Proceedings of the 17th World Congress
The International Federation of Automatic Control
Seoul, Korea, July 6-11, 2008

An LMI approach for robust stability of genetic networks

G. Chesi, Y.S. Hung

Department of Electrical and Electronic Engineering
University of Hong Kong
e-mail: {chesi,yshung}@eee.hku.hk

Abstract: This paper addresses the problem of establishing robust stability of uncertain genetic networks with SUM regulatory functions. For these networks we derive a sufficient condition for robust stability by introducing a bounding set of the uncertain nonlinearity, and we show that this condition can be formulated as a linear matrix inequality (LMI) optimization obtained via the square matricial representation (SMR) of polynomials by adopting polynomial Lyapunov functions and polynomial descriptions of the bounding set. Then, we propose a method for computing a family of bounding sets by means of convex optimizations. It is worthwhile to remark that these results are derived in spite of the fact that the variable equilibrium point cannot be computed being the solution of a system of parameter-dependent nonlinear equations, and is hence unknown.

Keywords: Genetic network, Uncertainty, Robust stability, SMR, LMI.

1. INTRODUCTION

The study of genetic regulatory networks has recently become a fundamental challenge in systems biology as it explains the interactions between genes and proteins to form a complex system that performs complicated biological functions, see for instance Jacob and Monod [1961], Smolen et al. [2000], Bower and Bolouri [2001]. Genetic networks are biochemically dynamical systems, and it is natural to model genetic networks by using dynamical system models which provide a powerful tool for studying gene regulation processes in living organisms. Basically, there are two types of genetic network models, the Boolean model and the differential equation model. In Boolean models, the activity of each gene is expressed in one of two states, ON or OFF, and the state of a gene is determined by a Boolean function of the states of other related genes. In the differential equation models, the variables describe the concentrations of gene products, such as mRNAs and proteins, as continuous values of the gene regulation systems. See also Bay et al. [2002], Kobayashi et al. [2002], Jong [2002], Wang et al. [2004], Aluru [2005], Davidson [2006] and references therein for a wider categorization of genetic networks models. Genetic networks with SUM regulatory functions are differential equation models where each transcription factor acts additively to regulate a gene, i.e., the regulatory function sums over all the inputs. For further details see for example Li et al. [2006] where the stability of these networks is studied in presence of time delays.

In modeling genetic networks, like any other biological or physical system, it is necessary to introduce estimation errors, which makes the mathematical model *uncertain*. This means that one has to investigate the stability of an uncertain nonlinear system. In the control literature, stability analysis of uncertain linear systems is a widely studied problem with a lot of contributions in recent years (see for example Chesi et al. [2005], Scherer [2006] and references therein) generally formulated as linear matrix inequality (LMI) optimizations Boyd et al. [1994]. Unfortunately, genetic networks are nonlinear systems, which means that not only the dynamics *but also the equilibrium point* are uncertain. Moreover, the relationship between this uncertain equilibrium point and the uncertainty *cannot be calculated* being the solution of a system of parameter-dependent nonlinear equations.

In spite of these difficulties, we propose in this paper a condition for establishing robust stability of uncertain genetic networks with SUM regulatory functions. Specifically, we assume that the coefficients of the genetic network are unknown being affected by uncertain parameters. We derive a condition for robust stability by substituting the uncertain nonlinearity with an auxiliary variable constrained in a bounding set. This condition ensures that, for each admissible value of the uncertainties, the system has only one equilibrium point and this equilibrium point is globally asymptotically stable in the positive octant. Moreover, we show that this condition can be formulated as an LMI optimization by exploiting the square matricial representation (SMR) of polynomials and adopting polynomially parameter-dependent Lyapunov functions and polynomial descriptions of the bounding set. Then, we consider the problem of calculating a family of bounding sets. The difficulty of this step is that, in order to reduce the conservatism, the bounding sets must be calculated on the basis of the variable equilibrium point which is an unknown function of the uncertainty. In order to overcome this problem we propose two procedures: the first one for obtaining an embedding set of the variable equilibrium, and the second one for calculating a family of bounding sets of the uncertain nonlinearity based on this estimate of the equilibrium point.

It is worthwhile to remark that the problem of establishing stability of uncertain genetic networks has not been considered yet in the literature.

2. PRELIMINARIES

2.1 Problem formulation

Notation: 0_n: origin of $\mathbb{R}^n$; $\mathbb{R}^n_+$: nonnegative real numbers set; I_n: identity matrix $n \times n$; A': transpose of matrix A; $A > 0$ ($A \geq 0$): symmetric positive definite (semidefinite) matrix A; diag(v): diagonal matrix whose diagonal components are the entries of the vector v; $A \otimes B$: Kronecker's product of matrices A and B; $[a, b]$ and $[a; b]$: row and column concatenations of vectors a, b; $\lceil c \rceil$: smallest integer greater than or equal to c.

A genetic regulatory network with SUM regulatory functions can be described by the model

$$\left\{ \begin{array}{rcl} \dot{m}(t) & = & Am(t) + b + Bg(p(t)) \\ \dot{p}(t) & = & Cp(t) + Dm(t) \end{array} \right. \tag{1}$$

where $m(t)$ and $p(t) \in \mathbb{R}^n$ are the concentration vectors of mRNA and protein of the i-th gene, A and $C \in \mathbb{R}^{n\times n}$ are diagonal Hurwitz matrices containing the degradation rates, $D \in \mathbb{R}^{n\times n}$ is a diagonal positive definite matrix, $B \in \mathbb{R}^{n\times n}$ is the coupling matrix, $b \in \mathbb{R}^n$ and β is a positive constant. The i-th component of the function $g(p(t))$ is

$$g_i(p(t)) = \frac{p_i(t)^H}{\beta^H + p_i(t)^H} \tag{2}$$

where H is the Hill coefficient. See for example Li et al. [2006] for details and illustrations of the structure and regulation mechanism of this genetic network and for the typical relation between b and B.

