{x_1, x_2, ..., x_n\}$, then we have

$$y = Yx \tag{15}$$

where Y is a coupling matrix which determine the relationship between x_i and y_i. Thus, $\bar{r}_i(x(t))$ satisfies the following sector condition

$$\bar{r}_i(x)[\bar{r}_i(x) - (K_{3i} + K_{4i}\sum_{j=1}^{n} Y_{ij})x_i] \leq 0, i = 1, 2, ..., n \tag{16}$$

where Y_{ij} is the ijth entry of the coupling matrix Y.

Theorem 1. *Suppose that there exist matrix function $P(\theta)$, diagonal matrix functions $\Lambda_h(\theta)$, $\Lambda_r(\theta)$, $\Lambda_{\bar{r}}(\theta)$, such that the following conditions hold $\forall \theta \in \Theta$:*

$$\begin{aligned} &M(\theta) = \begin{bmatrix} M_{11} & M_{12} & M_{13} & M_{14} \\ \# & -2\Lambda_h(\theta) & 0_n & 0_n \\ \# & 0_n & -2\Lambda_r(\theta) & 0_n \\ \# & 0_n & 0_n & -2\Lambda_{\bar{r}}(\theta) \end{bmatrix} < 0 \\ &P(\theta) > 0 \\ &\Lambda_h(\theta) = diag(\lambda_{h1}(\theta), ..., \lambda_{hn}(\theta)),\ \lambda_{hi}(\theta) > 0 \\ &\Lambda_r(\theta) = diag(\lambda_{r1}(\theta), ..., \lambda_{rn}(\theta)),\ \lambda_{ri}(\theta) > 0 \\ &\Lambda_{\bar{r}}(\theta) = diag(\lambda_{\bar{r}1}(\theta), ..., \lambda_{\bar{r}n}(\theta)),\ \lambda_{\bar{r}i}(\theta) > 0,\ i = 1, 2, ..., n \end{aligned} \tag{17}$$

where

$$\begin{aligned} M_{11} &= -P(\theta)(A(\theta) + E(\theta)) - (A(\theta) + E(\theta))^T P(\theta) \\ M_{12} &= P(\theta)B(\theta) + diag(K_1)\Lambda_h(\theta) \\ M_{13} &= P(\theta)C(\theta) + diag(K_2)\Lambda_r(\theta) \\ M_{14} &= P(\theta)D(\theta) + [diag(K_3) + diag(K_4)Y]\Lambda_{\bar{r}}(\theta). \end{aligned} \tag{18}$$

Then, the uncertain GRN (6) is asymptotically stable for any $\theta \in \Theta$.

Proof. Consider the following Lyapunov function:

$$V(x(t)) = x^T(t)Px(t). \tag{19}$$

Calculating the time derivative of V along (6), we have

$$\begin{aligned}\dot{V}(x(t)) = 2x^T(t)P\dot{x} &= 2x^T(t)P[-(A+E)x(t) + Bh(x(t)) + Cr(x(t)) + D\bar{r}(x(t))] \\ &\leq -2x^T(t)P(A+E)x(t) + 2x^T(t)PBh(x(t)) + 2x^T(t)PCr(x(t)) \\ &\quad + 2x^T(t)PD\bar{r}(x(t)) - 2\sum_{i=1}^{n}\lambda_{hi}h_i(x(t))[h_i(x(t)) - K_{1i}x_i(t)] \\ &\quad - 2\sum_{i=1}^{n}\lambda_{ri}r_i(x(t))[r_i(x(t)) - K_{2i}x_i(t)] \\ &\quad - 2\sum_{i=1}^{n}\lambda_{\bar{r}i}\bar{r}_i(x(t))[\bar{r}_i(x(t)) - (K_{3i} + K_{4i}\sum_{j=1}^{n}Y_{ij})x_i(t)] \\ &= \xi^T(t)M\xi(t) < 0\end{aligned} \tag{20}$$

where $\xi(t) = [x^T(t), h^T(x(t)), r^T(x(t)), \bar{r}^T(x(t))]^T$.

Then, the GRN (6) is globally asymptotically stable for all $\theta \in \Theta$. □

Let us observe that, in order to solve the conditions in Theorem 1, it is required the feasibility test of an infinite family of LMIs. Thus, by restricting our attention to the SMR introduced in Section 2.2, we could provide a sufficient condition for Theorem 1 via an LMI feasibility test. We can write:

$$\begin{aligned}&P(\theta) = \Delta(\bar{P}, \theta^{\{m_1\}}, I_n),\ M(\theta) = \Delta(\bar{M}, \theta^{\{m_2\}}, I_{4n}),\ \Lambda_h(\theta) = \Delta(\bar{\Lambda}_h, \theta^{\{m_2\}}, I_n) \\ &\Lambda_r(\theta) = \Delta(\bar{\Lambda}_r, \theta^{\{m_2\}}, I_n), \Lambda_{\bar{r}}(\theta) = \Delta(\bar{\Lambda}_{\bar{r}}, \theta^{\{m_2\}}, I_n)\end{aligned} \tag{21}$$

where $\bar{P}$, $\bar{M}$, $\bar{\Lambda}_h$, $\bar{\Lambda}_r$ and $\bar{\Lambda}_{\bar{r}}$ are symmetric matrices of suitable dimensions. The vector $\theta^{\{m_1\}}$ and $\theta^{\{m_2\}}$ contain all monomials of degree m_1 and m_2 in θ, respectively.

