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Robustness Analysis of Genetic Regulatory Networks Affected by Model Uncertainty

Graziano Chesi *

Abstract

A fundamental problem in systems biology consists of investigating robustness properties of genetic regulatory networks (GRNs) with respect to model uncertainty. This paper addresses this problem for GRNs where the coefficients are rationally affected by polytopic uncertainty, and where the saturation functions are not exactly known. First, it is shown that a condition for ensuring that the GRN has a globally asymptotically stable equilibrium point for all admissible uncertainties can be obtained in terms of a convex optimization problem with linear matrix inequalities (LMIs), hence generalizing existing results that mainly consider only the case of GRNs where the coefficients are linearly affected by the uncertainty and the regulatory functions are in SUM form. Second, the problem of estimating the worst-case convergence rate of the trajectories to the equilibrium point over all admissible uncertainties is considered, and it is shown that a lower bound of this rate can be computed by solving a quasi-convex optimization problem with LMIs. Third, the paper considers the problem of estimating the set of uncertainties for which the GRN has a globally asymptotically stable equilibrium point. This problem is addressed, firstly, by showing how one can compute estimates with fixed shape by solving a a quasi-convex optimization problem with LMIs, and secondly, by deriving a procedure for computing estimates with variable shape. Numerical examples illustrate the use of the proposed techniques.

Keywords: Genetic regulatory network; Model uncertainty; Stability; Robustness.

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1 Introduction

It is well-known that genetic regulatory networks (GRNs) play a key role in systems biology as they explain the interactions between genes and proteins. Analyzing these interactions is fundamental in order to understand and possibly control the complex mechanisms that regulate biological functions in living organisms. GRNs can be described either by Boolean models or by differential equation models. In the latter case, the time derivative of each concentration is expressed through a function that typically consists of two parts: a linear part defining the natural decay of the concentration, and a nonlinear part describing the interaction among the concentrations. The nonlinear part contains saturation functions, such as the Hill functions, which are combined via sums (in this case the GRN is said to have SUM regulatory functions) or products (in this case the GRN is said to have PROD regulatory functions). See e.g. [14, 2, 4, 19, 1, 5, 16, 17, 18, 6, 21] and references therein.

GRN models are unavoidably affected by uncertainty. A simple reason is that the coefficients and the saturation functions of a GRN cannot be measured exactly. Another reason is that one has often to consider a family of GRNs in order to study the behavior of a class of organisms and not of a specific one only. This means that GRN models contain uncertain parameters, which are generally constrained in a bounded set of interest. The reader is referred to [10] and references therein for models and techniques typically used to deal with uncertainty in the case of linear systems.

This paper investigates robustness properties of GRNs described by differential equation models and affected by model uncertainty. Specifically, it is assumed that the coefficients of the GRN depend rationally on an uncertain vector constrained in a polytope, and that the saturation functions are not exactly known. First, a condition for ensuring that the GRN has a globally asymptotically stable equilibrium point for all admissible uncertainties is provided in terms of a convex optimization problem with linear matrix inequalities (LMIs), hence generalizing existing results that mainly consider only the case of GRNs where the coefficients are linearly affected by the uncertainty and the regulatory functions are in SUM form, see e.g. our previous work [11]. This condition is built by introducing a variable Lyapunov function candidate polynomially parametrized by the uncertainty and by exploiting the square matrix representation (SMR). Second, the problem of estimating the worst-case convergence rate of the trajectories to the equilibrium point over all admissible uncertainties is considered. It is shown that a lower bound of this rate can be computed by solving a generalized eigen-

value problem (GEVP), which is a quasi-convex optimization problem with LMIs. Third, the paper considers the problem of estimating the set of uncertainties for which the GRN has a globally asymptotically stable equilibrium point. It is shown that inner estimates with fixed shape of this set can be computed via a GEVP, moreover a procedure for obtaining estimates with variable shape is derived. Some examples with real GRNs illustrate the use of the proposed techniques. A preliminary version of this paper is reported in [7].

The organization of the paper is as follows. Section 2 introduces some preliminaries. Section 3 derives the proposed results. Section 4 presents two illustrative examples. Lastly, Section 5 concludes the paper with some final remarks.

2 Preliminaries

The notation adopted in this paper is as follows:

- $\mathbb{R}$: real number space;
- $\mathbb{R}_+$: non-negative real number space;
- 0: null matrix of size specified by the context;
- I_n: identity matrix $n \times n$;
- A': transpose of matrix A;
- $A > 0$ (resp., $A \geq 0$): symmetric positive definite (resp., semidefinite) matrix A;
- $\mathrm{diag}(a)$ (resp., $\mathrm{diag}(a_1, a_2, \ldots)$): diagonal matrix with the entries of vector a (resp., scalars $a_1, a_2, \ldots$) on the diagonal;
- $\mathrm{conv}(a, b, \ldots)$: convex hull of vectors $a, b, \ldots$;
- $\|a\|$: Euclidean norm of vector a, i.e. $\|a\| = \sqrt{a'a}$;
- $\mathrm{he}(A)$: $A + A'$;
- $A \otimes B$: Kronecker's product of matrices A and B;
- s.t.: subject to.

2.1 Uncertain GRNs

GRNs described by differential equation models have typically the form

$$\begin{cases} \dot{m}(t) &= Am(t) + b(p(t)) \\ \dot{p}(t) &= Cp(t) + Dm(t) \end{cases} \tag{1}$$

where $m = (m_1, \ldots, m_n)' \in \mathbb{R}^n_+$ and $p = (p_1, \ldots, p_n)' \in \mathbb{R}^n_+$ are vectors containing the concentrations of mRNA and protein, $A, C \in \mathbb{R}^{n\times n}$ are negative definite diagonal matrices, $D \in \mathbb{R}^{n\times n}$ is a positive definite diagonal matrix, and $b : \mathbb{R}^n_+ \to \mathbb{R}^n_+$ is a nonlinear function.

