Uncertain Gene Regulatory Networks Simplified by Gramian-Based Approach

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Abstract

The complexity of gene regulatory networks described by coupled nonlinear differential equations is often an obstacle for analysis purposes. They are prone to internal parametrical fluctuations making thus robustness a crucial property of these networks to attenuate the effects of internal fluctuation. Therefore, the development of effective model reduction techniques for uncertain biological systems is of paramount importance in the field of systems biology. In this paper, we apply a Gramian-based approach for model reduction for gene regulatory networks based only on finding generalized Gramians and standard matrix transformations. The method is based on finding a generalized controllability and observability Gramian of the uncertain system and then based on a state transformation matrix a reduced-order representation. Under the assumption that the structured uncertainties are norm-bounded, we can prove that the reduced-order balanced system is also stable.

Key words: Gene regulatory network, uncertain system, model reduction

1 Introduction

Many gene regulatory networks are described by complex models which are difficult to analyze and also difficult to control. Analysis and synthetic design of such networks is very sensitive to parameter perturbations [1]. Errors in

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parameters such as external perturbations and modeling errors are caused by data inaccuracies or computation errors. These perturbations can lead to location errors of equilibria, to instabilities, and even to spurious states [7]. Therefore, a rigorous understanding of the qualitative robustness properties of gene regulatory networks with respect to parameter variations becomes imperative [2]. On the other hand, order reduction may overcome some of the difficulties but at the price of a significant loss of accuracy. Therefore, a stringent need arises to analyze it such that it is made useful for many applications. The idea is to employ a model simplification that leads to a model of lower complexity, easier to handle, and to a simplified synthesis procedure for design problems. In addition, this simplification is reducing the computational complexity.

Balanced truncation is known as a popular method for model reduction since it is relatively simple and the quality of the reduced model is guaranteed. The interpretation of most balancing techniques is based on the concept of past and future energy. The most important contribution was the balancing for stable minimal linear systems [3]. It is based on a state–space point of view of employing the well–known observability and controllability Gramians and related to the past input energy (controllability) and future input energy (observability). The idea behind transforming a system into balanced form is to easily detect and remove a state component of the initial system to obtain a reduced–order model. The importance of a component is based on Hankel singular values which determine if the output energy of a certain component is small and thus difficult to observe and if the input energy to reach this state is large. While for linear systems finding a balancing coordinate transformation via solutions of the controllability and observability Lyapunov equations is quite easy, for nonlinear systems this equations are almost impossible to solve and thus balancing becomes in general not a simple task [5]. In a previous work [6], we applied a nonlinear model reduction technique for gene regulatory networks. However the very important concept of uncertainty paired with model simplification was not taken into account so far. We propose to apply and enhance the theoretical concepts from [8] to gene regulatory networks to obtain a stable model reduction under consideration of norm-bounded uncertainties. To the author's best knowledge, this method has not been applied so far to the analysis of gene regulatory networks.

The general kinetic equation describing the temporal evolution of the concentration for the j-th state and its output of a N–gene regulatory network is:

$$\begin{aligned}\dot{x}_i &= -\sum_{j=1}^{N} a_{ij}x_j + \sum_{j=1}^{N} b_{ij}x_i x_j \\ &\quad + (\sum_{j=1}^{N} c_{ij}x_j + \sum_{j=1}^{N} d_{ij}x_j x_i)u_i \\ y_i &= x_i\end{aligned} \tag{1}$$

where x_i is the current concentration state, y_i the current output of the gene regulatory network, and u_i is the external input, and m_{ij} a_{ij}, b_{ij}, c_{ij} and d_{ij} are the kinetic parameters associated with these reaction equations.