In this paper we address the stability analysis of the genetic network (1) affected by time-invariant parametric uncertainties. In particular, we consider the model

$$\left\{ \begin{array}{rcl} \dot{m}(t) & = & A(\theta)m(t) + b(\theta) + B(\theta)g(p(t)) \\ \dot{p}(t) & = & C(\theta)p(t) + D(\theta)m(t) \\ \theta \in \Theta & & \end{array} \right. \tag{3}$$

where $\theta \in \mathbb{R}^r$ is the time-invariant uncertainty vector and Θ is the uncertainty set described by the hypercube

$$\Theta = \{\theta \in \mathbb{R}^r : \ \theta_i \in [0, 1] \ \forall i\}. \tag{4}$$

The functions $A(\theta), C(\theta), D(\theta), B(\theta) \in \mathbb{R}^{n\times n}$ and $b(\theta) \in \mathbb{R}^n$ are linear, with $A(\theta)$ and $C(\theta)$ diagonal Hurwitz for each $\theta \in \Theta$, and $D(\theta)$ diagonal and positive definite for each $\theta \in \Theta$. The problem we consider is as follows.

Problem P1: to establish if, for each $\theta \in \Theta$, system (3) has an equilibrium point in $\mathbb{R}^{2n}_+$ and whose domain of attraction includes $\mathbb{R}^{2n}_+$.

In the sequel the dependence on t will be omitted where appropriate for ease of notation. Let us observe that, if problem P1 has a positive answer, the equilibrium point is unique and globally asymptotically stable in $\mathbb{R}^{2n}_+$.

2.2 Square matricial representation (SMR)

Let us introduce a key representation of polynomials. Let $s(x)$ be a polynomial of degree $2m$ in $x \in \mathbb{R}^n$. This polynomial can be represented via the square matricial representation (SMR) of polynomials as

$$s(x) = x^{[m]'} S(\alpha) x^{[m]}. \tag{5}$$

In (5), $x^{[m]} \in \mathbb{R}^{\nu(n,m)}$ is a vector containing all monomials of degree less than or equal to m in x, and $S(\alpha) \in \mathbb{R}^{\nu(n,m)\times\nu(n,m)}$ is a symmetric matrix affine on a free vector $\alpha\mu(n, m)$. The quantities $\nu(n, m)$ and $\mu(n, m)$ are

$$\begin{array}{rcl} \nu(n,m) & = & \dfrac{(n+m)!}{n!m!} \\ \mu(n,m) & = & \dfrac{1}{2}\nu(n,m)(\nu(n,m)+1) - \nu(n,2m). \end{array} \tag{6}$$

For details see Chesi et al. [1999, 2003]. In the sequel we will refer to $S(\alpha)$ as SMR matrix of $s(x)$.

3. STABILITY CONDITION

Let $[m^*(\theta); p^*(\theta)] \in \mathbb{R}^{2n}$ be an equilibrium point of (3), that is a solution of the nonlinear equations

$$\left\{ \begin{array}{rcl} A(\theta)m + b(\theta) + B(\theta)g(p) & = & 0_n \\ C(\theta)p + D(\theta)m & = & 0_n \end{array} \right. \tag{7}$$

Let us first introduce the following remark.

Remark 1. By the nature of the problem, all trajectories of (3) starting in $\mathbb{R}^{2n}_+$ remain in $\mathbb{R}^{2n}_+$ for each $\theta \in \Theta$. In fact, from (1) one has that the derivatives of m when $m = 0_n$ and p when $p = 0_n$ are non-negative. Hence:

$$\begin{bmatrix} m(0) \\ p(0) \end{bmatrix} \in \mathbb{R}^{2n}_+ \Rightarrow \begin{bmatrix} m(t) \\ p(t) \end{bmatrix} \in \mathbb{R}^{2n}_+ \ \forall t \geq 0 \ \forall \theta \in \Theta. \tag{8}$$

Let us shift the unknown equilibrium point $[m^*(\theta); p^*(\theta)]$ in the origin by defining

$$\begin{array}{rcl} x & = & m - m^*(\theta) \\ y & = & p - p^*(\theta). \end{array} \tag{9}$$

System (3) becomes:

$$\left\{ \begin{array}{rcl} \dot{x} & = & A(\theta)x + B(\theta)h(y, p^*(\theta)) \\ \dot{y} & = & C(\theta)y + D(\theta)x \\ \theta \in \Theta & & \end{array} \right. \tag{10}$$

where the i-th component of the function $h(y, p^*(\theta))$ is

$$h_i(y, p^*(\theta)) = \frac{(y_i + p_i^*(\theta))^H}{\beta^H + (y_i + p_i^*(\theta))^H} - \frac{p_i^*(\theta)^H}{\beta^H + p_i^*(\theta)^H}. \tag{11}$$

Let $\mathcal{X}(\theta) \times \mathcal{Y}(\theta)$ be the image of $\mathbb{R}^{2n}_+$ via the map (9):

$$\begin{array}{rcl} \mathcal{X}(\theta) & = & \{x \in \mathbb{R}^n : \ x_i \geq -m_i^*(\theta) \ \forall i = 1, \ldots, n\} \\ \mathcal{Y}(\theta) & = & \{y \in \mathbb{R}^n : \ y_i \geq -p_i^*(\theta) \ \forall i = 1, \ldots, n\}. \end{array} \tag{12}$$

The following result provides a first step for building a solution of problem P1.

