RESEARCH ARTICLE

Polynomial Relaxation-based Conditions for Global Asymptotic Stability of Equilibrium Points of Genetic Regulatory Networks

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An important problem in systems biology consists of establishing whether an equilibrium point of a genetic regulatory network (GRN) is stable or not. This paper investigates this problem for GRNs with SUM or PROD regulatory functions. It is shown that sufficient conditions for global asymptotical stability of an equilibrium point of these networks can be derived in terms of convex optimizations with linear matrix inequality (LMI) constraints. These conditions are obtained by looking for a Lyapunov function through the use of suitable polynomial relaxations, and do not introduce approximations of the nonlinearities present in the GRNs. The benefit of these conditions is that their conservatism can be decreased by increasing the degree of the introduced polynomial relaxations. Numerical examples illustrate the usefulness of the proposed conditions.

Keywords: GRN, SUM form, PROD form, Stability, LMI.

1. Introduction

A primary research area in biomedical engineering is represented by genetic regulatory networks (GRNs), which explain the interactions between genes and proteins to form complex systems that perform complicated biological functions, see for instance Smolen et al. (2000), Jong (2002), Chen and Aihara (2002), Kobayashi et al. (2002), Li et al. (2007), Munsky and Khammash (2008) and references therein. A first classification divides GRNs into two main groups, specifically the Boolean model (or discrete model) and the differential equation model (or continuous 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 (i.e., mRNAs and proteins) as continuous values, and their time derivative is expressed as a function of the variables themselves.

The differential equation models can be divided into two main classes. One of these classes is characterized by the fact that each transcription factor acts additively to regulate a gene, i.e. the regulatory function sums over all the inputs, and it is known as GRN with SUM regulatory functions. The other class is described by a product rather than a sum among all the inputs, and it is known as GRN with PROD regulatory functions. See for instance Li et al. (2006, 2007), Chaves et al. (2008), Drulhe et al. (2008), Chesi and Hung (2008) and references therein.

An important issue in GRNs consists of establishing stability of equilibrium points. In fact, stability is related to the ability of an organism to robustly regulate its function in spite of

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the presence of changes that move the state of the organism away from the equilibrium. Unfortunately, this is a difficult issue since GRNs are nonlinear systems, in particular they are characterized by sums or products of saturation functions, and to determine whether an equilibrium point of such a system is globally asymptotically stable is known to be a NP-hard problem, see for instance Khalil (2001).

This paper proposes a possible solution for this problem. In particular, GRNs with SUM or PROD regulatory functions are considered. It is shown that sufficient conditions for global asymptotical stability of equilibrium points of these networks can be obtained in terms of linear matrix inequality (LMI) feasibility tests, which amount to solving convex optimization as explained in Boyd et al. (1994). These conditions are derived by searching for a Lyapunov function for the equilibrium point, and are constructed through the use of suitable polynomial relaxations. The advantage of these conditions is that their conservatism can be decreased by increasing the degree of the polynomial relaxations, since no approximation of the nonlinearities present in the GRNs is introduced. Some numerical examples are reported in order to illustrate the proposed approach and its usefulness.

The paper is organized as follows. Section 2 introduces some preliminaries on GRNs with SUM and PROD regulatory functions. Section 3 describes the proposed results. Section 4 presents some illustrative examples. Lastly, Section 5 concludes the paper with some final remarks.

2.   Preliminaries

Let us start by introducing the notation adopted in the following discussions:

- $\mathbb{R}$: space of real numbers;
- $\mathbb{R}_+$: space of positive real numbers;
- 0_n: origin of $\mathbb{R}^n$;
- I_n: $n \times n$ identity matrix;
- X': transpose of matrix X;
- e_i: i-th column of the identity matrix (with size specified by the context);
- TF: transcription factor.

