Title	On the Steady States of Uncertain Genetic Regulatory Networks
Author(s)	Chesi, G
Citation	IEEE Transactions on Systems, Man, and Cybernetics Part A:Systems and Humans, 2012, v. 42 n. 4, p. 1020-1024
Issued Date	2012
URL	http://hdl.handle.net/10722/155720
Rights	©2012 IEEE. Personal use of this material is permitted. However, permission to reprint/republish this material for advertising or promotional purposes or for creating new collective works for resale or redistribution to servers or lists, or to reuse any copyrighted component of this work in other works must be obtained from the IEEE.

On the Steady States of Uncertain Genetic Regulatory Networks

Graziano Chesi

***Abstract*—This correspondence addresses the analysis of the steady states of uncertain genetic regulatory networks (GRNs). The uncertainty is represented as a vector constrained in a given set that affects the coefficients of the mathematical model of the GRN. It is shown how regions containing all possible steady states can be estimated via an iterative strategy that progressively splits the concentration space into smaller sets, discarding those that are guaranteed not to contain equilibrium points of the considered model. This strategy is based on worst case evaluations of some appropriate functions of the uncertainty via linear matrix inequality optimization.**

***Index Terms*—Genetic regulatory network (GRN), robustness, steady state, uncertainty.**

I. Introduction

It is well known that genetic regulatory networks (GRNs) play a key role in living organisms. Various types of models are used to study GRNs, in particular, discrete models (such as Boolean models, which mainly aim to characterize qualitative behaviors), continuous models (which mainly focus on quantitative behaviors), and hybrid models (which are obtained by combining discrete and continuous models). GRNs are also classified depending on the time representation (e.g., continuous time or discrete time, possibly via Markov chains), the nature of the signals (e.g., deterministic or stochastic), the nature of the methods adopted for their study (e.g., analytic or via simulations as with Monte Carlo methods), etc., e.g., [1]–[6].

An important problem consists of determining the steady states of GRNs. In fact, knowledge of the steady states provides qualitative and quantitative information about the temporal evolution of messenger ribonucleic acid (mRNA) and protein concentrations. Moreover, this knowledge is often required in fundamental studies, such as stability analysis; see, e.g., [7]. Determining the steady states amounts to solving a system of nonlinear equations since the temporal derivative of the mRNA and protein concentrations is a nonlinear function of these concentrations, and this operation is nontrivial since there do not exist techniques that guarantee to find all solutions of a generic nonlinear system, e.g., [8]–[10].

The problem, however, is even more difficult in practice. In fact, mathematical models of GRNs are not exactly known. This is due to various reasons, in particular, to the fact that the experimental data used to identify the coefficients of the model are unavoidably affected by noise and measurement errors. Moreover, researchers have often to consider not only a specific mathematical model but also a family of mathematical models in order to analyze and synthesize a class of GRNs. This means that mathematical models of GRNs contain uncertain parameters, e.g., [11] and [12]. These uncertain parameters affect the steady states that, as a result, are uncertain as well. Clearly, one might think of repeating the determination of the steady states for all possible uncertainties, but this solution would require to solve a system of nonlinear equations an infinite number of times. It is worth mentioning that uncertain GRNs may present also steady states that are independent of the uncertainty depending on their structure, e.g., [13].

This correspondence addresses the analysis of the steady states of uncertain GRNs. Specifically, regulation functions of various types are considered through a generalized model that includes the standard case of Hill functions. The uncertainty is represented as a vector constrained in a given set that affects the coefficients of the mathematical model of the GRN via polynomial functions. It is shown how regions containing all possible steady states can be estimated via an iterative strategy that progressively splits the concentration space into smaller sets, discarding those that are guaranteed not to contain equilibrium points of the considered model. This strategy is based on worst case evaluations of some appropriate functions of the uncertainty via linear matrix inequality (LMI) optimization and allows one to select the tradeoff between conservatism of the found regions and computational time. The proposed strategy is illustrated through various numerical examples. It is worth mentioning that systematic approaches for investigating the steady states of uncertain GRNs have not been proposed yet in the literature.

This correspondence is organized as follows. Section II introduces some preliminaries on GRNs. Section III describes the proposed strategy. Section IV presents some numerical examples. Lastly, Section V concludes with some final remarks.

II. Preliminaries

Let us introduce the notations used throughout this correspondence: $\mathbb{R}$ is the space of real numbers, $\mathbb{R}_+$ is the space of nonnegative real numbers, 0_n is a null vector of size $n \times 1$, and Z' is the transpose of matrix/vector Z.