Theorem 1. Let $\mathcal{Z}(y, \theta) \subseteq \mathbb{R}^n$ be any set satisfying the following condition:

$$h(y, p^*(\theta)) \in \mathcal{Z}(y, \theta) \ \forall y \in \mathcal{Y}(\theta) \ \forall \theta \in \Theta. \tag{13}$$

Suppose there exists a parameter-dependent Lyapunov function $v(x, y, \theta)$ such that it is continuously differentiable and radially unbounded for each $\theta \in \Theta$ and

$$\left. \begin{array}{rcl} v(x, y, \theta) & > & 0 \\ \bar{v}(x, y, z, \theta) & < & 0 \end{array} \right\} \begin{array}{l} \forall [x; y] \in \mathbb{R}^{2n} \setminus 0_{2n} \\ \forall z \in \mathcal{Z}(y, \theta) \ \forall \theta \in \Theta \end{array} \tag{14}$$

where

$$\bar{v}(x, y, z, \theta) = \frac{\partial v(x, y, \theta)}{\partial [x; y]} \begin{bmatrix} A(\theta)x + B(\theta)z \\ D(\theta)x + C(\theta)y \end{bmatrix} \tag{15}$$

Then, problem P1 admits a positive answer.

Proof. Suppose that the conditions (13)–(14) are satisfied. From (15) one has that $v(x,y,\theta)$ is positive definite (with respect to x,y) for each $\theta \in \Theta$ and that the derivative of $v(x,y,\theta)$ along the trajectories of (10) is negative definite in $\mathcal{X}(\theta) \times \mathcal{Y}(\theta)$ for each $\theta \in \Theta$. In fact, from (13) one has that for all $y \in \mathcal{Y}(\theta)$ there exists $z \in \mathcal{Z}(y,\theta)$ such that $\bar{v}(x,y,z,\theta) = \dot{v}(x,y,\theta)$ for each $\theta \in \Theta$, being

$$\dot{v}(x,y,\theta) = \frac{\partial v(x,y,\theta)}{\partial [x;y]} \begin{bmatrix} A(\theta)x + B(\theta)h(y,p^*(\theta)) \\ D(\theta)x + C(\theta)y \end{bmatrix}.$$

Hence, let us consider any trajectory $[x(t);y(t)]$ of system (10) starting in $\mathcal{X}(\theta) \times \mathcal{Y}(\theta)$. From the positive definiteness of $v(x,y,\theta)$ and $-\dot{v}(x,y,\theta)$ in $\mathcal{X}(\theta) \times \mathcal{Y}(\theta)$ one has that $[x(t);y(t)]$ move on decreasing level sets of $v(x,y,\theta)$ asymptotically reaching the origin unless $[x(t);y(t)]$ exits from $\mathcal{X}(\theta) \times \mathcal{Y}(\theta)$. But the latter case is impossible because from (12) and the first condition in (13) one has that

$$[x(t);y(t)] \notin \mathcal{X}(\theta) \times \mathcal{Y}(\theta) \Rightarrow [m(t);p(t)] \notin \mathbb{R}_+^{2n}$$

which contradicts (8). Therefore, the theorem holds. □

Theorem 1 provides a sufficient condition for problem P1 based on the existence of a suitable set $\mathcal{Z}(y,\theta)$ and a suitable Lyapunov function $v(x,y,\theta)$.

Remark 2. Let us observe that we have derived this condition in spite of the fact that the equilibrium point $[m^*(\theta);p^*(\theta)]$ of system (3) cannot be calculated being the solution of a system of parameter-dependent nonlinear equations.

Remark 3. Let us also observe that Theorem 1 provides a guaranteed domain of attraction of the unknown equilibrium point $[m^*(\theta);p^*(\theta)]$ without requiring that the derivative of the Lyapunov function is negative definite in a sublevel set of the Lyapunov function including $\mathbb{R}_+^{2n}$ nor in the whole space $\mathbb{R}^{2n}$.

The condition of Theorem 1 can be tackled through convex LMI optimizations by restricting our attention to polynomial Lyapunov functions and polynomial descriptions of the set $\mathcal{Z}(y,\theta)$. In particular, let us select $v(x,y,\theta)$ as a parameter-dependent quadratic Lyapunov functions with polynomial dependence according to

$$\begin{aligned} v(x,y,\theta) &= [x;y]'\bar{V}(\theta)[x;y] \\ \bar{V}(\theta) &= V\left(\theta^{[\delta_v]} \otimes I_{2n}\right) \end{aligned} \tag{16}$$

where δ_v is the degree of the dependence and V is a matrix of suitable dimension such that $\bar{V}(\theta) = \bar{V}(\theta)'$. Then, we describe $\mathcal{Z}(y,\theta)$ as follows:

$$\mathcal{Z}(y,\theta) = \{z \in \mathbb{R}^n : \; a_i(y,z,\theta) \geq 0 \; \forall i = 1,\ldots,n_a\} \tag{17}$$

where $a_i(y,z,\theta)$ are suitable polynomials of degree δ_a in θ such that condition (13) holds (the computation of these polynomials will be dealt with in Section 4).