In this paper we consider two classes of GRNs. The first class is characterized by SUM regulatory functions, which can be described by the model

$$
\begin{cases}
\dot{m}_i(t) = -a_i m_i(t) + \sum_{j=1}^{n} b_{i,j}^S(p_j(t)) \\
\dot{p}_i(t) = -c_i p_i(t) + d_i m_i(t) \\
\qquad i = 1, \ldots, n
\end{cases}
\tag{1}
$$

where $m_i(t), p_i(t) \in \mathbb{R}_+$ are the concentrations of mRNA and protein of the i-th node, and $a_i, c_i, d_i \in \mathbb{R}_+$ are positive coefficients. The function $b_{i,j}(p_j(t), 0)$ is given by

$$
b_{i,j}^S(p_j(t)) = \begin{cases}
\alpha_{i,j} f(p_j(t)) & \text{if TF } j \text{ is an} \\
& \text{activator of gene } i \\
\alpha_{i,j}(1 - f(p_j(t))) & \text{if TF } j \text{ is a} \\
& \text{repressor of gene } i \\
0 & \text{otherwise}
\end{cases}
\tag{2}
$$

where $\alpha_{i,j}$ are positive coefficients and $f(\cdot)$ is a saturation function satisfying

$$f : \mathbb{R}_+ \to [0,1], \ f(0) = 0, \ f(\infty) = 1, \ f \text{ monotic.} \tag{3}$$

This function $f(\cdot)$ is selected in the class of the Hill's functions, and is given by

$$f(p_i(t)) = \frac{p_i(t)^H}{\beta^H + p_i(t)^H} \tag{4}$$

where $\beta \in \mathbb{R}$ and H is an integer. By defining the vectors

$$m(t) = \begin{pmatrix} m_1(t) \\ \vdots \\ m_n(t) \end{pmatrix}, \quad p(t) = \begin{pmatrix} p_1(t) \\ \vdots \\ p_n(t) \end{pmatrix} \tag{5}$$

the model (1) can be rewritten in matricial form as (see for instance Li et al. (2006, 2007) for details)

$$\begin{cases} \dot{m}(t) = -Am(t) + r + Rg^S(p(t)) \\ \dot{p}(t) = -Cp(t) + Dm(t) \end{cases} \tag{6}$$

where $A, C, D \in \mathbb{R}_+^{n \times n}$ are diagonal matrices with positive entries, $R \in \mathbb{R}^{n \times n}$ is the matrix given by

$$R_{i,j} = \begin{cases} \alpha_{i,j} & \text{if TF } j \text{ is an activator of gene } i \\ -\alpha_{i,j} & \text{if TF } j \text{ is a repressor of gene } i \\ 0 & \text{otherwise,} \end{cases} \tag{7}$$

$r \in \mathbb{R}_+^n$ is the vector defined according to

$$r_i = - \sum_{j: \ R_{i,j} < 0} R_{i,j}, \tag{8}$$

and the function $g^S : \mathbb{R}_+^n \to [0,1]^n$ has the expression

$$g^S(p(t)) = \begin{pmatrix} f(p_1(t)) \\ \vdots \\ f(p_n(t)) \end{pmatrix}. \tag{9}$$

It is worth observing that r_i in (8) is affected only by the terms $R_{i,j}$ for which the TF j is a repressor of gene i.

The second class of GRNs we consider is characterized by PROD regulatory functions, which can be described by the model

$$\begin{cases} \dot{m}_i(t) = -a_i m_i(t) + \prod_{j=1}^n b_{i,j}^P(p_j(t)) \\ \dot{p}_i(t) = -c_i p_i(t) + d_i m_i(t) \\ \qquad i = 1, \dots, n \end{cases} \tag{10}$$

where the derivative of the mRNA depends on the product of the nonlinear terms $b_{i,j}^P(p_j(t))$, which are defined as the terms $b_{i,j}^S(p_j(t))$ in (2) except for the fact that $b_{i,j}^P(p_j(t)) = 1$ if TF j is neither an activator nor a repressor of gene i. In matricial form, the system (10) can be rewritten as

$$\begin{cases} \dot{m}(t) = -Am(t) + g^P(p(t)) \\ \dot{p}(t) = -Cp(t) + Dm(t) \end{cases} \tag{11}$$

where

$$g^P(p(t)) = \begin{pmatrix} \prod_{j=1}^n b_{1,j}^P(p_j(t)) \\ \vdots \\ \prod_{j=1}^n b_{n,j}^P(p_j(t)) \end{pmatrix}. \tag{12}$$