The author considers GRNs expressed by

$$\begin{cases} \dot{m}(t) = A_1 m(t) + B b\left(p(t)\right) + c \\ \dot{p}(t) = A_2 p(t) + A_3 m(t) \end{cases} \tag{1}$$

where the vectors m and $p \in \mathbb{R}_+^n$ contain the mRNA and protein concentrations, A_1, A_2, and A_3 are diagonal matrices, B and c are a matrix and a vector, and the function $b(p)$ is obtained by saturation functions, i.e., functions $f(p_1), \ldots, f(p_n)$ where $f : \mathbb{R}_+ \to [0, 1]$ with $f(0) = 0$, $\lim_{z\to\infty} f(z) = 1$, and $f(z)$ monotonically increasing. In the case of Hill functions, one has

$$f(p_l) = \frac{p_l^\alpha}{\beta^\alpha + p_l^\alpha}, \qquad l = 1, \ldots, n \tag{2}$$

for some α and $\beta \in \mathbb{R}_+$. The GRN (1) can be rewritten in compact form

$$\dot{x}(t) = Ex(t) + Gg\left(x(t)\right) + h \tag{3}$$

where $x \in \mathbb{R}^N$, E and G are matrices, h is a vector, and $g(x)$ is composed of Hill functions. Indeed, (3) coincides with (1) by simply

Manuscript received November 10, 2010; revised March 22, 2011; accepted August 6, 2011. Date of publication January 5, 2012; date of current version June 13, 2012. This paper was recommended by Associate Editor G. Calafiore.

The author is with the Department of Electrical and Electronic Engineering, The University of Hong Kong, Pokfulam, Hong Kong (e-mail: http://www.eee.hku.hk/~chesi).

Digital Object Identifier 10.1109/TSMCA.2011.2178829

defining

$$x = \begin{pmatrix} m \\ p \end{pmatrix} \qquad E = \begin{pmatrix} A_1 & 0 \\ A_3 & A_2 \end{pmatrix} \qquad G = \begin{pmatrix} B \\ 0 \end{pmatrix}$$
$$h = \begin{pmatrix} c \\ 0 \end{pmatrix} \qquad g(x) = b(p). \tag{4}$$

In this correspondence, the author considers the model (3) affected by parametric uncertainty, in particular

$$\dot{x}(t) = E(\theta)x(t) + G(\theta)g\left(x(t)\right) + h(\theta) \tag{5}$$

where $\theta \in \mathbb{R}^r$ is an uncertain vector constrained according to

$$\theta \in \Theta \tag{6}$$

where the set Θ is expressed as

$$\Theta = \{\theta \in \mathbb{R}^r : \quad a_l(\theta) \geq 0, \quad l = 1, \ldots, n_a\} \tag{7}$$

for some polynomials $a_l(\theta)$. The functions $E(\theta)$, $G(\theta)$, and $h(\theta)$ are assumed polynomial, with $E(\theta)$ invertible for all $\theta \in \Theta$. Each entry of $g(x)$ is assumed to be either one or a product of the functions $f(x_1), \ldots, f(x_n)$ (with each x_i appearing in not more than one entry), e.g.,

$$g(x) = \left(f(x_1), f(x_2)f(x_3)\right)'. \tag{8}$$

The problem addressed in this correspondence consists of estimating the set of steady states of (5), i.e.,

$$\mathcal{S} = \left\{x \in \mathbb{R}^N_+ : \quad E(\theta)x + G(\theta)g(x) + h(\theta) = 0_n \right. \\ \left. \text{for some } \theta \in \Theta\right\}. \tag{9}$$

Remark 1: The considered framework allows one to consider GRNs with time delays. Indeed, in such a case, (5) can be rewritten as

$$\dot{x}(t) = E(\theta)x(t) + G(\theta)g\left(x(t)\right) + h(\theta) \\ + \sum_{l=1}^{n_\tau} \left(E_l(\theta)x(t-\tau_l) + G_l(\theta)g\left(x(t-\tau_l)\right)\right) \tag{10}$$

where τ_l is the lth time delay and $E_l(\theta)$ and $G_l(\theta)$ are analogous to $E(\theta)$ and $G(\theta)$. At the equilibrium, one has that $x(t)$ and $x(t-\tau_l)$ coincide, i.e.,

$$\lim_{t\to\infty} x(t) = \lim_{t\to\infty} x(t-\tau_l) \qquad \forall l \tag{11}$$

and hence, the set of steady states for the time-delay system is obtained by simply replacing $E(\theta)$ and $G(\theta)$ with $E(\theta) + \sum_{l=1}^{n_\tau} E_l(\theta)$ and $G(\theta) + \sum_{l=1}^{n_\tau} G_l(\theta)$, respectively. See, e.g., [14] for more information about models of GRNs with time delays.