2 Global Asymtotic Stability Criteria for Quadratic Differential Equations

The general kinetic equation describing the temporal evolution of the gene regulatory networks (1) has a quadratic nonlinear term given as:

$$\dot{x}_i = -\sum_{j=1}^{N} a_{ij}x_j + \sum_{i=1}^{N} b_{ij}x_i x_j \tag{2}$$

In state space representation, we obtain the following general form:

$$\dot{x} = Ax + [B_1^T x, \cdots, B_N^T x]^T x \tag{3}$$

where $A = a_{ij}$ and B_i^T is given as

$$B_i^T = \begin{pmatrix} 0 & \cdots & 0 \\ b_{1i} & \cdots & b_{Ni} \\ 0 & \cdots & 0 \end{pmatrix} \tag{4}$$

A Lyapunov function for the above system is given as [4]

$$V = x^T P x, \quad P > 0 \quad P = P^T \tag{5}$$

with

$$A^T P + PA = -Q, \quad Q > 0, \quad Q = Q^T \tag{6}$$

guaranteeing thus the asymptotic stability of system (3) in the whole. Additionally, we need to require that $\dot{V} < 0$ for all $x \neq 0$. This leads to

$$\dot{V} = x^T(PA + A^T P)x + 2x^T P[B_1^T x, \cdots, B_N^T x]^T x \tag{7}$$

$\dot{V}$ is negative definite if and only if all the third-order terms it contains are identically zero, i.e.

$$x^T P[B_1^T x, \cdots, B_N^T x]^T x = 0 \tag{8}$$

By choosing $Q = I$, we obtain assuming A is symmetric:

$$P = -\frac{1}{2}A^{-1} \tag{9}$$

The resulting stability condition for our system is:

$$\sum_{i=1}^{N} \tilde{a}_{ij} x_i^2 \sum_{j=1}^{N} b_{ij} x_j = 0 \tag{10}$$

where $\tilde{a}_{ij}$ represent the elements of the inverse matrix.

3 Problem Statement

Notations:

$L_2^m = L_2^m[0, \infty)$ is the space of square integrable functions in R^m.

$||\Delta|| = sup_{z \in L_2^m[0,\infty), z \neq 0}(||\Delta z||/||z||)$ is the gain of an operator Δ in $\mathcal{L}(L_2^m)$

Δ^T is the adjoint operator of Δ if Δ is linear.

If $\Delta = \Delta^T$, then $\Delta < 0$ means that $x^T \Delta x < 0$, $\forall x \neq 0$ in R^m.

$\mathcal{L}(L_2^m)$ is the space of all linear bounded operators mapping from L_2^m to L_2^m.

$|\cdot|$ is the Euclidean norm in R^n.

M^T is the transpose of a complex matrix M.

$|z|_\Lambda^2 = z^T \Lambda z$ for $z \in R^m$ and a nonnegative matrix $\Lambda \in R^{m \times m}$.

State space representation of a transfer matric is given as $G(s) = \left[\begin{array}{c|c} A & B \\ \hline C & D \end{array}\right] = C(sI - A)^{-1}B + D$

In the following, we will demonstrate the application of the model reduction based on balanced truncation.

For the sake of simplicity, we will consider a restricted state domain where the nonlinearity can be approximated by a linear function, $f(x_i) = x_i$.

$$\dot{x}_j = -l_j x_j + \sum_{i=1}^{N} D_{ij} x_i + \sum_{i=1}^{p} m_{ij} u_i \tag{11}$$

Thus, the system has a linear representation of the form

$$\begin{aligned} \dot{x}(t) &= Ax(t) + Bu(t)) \\ y(t) &= Cx(t) \end{aligned} \tag{12}$$

with $C = I$ and

$$A = D - L \quad \text{and} \quad B = M \tag{13}$$

It is assumed that the linear system is stable: $A = D - L$ is Hurwitz. We will assume that matrix D is a symmetric matrix.