For instance, in GRNs with SUM regulatory functions the j-th entry of $b(p)$ is given by

$$b_i(p) = \sum_{j=1}^{n} \alpha_{i,j} b_{i,j}(p_j) \tag{2}$$

where the functions $b_{i,j} : \mathbb{R}_+ \to \mathbb{R}_+$ can be expressed as

$$b_{i,j}(p_j) = \begin{cases} f_j(p_j) & \text{if TF } j \text{ is an activator} \\ & \text{of gene } i \\ 1 - f_j(p_j) & \text{if TF } j \text{ is a repressor} \\ & \text{of gene } i \\ 0 & \text{otherwise} \end{cases} \tag{3}$$

for some saturation functions $f_j : \mathbb{R}_+ \to \mathbb{R}_+$, which typically are chosen of Hill form according to

$$f_j(p_j) = \frac{p_j^{h_j}}{\beta_j^{h_j} + p_j^{h_j}} \tag{4}$$

for some positive scalars β_j and h_j. In GRNs with PROD regulatory functions, $b_i(p)$ is a product of functions like $b_{i,j}(p_j)$. In general, hence, $b(p)$ can be expressed as

$$b(p) = Bg(p) + \theta \tag{5}$$

for some $B \in \mathbb{R}^{n\times l}$ and $\theta \in \mathbb{R}^n_+$, where the entries of the function $g : \mathbb{R}^n_+ \to \mathbb{R}^l_+$ are a subset of the functions $f_1(p_1), \ldots, f_n(p_n)$ and their products. For instance, one can have

$$g(p) = (f_1(p_1), f_3(p_3), f_1(p_1)f_2(p_2))'. \tag{6}$$

In this paper we consider GRNs as in (1) affected by parametric model uncertainty, in particular

$$\begin{cases} \dot{m}(t) &= A(u)m(t) + B(u)\phi(p(t)) + \theta(u) \\ \dot{p}(t) &= C(u)p(t) + D(u)m(t) \end{cases} \tag{7}$$

where $u \in \mathbb{R}^q$ is a time-invariant uncertain vector, and the function $\phi : \mathbb{R}^n_+ \to \mathbb{R}^l_+$ account for uncertainty on the function $g(p)$ in (5). We consider that u is constrained in a polytope according to

$$\begin{array}{rcl} u & \in & \mathcal{U} \\ \mathcal{U} & = & \text{conv}\left\{u^{(1)}, \ldots, u^{(r)}\right\} \end{array} \tag{8}$$

for some $u^{(i)} \in \mathbb{R}^q$. The functions of u in (7) are assumed rational, and we express them as

$$A(u) = \frac{\hat{A}(u)}{\tau(u)}, \ldots, \theta(u) = \frac{\hat{\theta}(u)}{\tau(u)} \tag{9}$$

where $\hat{A}(u), \ldots, \hat{\theta}(u)$ are matrix polynomials, and $\tau(u)$ is a polynomial positive on $\mathcal{U}$, i.e.

$$\tau(u) > 0 \quad \forall u \in \mathcal{U}. \tag{10}$$

Moreover, we consider that $\phi(p)$ is constrained as

$$\begin{array}{c} (\phi_i(y+p) - \phi_i(p))\left(\displaystyle\sum_{j=1}^{n} \lambda_{i,j} y_j - \phi_i(y+p) + \phi_i(p)\right) \geq 0 \\ \forall p, y \in \mathbb{R}^n : \ p_i \geq 0, \ y_i \geq -p_i \ \forall i = 1, \ldots, l \end{array} \tag{11}$$

for some scalars $\lambda_{i,j}$. We denote with Φ the set of functions $\phi(p)$ satisfying (11), i.e.

$$\Phi = \{\phi(\cdot) : \ (11) \text{ holds}\}. \tag{12}$$

The problems addressed in this paper are as follows:

1. to establish whether the uncertain GRN (7) has a globally asymptotically stable equilibrium point in $\mathbb{R}^n_+ \times \mathbb{R}^n_+$ for all $u \in \mathcal{U}$ and for all $\phi(\cdot) \in \Phi$, which is denoted by (m^*, p^*);

2. to estimate the worst-case convergence rate of the concentrations, i.e.

$$\begin{array}{rcl} \gamma^* & = & \displaystyle\inf_{u \in \mathcal{U}, \phi(\cdot) \in \Phi} \sup \Big\{ \gamma \in \mathbb{R} : \ \|z(t)\|^2 \leq \xi e^{-\gamma t} \\ & & \forall t \geq 0 \text{ for some } \xi \in \mathbb{R} \Big\} \end{array} \tag{13}$$

and

$$z = \begin{pmatrix} x \\ y \end{pmatrix}, \quad x = m - m^*, \quad y = p - p^*; \tag{14}$$

3. to estimate the set of vectors u for which (7) has a globally asymptotically stable equilibrium point in $\mathbb{R}^n_+ \times \mathbb{R}^n_+$, i.e.

$$\begin{aligned} \mathcal{S} \;=\; \Big\{ & u \in \mathbb{R}^q : \; (m^*, p^*) \in \mathbb{R}^n_+ \times \mathbb{R}^n_+ \text{ is globally} \\ & \text{asymptotically stable for all } \phi(\cdot) \in \Phi \Big\}. \end{aligned} \tag{15}$$

Remark 1. Let us observe that the function $\phi(p)$ in (7) can be either known or unknown, and can contain Hill and non-Hill saturation functions, provided that condition (11) holds. Also, let us observe that (7) includes GRN models typically adopted in the literature, such as GRNs in SUM form or in PROD form, for instance GRNs in SUM form can be considered by choosing

$$\phi(p) = (f_1(p_1), \ldots, f_n(p_n))'. \tag{16}$$

Remark 2. Whenever the generic i-th entry of $\phi(p)$ is a Hill function $f_j(p_j)$ as in (4) with $\beta_j > 0$ and $h_j > 1$, condition (11) can be satisfied for such an index i by simply choosing $\lambda_{i,k} = 0$ for $k \neq j$, and

$$\lambda_{i,j} = \frac{h_j^2 - 1}{4\beta_j h_j} \left(\frac{h_j + 1}{h_j - 1} \right)^{1/h_j}. \tag{17}$$

Moreover, if the constants β_j and h_j are unknown in the ranges $[\beta_j^-, \beta_j^+]$ and $[h_j^-, h_j^+]$ with $\beta_j^- > 0$ and $h_j^- > 1$, then condition (11) can be satisfied for the considered index i as just mentioned by replacing β_j and h_j with β_j^- and h_j^+, respectively.

2.2 Forms and SMR

The techniques proposed in this paper exploit forms, i.e. polynomials with all monomials of the same degree (also known as homogeneous polynomials). Forms can be represented through the square matrix representation (SMR) introduced in [12]. Specifically, let $s(x)$ be a form of degree $2d$ in $x \in \mathbb{R}^n$, and let $b_s(x)$ be a vector containing all monomials of degree equal to d in x. Then, $s(x)$ can be written as

$$s(x) = b_s(x)' \left(S + L(\alpha) \right) b_s(x) \tag{18}$$

where $S = S'$ is such that

$$s(x) = b_s(x)' S b_s(x), \tag{19}$$

$L(\alpha)$ is a linear parametrization of the subspace

$$\mathcal{L}(b_s) = \left\{ L = L' : \; b_s(x)' L b_s(x) = 0 \; \forall x \right\} \tag{20}$$

and α is a free vector of length equal to the dimension of $\mathcal{L}(b_s)$. The matrices S and $S + L(\alpha)$ are called SMR matrices of $s(x)$ (also known as Gram matrices). The SMR allows one to establish whether a form $s(x)$ is a sum of squares of forms (SOS), i.e. $s(x) = \sum_{i=1}^{k} s_i(x)^2$ for some forms $s_1(x), \ldots, s_k(x)$. Indeed, $s(x)$ is SOS if and only if there exists α satisfying the LMI

$$S + L(\alpha) \geq 0. \tag{21}$$

Similarly, the SMR can be employed to represent also matrix forms. In particular, a matrix form $S(x) = S(x)' \in \mathbb{R}^{r \times r}$ of degree $2d$ in $x \in \mathbb{R}^n$ can be written as

$$S(x) = \Delta(M_S + L(\alpha), b_s(x), I_r) \tag{22}$$

where Δ denotes the notation

$$\begin{array}{rcl} \Delta(M_S + L(\alpha), b_s(x), I_r) & = & (b_s(x) \otimes I_r)' \, (M_S + L(\alpha)) \\ & & \cdot \, (b_s(x) \otimes I_r) \, , \end{array} \tag{23}$$