Remark 2: The derivative $\dot{x}$ in (5) is expressed as a sum of a linear term in x [i.e., $E(\theta)x$], a nonlinear term [i.e., $G(\theta)g(x)$], and a constant [i.e., $h(\theta)$]. Let us observe that each entry of the nonlinear term $G(\theta)g(x)$ is allowed to be a sum of products of the saturation functions, e.g.,

$$G(\theta)g(x) = \left(\theta_2 f(x_1), -f(x_1) + \theta_1 f(x_2)f(x_3)\right)'. \tag{12}$$

See, e.g., [15] for more information about structural properties of GRNs.

Remark 3: The uncertainty description introduced in (5) includes several cases of interest. For instance, one can consider the standard case where the coefficients are linear or quadratic functions of θ. Moreover, the vector θ can be constrained in standard sets such as boxes, polytopes, and ellipsoids.

III. Estimating the Steady States

This section describes the proposed strategy. The idea consists of shrinking the concentration space via a fixed-point algorithm that guarantees not to lose any admissible steady state. Then, the shrunk set is divided into subsets of appropriate form, and the algorithm is reapplied to each of them. Hence, the procedure is repeated for a chosen number of times, which determines the accuracy of the estimates.

Specifically, let us denote with $\mathcal{H}$ a hyperrectangle in $\mathbb{R}^N_+$, and define the function

$$\mathcal{A}(\mathcal{H}) = \left\{x \in \mathbb{R}^N_+ : \quad x_i \in \left[q_i^-, q_i^+\right]\right\} \tag{13}$$

where q_i^- and q_i^+ are any quantities satisfying

$$q_i^- \leq \min_{x \in ver(\mathcal{H})} \min_{\theta\in\Theta} u_i(x,\theta)$$
$$q_i^+ \geq \max_{x \in ver(\mathcal{H})} \max_{\theta\in\Theta} u_i(x,\theta) \tag{14}$$

where $ver(\mathcal{H})$ is the set of vertices of $\mathcal{H}$ and $u_i(x,\theta)$ is the ith entry of the vector

$$u(x,\theta) = -E(\theta)^{-1}\left(G(\theta)g(x) + h(\theta)\right). \tag{15}$$

Theorem 1: The function $\mathcal{A}(\mathcal{H})$ satisfies

$$p \in \mathcal{H} \cap \mathcal{S} \Rightarrow p \in \mathcal{A}(\mathcal{H}) \tag{16}$$
$$\mathcal{H} \cap \mathcal{A}(\mathcal{H}) = \emptyset \Rightarrow \mathcal{H} \cap \mathcal{S} = \emptyset. \tag{17}$$

Evaluating the function $\mathcal{A}(\mathcal{H})$ requires the computation of the quantities q_i^- and q_i^+. The author will explain how this step can be addressed after Theorem 3. From $\mathcal{A}(\mathcal{H})$, the author defines the following function.

Theorem 2: Let $\mathcal{H}$ be a hyperrectangle in $\mathbb{R}^N_+$, and define the algorithm $\mathcal{B}(\mathcal{H})$ as follows.

Step B1) Set $\mathcal{H}^{(0)} = \mathcal{H}$ and $j = 0$.
Step B2) Set $\mathcal{B}_1 = \mathcal{H}^{(j)} \cap \mathcal{A}(\mathcal{H}^{(j)})$.
Step B3) If $\mathcal{B}_1 = \emptyset$, set $\mathcal{B}(\mathcal{H}) = \mathcal{B}_1$ and exit.
Step B4) If $\mathcal{B}_1 = \mathcal{H}^{(j)}$, set $\mathcal{B}(\mathcal{H}) = \mathcal{B}_1$ and exit.
Step B5) If $j = j_{\max}$, set $\mathcal{B}(\mathcal{H}) = \mathcal{B}_1$ and exit.
Step B6) Set $j = j + 1$ and $\mathcal{H}^{(j)} = \mathcal{B}_1$, and go to Step B2.