In this paper we address the following problem. Let $(m^*, p^*) \in \mathbb{R}_+^{2n}$ be an equilibrium point of the GRN (6) (respectively, (11)). Then, the problem consists of establishing whether (m^*, p^*) is globally asymptotically stable, i.e.

$$\forall \varepsilon > 0 \ \exists \delta > 0 : \ \left\| \begin{pmatrix} m(0) \\ p(0) \end{pmatrix} \right\| < \delta \ \Rightarrow \ \left\| \begin{pmatrix} m(t) \\ p(t) \end{pmatrix} - \begin{pmatrix} m^* \\ p^* \end{pmatrix} \right\| < \varepsilon \quad \forall t \geq 0 \tag{13}$$

and

$$\lim_{t \to \infty} \begin{pmatrix} m(t) \\ p(t) \end{pmatrix} = \begin{pmatrix} m^* \\ p^* \end{pmatrix} \quad \forall \begin{pmatrix} m(0) \\ p(0) \end{pmatrix} \in \mathbb{R}_+^{2n} \tag{14}$$

where $m(0)$ and $p(0)$ are the initial conditions for $m(t)$ and $p(t)$ respectively.

Let us observe that, if one can establish that this problem has a positive answer, then one also establishes that the equilibrium point (m^*, p^*) is unique since the absence of other equilibrium points is a necessary condition for global asymptotical stability of (m^*, p^*).

In the sequel the dependence on the time t of the considered signals will be omitted for ease of notation unless indicated otherwise.

3. Stability conditions

In this section we describe the proposed approach for investigating global asymptotical stability of the GRNs (6) and (11). This approach is based on searching for a Lyapunov function for the equilibrium (m^*, p^*) through the use of suitable polynomial relaxations.

Specifically, let us introduce the new variables $x, y \in \mathbb{R}^n$

$$\begin{aligned} x &= m - m^* \\ y &= p - p^*. \end{aligned} \tag{15}$$

By rewriting the GRNs (6) and (11) with respect to these new variables, one has that the equilibrium point (m^*, p^*) is shifted into the origin. Let us indicate with $v(x, y)$ a Lyapunov function candidate. For reasons that will become clear in the sequel, we select this function of polynomial type. Hence, $v(x, y)$ can be written as

$$v(x, y) = \sum_{i_1 + \ldots i_{2n} = 2\delta_v} v_{i_1, \ldots, i_{2n}} x_1^{i_1} \cdots x_n^{i_n} y_1^{i_{n+1}} \cdots y_n^{i_{2n}} \tag{16}$$

where $i_1, \ldots, i_{2n}$ are positive integers, $2\delta_v$ is the degree of $v(x, y)$ for some integer δ_v, and the quantities $v_{i_1, \ldots, i_{2n}} \in \mathbb{R}$ are the coefficients of $v(x, y)$.

Let us consider now the time derivative $\dot{v}(x, y)$ of the Lyapunov function $v(x, y)$ along the trajectory of the system (6). This is given by

$$\dot{v}(x, y) = \nabla v(x, y) \begin{pmatrix} -Ax + R(g^S(y + p^*) - g^S(p^*)) \\ -Cy + Dx \end{pmatrix}. \tag{17}$$

In order to consider $\dot{v}(x, y)$ we introduce the function

$$w_0(x, y, z) = \nabla v(x, y) \begin{pmatrix} -Ax + Rz \\ -Cy + Dx \end{pmatrix} \tag{18}$$

where $z \in \mathbb{R}^n$ is an additional variable. This variable is related to y by the relationship

$$z = g^S(y + p^*) - g^S(p^*). \tag{19}$$

It is easy to verify that

$$w_0(x, y, z) = \dot{v}(x, y) \quad \forall z : \ (19) \text{ holds}. \tag{20}$$