$M_S = M_S'$ is such that

$$S(x) = \Delta(M_S, b_s(x), I_r), \tag{24}$$

$L(\alpha)$ is a linear parametrization of the subspace

$$\mathcal{L}(b_s, I_r) = \left\{ L = L' : \; \Delta(L, b_s(x), I_r) = 0 \; \forall x \right\} \tag{25}$$

and α is a free vector of length equal to the dimension of $\mathcal{L}(b_s, I_r)$. By using the SMR one can establish whether a matrix form $S(x)$ is SOS, i.e. $S(x) = \sum_{i=1}^{k} S_i(x)' S_i(x)$ for some matrix forms $S_1(x), \ldots, S_k(x)$. Indeed, $S(x)$ is SOS if and only if there exists α satisfying the LMI

$$M_S + L(\alpha) \geq 0. \tag{26}$$

The reader is referred to [10, 8] for details and algorithms about the SMR and SOS polynomials.

3 Robustness Analysis

Here we describe the proposed results for robustness analysis. Specifically, we provide a condition for the existence of a globally asymptotically stable equilibrium point for all $u \in \mathcal{U}$ and for all $\phi(\cdot) \in \Phi$ in Section 3.1. Then, we address the estimation of γ^* in Section 3.2. Lastly, we consider the estimation of $\mathcal{S}$ in Section 3.3.

3.1 Robust Stability

Let d be the maximum degree of the matrix polynomials $\hat{A}(u), \ldots, \hat{\theta}(u)$, and let us express $\hat{A}(u)$ as

$$\hat{A}(u) = \sum_{i=0}^{d} \hat{A}^{(i)}(u) \tag{27}$$

where $\hat{A}^{(i)}(u)$ is a matrix form of degree i in u. Any vector $u \in \mathcal{U}$ can be written as

$$u = \sum_{i=1}^{r} w_i u^{(i)} \tag{28}$$

for some $w \in \mathcal{W}$ where $\mathcal{W}$ is the simplex:

$$\mathcal{W} = \left\{ w \in \mathbb{R}_+^r : \ \sum_{i=1}^{r} w_i = 1 \right\}. \tag{29}$$

Let us define

$$\bar{A}(w) = \sum_{i=0}^{d} \left(\sum_{j=1}^{r} w_j \right)^{d-i} \hat{A}^{(i)} \left(\sum_{j=1}^{r} w_j u^{(j)} \right). \tag{30}$$

We have that $\bar{A}(w)$ is a matrix form of degree d in w. Moreover,

$$\begin{array}{c} \forall u \in \mathcal{U} \ \exists w \in \mathcal{W} : \ \hat{A}(u) = \bar{A}(w) \\ \forall w \in \mathcal{W} \ \exists u \in \mathcal{U} : \ \hat{A}(u) = \bar{A}(w). \end{array} \tag{31}$$

Similarly, we obtain the matrix forms $\bar{B}(w)$, $\bar{C}(w)$, $\bar{D}(w)$, $\bar{\theta}(w)$ and $\bar{\tau}(w)$, and hence (7) can be equivalently rewritten as

$$\left\{ \begin{array}{rcl} \dot{m}(t) & = & \dfrac{\bar{A}(w)m(t) + \bar{B}(w)\phi(p(t)) + \bar{\theta}(w)}{\bar{\tau}(w)} \\ \dot{p}(t) & = & \dfrac{\bar{C}(w)p(t) + \bar{D}(w)m(t)}{\bar{\tau}(w)}. \end{array} \right. \tag{32}$$

Now, let $P(w) = P(w)' \in \mathbb{R}^{2n \times 2n}$ be a matrix form of degree δ in w, and let us define $Q(w) = Q(w)' \in \mathbb{R}^{2n+l \times 2n+l}$ as

$$Q(w) = \mathrm{he} \left(\begin{array}{c} P(w) \left(\begin{array}{ccc} \bar{A}(w) & 0 & \bar{B}(w) \\ \bar{D}(w) & \bar{C}(w) & 0 \end{array} \right) \\ 0 \end{array} \right) \tag{33}$$

where the "0"-blocks are null matrices of suitable size. Also, let $s(w) \in \mathbb{R}^l$ be a vector form of degree $\delta + d$ in w, and let us define $R(w) = R(w)' \in \mathbb{R}^{2n+l \times 2n+l}$ as

$$R(w) = \mathrm{he} \begin{pmatrix} 0 & 0 \\ 0 & \Lambda' \mathrm{diag}(s(w)) \\ 0 & -2\mathrm{diag}(s(w)) \end{pmatrix} \tag{34}$$

where the "0"-blocks are null matrices of suitable size, and $\Lambda \in \mathbb{R}^{l \times n}$ is the matrix having on its (i,j)-th entry the scalar $\lambda_{i,j}$ introduced in condition (11).

Let $b_P(w)$ and $b_Q(w)$ be vectors containing all monomials in w of degrees δ and $\delta + d$, respectively, and let us parametrize $P(w)$ and $s(w)$ as

$$\begin{array}{rcl} P(w) & = & C_P \left(b_P(w) \otimes I_{2n} \right) \\ s(w) & = & c_s' b_Q(w) \end{array} \tag{35}$$

where the matrix C_P and the vector c_s are variables to be determined. Let us introduce the notation

$$\mathrm{sq}(w) = \left(w_1^2, \ldots, w_q^2 \right)' \tag{36}$$

and let us express $P(\mathrm{sq}(w))$, $Q(\mathrm{sq}(w))$ and $R(\mathrm{sq}(w))$ as

$$\begin{array}{rcl} P(\mathrm{sq}(w)) & = & \Delta(M_P, b_P(w), I_{2n}) \\ Q(\mathrm{sq}(w)) & = & \Delta(M_Q, b_Q(w), I_{2n+l}) \\ R(\mathrm{sq}(w)) & = & \Delta(M_R, b_Q(w), I_{2n+l}) \end{array} \tag{37}$$

for some matrices $M_P = M_P'$, $M_Q = M_Q'$ and $M_R = M_R'$.