The next step for obtaining an LMI formulation of Theorem 1 consists of exploiting the Hilbert's positivstellensatz and a parameter-dependent extension of the SMR of polynomials. In particular, let us define $c = [x;y;z]$ and

$$\begin{aligned} t_1(c,\theta) &= v(x,y,\theta) - \sum_{i=1}^{r} \theta_i(1-\theta_i)s_{1,i}(c,\theta) \\ t_2(c,\theta) &= -\bar{v}(x,y,z,\theta) - \sum_{i=1}^{r} \theta_i(1-\theta_i)s_{2,i}(c,\theta) \\ &\quad - \sum_{i=1}^{n_a} a_i(y,z,\theta)s_{3,i}(c,\theta) \end{aligned} \tag{18}$$

where $s_{1,i}(c,\theta), s_{2,i}(c,\theta)$ and $s_{3,i}(c,\theta)$ are auxiliary polynomials to determine known as Hilbert's polynomials. Let us select $\delta_1 \geq \left\lceil \frac{\delta_v}{2} \right\rceil$, $\delta_2 \geq \left\lceil \frac{\max\{\delta_v+1, 2\delta_3+\delta_a\}}{2} \right\rceil$, $\delta_3 \geq 0$ and let us express these polynomials as

$$\begin{aligned} t_k(c,\theta) &= \left(\theta^{[\delta_k+1]} \otimes \xi_k(c)\right)' T_k \left(\theta^{[\delta_k+1]} \otimes \xi_k(c)\right) \\ s_{k,i}(c,\theta) &= \left(\theta^{[\delta_k]} \otimes \xi_k(c)\right)' S_{k,i} \left(\theta^{[\delta_k]} \otimes \xi_k(c)\right) \end{aligned} \tag{19}$$

where T_k and $S_{k,i}$ are SMR matrices and $\xi_k(c)$ are chosen vectors containing bases for these polynomials. For example, if $t_2(c,\theta)$ is quadratic in c, one can simply select $\xi_k(c) = c$ since $t_2(c,\theta) = \left(\theta^{[\delta_2+1]} \otimes c\right)' T_2 \left(\theta^{[\delta_2+1]} \otimes c\right)$. Lastly, for $k = 1,2$ let us define the linear sets

$$\begin{aligned} \mathcal{N}_k = \Big\{ N_k = N_k' : \; &\left(\theta^{[\delta_k+1]} \otimes \xi_k(c)\right)' N_k \\ &\cdot \left(\theta^{[\delta_k+1]} \otimes \xi_k(c)\right) = 0 \; \forall c \; \forall \theta \Big\} \end{aligned} \tag{20}$$

and let $N_k(\alpha_k)$ be linear parameterizations of $\mathcal{N}_k$ where α_k is a free vector of suitable dimension.

Theorem 2. Suppose there exist V, S_*, α_* such that the following LMIs are satisfied:

$$\begin{aligned} T_k + N_k(\alpha_k) &> 0 \quad \forall k = 1,2 \\ S_{k,i} &> 0 \quad \forall k = 1,2 \; \forall i = 1,\ldots,r \\ S_{3,i} &> 0 \quad \forall i = 1,\ldots,n_a \end{aligned} \tag{21}$$

Then, problem P1 admits a positive answer.

Proof. Suppose that (21) is satisfied. By multiplying the inequality $T_2 + N_2(\alpha_2) > 0$ by $\theta^{[\delta_2]} \otimes \xi_2(c)$ on the left and right sides and exploiting the definition of $N_2(\alpha_2)$ one obtains that $t_2(c,\theta) > 0$. Similarly, from the other LMIs one obtains analogous positivity conditions for the polynomials in (18). Now, let us consider any $\theta \in \Theta$ and $c = [x;y;z]$ such that $[x;y] \neq 0_{2n}$ and $z \in \mathcal{Z}(y,\theta)$. It follows from (17) that $a_i(y,z,\theta) \geq 0$ for all $i = 1,\ldots,n_a$. Moreover, from the definition of $t_2(c,\theta)$ in (18) and Θ in (4) one has that the condition $t_2(c,\theta) > 0$ implies $\bar{v}(x,y,z,\theta) < 0$ as required by condition (14). Analogously, one proves from the definition of $t_1(c,\theta)$ in (18) that $v(x,y,\theta)$ satisfies condition (14). □

Theorem 2 provides a sufficient condition for problem P1 via an LMI feasibility test, which is a convex optimization. This condition is obtained by exploiting a polynomial description of the set $\mathcal{Z}(y,\theta)$ which contains the uncertain nonlinearity of system (10) under the assumption that condition (13) is satisfied. The SMR matrices $T_1, T_2, N_1(\alpha_1)$ and $N_2(\alpha_2)$ involved in the condition of Theorem 2 can be computed via simple algorithms, see for example Chesi et al. [2003].

4. COMPUTATION OF THE UNCERTAIN NONLINEARITY BOUNDING SET

In this section we consider the problem of computing polynomials $a_i(y,z,\theta)$ such that the set $\mathcal{Z}(y,\theta)$ in (17) satisfies the condition (13). We proceed according to the following steps:

(1) characterizing the variable equilibrium point of system (3);
(2) computing $a_i(y,z,\theta)$ on the base of this characterization.

4.1 Characterizing the variable equilibrium point

Let us define the set $\mathcal{P}$ of possible values for the p-component of the equilibrium points of (3) as

$$\mathcal{P} = \big\{p \in \mathbb{R}^n_+ : \; [m;p] \text{ is a solution of (7)} \\ \text{for some } m \in \mathbb{R}^n \text{ and } \theta \in \Theta\big\}. \quad (22)$$

Since the computation of $\mathcal{P}$ is a difficult task, we proceed by computing an embedding set of $\mathcal{P}$.