Let us define the function

$$h_i(y, z) = (z_i + f(p_i^*)) \left(\beta^H + (y_i + p_i^*)^H\right) - (y_i + p_i^*)^H. \tag{21}$$

Since

$$(19) \text{ holds} \iff h_1(y, z) = \ldots = h_n(y, z) = 0 \tag{22}$$

one has that (20) can be rewritten as

$$w_0(x, y, z) = \dot{v}(x, y) \ \forall z : \ h_1(y, z) = \ldots = h_n(y, z) = 0. \tag{23}$$

Next, let us define the function

$$w_1(x, y, z) = w_0(x, y, z) + \sum_{i=1}^{n} u_i(x, y, z) h_i(y, z) \tag{24}$$

where $u_i(x, y, z)$, $1 \leq i \leq n$, are auxiliary polynomials of some degree δ_u. For any polynomials $u_1(x, y, z), \ldots, u_n(x, y, z)$ one has that

$$w_1(x, y, z) = \dot{v}(x, y) \ \forall z : \ h_1(y, z) = \ldots = h_n(y, z) = 0. \tag{25}$$

The next step consists of introducing an appropriate representation of the Lyapunov function $v(x, y)$ and the function $w_1(x, y, z)$. We can express $v(x, y)$ as

$$v(x, y) = b_v(x, y)' V b_v(x, y) \tag{26}$$

where $b_v(x, y)$ is a vector of polynomials in x and y, and $V = V'$ is a symmetric matrix containing the coefficients of $v(x, y)$ with respect to $b_v(x, y)$. The vector $b_v(x, y)$ is chosen under two

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conditions. The first is that its entries form a base for the polynomials of degree δ that vanishes in the origin, i.e. for all polynomials $q(x, y)$ of degree δ such that $q(0_n, 0_n) = 0$ there exists a vector $\bar{q}$ such that

$$q(x, y) = \bar{q}' b_v(x, y). \tag{27}$$

The second condition is that $b_v(x, y)$ vanishes if and only if (x, y) is the origin, i.e.

$$\|b_v(x, y)\| = 0 \iff (x, y) = 0_{2n}. \tag{28}$$

Similarly, we express the function $w_1(x, y, z)$. Indeed, let us write the polynomials $u_1(x, y, z), \dots, u_n(x, y, z)$ as

$$u_i(x, y, z) = u_i' b_u(x, y, z) \quad \forall i = 1, \dots, n \tag{29}$$

where $b_u(x, y, z)$ is a chosen polynomial base for the polynomials of degree δ_u, and u_i is the corresponding vector of coefficients. Let us define the matrix

$$U = (u_1, \dots, u_n). \tag{30}$$

Then, we can rewrite $w_1(x, y, z)$ as

$$w_1(x, y, z) = b_w(x, y, z)' \left(W(U, V) + L(\alpha) \right) b_w(x, y, z) \tag{31}$$

where $b_w(x, y, z)$ is a polynomial base such that

$$\|b_w(x, y, z)\| = 0 \iff (x, y, z) = 0_{3n}, \tag{32}$$

and $W(U, V)$ is an affine linear symmetric matrix function of U and V containing the coefficients of $w_1(x, y, z)$ with respect to the chosen $b_w(x, y, z)$, and $L(\alpha)$ is a linear parametrization of the set

$$\mathcal{L} = \left\{ L = L' : \ b_w(x, y, z)' L b_w(x, y, z) = 0 \ \forall x, y, z \right\} \tag{33}$$

being α is a vector of free parameters. The following theorem shows how the sought Lyapunov function can be obtained via a convex optimization.

Theorem 3.1 : *Let $(m^*, p^*) \in \mathbb{R}_+^{2n}$ be an equilibrium point of the system (6). Let us suppose that there exist matrices V and U and a vector α satisfying the system of LMIs*

$$\begin{cases} V > 0 \\ W(U, V) + L(\alpha) < 0 \end{cases} \tag{34}$$

for some integers δ_v and δ_u. Then, (m^*, p^*) is globally asymptotically stable.