Theorem 1 *The uncertain GRN* (7) *has a globally asymptotically stable equilibrium point in* $\mathbb{R}_+^n \times \mathbb{R}_+^n$ *for all* $u \in \mathcal{U}$ *and for all* $\phi(\cdot) \in \Phi$ *if there exist* C_P, c_s, α *and* β *satisfying the LMIs*

$$\left\{ \begin{array}{rcl} 0 & < & M_P + L_P(\alpha) \\ 0 & > & M_Q + M_R + L_Q(\beta) \end{array} \right. \tag{38}$$

where $L_P(\alpha)$ *and* $L_Q(\beta)$ *are linear parametrizations of* $\mathcal{L}(b_P, I_{2n})$ *and* $\mathcal{L}(b_Q, I_{2n+l})$.

Proof. Let us pre- and post- multiply the first LMI in (38) by $(b_P(w) \otimes I_{2n})'$ and $b_P(w) \otimes I_{2n}$, respectively. We obtain:

$$\begin{array}{rcl} 0 & < & \left(b_P(w) \otimes I_{2n} \right)' \left(M_P + L_P(\alpha) \right) \left(b_P(w) \otimes I_{2n} \right) \\ & = & \Delta(M_P, b_P(w), I_{2n}) \\ & = & P(\mathrm{sq}(w)) \end{array} \tag{39}$$

i.e. $P(\mathrm{sq}(w)) > 0$ for all $w \neq 0$. From Theorem 1.17 in [10] this holds if and only if

$$P(w) > 0 \quad \forall w \in \mathcal{W}. \tag{40}$$

Let us pre- and post- multiply the second LMI in (38) by $(b_Q(w) \otimes I_{2n+l})'$ and $b_Q(w) \otimes I_{2n+l}$, respectively. We analogously obtain that

$$Q(w) + R(w) < 0 \quad \forall w \in \mathcal{W}. \tag{41}$$

Let us define x, y and z as in (14) where (m^*, p^*) is an unknown equilibrium point of (32) in $\mathbb{R}^n_+ \times \mathbb{R}^n_+$. Let us also define the function

$$v(z, w) = z' P(w) z. \tag{42}$$

One has that the time derivative of $v(z, w)$ along the trajectories of (32) is given by

$$\dot{v}(\zeta, w) = \frac{\zeta' Q(w) \zeta}{\bar{\tau}(w)} \tag{43}$$

where

$$\begin{array}{rcl} \zeta & = & \left(z', z'_\phi\right)' \\ z_\phi & = & \phi(y + p^*) - \phi(p^*). \end{array} \tag{44}$$

Let us observe that the condition $Q(w) + R(w) < 0$ for all $w \in \mathcal{W}$ implies that the entries of $s(w)$ are positive for all $w \in \mathcal{W}$. This fact and the definition of z_ϕ imply that

$$\zeta' R(w) \zeta \geq 0 \quad \forall w \in \mathcal{W} \; \forall \phi(\cdot) \in \Phi. \tag{45}$$

Consequently, one has that

$$0 > \zeta' \left(Q(w) + R(w)\right) \zeta \geq \zeta' Q \zeta \tag{46}$$

hence implying that $v(x, y, w) > 0$ and $\dot{v}(\zeta, w) < 0$ for all $(x, y) \neq 0$ for all $w \in \mathcal{W}$ and for all $\phi(\cdot) \in \Phi$ since (10) holds. Therefore, (m^*, p^*) is a globally asymptotically stable equilibrium point in $\mathbb{R}^n_+ \times \mathbb{R}^n_+$. □

Theorem 1 provides a condition for establishing the existence of a globally asymptotically stable equilibrium point in the GRN (7) for all admissible uncertainties. This condition consists of an LMI feasibility test, which amounts to solving a convex optimization problem, see e.g. [3]. Also, this condition depends on the chosen integer δ. It can be shown that the conservatism of the condition does not increase as δ increases, moreover there can be cases where the condition is satisfied for $\delta + 1$ but it is not for δ. On the

other hand, the computational burden increases as δ increases, and hence a trade-off is necessary when choosing δ.

One way to select δ consists of starting with the smallest allowed value, i.e. $\delta = 0$, and then increasing δ till either the condition of Theorem 1 is satisfied or the computational burden becomes too large: this is motivated by the fact that the computational burden for $\delta + 1$ is always much larger than that for δ. Another way consists of choosing the largest δ for which the maximum number of scalar variables in the LMI feasibility test (38) (and, hence, the computational burden) is smaller than a specified limit: this allows one obtain the least conservative condition for a selected price without trying different values of δ.

From the biological viewpoint the condition of Theorem 1 allows one to ensure that the concentrations of mRNA and protein converge to some constant values for all admissible uncertainties. This also means that, whenever the condition holds, the GRN has no multiple equilibria and no limit cycles, which may represent an undesired condition for the organism under study such as a disease. See e.g. [15] regarding undesired multiple equilibria.

3.2 Worst-Case Convergence Rate

Here we consider the problem of estimating the worst-case convergence rate γ^* defined in (13). It is known that the convergence rate of the trajectories can be estimated by means of Lyapunov functions, in particular by imposing that the time derivative of the Lyapunov function is smaller than the Lyapunov function scaled by the convergence rate. In our case this translates into the condition

$$\dot{v}(\zeta, w) \leq -\gamma v(z, w) \quad \forall x, y \; \forall w \in \mathcal{W} \; \forall \phi(\cdot) \in \Phi \tag{47}$$

where $v(z, w)$ and $\dot{v}(\zeta, w)$ are defined as in (42)–(43), and γ is the guaranteed convergence rate. In fact, (47) ensures that

$$v(z(t), w) \leq v(z(0), w) e^{-\gamma t} \quad \forall z(0) \; \forall t \geq 0. \tag{48}$$

However, a difficulty arises: in fact, the condition (47) cannot be expressed via LMIs since both γ and $v(z, w)$ are variables. This means that estimating the worst-case convergence rate γ^* would require the use of bilinear matrix inequalities (BMIs), which unfortunately lead to nonconvex optimization.

In order to cope with this problem, we proceed as follows. Let us redefine the integer d as the maximum degree of the matrix polynomials $\hat{A}(u), \ldots, \hat{\theta}(u)$ and $\tau(u)$ (i.e., considering also $\tau(u)$), and for such a new d

let us redefine all the quantities introduced in Section 3.1. Moreover, let us define $S(w) = S(w)' \in \mathbb{R}^{2n+l \times 2n+l}$ as

$$S(w) = \begin{pmatrix} \bar{\tau}(w)P(w) & 0 \\ 0 & 0 \end{pmatrix} \tag{49}$$

where the "0"-blocks are null matrices of suitable size, and let us express $S(\mathrm{sq}(w))$ as

$$S(\mathrm{sq}(w)) = \Delta(M_S, b_Q(w), I_{2n+l}) \tag{50}$$

for some matrix $M_S = M_S'$.