Theorem 3. Let $\Theta_v = \{0,1\}^r$ be the set of vertices of Θ and let ϕ_i^- and ϕ_i^+ be any quantities satisfying

$$\begin{aligned} \phi_i^- &\leq \min_{\theta\in\Theta} \frac{D_{i,i}(\theta)}{A_{i,i}(\theta)C_{i,i}(\theta)} \\ \phi_i^+ &\geq \max_{\theta\in\Theta} \frac{D_{i,i}(\theta)}{A_{i,i}(\theta)C_{i,i}(\theta)} \end{aligned} \quad (23)$$

for all $i = 1,\dots,n$. For $i = 1,\dots,n$ let us define $u_{0,i}^- = 0$ and $u_{0,i}^+ = +\infty$. Moreover, for $k \geq 1$ let us define the set

$$\mathcal{U}_k = \left\{u \in \mathbb{R}^n : \; u_{k,i}^- \leq u_i \leq u_{k,i}^+ \;\; \forall i = 1,\dots,n\right\} \quad (24)$$

where

$$\begin{aligned} u_{k,i}^- &= \max\{u_{k-1,i}^-, \phi_i^- \psi_{k,i}^-\} \\ u_{k,i}^+ &= \min\{u_{k-1,i}^+, \phi_i^+ \psi_{k,i}^+\} \end{aligned} \quad (25)$$

and

$$\begin{aligned} \psi_{k,i}^- &= \min_{[\theta;q]\in\Theta_v\times\mathcal{Q}_{k-1}} e_i'\,(b(\theta) + B(\theta)q) \\ \psi_{k,i}^+ &= \max_{[\theta;q]\in\Theta_v\times\mathcal{Q}_{k-1}} e_i'\,(b(\theta) + B(\theta)q) \end{aligned} \quad (26)$$

being $e_i \in \mathbb{R}^n$ the i-th column of I_n and

$$\mathcal{Q}_k = \left\{g(u) : \; u_i = u_{k,i}^-, u_{k,i}^+\right\} \quad (27)$$

with $g(\cdot)$ as in (2). Then,

$$\mathcal{U}_k \supseteq \mathcal{U}_{k+1} \supseteq \mathcal{P} \quad \forall k \geq 1. \quad (28)$$

Proof. Let us consider first $k = 1$. From the definition of equilibrium points of the system (3) in (7), one has that $p \in \mathcal{P}$ if and only if

$$-A(\theta)D(\theta)^{-1}C(\theta)p + b(\theta) + B(\theta)g(p) = 0_n \\ p \in \mathbb{R}^n_+$$

for some $\theta \in \Theta$. If $p \in \mathbb{R}^n_+$ one has that $g(p) \in [0,1]^n$ and, hence, each p satisfying the previous conditions satisfies also

$$p = C(\theta)^{-1}D(\theta)A(\theta)^{-1}\,(b(\theta) + B(\theta)q)$$

for some $q \in [0,1]^n$. Hence, taking into account that $A(\theta), C(\theta), D(\theta)$ are diagonal one has

$$\min_{p\in\mathcal{P}} p_i \geq \bar{u}_{1,i}^-$$

$$\bar{u}_{1,i}^- = \min_{[\theta;q]\in\Theta\times[0,1]^n} \frac{D_{i,i}(\theta)e_i'\,(b(\theta) + B(\theta)q)}{A_{i,i}(\theta)C_{i,i}(\theta)}.$$

Moreover,

$$\begin{aligned} \bar{u}_{1,i}^- &\geq \phi_i^- \min_{[\theta;q]\in\Theta\times[0,1]^n} e_i'\,(b(\theta) + B(\theta)q) \\ &= \phi_i^- \psi_{1,i}^- \end{aligned}$$

because $e_i'\,(b(\theta) + B(\theta)q)$ is a multi-linear function and hence the minimum over the hypercube $\Theta \times [0,1]^n$ is taken on the vertices of this hypercube. Hence, taking into account that $p_i \geq u_{0,i}^- = 0$ for all $p \in \mathcal{P}$ one has immediately shows that $\mathcal{U}_1 \supseteq \mathcal{P}$. Then, from (25) it is clear that $\mathcal{U}_k \supseteq \mathcal{U}_{k+1}$ because the limits of the set $\mathcal{U}_k$ do not increase with k. Hence, the theorem holds. □

Theorem 3 provides an iterative strategy for computing an embedding set of $\mathcal{P}$ which consists of the following steps:

(1) calculate ϕ_i^- and ϕ_i^+ which are respectively a lower and an upper bound of a rational function over the hypercube Θ;
(2) calculate $\psi_{k,i}^-$ and $\psi_{k,i}^+$ which are respectively the minimum and maximum of a function on the set of vertices $\Theta_v \times \mathcal{Q}_{k-1}$;
(3) iterate the calculation of $\psi_{k,i}^-$ and $\psi_{k,i}^+$ based on the estimate found at the previous iteration.

The computation of $\psi_{k,i}^-$ and $\psi_{k,i}^+$ is trivial. For the computation of the ϕ_i^- and ϕ_i^+ in the general case one can readily exploit dedicated software based on convex LMI optimizations, see for example Henrion and Lasserre [2002], Chesi et al. [2003]. Moreover, there are special cases in which also the computation of ϕ_i^- and ϕ_i^+ is trivial, such as $r = 1$ (one has to find the minimum and maximum of a rational function of a scalar parameter). The following simple numerical example illustrates the proposed procedure.