Let $L(\alpha)$ be a linear parameterization of

$$\mathfrak{L} = \{L = L^T : \Delta(L, \theta^{\{m_2\}}, I_{4n}) = 0_{4n\times 4n} \quad \forall\theta \in \mathbb{R}^r\}. \tag{22}$$

Let $2b_i$ be the degree of $t_i(\theta)$, and let us define the matrix polynomial

$$T_i(\theta) = \sum_{i=0}^{r} t_i(\theta)\Delta(U_i, \theta^{\{m_2-b_i\}}, I_{4n}) \tag{23}$$

where $U_i = U_i^T$, and let $Z_i(U_i) = Z_i(U_i)^T$ be linear matrix functions satisfying

$$T_i(\theta) = \Delta(Z_i(U_i), \theta^{\{m_2\}}, I_{4n}). \tag{24}$$

Theorem 2. *Suppose there exist symmetric matrices* $\bar{P}$, $\bar{M}$, $\bar{\Lambda}_h$, $\bar{\Lambda}_r$, $\bar{\Lambda}_{\bar{r}}$ *and a vector* α, *satisfying the following LMIs:*

$$\bar{M} + L(\alpha) + \sum_{i=1}^{r} Z_i(U_i) < 0,\ \bar{P} > 0,\ \bar{\Lambda}_h > 0,\ \bar{\Lambda}_r > 0,\ \bar{\Lambda}_{\bar{r}} > 0. \tag{25}$$

Then, Theorem 1 holds.

Proof. Suppose that (25) holds. Since $\bar{P} > 0\ \bar{\Lambda}_h > 0,\ \bar{\Lambda}_r > 0,\ \bar{\Lambda}_{\bar{r}} > 0$, one gets from (21) that:

$$P(\theta) > 0,\ \Lambda_h(\theta) > 0,\ \Lambda_r(\theta) > 0,\ \Lambda_{\bar{r}}(\theta) > 0 \quad \forall \theta. \tag{26}$$

Now, let us consider $M(\theta)$. From $\bar{M} + L(\alpha) + \sum_{i=1}^{r} Z_i(U_i) < 0$, pre- and post-multiplying by $(\theta^{\{m_2\}} \otimes I_{4n})^T$ and $(\theta^{\{m_2\}} \otimes I_{4n})$, since $\Delta(L, \theta^{\{m_2\}}, I_{4n}) = 0_{4n \times 4n}$, one gets

$$0 > \Delta(\bar{M} + L(\alpha) + \sum_{i=1}^{r} Z_i(U_i), \theta^{\{m_2\}}, I_{4n}) = M(\theta) + \sum_{i=1}^{r} T_i(\theta). \tag{27}$$

Consider any $\theta \in \Theta$. Since $U_i > 0$, from (2) and (23) we have

$$t_i(\theta) \geq 0,\ \Delta(U_i, \theta^{\{m_2 - b_i\}}, I_{4n}) > 0, \forall i. \tag{28}$$

This implies that:

$$T_i(\theta) \geq 0 \quad \forall \theta \in \Theta. \tag{29}$$

Therefore, from (27) and (29) it follows that:

$$M(\theta) < 0 \quad \forall \theta \in \Theta. \tag{30}$$

Consequently, the conditions of Theorem 1 hold since there exist $P(\theta)$, $\Lambda_h(\theta)$, $\Lambda_r(\theta)$ and $\Lambda_{\bar{r}}(\theta)$ fulfilling (17) $\forall \theta \in \Theta$. □

4 Illustrative Example

In this example, we will illustrate the application of the proposed results to an well-known Cdc2-Cyclin B/Wee1 system [7]. In this system, Cdc2-Cyclin B complex and Wee1 are two proteins, and the inhibition of each kinase by the other is assumed to be approximated by a Hill function. The system has the form:

$$\begin{cases} \dfrac{dz_1(t)}{dt} = \alpha_1(1 - z_1) - \dfrac{\beta_1 z_1 (v z_2)^{\nu_1}}{Q_1 + (v z_2)^{\nu_1}} \\ \dfrac{dz_2(t)}{dt} = \alpha_2(1 - z_2) - \dfrac{\beta_2 z_2 z_1^{\nu_2}}{Q_2 + z_1^{\nu_2}} \end{cases} \tag{31}$$

where z_1 and z_2 denote Cdc2, Wee1 respectively; α_1, α_2, β_1, β_2 are rate constants; $Q_1 = 30$, $Q_2 = 1$ are Michaelis (saturation) constants; $\nu_1 = \nu_2 = 4$ are Hill coefficients; and v is a coefficient reflects the strength of the influence of Wee1 on Cdc2-cyclin B. Here, we select $v = 2$.