Theorem 2 *Let us define the quantity*

$$\hat{\gamma}_\delta = \frac{1}{\hat{\mu}} \tag{51}$$

where

$$\begin{aligned} & \hat{\mu} = \inf_{C_P, c_s^{(i)}, \alpha, \beta^{(i)}, \mu} \mu \\ s.t. \quad & \begin{cases} 0 < M_P + L_P(\alpha) \\ 0 > \mu(M_Q + M_R^{(1)} + L_Q(\beta^{(1)})) + M_S \\ \qquad + M_R^{(2)} + L_Q(\beta^{(2)}) \\ 0 < M_Q + M_R^{(1)} + L_Q(\beta^{(1)}) \\ 0 < \mu \end{cases} \end{aligned} \tag{52}$$

where $L_P(\alpha)$ and $L_Q(\cdot)$ are linear parametrizations of $\mathcal{L}(b_P, I_{2n})$ and $\mathcal{L}(b_Q, I_{2n+l})$, and $M_R^{(i)}$ is built as M_R by replacing c_s with $c_s^{(i)}$. Then,

$$\hat{\gamma}_\delta \leq \gamma^*. \tag{53}$$

Proof. Let us suppose that the inequalities in (52) hold. From the first inequality, by proceeding as in the proof of Theorem 1, one obtains that $P(w) > 0$ for all $w \in \mathcal{W}$. Let us pre- and post- multiply the second inequality in (38) by $(b_Q(w) \otimes I_{2n+l})'$ and $b_Q(w) \otimes I_{2n+l}$, respectively. We obtain that

$$\begin{aligned} 0 > & \Delta(\mu(M_Q + M_R^{(1)} + L_Q(\beta^{(1)})) + M_S + M_R^{(2)} \\ & + L_Q(\beta^{(2)}), b_Q(w), I_{2n+l}) \\ = & \mu(Q(\mathrm{sq}(w)) + R^{(1)}(\mathrm{sq}(w))) + P(\mathrm{sq}(w)) \\ & + R^{(2)}(\mathrm{sq}(w)) \end{aligned} \tag{54}$$

for all $w \neq 0$, and hence that

$$Q(w) + R^{(1)}(w) + \frac{1}{\mu}\left(\bar{\tau}(w)P(w) + R^{(2)}(w)\right) < 0 \tag{55}$$

for all $w \in \mathcal{W}$. Let us observe that

$$\zeta' R^{(i)} \zeta \geq 0 \quad \forall w \in \mathcal{W}\ \forall i = 1, 2\ \forall \phi(\cdot) \in \Phi, \tag{56}$$

and hence

$$\bar{\tau}(w)\left(\dot{v}(\zeta, w) + \frac{1}{\mu} v(z, w)\right) < 0 \quad \forall w \in \mathcal{W}\ \forall \phi(\cdot) \in \Phi. \tag{57}$$

From (10) this implies that $\mu^{-1} < \gamma^*$, and therefore (53) holds. □

Theorem 2 provides a lower bound of the worst-case convergence rate of the concentrations γ^* in (13). This lower bound is obtained by solving (52), which is a GEVP and belongs to the class of quasi-convex optimization problems, see e.g. [3]. It is worth observing that the fourth inequality in (52), which ensures that the obtained lower bound is positive, is not conservative since γ^* is clearly positive if the GRN (7) is globally asymptotically stable. Moreover, the third inequality in (52) guarantees that the optimization problem is a GEVP, and the variable $\beta^{(1)}$ has the role of exploiting additional degrees of freedom through the matrix $L_Q(\beta^{(1)})$ in this inequality.

The lower bound provided by Theorem 2 is a function of the chosen δ. It can be shown that the conservatism of this lower bound does not increase as δ increases, i.e.

$$\hat{\gamma}_{\delta+1} \geq \hat{\gamma}_{\delta}. \tag{58}$$

As in the case of Theorem 1, a trade-off between non-conservatism of the condition and computational burden of the optimization problem is necessary when choosing δ, which can be done following the guidelines at the end of Section 3.1.

The biological implication of Theorem 2 is to provide a guaranteed minimum speed of the convergence of the concentrations of mRNA and protein to their equilibrium values. This allows one to establish how fast the GRN can recover for all admissible uncertainties from an abnormal state.

3.3 Stable Uncertainty Sets

The third problem we consider consists of estimating $\mathcal{S}$ in (15). Let us start by noticing that this problem could be addressed by letting the vertices

$u^{(1)}, \ldots, u^{(r)}$ in (8) vary in $\mathbb{R}^q$, and by maximizing the volume of the convex polytope $\mathcal{U}$ under the condition provided by Theorem 1. Unfortunately, this would result in a nonconvex optimization problem since the second inequality in (38) would become a polynomial matrix inequality.

Hence, we consider a slightly different problem, which consists of determining the largest set of fixed shape contained in $\mathcal{S}$. Specifically, let us express the vertex $u^{(i)}$ as

$$u^{(i)} = u_0^{(i)} + \varsigma u_1^{(i)} \tag{59}$$

where $u_0^{(i)} \in \mathbb{R}^q$ denotes a starting value for the i-th vertex, and $u_1^{(i)} \in \mathbb{R}^q$ denotes its direction of extension. The problem is hence to determine the maximum value of ς for which $\mathcal{U}$ is a subset of $\mathcal{S}$, i.e.

$$\varsigma^* = \sup_{\mathcal{U} \subseteq \mathcal{S}} \varsigma. \tag{60}$$

Clearly, in order for the above problem to be well-posed, it is necessary to assume that the convex polytope $\mathcal{U}$ built with the vertices $u_0^{(1)}, \ldots, u_0^{(r)}$ is a subset of $\mathcal{S}$, i.e.

$$\mathcal{U}|_{\varsigma=0} \subseteq \mathcal{S}. \tag{61}$$

The above condition can be guaranteed by using Theorem 1.