Let us consider the uncertainty structure

$$\Delta^c = \left\{ \text{diag}(\Delta_1, \cdots, \Delta_k) : \Delta_i \in \mathcal{L}(L_2^{h_i}), \Delta_i \quad \text{causal}, ||\Delta_i|| \leq 1 \right\} \tag{14}$$

resulting into the following uncertain gene regulatory network:

$$\begin{aligned} \dot{x}(t) &= Ax(t) + E\zeta + Bu(t)) \\ z(t) &= Kx(t) \\ y(t) &= Cx(t) \\ \zeta(t) &= \Delta z(t), \quad \Delta \in \Delta^c \end{aligned} \tag{15}$$

with $C = I$ and B, E, K are diagonal matrices. $x(t) \in R^n$ is the state, $u(t) \in R^m$ is the control input, $z(t) \in R^h$ is the uncertainty output, $y(t) \in R^l$ is

the measured output and $\zeta(t) \in R^h$ is the uncertainty input. We also have $h = h_1 + \cdots, h_k$.

We thus obtain a nominal system as

$$M = \begin{bmatrix} M_{11} & M_{12} \\ M_{21} & M_{22} \end{bmatrix} = \left(\begin{array}{c|cc} A & E & B \\ \hline K & 0_{h\times h} & 0_{h\times m} \\ C & 0_{l\times h} & 0_{l\times m} \end{array}\right) \tag{16}$$

The uncertain system (15) is defined by a linear fractional transformation representation as $\mathcal{F}_u(M, \Delta) := M_{22} + M_{21}\Delta(I - M_{11}\Delta)^{-1}M_{12}$ if $I - M_{11}\Delta$ is non-singular.

We will define the following operators:

$$\begin{bmatrix} A_\Delta & B_\Delta \\ C_\Delta & 0 \end{bmatrix} = \begin{bmatrix} A + E\Delta K & B \\ C & 0 \end{bmatrix} \tag{17}$$

In the following, we will give the definition of robust stability.

Definition 1 (Robust Stability): The uncertain system (15) is robustly stable if $(I - M_{11}\Delta)^{-1}$ exists in $\mathcal{L}(L_2^h)$ and is causal for all $\Delta \in \Delta^c$.

The next lemma states a necessary condition for robust stability.

Lemma [8]: The uncertain system (15) is robustly stable if and only if there exists a $\Theta \in P_\Theta$ and $X > 0$ such that

$$A^T X + XA + K^T \Theta K + KE\Theta^{-1}E^T X < 0 \tag{18}$$

where

$$P_\Theta = \{\mathrm{diag}(\theta_1 I_{h_1}, \cdots, \theta_k I_{h_K}) : \theta_i > 0\} \tag{19}$$

is the positive commutant set corresponding to Δ^c.

We further introduce the generalized Gramians for the uncertain system from equation (15).

Definition: The matrices $S > 0$ and $P > 0$ are said to be generalized controllability or observability Gramians for the uncertain system (15) if the following inequalities hold:

$$\begin{aligned} &\mathcal{A}_\Delta S + S\mathcal{A}_\Delta^T + \mathcal{B}_\Delta \mathcal{B}_\Delta^T < 0 \quad \forall \Delta \in \Delta^c \\ &\mathcal{A}_\Delta^T P + P\mathcal{A}_\Delta + \mathcal{C}_\Delta^T \mathcal{C}_\Delta < 0 \quad \forall \Delta \in \Delta^c. \end{aligned} \tag{20}$$

As shown in [8], we can define the following algebraic Riccati inequalities for the uncertain system (15)

$$AS + SA^T + SK^T \Lambda_C K S + E\Lambda_C^{-1} E^T + BB^T < 0 \tag{21}$$

and

$$A^T P + PA + PE\Lambda_0^{-1} E^T P + K^T \Lambda_0 K + C^T C < 0 \tag{22}$$

with $S, P > 0$, $\Lambda_C^{-1}, \Lambda_0 > 0$ and $\Lambda_C, \Lambda_0 \in P_\Theta$.

Theorem: The following statements are equivalent assuming $K = E$:

(i) The uncertain system (15) is robustly stable.

(ii) The Riccati inequalities (21) and (22) admit a solution $S, P > 0$ for some $\Lambda_C, \Lambda_0 \in P_\Theta$.

Proof: We will prove the equivalence between (ii) and (i). We start from inequality (21) and we can easily show that inequality (21) holds with $X = S$, $\Lambda_C = \Theta^{-1}$ and $K = E$. The other inequality can be proven similarly as well as the equivalence between (i) and (ii).