Example A. Let us consider system (3) with $H = 2$, $\beta = 1$, $n = 2$, $r = 1$ and

$$\begin{aligned} A(\theta) &= \mathrm{diag}(-1 + 0.2\theta_1, -1) \\ C(\theta) &= \mathrm{diag}(-1 - 0.3\theta_1, -1) \\ D(\theta) &= \mathrm{diag}(1 + 0.2\theta_1, 1 + 0.1\theta_1) \\ B(\theta) &= \begin{bmatrix} 0 & -0.3 - 0.2\theta_1 \\ 0.2 + 0.5\theta_1 & 0 \end{bmatrix} \\ b(\theta) &= [0.5 + 0.3\theta_1; 0]. \end{aligned} \quad (29)$$

The first step consists of computing the quantities ϕ_i^-, ϕ_i^+ satisfying the condition (23). For $i = 1$ we have:

$$\phi_1^- \leq \frac{1 + 0.2\theta_1}{(1 - 0.2\theta_1)(1 + 0.3\theta_1)} \leq \phi_1^+ \;\forall\theta_1 \in [0,1] \quad (30)$$

and, by simply looking at the zeros of the first derivative, one sees that ϕ_1^- and ϕ_1^+ can be selected respectively as 1 and 1.154. Analogously, one finds that ϕ_2^- and ϕ_2^+ can be selected as $\phi_2^- = 1$ and $\phi_2^+ = 1.1$.

The next step consists of computing the embedding set $\mathcal{U}_k$ in (24) by simply evaluating the function $e_i'\,(b(\theta) + B(\theta)q)$ on the set of vertices $\Theta_v \times \mathcal{Q}_{k-1}$. Table 1 shows the estimates obtained for some values of k. Let us observe that the convergence is quite fast as the final value (shown at the 20-th iteration) is reached in about 4 iterations. Figure 1 shows the set $\mathcal{U}_4$ and the true equilibrium point $p^*(\theta)$ computed by solving the system of nonlinear equations (7) for $\theta = 0, 0.1, \dots, 0.9, 1$: as we can see $p^*(\theta)$ belongs to $\mathcal{U}_4$ for each $\theta \in \Theta$ according to Theorem 3.

k	$u^-_{k,1}$	$u^+_{k,1}$	$u^-_{k,2}$	$u^+_{k,2}$
1	0	0.577	0	0.77
2	0.188	0.577	0	0.192
3	0.289	0.577	0.00685	0.192
4	0.289	0.577	0.0154	0.192
⋮	⋮	⋮	⋮	⋮
20	0.289	0.577	0.0154	0.192

Table 1. Example A: embedding sets $\mathcal{U}_k$ of $\mathcal{P}$.

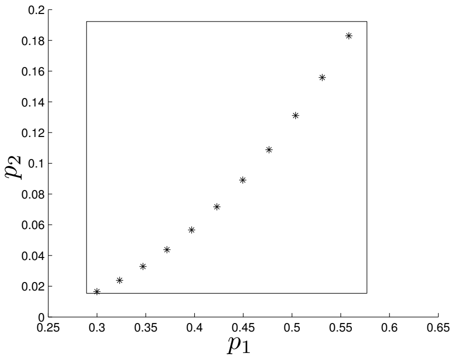

Fig. 1. Example A: box $\mathcal{U}_4$ (solid line) and true equilibrium point $p^*(\theta)$ for $\theta = 0, 0.1, \ldots, 1$ ("$*$" marks).

4.2 Uncertain nonlinearity bounding set

In this section we consider the problem of computing bounding sets $\mathcal{Z}(y,\theta)$ satisfying the condition (13) based on the embedding set $\mathcal{U}_k$ of $\mathcal{P}$ provided by Theorem 3. The first step consists of selecting a structure for the polynomials $a_i(y,z,\theta)$ in (17). Since $h_i(y,p^*(\theta))$ for $y \in \mathcal{Y}(\theta)$ is a monotonically increasing function with saturation and vanishing at $y = 0_n$, one can select for example the linear set

$$a_i(y,z,\theta) = z_i(\sigma_i y_i - z_i) \tag{31}$$

or the parameter-dependent quadratic set

$$a_i(y,z,\theta) = z_i((\sigma_{i,1} + \sigma_{i,2}'\theta)y_i - z_i(\sigma_{i,3} + \sigma_{i,4}'\theta + y_i)) \tag{32}$$

where $\sigma_i, \sigma_{i,1}, \sigma_{i,3} \in \mathbb{R}$ and $\sigma_{i,2}, \sigma_{i,4} \in \mathbb{R}^r$ are constants.

For clarity and conciseness, we illustrate the technique for the structure (31). With this definition of $\mathcal{Z}(y,\theta)$, the condition (13) is fulfilled if and only if

$$h_i(y,p)\left(\sigma_i y_i - h_i(y,p)\right) \geq 0 \quad \begin{array}{r}\forall i = 1,\ldots,n \\ \forall y_i \geq -p_i \ \forall p \in \mathcal{P}\end{array} \tag{33}$$

From the definition of the function $h_i(y,p)$ in (11), one has that this condition holds if and only if

$$o_i(y_i,p_i) \geq 0 \quad \forall i = 1,\ldots,n \ \forall y_i \geq -p_i \ \forall p \in \mathcal{P} \tag{34}$$

where

$$\begin{array}{l} o_i(y_i,p_i) = \sigma_i y_i(\beta^H + p_i^H)\left(\beta^H + (y_i+p_i)^H\right) \\ \cdot\left((y_i+p_i)^H - p_i^H\right) - \beta^H\left((y_i+p_i)^H - p_i^H\right)^2. \end{array} \tag{35}$$