Estimating ς^* can be done in the general case by a one-parameter sequence of stability tests: in particular, for each fixed value ς_1 of ς, one can establish whether $\bar{\varsigma} \leq \varsigma^*$ by using the condition provided by Theorem 1. This one-parameter search can be performed via a bisection search in order to speed up the convergence since

$$\varsigma_1 \leq \varsigma_2 \Rightarrow \mathcal{U}|_{\varsigma_1} \subseteq \mathcal{U}|_{\varsigma_2}. \tag{62}$$

In the case of affine linear dependence of the uncertain GRN (7) on the uncertainty, the sought estimate of ς^* can be obtained via a GEVP. Specifically, let us define all the quantities introduced in Section 3.1, and let us observe that if the functions of u in (7) are affine linear, then the functions of w in (32) are linear. Taking into account that (28) boils down to

$$u = \sum_{i=1}^{r} w_i u_0^{(i)} + \varsigma \sum_{i=1}^{r} w_i u_1^{(i)} \tag{63}$$

one has that $\bar{A}(w), \ldots, \bar{\theta}(w)$ can be written as

$$\bar{A}(w) = \bar{A}_0(w) + \varsigma \bar{A}_1(w), \ldots, \bar{\theta}(w) = \bar{\theta}_0(w) + \varsigma \bar{\theta}_1(w) \tag{64}$$

where $\bar{A}_0(w), \ldots, \bar{\theta}_0(w)$ depend on the vertices $u_0^{(1)}, \ldots, u_0^{(r)}$, and $\bar{A}_1(w), \ldots, \bar{\theta}_1(w)$ depend on the directions $u_1^{(1)}, \ldots, u_1^{(r)}$. For $i = 0, 1$ let us define $T_i(w) = T_i(w)' \in \mathbb{R}^{2n+l \times 2n+l}$ as

$$T_i(w) = \mathrm{he} \left(\begin{array}{c} P(w) \left(\begin{array}{ccc} \bar{A}_i(w) & 0 & \bar{\Phi}(w) \\ \bar{D}_i(w) & \bar{C}_i(w) & 0 \end{array} \right) \\ 0 \end{array} \right) \tag{65}$$

where the "0"-blocks are null matrices of suitable size, and let us express $T_i(\mathrm{sq}(w))$ as

$$T_i(\mathrm{sq}(w)) = \Delta(M_{T_i}, b_Q(w), I_{2n+l}) \tag{66}$$

where $M_{T_i} = M'_{T_i}$ is built with respect to the vector $b_Q(w)$ used in (37).

Theorem 3 *Let us define the quantity*

$$\hat{\varsigma}_\delta = \frac{1}{\hat{\mu}} \tag{67}$$

where

$$\begin{array}{rl} & \hat{\mu} = \inf_{C_P, c_s^{(i)}, \alpha, \beta^{(i)}, \mu} \mu \\ s.t. & \left\{ \begin{array}{rcl} 0 & < & M_P + L_P(\alpha) \\ 0 & > & \mu(M_{T_0} + M_R^{(1)} + L_Q(\beta^{(1)})) + M_{T_1} \\ & & + M_R^{(2)} + L_Q(\beta^{(2)}) \\ 0 & < & M_{T_0} + M_R^{(1)} + L_Q(\beta^{(1)}) \\ 0 & < & \mu \end{array} \right. \end{array} \tag{68}$$

$L_P(\alpha)$ and $L_Q(\cdot)$ are linear parametrizations of $\mathcal{L}(b_P, I_{2n})$ and $\mathcal{L}(b_Q, I_{2n+l})$, and $M_R^{(i)}$ is built as M_R by replacing c_s with $c_s^{(i)}$. Then,

$$\hat{\varsigma}_\delta \leq \varsigma^*. \tag{69}$$

Proof. Let us suppose that the inequalities in (68) hold. From the first inequality one obtains that $P(w) > 0$ for all $w \in \mathcal{W}$. From the second inequality we obtain that

$$\begin{array}{rcl} 0 & > & \Delta(\mu(M_{T_0} + M_R^{(1)} + L_Q(\beta^{(1)})) + M_{T_1} + M_R^{(2)} \\ & & + L_Q(\beta^{(2)}), b_Q(w), I_{2n+l}) \\ & = & \mu(T_0(\mathrm{sq}(w)) + R^{(1)}(\mathrm{sq}(w))) + T_1(\mathrm{sq}(w)) \\ & & + R^{(2)}(\mathrm{sq}(w)) \end{array} \tag{70}$$

for all $w \neq 0$, and hence that

$$\mu \left(T_0(w) + \frac{1}{\mu} M_{T_1} \right) + \mu M_R^{(1)} + M_R^{(2)} < 0 \quad \forall w \in \mathcal{W}. \tag{71}$$

Since $\zeta' R^{(i)} \zeta \geq 0$ for all $w \in \mathcal{W}$ and for all $\phi(\cdot) \in \Phi$, one has that $\dot{v}(\zeta, w) < 0$ at all the vertices

$$u^{(i)} = u_0^{(i)} + \frac{1}{\mu} u_1^{(i)}. \tag{72}$$

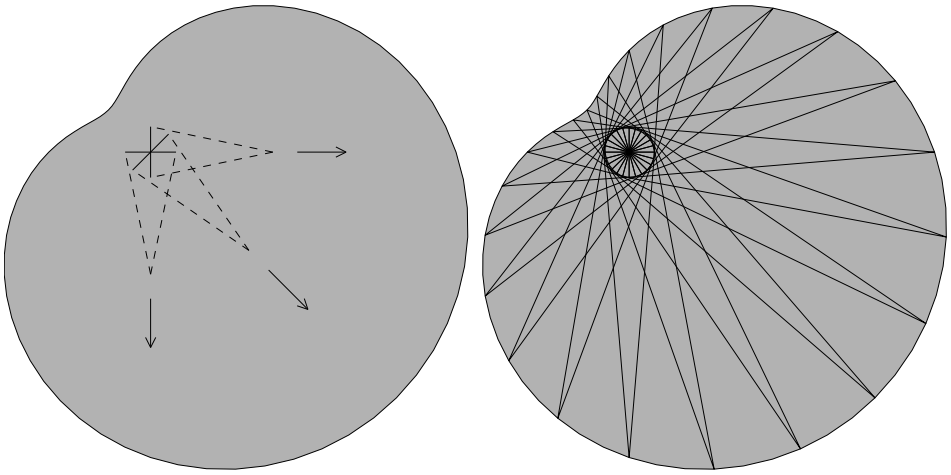
Hence, $\mu^{-1} < \varsigma^*$, and therefore (69) holds. □

Hereafter we describe a procedure that can be used in order to estimate $\mathcal{S}$ via a sequence of problems in the form (59)–(60). Specifically, the idea is to use in each of these problems an elementary set of the uncertainty with variable size in one direction and with fixed size in all the other ones. These elementary sets are chosen in order to cover all the possible directions from a common point. Problem (59)–(60) is hence solved for each of these sets in order to determine the maximum extension of $\mathcal{S}$ along the considered variable directions. A guaranteed estimate of $\mathcal{S}$ is therefore obtained by taking the union of the computed estimates in the sequence. Figure 1 illustrates this process in the planar case (i.e., $u \in \mathbb{R}^2$) by using triangles as elementary sets. These triangles have constant base and variable height, and are chosen with different orientations.