Let us rewrite this network in the form of the GRN (6), we have

$$\frac{dx(t)}{dt} = -[A(\theta) + E(\theta)]x(t) + C(\theta)r(x(t)) + D(\theta)\bar{r}(x(t)) \tag{32}$$

where
$A(\theta) = \begin{bmatrix} \alpha_1 & 0 \\ 0 & \alpha_2 \end{bmatrix}$, $C(\theta) = \begin{bmatrix} w_1^* & 0 \\ 0 & w_2^* \end{bmatrix}$, $D(\theta) = \begin{bmatrix} 0 & -\beta_1 \\ -\beta_2 & 0 \end{bmatrix}$, $E(\theta) = \begin{bmatrix} \beta_1 r_1(z_2^*) & 0 \\ 0 & \beta_2 r_2(z_1^*) \end{bmatrix}$,

and the regulation function $r_i(x(t))$ equals to $x_i^4/(1 + x_i^4)$. It is easy to know that the maximal value of the derivative of $r_i(x(t))$ is less than 1.0652.

Let us choose the matrix variables as

$A(\theta) = diag(0.9 - 0.2\theta_1 + 0.3\theta_2, 0.5 + 0.1\theta_1 - 0.1\theta_2)$, $C(\theta) = diag(1 + \theta_1, 1 + \theta_1)$,

$E(\theta) = diag(0.95, 0.95) * diag(10 + 8\theta_1, 5 + 2\theta_1)$, $D(\theta) = \begin{bmatrix} 0 & -10 - 8\theta_1 \\ -5 - 2\theta_1 & 0 \end{bmatrix}$.

Remark 1. Let us observe that, the value of w_1^*, w_2^*, $r_1(z_2^*)$ and $r_2(z_1^*)$ in $C(\theta)$ and $E(\theta)$ are unknown which are depended on the uncertainty parameter θ. Depending on the properties of $r_i(x(t))$, we simply choose $r_1(z_2^*) = r_2(z_1^*) = 0.95$ and $w_1^* = w_2^* = 1 + \theta_1$ in the calculations.

The set $\Theta = [0, 1]^2$ can be expressed as in (2) with $t_i(\theta) = \theta_i(1 - \theta_i), i = 1, 2$. Let us select $K_2 = K_3 = diag(1.0652, 1.0652)$, $K_4 = diag(1, 1)$ and $Y = \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix}$ in order to fulfill the sector conditions.

The state trajectories of the uncertain GRN (32) are shown in Fig. 1 with different uncertainty parameter θ_1, θ_2 and different concentrations of $Cdc2$ and $Wee1$. It shows that, by solving the conditions in Theorem 2, the Cdc2-Cyclin B/Wee1 system is asymptotically stable with all admissible parametric uncertainties.

5 CONCLUSIONS

In this paper, we addressed the problem of establishing robust stability of uncertain GRNs. Specifically, based on the Lyapunov functional method and LMI techniques, a criteria has been established to ensure the robust asymptotical stability of the uncertain GRNs with multivariable regulation functions. Then, by using SMR and by adopting polynomially parameter-dependent Lyapunov functions, the conditions for robust stability for all admissible uncertainties can be obtained in terms of LMIs. An example with real biological model has been used to illustrate the use of proposed methodology.

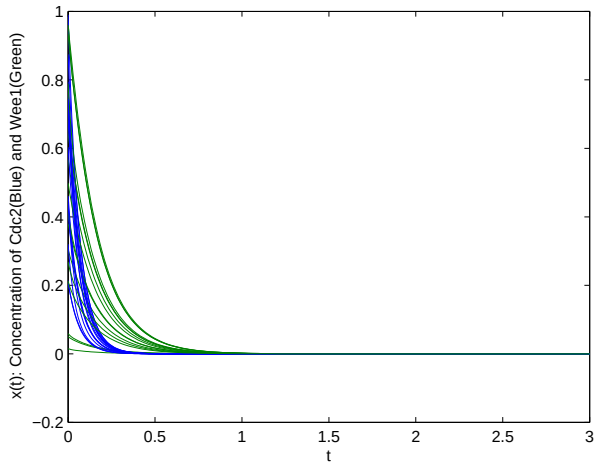

Fig. 1. State trajectories of the Cdc2-Cyclin B/Wee1 system.

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