In order to determine σ_i satisfying (34), we can exploit the SMR of polynomials and LMI optimizations. To this end, let us observe that $o_i(y_i,p_i)$ is a polynomial in y_i whose coefficients depend on p_i, and hence we can adopt a parameter-dependent structure where the parameter is p_i. Specifically, let us define the polynomial

$$\begin{array}{rl} t_{4,i}(y_i,p_i) = & o_i(y_i,p_i) - (y_i+p_i)s_{4,i}(y_i,p_i) \\ & -(p_i - u^-_{k,i})(u^+_{k,i} - p_i)s_{5,i}(y_i,p_i) \end{array} \tag{36}$$

where $s_{4,i}(y_i,p_i)$ and $s_{5,i}(y_i,p_i)$ are auxiliary polynomials and $u^-_{k,i}$ and $u^+_{k,i}$ are the bounds of the set $\mathcal{U}_k$ in (24). Let us select $\delta_4 \geq \lceil \frac{2H+1}{2} \rceil$, $\delta_5 \geq \lceil \frac{3H-1}{2} \rceil$ and the following structures:

$$\begin{array}{rcl} t_{4,i}(y_i,p_i) & = & \left(p_i^{[\delta_4]} \otimes y_i^{[\delta_5]}\right)' T_{4,i} \left(p_i^{[\delta_4]} \otimes y_i^{[\delta_5]}\right) \\ s_{4,i}(y_i,p_i) & = & \left(p_i^{[\delta_4-1]} \otimes y_i^{[\delta_5-1]}\right)' S_{4,i} \left(p_i^{[\delta_4-1]} \otimes y_i^{[\delta_5-1]}\right) \\ s_{5,i}(y_i,p_i) & = & \left(p_i^{[\delta_4-1]} \otimes y_i^{[\delta_5]}\right)' S_{5,i} \left(p_i^{[\delta_4-1]} \otimes y_i^{[\delta_5]}\right) \end{array} \tag{37}$$

where $T_{4,i}, S_{4,i}$ and $S_{5,i}$ are SMR matrices of suitable dimension. Moreover, let $N_4(\alpha_4)$ be a linear parametrization of the set $\{N = N' : \ \left(p_i^{[\delta_4]} \otimes y_i^{[\delta_5]}\right)' N \left(p_i^{[\delta_4]} \otimes y_i^{[\delta_5]}\right) = 0 \ \forall y_i \ \forall p_i\}$ where α_4 is a free vector of suitable dimension.

Lastly, let us observe that there exist multiple constants σ_i satisfying (13), and clearly one wants to pick up the smallest one in order to reduce the conservatism of $\mathcal{Z}(y,\theta)$. The computation of an upper bound of this optimal constant is considered in the following result.

Theorem 4. For all $i = 1,\ldots,n$ let $\bar{\sigma}_i$ be the solution of the following EVP:

$$\begin{array}{c} \bar{\sigma}_i = \displaystyle\min_{\sigma_i, S_{4,i}, S_{5,i}, \alpha_{4,i}} \sigma_i \\ \text{s.t.} \begin{cases} T_{4,i} + N_4(\alpha_{4,i}) \geq 0 \\ S_{j,i} \geq 0 \quad \forall j = 4,5 \end{cases} \end{array} \tag{38}$$

Then, the set $\mathcal{Z}(y,\theta)$ defined with $a_i(y,z,\theta)$ as in (31) for $\sigma_i = \bar{\sigma}_i$ satisfies the condition (13).

Proof. Similarly to the proof of Theorem 2 one proves that $t_{4,i}(y_i,p_i)$ and $s_{j,i}(y_i,p_i)$ are nonnegative. Then, for any y_i and p_i such that $y_i \in [-p_i, +\infty)$ and $p \in \mathcal{P}$, one has that the non-negativity of $t_{4,i}(y_i,p_i)$ and $s_{j,i}(y_i,p_i)$ and the fact that $U_k \supseteq \mathcal{P}$ for all $k \geq 1$ (see Theorem 3) imply that $o_i(y_i,p_i) \geq 0$ as required by condition (34). Lastly, the optimization (38) is an EVP because the cost is a linear function of the LMI variables Boyd et al. [1994]. □

Theorem 4 provides a technique to find the set $\mathcal{Z}(y,\theta)$ which amounts to solving an EVP (that is a convex optimization constrained by LMIs).

5. AN EXAMPLE

Let us consider the uncertain genetic network described by (3) with $H = 2$, $\beta = 1$, $n = 5$, $r = 1$ and

$$\begin{array}{rcl} A(\theta) & = & \mathrm{diag}(-1-0.2\theta_1, -1, -1, -1, -1) \\ C(\theta) & = & \mathrm{diag}(-1, -1-0.2\theta_1, -1, -1, -1) \\ D(\theta) & = & \mathrm{diag}(0.8+0.2\theta_1, 0.8, 0.8, 0.8, 0.8+0.1\theta_1) \\ B(\theta) & = & \begin{bmatrix} 0 & -0.5 & 0.5+0.1\theta_1 & 0 & 0 \\ -0.5 & 0 & 0 & 0.5 & 0.5+0.2\theta_1 \\ 0 & 0.5 & 0 & 0 & 0 \\ 0.5 & -0.5 & 0 & 0 & 0 \\ 0.1\theta_1 & 0 & 0 & 0.5 & 0 \end{bmatrix} \\ b(\theta) & = & [0.5; 0.5; 0; 0.5; 0]. \end{array}$$

The model for $\theta_1 = 0$ is considered in Li et al. [2006].

Let us consider first problem P1. We compute an embedding set $\mathcal{U}_k$ of $\mathcal{P}$ as described in Section 4.1, and then constants σ_i satisfying the condition (13). We find the set $\mathcal{U}_{11}$ shown in Table 2 (after the 11-th iteration of the procedure in Theorem 3 these values remain constant). Table 2 also shows the constants $\bar{\sigma}_i$ obtained from Theorem 4. We select a parameter-dependent quadratic Lyapunov

i	1	2	3	4	5
$u_{11,i}^{-}$	0.341	0.335	0.0404	0.382	0.0509
$u_{11,i}^{+}$	0.376	0.419	0.0597	0.409	0.0757
$\bar{\sigma}_i$	0.633	0.639	0.529	0.638	0.536

Table 2. Example 1: embedding set $\mathcal{U}_{11}$ of $\mathcal{P}$ and constants σ_i based on this set.

function with polynomial dependence of degree $\delta_v = 0$ (common quadratic Lyapunov function) and find that the LMI (21) is satisfied. Hence, according to Theorem 2 we find that, for each $\theta \in \Theta$, the system considered in this example has an equilibrium point in $\mathbb{R}_+^{2n}$ and whose domain of attraction includes $\mathbb{R}_+^{2n}$.