From the biological viewpoint, the obtained estimate represents a set of the uncertainties for which the concentrations of mRNA and protein are guaranteed to converge to some constant values. This can help biologists in analyzing and synthesizing GRNs with stable behaviors.

4 Examples

Here we present some illustrative examples with GRNs in SUM form, see also [7] for examples with other kinds of GRNs. The computations are done in Matlab with the toolbox SeDuMi. The SMR matrices involved in the LMI problems are built with the algorithms reported in [10].



(a) (b)

Figure 1: Procedure for estimating $\mathcal{S}$. (a) Three elementary sets with different orientations are used to estimate the extension of $\mathcal{S}$ in three different directions via Theorem 3. (b) Final estimate of $\mathcal{S}$ obtained as union of the found elementary estimates.

4.1 Example 1

Let us consider the repressilator investigated in *Escherichia coli* [13] and described by the model

$$\begin{cases} \dot{m}_i(t) = -a_i^{rep} m_i(t) + b_i^{rep}(1 - f_j(p_j(t))) \\ \dot{p}_i(t) = -c_i^{rep}(p_i(t) - m_i(t)) \\ i = lacl, tetR, cl \\ j = cl, lacl, tetR \end{cases}$$

where $f_j(p_j)$ is the Hill function in (4) with $\beta_j = 1$ and $h_j = 2$. Here we consider a plausible family of such repressilator models parametrized by three unknown parameters u_1, u_2 and u_3:

$$\begin{gathered} a_1^{rep} = 2, \quad a_2^{rep} = 3, \quad a_3^{rep} = 1 \\ b_1^{rep} = u_1, \quad b_2^{rep} = u_2, \quad b_3^{rep} = u_3 \\ c_1^{rep} = 1, \quad c_2^{rep} = 1, \quad c_3^{rep} = 1 \\ u_i \geq 0, \quad u_1 + u_2 + u_3 = 6. \end{gathered}$$

In this family, the coefficients a_i^{rep} and c_i^{rep} expressing the decay rate of mRNA and protein are chosen, whereas the interaction coefficients b_i^{rep} are

let free under a normalization constraint. The motivation for considering such a family is to investigate the effect of different interaction coefficients.

Let us define $u = (u_1, u_2, u_3)'$ and $w = u/6$. This system can be rewritten as in (32) by choosing

$$\begin{array}{rcl} \bar{A}(w) & = & (w_1 + w_2 + w_3)\mathrm{diag}(-2, -3, -1) \\ \bar{B}(w) & = & -6\mathrm{diag}(w_1, w_2, w_3) \\ \bar{C}(w) & = & (w_1 + w_2 + w_3)\mathrm{diag}(-1, -1, -1) \\ \bar{D}(w) & = & (w_1 + w_2 + w_3)\mathrm{diag}(1, 1, 1) \\ \phi(p) & = & (f_3(p_3), f_1(p_1), f_2(p_2))' \\ \bar{\theta}(w) & = & 6w \\ \bar{\tau}(w) & = & 1. \end{array}$$

The conditions in (11) are simply satisfied by selecting the entries $\lambda_{i,j}$ of Λ according to Remark 2, i.e.

$$\Lambda = \begin{pmatrix} 0 & 0 & 0.650 \\ 0.650 & 0 & 0 \\ 0 & 0.650 & 0 \end{pmatrix}.$$

First, we consider the problem of establishing whether this family of repressilator models has a globally asymptotically stable equilibrium point in $\mathbb{R}^3_+ \times \mathbb{R}^3_+$. Hence, we use Theorem 1, and find that (38) does not hold for $\delta = 0$, but it holds for $\delta = 1$ (the number of scalar variables in the LMIs is 138 for $\delta = 0$ and 936 for $\delta = 1$). This implies that, for all models of the family, the concentrations of mRNA and protein converge to some constant values, and hence that there are no multiple equilibria or limit cycles.

Second, in order to investigate more deeply this family, we consider the problem of estimating the worst-case convergence rate of the concentrations, i.e. γ^* in (13). Hence, we use Theorem 2, and we find the lower bound $\hat{\gamma}_1 = 0.570$ for $\delta = 1$. Figure 2 shows the normalized magnitude of the trajectories for some random admissible values of u, $m(0)$ and $p(0)$ and the function $e^{-\hat{\gamma}_1 t}$.

From the biological viewpoint, $\hat{\gamma}$ provides a guaranteed minimum speed of convergence of the concentrations of mRNA and protein to their equilibrium values. In fact, each model of the family under study has a different dynamical behavior, and this guaranteed minimum speed allows one to establish how fast the repressilator can recover (for all admissible interaction coefficients) from an abnormal state, which in living organisms can be caused for instance by diseases.

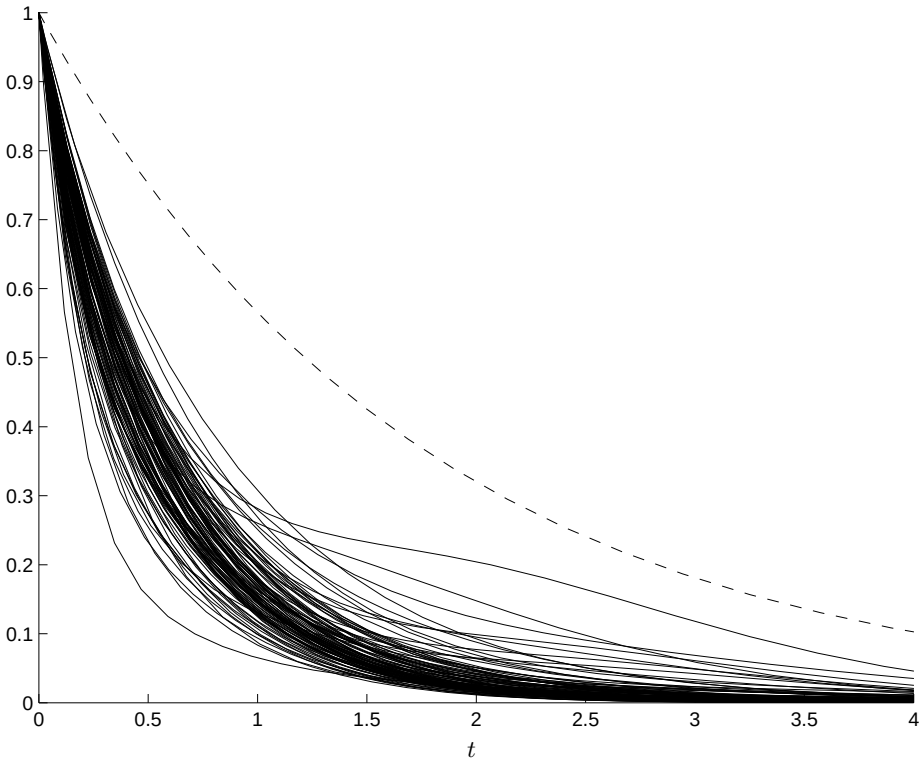


Figure 2: (Example 1) Functions $e^{-\hat{\gamma}_1 t}$ (dashed line) and $\|z(t)\|^2/\|z(0)\|^2$ for some random admissible values of u, $m(0)$ and $p(0)$ (solid line).