Then, $\mathcal{B}(\mathcal{H})$ provides either the empty set, a point, or a hyperrectangle. Moreover

$$\mathcal{B}(\mathcal{H}) \subseteq \mathcal{H} \tag{18}$$
$$p \in \mathcal{H} \cap \mathcal{S} \Rightarrow p \in \mathcal{B}(\mathcal{H}). \tag{19}$$

Observe that the algorithm $\mathcal{B}(\mathcal{H})$ stops whenever $\mathcal{B}_1$ is empty, $\mathcal{B}_1$ is the hyperrectangle $\mathcal{H}^{(j)}$ found at the previous iteration, or a maximum number of iterations (denoted by $j_{\max}$) are reached. From $\mathcal{B}(\mathcal{H})$, the author derives the algorithm for the computation of the sought set $\mathcal{S}$ as follows.

Theorem 3: Let $\mathcal{H}$ be a hyperrectangle in $\mathbb{R}^N_+$, and let k be a nonnegative integer. Let us define the algorithm $\mathcal{C}(\mathcal{H}, k)$ as follows.

Step C1) If $k = 0$, set $\mathcal{C}(\mathcal{H}, k) = \mathcal{H}$ and exit.
Step C2) If $k = 1$, set $\mathcal{C}(\mathcal{H}, k) = \mathcal{B}(\mathcal{H})$ and exit.
Step C3) If $\mathcal{B}(\mathcal{H})$ is either the empty set or a point, set $\mathcal{C}(\mathcal{H}, k) = \mathcal{B}(\mathcal{H})$ and exit.
Step C4) Divide $\mathcal{B}(\mathcal{H})$ into disjoint hyperrectangles $\mathcal{H}_1, \ldots, \mathcal{H}_s$ such that

$$\bigcup_{i=1,\ldots,s} \mathcal{H}_i = \mathcal{B}(\mathcal{H}). \tag{20}$$

Step C5) Set

$$\mathcal{C}(\mathcal{H},k)=\bigcup_{i=1,\ldots,s}\mathcal{C}(\mathcal{H}_i,k-1) \tag{21}$$

and exit.

Then, the set $\mathcal{S}$ is estimated by calling the algorithm $\mathcal{C}(\mathbb{R}^N_+,k)$ (i.e., choosing as initial hyperrectangle the set $\mathbb{R}^N_+$). Indeed, for all $k\geq 0$, one has that

$$\mathcal{S}\subseteq\mathcal{C}\left(\mathbb{R}^N_+,k+1\right)\subseteq\mathcal{C}\left(\mathbb{R}^N_+,k\right). \tag{22}$$

Observe that the algorithm $\mathcal{C}(\mathbb{R}^N_+,k)$ stops after k divisions of the current hyperrectangle in subhyperrectangles. The number of subhyperrectangles can be freely chosen, and a simple choice consists of dividing each side of the current hyperrectangle into two equal segments.

Concerning the numerical complexity of this algorithm, let us observe that this depends on the GRN dimension N through the number of vertices of the hyperrectangles which determines the number of evaluations in $\mathcal{A}(\mathcal{H})$. Although this number grows quickly with N, the overall computational time of the procedure is alleviated by the fact that numerous hyperrectangles are typically discarded in Step B3 owing to the properties of $\mathcal{B}(\mathcal{H})$.

Next, let us address the construction of the quantities q_i^- and q_i^+. These quantities can be found by solving convex optimization problems with LMIs. Specifically, for any $x\in ver(\mathcal{H})$, let us define

$$\begin{aligned}w_-(\theta)=&num\left(u_i(x,\theta)\right)-\gamma den\left(u_i(x,\theta)\right)\\&-\sum_{l=1}^{n_a}s_l(\theta)a_l(\theta)\\w_+(\theta)=&den\left(u_i(x,\theta)\right)\gamma-num\left(u_i(x,\theta)\right)\\&-\sum_{l=1}^{n_a}s_l(\theta)a_l(\theta)\end{aligned} \tag{23}$$

where $num(u_i(x,\theta))$ and $den(u_i(x,\theta))$ are the numerator and denominator of $u_i(x,\theta)$, respectively, and $s_l(\theta)$ represents free polynomials. One has that, for any degree of $s_l(\theta)$, q_i^- and q_i^+ can be chosen as

$$\begin{aligned}q_i^-&=\max_{\gamma,s_k(\cdot)}\gamma\ \text{s.t.}\begin{cases}w_-(\theta)\ \text{is SOS}\\ s_l(\theta)\ \text{is SOS}\end{cases}\quad\forall l=1,\ldots,n_a\\q_i^+&=\min_{\gamma,s_k(\cdot)}\gamma\ \text{s.t.}\begin{cases}w_+(\theta)\ \text{is SOS}\\ s_l(\theta)\ \text{is SOS}\end{cases}\quad\forall l=1,\ldots,n_a\end{aligned} \tag{24}$$