   <u>Proof</u>. Let us suppose that there exist variables V, U, and α such that the system of LMIs (34) holds. From the first inequality of (34) and (26) one has that

$$\begin{cases} v(x, y) > 0 \ \ \forall (x, y) \neq 0_{2n} \\ v(0_n, 0_n) = 0. \end{cases} \tag{35}$$

Then, from the second inequality of (34) and (31) one has that

$$
\begin{cases}
w_1(x,y,z) < 0 \quad \forall (x,y,z) \neq 0_{3n} \\
w_1(0_n, 0_n, 0_n) = 0.
\end{cases}
\tag{36}
$$

Let z be any value for which (19) holds. Then, from (22) one has

$$
h_1(y,z) = \ldots = h_n(y,z) = 0,
\tag{37}
$$

and hence from (25) it follows that

$$
\begin{aligned}
0 &> w_1(x,y,z) \\
&= \dot{v}(x,y)
\end{aligned}
\tag{38}
$$

for all $(x,y,z) \neq 0_{3n}$ with z satisfying (19). This implies that

$$
\dot{v}(x,y) < 0 \quad \forall (x,y) \neq 0_{2n}.
\tag{39}
$$

Therefore, we have that the function $v(x,y)$ is radially unbounded and positive outside the origin, moreover $v(x,y)$ vanishes in the origin, and hence the origin represents the global minimum of $v(x,y)$. Moreover, from (39) we have that the time derivative $\dot{v}(x,y)$ is negative outside the origin, hence implying that $v(x,y)$ is decreasing along the trajectories of the system (6). Therefore, the theorem holds. $\qquad\square$

Theorem 3.1 provides a condition for establishing whether an equilibrium point (m^*, p^*) of the GRN (6) is globally asymptotically stable in the positive octant. This condition amounts to finding variables U, V and α such that the inequalities (34) are fulfilled. These inequalities are LMIs, and hence this search amounts to solving an LMI feasibility test, which is a convex optimization. See for instance Boyd et al. (1994) for details about LMI problems.

The construction of the matrices $W(U,V)$ and $L(\alpha)$ can be performed by using simple algorithms, see for instance the algorithms proposed in Chesi et al. (2003, 2009). Moreover, the LMI feasibility test (34) can readily be solved by using dedicated software, such as the LMI toolbox for MATLAB and SeDuMi, see respectively Gahinet et al. (1995) and Sturm (1999).

Before proceeding it is worth mentioning that the representation introduced in (26) and (31) for $v(x,y)$ and $w_1(x,y,z)$ is known as Gram matrix method and square matricial representation (SMR), see for instance Choi et al. (1995) and Chesi et al. (1999) respectively. This representation is useful because allows one to establish whether a polynomial is a sum of squares of polynomials (SOS) via an LMI, see for instance Chesi et al. (1999). Also, this representation allows one to establish whether a matrix polynomial is SOS via an LMI, see for instance Chesi et al. (2003, 2005).

Now, let us consider the GRN with PROD regulatory functions in (11). The stability of this system can be investigated through a condition analogous to that provided in Theorem 3.1. This is explained in the following result.

Theorem 3.2 : *Let $(m^*, p^*) \in \mathbb{R}_+^{2n}$ be an equilibrium point of the system (11). Let us suppose that there exist, for some integers δ_v and δ_u, matrices V and U and a vector α satisfying the system of LMIs (34) constructed as in the previous case by:*

(1) selecting $R = I_n$;

(2) redefining the polynomial $h_i(y,z)$ in (21) with the polynomial

$$h_i(y,z) = \left(z_i + g_i^P(p^*)\right)\psi_i(y+p^*) - \phi_i(y+p^*). \tag{40}$$

where $\phi_i(p)$ and $\psi_i(p)$ are polynomials satisfying

$$g_i^P(p) = \frac{\phi_i(p)}{\psi_i(p)}. \tag{41}$$

Then, (m^*, p^*) is globally asymptotically stable.