4.2 Example 2

Let us consider the motif of genes Gal3 and Gal80 in *Saccharomyces cerevisiae galactose regulation* (see e.g. [20] and references therein) which can be expressed in the form of system (1)–(5) as

$$\begin{cases} \dot{m}_1(t) &= -a_1 m_1(t) + e_{12} f_2(p_2(t)) + \theta_1 \\ \dot{m}_2(t) &= -a_2 m_2(t) + e_{21} f_1(p_1(t)) + \theta_2 \\ \dot{p}_1(t) &= -c_1 p_1(t) + d_1 m_1(t) \\ \dot{p}_2(t) &= -c_2 p_2(t) + d_2 m_2(t) \\ \theta_1 &= -\min\{0, e_{12}\} \\ \theta_2 &= -\min\{0, e_{21}\} \end{cases}$$

where $f_i(p_i)$ is the Hill function in (4) with

$$\begin{aligned} \beta_i &\in [0.5, 2] \\ h_i &\in \{2, 3\}. \end{aligned}$$

The problem is to estimate the set of interaction coefficients e_{12} and e_{21} for which the GRN has a globally asymptotically stable equilibrium point in $\mathbb{R}^2_+ \times \mathbb{R}^2_+$.

We express e_{12} and e_{21} as $e_{12} = e_{120} + u_1$ and $e_{21} = e_{210} + u_2$, where e_{120} and e_{210} represent the nominal value for the interaction coefficients, and u_1 and u_2 are uncertainties. The problem, hence, is to estimate $\mathcal{S}$ in (15). We consider the following plausible case:

$$\begin{gathered} a_1 = 1.1, \quad a_2 = 0.8, \quad c_1 = 1.3, \quad c_2 = 0.6 \\ d_1 = 0.9, \quad d_2 = 0.5, \quad e_{120} = -0.5, \quad e_{210} = -0.5. \end{gathered}$$

We proceed as described in Section 3.3 by using as elementary sets 144 triangles centered in the origin with orientations equally distributed in the interval $[0, 360]$ deg. For each triangle we solve the GEVP (68), which has 113 scalar variables. We hence obtain the inner estimates of the set $\mathcal{S}$ shown in Figure 3. The conditions in (11) are simply satisfied by selecting, e.g., $\phi(p) = (f_1(p_1), f_2(p_2))'$ and $\Lambda = 1.680 I_2$.

From the biological viewpoint, the area obtained in Figure 3 represents a set of the interaction coefficients of the two genes for which the concentrations of mRNA and protein are guaranteed to converge to some constant values. This means that, whenever the interaction coefficients lie inside such a set, the motif has no multiple equilibria (i.e., the equilibrium values of the concentrations are unique) and no limit cycles (i.e., the concentrations do not present periodic oscillations).

5 Conclusion

Robustness analysis of GRNs with respect to model uncertainty is a key problem in systems biology. This paper has addressed this problem for GRNs where the coefficients are rationally affected by polytopic uncertainty, and where the saturation functions are not exactly known. The proposed techniques are based on the construction of a variable Lyapunov function candidate parametrized by the uncertainty, and amount to solving convex and quasi-convex optimization problems obtained by using the SMR.

From the biological viewpoint, these techniques allow one to ensure that the concentrations of mRNA and protein converge to some constant values

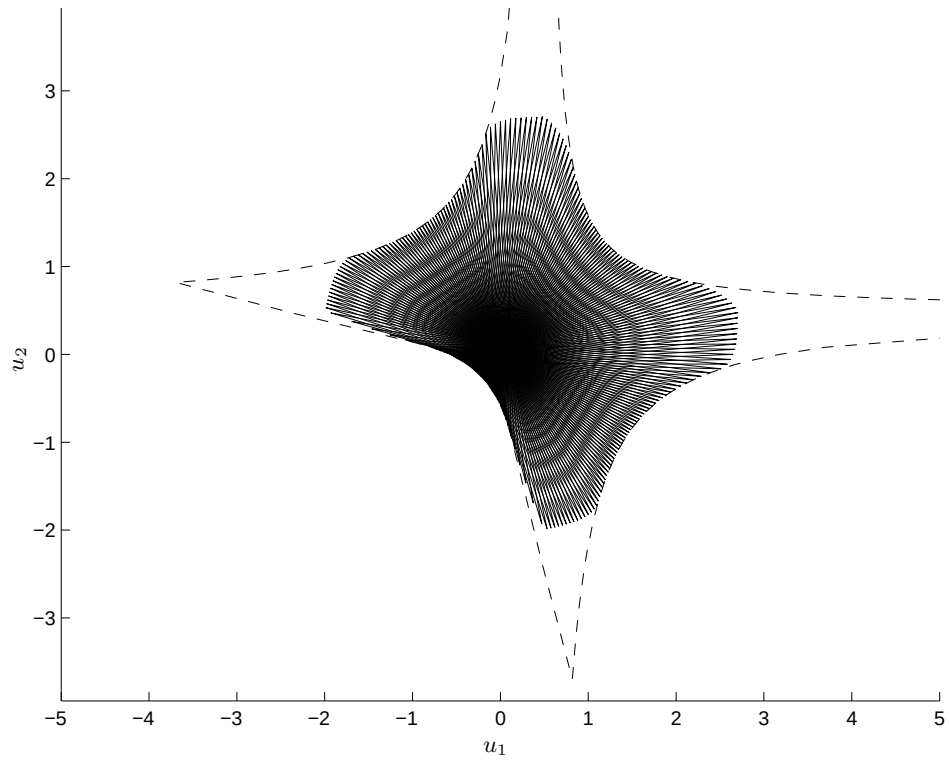


Figure 3: (Example 2) Set of interaction coefficients for which the GRN has a globally asymptotically stable equilibrium point in $\mathbb{R}^2_+ \times \mathbb{R}^2_+$: estimate obtained for $\delta = 0$ (solid line) and $\delta = 1$ (dashed line).

for all admissible uncertainties, provide a guaranteed minimum speed of this convergence, and allow one to estimate the set of the uncertainties for which this convergence can be achieved. Therefore, these techniques can help biologists in understanding and classifying the GRN models that present typical behaviors of healthy organisms.

Future work will be devoted to investigate the conservatism of the proposed methodology and possibly reduce it, e.g. by following the ideas proposed in [9] for the case of certain GRNs.

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