In addition to problem P1 we also consider the following problem:

Problem P2: to compute a lower bound of the stability margin

$$\begin{aligned} \varrho^* &= \sup\{\varrho : \text{ problem P1 has a positive} \\ &\qquad \text{answer with } \Theta \text{ replaced by } \Theta(\varrho)\} \\ \Theta(\varrho) &= \{\theta \in \mathbb{R}^r : \ \theta_i \in [0, \varrho] \ \forall i\}. \end{aligned} \quad (39)$$

We can address problem P2 via a bisection algorithm on ϱ where, at each step, the robust stability for each $\theta \in \Theta(\varrho)$ is established by using Theorem 2. By using a common Lyapunov function we find the lower bound $\varrho_0^* = 21.4$. This lower bound can be improved by increasing δ_v. In particular, with $\delta_v = 1$ we find $\varrho_1^* = 31.1$.

Regarding the complexity of the proposed approach, we have that the number of scalar variables in the LMI optimization (21) for this example is 296 for the case $\delta_v = 0$ and 451 for the case $\delta_v = 1$ (see also Table 3 where different values of n are also shown). The computational time for these two cases are less than 10 seconds on a standard PC.

$\delta_v \mid n$	1	2	3	4	5
0	16	53	112	193	296
1	23	79	169	293	451

Table 3. Example 1: number of scalar variables in the LMI optimization (21).

6. CONCLUSION

In this paper we have addressed the problem of establishing robust stability of genetic regulatory networks affected by parametric uncertainties. We have proposed a sufficient condition for robust stability by introducing a bounding set of the uncertain nonlinearity which ensures that, for each admissible value of the uncertainties, the system has only one equilibrium point and this equilibrium point is globally asymptotically stable in the positive octant. Moreover, we have shown that this condition can be formulated as an LMI optimization by considering polynomial Lyapunov functions and polynomial descriptions of the bounding set and by exploiting the square matricial representation (SMR) of polynomials. Then, we have shown that a family of bounding sets can be computed by means of convex optimizations in spite of the fact that the variable equilibrium point cannot be calculated being the solution of a system of parameter-dependent nonlinear equations.

ACKNOWLEDGEMENT

The authors would like to thank the Associate Editor and Reviewers for their comments.

REFERENCES

S. Aluru, editor. *Handbook of Computational Molecular Biology.* Computer and Information Science Series. Chapman and All/Crc, 2005.

S. D. Bay, J. Shrager, A. Pohorille, and P. Langley. Revising regulatory networks: From expression data to linear causal models. *Journal of Biomedical Informatics*, 35(5):289–297, 2002.

J. M. Bower and H. Bolouri, editors. *Computational Modeling of Genetic and Biochemical Networks.* Computational Molecular Biology. MIT Press, 2001.

S. Boyd, L. El Ghaoui, E. Feron, and V. Balakrishnan. *Linear Matrix Inequalities in System and Control Theory.* SIAM, Philadelphia, 1994.

G. Chesi, A. Tesi, A. Vicino, and R. Genesio. On convexification of some minimum distance problems. In *5th European Control Conf.*, Karlsruhe, Germany, 1999.

G. Chesi, A. Garulli, A. Tesi, and A. Vicino. Solving quadratic distance problems: an LMI-based approach. *IEEE Trans. on Automatic Control*, 48(2):200–212, 2003.

G. Chesi, A. Garulli, A. Tesi, and A. Vicino. Polynomially parameter-dependent Lyapunov functions for robust stability of polytopic systems: an LMI approach. *IEEE Trans. on Automatic Control*, 50(3):365–370, 2005.

E. H. Davidson. *The Regulatory Genome: Gene Regulatory Networks In Development And Evolution.* Academic Press, 2006.

D. Henrion and J. B. Lasserre. GloptiPoly: Global Optimization over Polynomials with Matlab and SeDuMi. In *Proc. of 41st IEEE Conf. on Decision and Control*, Las Vegas, Nevada, 2002.

F. Jacob and J. Monod. Genetic regulatory mechanisms in the synthesis of proteins. *Journal of Molecular Biology*, 3:318–356, 1961.

H. De Jong. Modeling and simulation of genetic regulatory systems: A literature review. *Journal of Computation Biology*, 9:67–103, 2002.

T. Kobayashi, L. Chen, and K. Aihara. Modeling genetic switches with positive feedback loops. *Journal of Theoretical Biology*, 221:379–399, 2002.

C. Li, L. Chen, and K. Aihara. Stability of genetic networks with sum regulatory logic: Lure system and lmi approach. *IEEE Trans. on Circuits and Systems-I*, 53(11):2451–2458, 2006.

C. W. Scherer. LMI relaxations in robust control. *European Journal of Control*, 12(1):3–29, 2006.

P. Smolen, D. A. Baxter, and J. H. Byrne. Mathematical modeling of gene networks. *Neuron*, 26(3):567–580, 2000.

R. Wang, T. Zhou, Z. Jing, and L. Chen. Modelling periodic oscillation of biological systems with multiple time scale networks. *Systems Biology*, 1:71–84, 2004.