Proof. Let us observe that

$$\dot{v}(x,y) = \nabla v(x,y)\begin{pmatrix} -Ax + g^P(y+p^*) - g^P(p^*)) \\ -Cy + Dx \end{pmatrix}. \tag{42}$$

Moreover,

$$w_1(x,y,z) = \nabla v(x,y)\begin{pmatrix} -Ax + Rz \\ -Cy + Dx \end{pmatrix} + \sum_{i=1}^{n} u_i(x,y,z)h_i(y,z). \tag{43}$$

Hence, it follows that

$$w_1(x,y,z) = \dot{v}(x,y) \ \ \forall z: \ h_1(y,z) = \ldots = h_n(y,z) = 0 \tag{44}$$

provided that $R = I_n$ and $h_i(y,z)$ is defined as in (40). Therefore, the theorem holds. $\qquad\square$

The following result clarifies that the conservatism of the stability conditions provided in Theorems 3.1 and 3.2 does not increase by increasing the integers δ_v and δ_u, i.e. the degrees of the Lyapunov function candidate $v(x,y)$ and auxiliary polynomials $u_1(x,y,z), \ldots, u_n(x,y,z)$.

Theorem 3.3 : *Let us consider the stability conditions provided in Theorems 3.1 and 3.2. One has that*

$$\begin{array}{c} \text{(34) is feasible for some } \delta_v, \delta_u \\ \Downarrow \\ \text{(34) is feasible for } \delta_v + i, \delta_u + j \text{ for all } i, j \geq 0. \end{array} \tag{45}$$

i.e., if there exist matrices V and U and a vector α satisfying the system of LMIs (34) for some δ_v and δ_u, then there also exist such matrices and such a vector for $\delta_v + i$ and $\delta_u + j$, where i and j are any positive integers.

Proof. Let us suppose that there exist matrices V and U and a vector α satisfying the system of LMIs (34) for some δ_v and δ_u. Then, let us define the polynomial

$$\bar{v}(x,y) = b_v(x,y)'V b_v(x,y) + \hat{v}(x,y) \tag{46}$$

where $\hat{v}(x,y) \in \mathbb{R}$ is a polynomial composed by monomials of degree greater than or equal to $2\delta_v$, and for $i = 1, \ldots, n$ the polynomials

$$\bar{u}_i(x,y,z) = e_i'U'b_u(x,y,z) + \hat{u}_i(x,y,z) \tag{47}$$

where $\hat{u}_i(x, y, z)$ is a polynomial of degree greater than or equal to δ_u (e_i is the i-th column of the $n \times n$ identity matrix). Let us observe that $\hat{v}(x, y)$ can be chosen such that $\bar{v}(x, y)$ admits a representation analogous to (26) with a positive definite matrix $\bar{V}$ since $V > 0$ for assumption. In particular, this can be done by selecting $\hat{v}(x, y)$ of the form

$$\hat{v}(x, y) = b_{\hat{v}}(x, y)' \hat{V} b_{\hat{v}}(x, y) \tag{48}$$

where $b_{\hat{v}}(x, y)$ is a vector containing a base for the polynomials in x and y with monomials of degree greater than or equal to δ_v, and $\hat{V}$ is a positive definite matrix. One has hence:

$$\bar{v}(x, y) = \begin{pmatrix} b_v(x, y) \\ b_{\hat{v}}(x, y) \end{pmatrix}' \bar{V} \begin{pmatrix} b_v(x, y) \\ b_{\hat{v}}(x, y) \end{pmatrix} \tag{49}$$

where

$$\bar{V} = \begin{pmatrix} V & \\ & \hat{V} \end{pmatrix}. \tag{50}$$

Moreover, $\hat{v}(x, y)$ can be chosen as a power of a quadratic function. Let us observe, in fact, that the system considered in the construction of $w_0(x, y, z)$ in (18) is

$$\begin{aligned} \dot{x} &= -Ax + Rz \\ \dot{y} &= -Cy + Dx \end{aligned} \tag{51}$$

which depends linearly on the state. This implies that, by simply selecting null polynomials $\hat{u}_1(x, y, z), \ldots, \hat{u}_n(x, y, z)$, the polynomial $\bar{w}_1(x, y, z)$ defined analogously to $w_1(x, y, z)$ in (24) admits the representation