Definition: An uncertain system of the form (15) is said to be balanced if it has generalized observability and controllability Gramians which are identical diagonal matrices.

The diagonal entries are called generalized Hankel singular values for the uncertain system.

We propose following the theoretical background in [8] a model reduction algorithm:

1. Solve the inequality system in (20) to obtain the generalized Gramians $S, P > 0$.

2. Balance S, P by choosing a state transformation matrix T such that

$$TST^T = (T^{-1})^T P T^{-1} = \text{diag}(\Sigma_1, \Sigma_2) = \text{diag}(\gamma_1, \cdots, \gamma_n) \tag{23}$$

where $\gamma_1 \geq \cdots \gamma_d > \gamma_{d+1} \geq \cdots \geq \gamma_n > 0$, $\Sigma_1 = diag(\gamma_1, \cdots, \gamma_d)$ and $\Sigma_2 = diag(\gamma_{d+1}, \cdots, \gamma_n)$.

3. Obtain the transformed nominal system as

$$M = \left(\begin{array}{c|cc} \bar{A} & \bar{E} & \bar{B} \\ \hline \bar{K} & 0_{h\times h} & 0_{h\times m} \\ \bar{C} & 0_{l\times h} & 0_{l\times m} \end{array}\right) \tag{24}$$

with $\bar{A} = TAT^{-1}$, $\bar{E} = TE$, $\bar{B} = TB$, $\bar{C} = CT^{-1}$ and $\bar{K} = KT^{-1}$.

The reduced order uncertain system of order d is defined as

$$M_r = \left(\begin{array}{c|cc} \bar{A}_r & \bar{E}_r & \bar{B}_r \\ \hline \bar{K}_r & 0_{h\times h} & 0_{h\times m} \\ \bar{C}_r & 0_{l\times h} & 0_{l\times m} \end{array}\right) \tag{25}$$

4. Represent the reduced dimension uncertain system as $\mathcal{G}_{r\Delta} = \mathcal{F}_u(M_r, \Delta), \Delta \in \Delta^c$.

In the following, we will give a useful theorem without proof adapted from [8]:

Theorem: Consider a robustly stable uncertain system as given in (15) and suppose we can derive a reduced dimension uncertain system $\mathcal{G}_{r\Delta}$ based on generalized Gramians and state transformation. Then the system $\mathcal{G}_{r\Delta}$ is also balanced and robustly stable. We also have

$$\sup_{\delta\in[-1,1]} ||\mathcal{G}_\Delta(s) - \mathcal{G}_{r\Delta}(s)||_\infty \leq 2(\gamma_1^t + \cdots + \gamma_q^t) \tag{26}$$

where γ_i^t denote the distinct generalized Hankel values of $\gamma_{d+1}, \cdots, \gamma_n$.

Example: Consider the following uncertain system of the form (15) with $\Delta = \delta \in [-1, 1]$ and with $B = C = K = E = \text{diag}(1 \quad 1)$ and $A = \begin{bmatrix} -9.7 & 0 & 0 \\ 1 & -1.7 & 0 \\ 0 & 1 & -2.7 \end{bmatrix}$. We choose $|\delta| = 0.3$. Based on the described balanced truncation procedure, we obtain the balanced Gramian $\Sigma = \text{diag}(0.33 \quad 0.17 \quad 0.05)$. A natural choice is to truncate the last state and keep the first two. The upper bound of the error is given according to (26) as $\sup_{\delta\in[-1,1]} ||\mathcal{G}_\Delta(s) - \mathcal{G}_{r\Delta}(s)||_\infty \leq 0.1$.

4 Conclusions

We present a model reduction of an uncertain gene regulatory network based on balanced truncation. The method is based on solving generalized Gramian inequalities and matrix transformations. We assume that structured uncertainty is norm bounded. When applied to linear systems, the reduced model corresponds to the usual balanced truncation of the system. A simple example is illustrating this novel approach of model reduction for gene regulatory networks.

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