where "SOS" means "sum of squares of polynomials." In fact, consider, e.g., q_i^-. One has that $w_-(\theta)$ and $s_l(\theta)$ are SOS and hence nonnegative. Therefore, from the definition of $w_-(\theta)$, one gets that, for all $\theta\in\Theta$

$$\begin{aligned}0\leq& w_-(\theta)\\=&num\left(u_i(x,\theta)\right)-\gamma den\left(u_i(x,\theta)\right)-\sum_{l=1}^{n_a}s_l(\theta)a_l(\theta)\\\leq& num\left(u_i(x,\theta)\right)-\gamma den\left(u_i(x,\theta)\right)\end{aligned} \tag{25}$$

i.e., $\gamma\leq u_i(x,\theta)$. Establishing whether a polynomial is SOS is equivalent to an LMI feasibility test; see, e.g., [16] and [17] for details. Hence, the constraints in (24) can be expressed via LMIs, and therefore, (24) amounts to solving two convex optimization problems with LMIs.

IV. Illustrative Examples

This section presents some illustrative examples where the proposed strategy is adopted to estimate the steady states of uncertain GRNs.

A. Example 1

Let us start by considering a simple example with an uncertain GRN described by

$$\begin{cases}\dot m_1(t)=-m_1(t)+\theta\left(1-f\left(p_2(t)\right)\right)\\ \dot m_2(t)=-m_2(t)+2.5\left(1-f\left(p_1(t)\right)\right)\\ \dot p_1(t)=-2p_1(t)+m_1(t)\\ \dot p_2(t)=-p_2(t)+0.5\theta m_2(t)\end{cases} \tag{26}$$

where $f(\cdot)$ is the Hill function in (2) with $\alpha=2$ and $\beta=1$ and the uncertain parameter θ is constrained according to

$$\theta\in[1,2]. \tag{27}$$

This GRN is characterized by the fact that TF 1 is a regressor of gene 2 and TF 2 is a regressor of gene 1. The uncertain parameter θ affects the coefficients of the GRN.

Let us consider the problem of estimating the set $\mathcal{S}$. To this end, the author uses the algorithm described in Theorem 3. With $k=1$, the set $\mathbb{R}^+_N$ is shrunk via the function $\mathcal{B}(\cdot)$, and for the p-components, the author obtains the rectangle shown in Fig. 1(a). With $k=2$, this rectangle is divided into four equal rectangles, and $\mathcal{B}(\cdot)$ is reapplied to each of them. This provides the three rectangles shown in Fig. 1(b): Observe, in fact, that one rectangle has been shrunk to the empty set. Proceeding in this way, the author obtains the estimates shown in Fig. 1(c) (with $k=3$) and Fig. 1(d) (with $k=4$).

B. Example 2

Let us consider the system (28), shown at the bottom of the page, where M denotes an mRNA concentration while P_0, P_1, P_2, and P_N denote protein concentrations. This system summarizes the model proposed in [18] for investigating dynamical behaviors in Drosophila period protein (PER). The model is based on multiple phosphorylation of PER and on the negative feedback exerted by PER on the transcription of the period gene. The author considers the case where some coefficients are fixed while others are uncertain. In particular, the fixed coefficients are chosen as $n=1$, $v_s=2$, $v_m=0.8$, $v_d=1.2$, $V_4=2.6$, $k_s=0$, $k_1=2$, $k_2=1$, $K_d=0.5$, $K_i=0.5$, and $a_i=1$ for all i, while the uncertain coefficients are

$$V_1\in[1,3]\qquad V_2\in[1,2]\qquad V_3=[2,5]. \tag{29}$$

Hence, $\theta=[V_1,V_2,V_3]$. The author estimates the steady states via the algorithm $\mathcal{C}(\mathbb{R}^N_+,k)$, obtaining the results shown in Fig. 2 (where the

$$\begin{cases}\dot M(t)=v_s\frac{K_1^n}{K_1^n+P_N(t)^n}-a_1M(t)-v_m\frac{M(t)}{K_m+M(t)}\\ \dot P_0(t)=k_sM(t)-a_2P_0(t)-V_1\frac{P_0(t)}{K_1+P_0(t)}+V_2\frac{P_1(t)}{K_2+P_1(t)}\\ \dot P_1(t)=V_1\frac{P_0(t)}{K_1+P_0(t)}-a_3P_1(t)-V_2\frac{P_1(t)}{K_2+P_1(t)}-V_3\frac{P_1(t)}{K_3+P_1(t)}+V_4\frac{P_2(t)}{K_4+P_2(t)}\\ \dot P_2(t)=V_3\frac{P_1(t)}{K_3+P_1(t)}-V_4\frac{P_2(t)}{K_4+P_2(t)}-(a_4+k_1)P_2(t)+k_2P_N(t)-v_d\frac{P_2(t)}{K_d+P_2(t)}\\ \dot P_N(t)=k_1P_2(t)-(a_5+k_2)P_N(t)\end{cases} \tag{28}$$