$$\bar{w}_1(x, y, z) = b_{\bar{w}}(x, y, z)' \left(\bar{W}(\bar{U}, \bar{V}) + \bar{L}(\bar{\alpha}) \right) b_{\bar{w}}(x, y, z) \tag{52}$$

with

$$\bar{W}(\bar{U}, \bar{V}) + \bar{L}(\bar{\alpha}) < 0 \tag{53}$$

where $\bar{U}$ and $\bar{L}(\bar{\alpha})$ are defined analogously to (30) and (33) respectively. See for instance Chesi et al. (2003) for details on the construction of such a matrix in an analogous case. Therefore, the theorem holds. $\qquad\qquad\square$

Theorem 3.3 provides a monotonicity property of the stability conditions provided in Theorems 3.1 and 3.2 with respect to the integers δ_v and δ_u. In addition to this property, it is expected that the conservatism of these stability conditions may be arbitrary decreased by selecting δ_v and δ_u sufficiently large, since in this way one reduces the gap introduced by the constructed polynomial relaxations. Regarding this gap, the reader is referred to Putinar (1993), Reznick (2000), Chesi (2007) and references therein.

Remark 1. It is worth observing that the stability conditions provided in Theorems 3.1 and 3.2 differ from existing stability conditions for GRNs based on LMIs such as the one proposed in Chesi and Hung (2008). In fact, these existing stability conditions introduce suitable approximations of the nonlinearities present in the GRNs, for instance via sector representations. Instead, the stability conditions provided in Theorems 3.1 and 3.2 take into account the exact structure of these nonlinearities through the polynomials $h_1(y, z), \ldots, h_n(y, z)$.

Remark 2. Another useful remark concerns the application of the proposed approach to GRNs with noise and/or time delay. Specifically, time delay can be considered by adopting Lyapunov-Krasovskii functionals and parametrizing them via the SMR in a way analogous to the one described in this paper for Lyapunov functions. The reader is referred to the works Xu and Lam (2008), Zhang et al. (2009) and references therein for more details about Lyapunov-Krasovskii functionals. The presence of noise can be considered as well, indeed the proposed approach can be extended to investigate stochastic stability rather than the classical notion of stability. In particular, one can analyze the convergence properties of the statistical expectation of the states of the GRN, see for instance Li et al. (2007).

Remark 3. A final remark concerns the possibility of considering GRNs that cannot be expressed with SUM or PROD regulatory functions. It is useful to observe that the approach we have described can be applied also to different regulatory functions, provided that the GRN is described by differential equations that are polynomial in the state. In fact, this still allows one to investigate the existence of a Lyapunov function proving global asymptotical stability of the equilibrium point via the SMR and LMIs. Instead, for different models of GRNs such as Boolean models, the proposed approach cannot be directly applied, and at present the only viable way is to resort to suitable approximations of these models described through polynomials.

4.   Illustrative examples

This section illustrates the proposed stability conditions with some numerical examples. The matrices $W(U, V)$ and $L(\alpha)$ are built by using the algorithms proposed in Chesi et al. (2003, 2009), and the LMI feasibility tests are solved by using MATLAB and SeDuMi, see Sturm (1999). The computational time for these examples on a standard personal computer is less than 5 seconds.

4.1.   *Example 1*

Let us consider as first example a GRN with SUM regulatory functions, in particular the repressilator investigated in *Escherichia coli* in Elowitz and Leibler (2000):

$$\begin{cases} \dot{m}_i = -m_i + \dfrac{\gamma_i}{1 + p_j^2} \\ \dot{p}_i = -(p_i - m_i) \\ \quad i = lacl, tetR, cl \\ \quad j = cl, lacl, tetR. \end{cases} \tag{54}$$