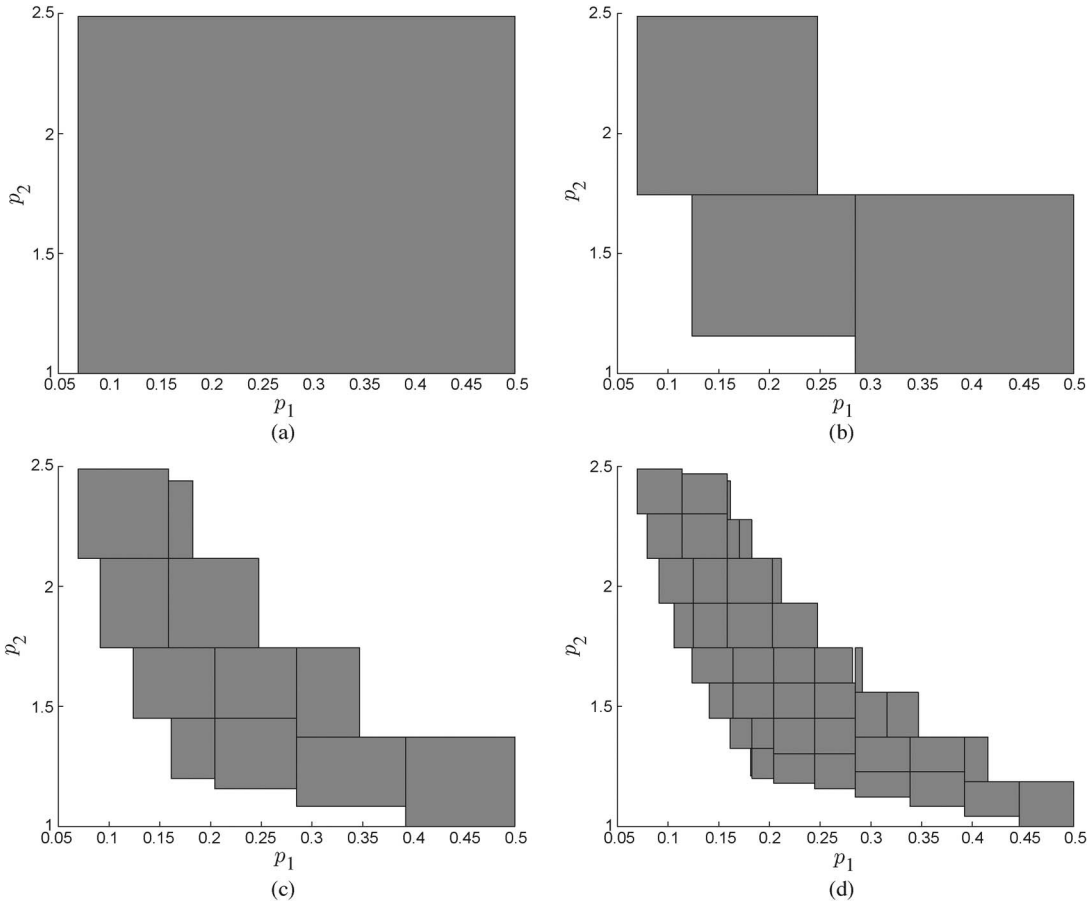

Fig. 1. Example 1. Estimates of the steady states with (a) $k = 1$, (b) $k = 2$, (c) $k = 3$, and (d) $k = 4$.

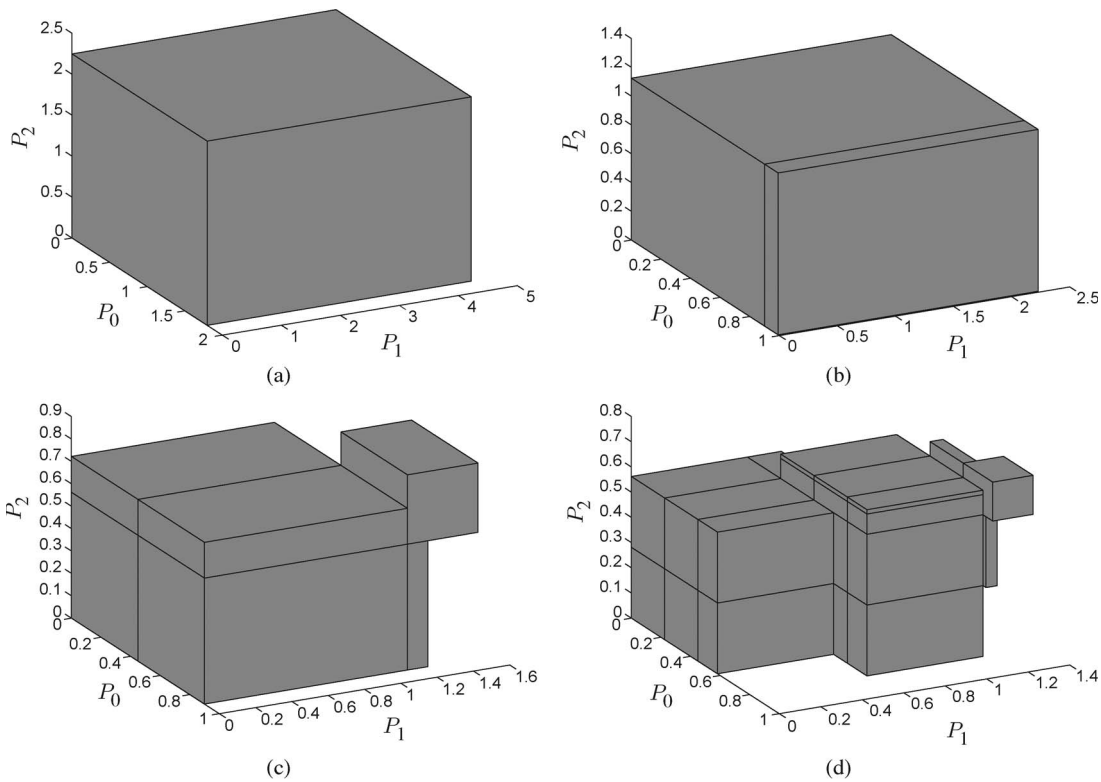

Fig. 2. Example 2. Projections of the estimates of the steady states with (a) $k = 1$, (b) $k = 2$, (c) $k = 3$, and (d) $k = 4$.

projection of the estimates on the 3-D space with coordinates P_0, P_1, and P_2 is reported).

From a biological point of view, the found estimates provide bounds to the equilibrium values of the concentrations in (28) that are guaranteed for all admissible parameters. These bounds are useful for a number of studies, for instance, in order to provide information about the evolution of the concentrations.

V. Conclusion

The author has proposed an iterative strategy for estimating the steady states of uncertain GRNs. This strategy is based on worst case evaluations of some appropriate functions and provides a region containing all possible steady states. This algorithm can be useful in numerous tasks since knowledge of the steady states is typically required when studying stability of GRNs. Future work will consider the possibility of extending the proposed strategy in order to estimate limit cycles.

Appendix

Proof of Theorem 1: Let $y \in \mathcal{S}$. One has that, for some $\theta \in \Theta$, $y = -E(\theta)^{-1}(G(\theta)g(y) + h(\theta))$. Moreover, if y belongs to $\mathcal{H}$, one has that

$$y_i \in \left[\min_{x \in ver(\mathcal{H})} u_i(x,\theta), \max_{x \in ver(\mathcal{H})} u_i(x,\theta)\right]$$

since each entry of $-E(\theta)^{-1}(G(\theta)g(y) + h(\theta))$ is monotonic due to the structure of $g(y)$. This implies that

$$y_i \in \left[q_i^-, q_i^+\right]$$

and hence, (16) holds. Then, suppose for contradiction that $\mathcal{H} \cap \mathcal{A}(\mathcal{H})$ is empty but $\mathcal{H} \cap \mathcal{S}$ is not. Let y be in $\mathcal{H} \cap \mathcal{S}$. Then, from (16), one has that $p \in \mathcal{A}(\mathcal{H})$, but y belongs also to $\mathcal{H}$, hence contradicting that $\mathcal{H} \cap \mathcal{A}(\mathcal{H})$ is empty. Therefore, (17) holds.

Proof of Theorem 2: Let us observe that the output of $\mathcal{B}(\mathcal{H})$ can be either the empty set (Step B3), a point (Step B4), or a hyperrectangle (Steps B4–B6). Then, (18) follows from the fact that $\mathcal{B}(\mathcal{H})$ is a subset of $\mathcal{H}^{(0)} = \mathcal{H}$. Lastly, (19) holds since $\mathcal{B}(\mathcal{H})$ is a sequence of applications of the function $\mathcal{A}(\cdot)$ for which (16) ensures that no point of $\mathcal{H} \cap \mathcal{S}$ can be lost.