This GRN can be expressed as in (6) with $n = 3$, $H = 2$, $\beta = 1$ and

$$\begin{aligned} A &= -I_3 \\ C &= -I_3 \\ D &= I_3 \\ R &= \begin{pmatrix} 0 & 0 & -\gamma_1 \\ -\gamma_2 & 0 & 0 \\ 0 & -\gamma_3 & 0 \end{pmatrix} \\ r &= (\gamma_1, \gamma_2, \gamma_3)'. \end{aligned} \tag{55}$$

We select the plausible values

$$\gamma_1 = 1, \quad \gamma_2 = 2, \quad \gamma_3 = 5. \tag{56}$$

It follows that this system has an equilibrium point in $(m^*, p^*) = (0.27, 1.34, 1.29, 0.27, 1.34, 1.29)'$. The problem consists of establishing whether (m^*, p^*) is globally asymptotically stable. To this end, let us use Theorem 3.1. We hence build the system of LMIs (34) for $\delta_v = \delta_u = 1$, and we find out that there exist matrices U and V and a vector α fulfilling these LMIs. Therefore, we conclude that (m^*, p^*) is globally asymptotically stable.

For comparison purpose, we attempt to solve the same problem by using existing stability conditions. We find out that the condition in Lu (2000) (which is based on the spectral radius of suitable matrices) and the condition in Chesi and Hung (2008) (which is based on LMIs via nonlinearities approximation) are not satisfied and do not allow one to conclude global asymptotical stability.

4.2. *Example 2*

As second example we consider a GRN in PROD form, in particular

$$\begin{cases} \dot{m}_1(t) = -0.9m_1(t) + \dfrac{4p_2^2}{(1+p_2^2)(1+p_3^2)} \\[2mm] \dot{m}_2(t) = -0.8m_2(t) + \dfrac{3}{1+p_3^2} \\[2mm] \dot{m}_3(t) = -0.6m_3(t) + \dfrac{2}{1+p_1^2} \\[2mm] \dot{p}_1(t) = -p_1(t) + 0.5m_1(t) \\[1mm] \dot{p}_2(t) = -p_2(t) + 0.7m_2(t) \\[1mm] \dot{p}_3(t) = -p_3(t) + 0.4m_3(t). \end{cases} \tag{57}$$

This GRN is characterized by the fact that TF 1 is a regressor of gene 3, TF 2 is an activator of gene 1, and TF 3 is regressor of genes 1 and 2. The system can be expressed as in (11) with $n = 3$, $H = 2$, $\beta = 1$ and

$$\begin{aligned} A &= \operatorname{diag}(-0.9, -0.8, -0.6) \\ C &= -I_3 \\ D &= \operatorname{diag}(0.5, 0.7, 0.4) \\ g^P(p) &= \left(\dfrac{4p_2^2}{(1+p_2^2)(1+p_3^2)}, \dfrac{3}{1+p_3^2}, \dfrac{2}{1+p_1^2} \right)'. \end{aligned} \tag{58}$$

It follows that this system has an equilibrium point in $(m^*, p^*) = (3.34, 3.34, 0.88, 1.67, 2.34, 0.35)'$. In order to establish whether (m^*, p^*) is globally asymptotically stable, we use Theorem 3.2, finding out that there exist matrices U and V and a vector α fulfilling the system of LMIs for $\delta_v = 1$ and $\delta_u = 2$. Therefore, we conclude that (m^*, p^*) is globally asymptotically stable.

It is interesting to observe that other existing stability conditions for GRNs, as those considered in Example 1, cannot be used in this case since this GRN has PROD regulatory functions.

5. Conclusion

Sufficient conditions for global asymptotic stability of equilibrium points of GRNs with SUM or PROD regulatory functions have been proposed based on convex optimizations with LMI constraints. The nice feature of these conditions is that they do not rely on approximations of the nonlinearities present in the GRNs. Moreover, the conservatism of these conditions can be decreased by increasing the degree of the constructed relaxations. As shown by some numerical examples, the proposed conditions compare favorably with some existing methods.

Future work will investigate the possibility of establishing upper bounds of the degrees of the polynomials required to achieve necessity of the conditions. Moreover, the extension of the proposed approach to the case of GRNs described by different models will be considered.

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14   REFERENCES

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