Proof of Theorem 3: Observe that $\mathcal{C}(\mathcal{H}, k)$ is either $\mathcal{H}$ (Step C1) or the union of the output sets of the function $\mathcal{B}(\cdot)$ applied to subsets of $\mathcal{H}$ (Steps C2–C5). Each of these output sets is included in the corresponding input set due to (18). Therefore, (22) holds.

Acknowledgment

The author would like to thank the Editors and the Reviewers for their useful comments that have greatly improved this correspondence.

References

[1] F. Jacob and J. Monod, "Genetic regulatory mechanisms in the synthesis of proteins," *J. Mol. Biol.*, vol. 3, pp. 318–356, Jun. 1961.

[2] J. M. Bower and H. Bolouri, Eds., *Computational Modeling of Genetic and Biochemical Networks*. Cambridge, MA: MIT Press, 2001, ser. Computational Molecular Biology.

[3] H. Toh and K. Horimoto, "System for automatically inferring a genetic network from expression profiles," *J. Biol. Phys.*, vol. 28, pp. 449–464, 2002.

[4] S. R. Taylor, R. Gunawan, L. R. Petzold, and F. J. Doyle, "Sensitivity measures for oscillating systems: Application to mammalian circadian gene network," *IEEE Trans. Autom. Control*, vol. 53, no. 1, pp. 177–188, Jan. 2008, IEEE Trans. Circuits Syst. I, Reg. Papers Joint Special Issue on Systems Biology.

[5] L. Chen, R. Wang, C. Li, and K. Aihara, *Modelling Biomolecular Networks in Cells: Structures and Dynamics*. London, U.K.: Springer-Verlag, 2010.

[6] T. J. Perkins, R. Wilds, and L. Glass, "Robust dynamics in minimal hybrid models of genetic networks," *Philos. Trans. Roy. Soc. A*, vol. 368, no. 1930, pp. 4961–4975, Nov. 2010.

[7] G. Chesi, "Polynomial relaxation-based conditions for global asymptotic stability of equilibrium points of genetic regulatory networks," *Int. J. Syst. Sci.*, vol. 41, no. 1, pp. 65–72, Jan. 2010.

[8] G. Chesi, A. Garulli, A. Tesi, and A. Vicino, "Characterizing the solution set of polynomial systems in terms of homogeneous forms: An LMI approach," *Int. J. Robust Nonlinear Control*, vol. 13, no. 13, pp. 1239–1257, Nov. 2003.

[9] J. Nocedal and S. Wright, *Numerical Optimization*. New York: Springer-Verlag, 2006.

[10] G. Chesi, "Computing equilibrium points of genetic regulatory networks," in *Transactions on Computational Systems Biology XI*. Berlin, Germany: Springer-Verlag, 2009, pp. 268–282.

[11] G. Chesi and Y. S. Hung, "Stability analysis of uncertain genetic sum regulatory networks," *Automatica*, vol. 44, no. 9, pp. 2298–2305, Sep. 2008.

[12] G. Chesi, "Robustness analysis of genetic regulatory networks affected by model uncertainty," *Automatica*, vol. 47, no. 6, pp. 1131–1138, Jun. 2011.

[13] M. Feinberg and F. J. M. Horn, "Dynamics of open chemical systems and the algebraic structure of the underlying reaction network," *Chem. Eng. Sci.*, vol. 29, pp. 775–787, 1974.

[14] J. Goutsias and S. Kim, "Stochastic transcriptional regulatory systems with time delays: A mean-field approximation," *J. Comput. Biol.*, vol. 13, no. 5, pp. 1049–1076, 2006.

[15] J. Goutsias and S. Kim, "A nonlinear discrete dynamical model for transcriptional regulation: Construction and properties," *Biophys. J.*, vol. 86, no. 4, pp. 1922–1945, 2004.

[16] G. Chesi, A. Garulli, A. Tesi, and A. Vicino, *Homogeneous Polynomial Forms for Robustness Analysis of Uncertain Systems*. Berlin, Germany: Springer-Verlag, 2009.

[17] G. Chesi, "LMI techniques for optimization over polynomials in control: A survey," *IEEE Trans. Autom. Control*, vol. 55, no. 11, pp. 2500–2510, Nov. 2010.

[18] A. Goldbeter, "A model for circadian oscillations in the Drosophila period protein (PER)," in *Proc. Roy. Soc. B*, 1995, vol. 261, pp. 319–324.