# Gene Regulatory Networks Simplified by Nonlinear Balanced Truncation

Anke Meyer-Bäse[a] and Fabian Theis[b]
[a] Department of Electrical and Computer Engineering,
Florida State University, Tallahassee, Florida 32310-6046 USA,
[b]Institute for Bioinformatics and Systems Biology,
Helmholtz Center Munich, Neuherberg 85764 Germany

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**Abstract**

The complexity of gene regulatory networks described by coupled nonlinear differential equations is often an obstacle for analysis purposes. Therefore, the development of effective model reduction techniques is of paramount importance in the field of systems biology. In this paper, we apply the theory of nonlinear balanced truncation for model reduction for gene regulatory networks based only on standard matrix computations. The method is based on finding a controllability and observability function of the nonlinear system and thus obtain a balanced representation that produces singular value functions which are functions of the state. As a result, we obtain a ranked contribution of the states from an input–output perspective.

## 1 Introduction

Many gene regulatory networks are described by complex models which are difficult to analyze and also difficult to control. 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 based on this analysis resulting in a model of lower complexity, easier to handle, and in 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 [2]. 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 [3].

In this paper, we propose to apply an nonlinear model reduction for gene regulatory networks. 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:

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

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 [1]

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

with

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

guaranteeing thus the asymtotic 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 Balancing for Nonlinear Systems

The ideas from the linear case can to some extent be extended to the nonlinear case. In this context, the controllability function is defined as the past input energy while the observability function as the future output energy. These functions can be transformed into a form that defines a measure of importance of a state component. This form is defined as a balanced representation and singular value functions are defined in dependence of the state component [3]. For the linear case, these functions are constant and equal to the squared Hankel singular values.

We will consider a smooth, $C^\infty$ nonlinear system such as

$$\begin{aligned} \dot{x} &= f(x) + g(x)u \\ y &= h(x) \end{aligned} \tag{11}$$

where $u = (u_1, \cdots, u_m) \in R^m, y = (y_1, \cdots, y_p) \in R^p$, and $x = (x_1, \cdots, x_n)$ are the local coordinates of the smooth state space manifold $M$. $f, g = (g_1, \cdots, g_m)$ are smooth vector fields on $M$ with $h = (h_1, h_2, \cdots, h_p)$ being the smooth output map of the system.

**Definition 1:** The controllability and observability function of the nonlinear system (11) are defined as

$$L_c(x_0) = \min_{\substack{u \in L_2(\infty,0) \\ x(-\infty)=0, x(0)=x_0}} \frac{1}{2} \int_{-\infty}^{0} ||u(t)||^2 dt \tag{12}$$

and

$$L_o(x_0) = \frac{1}{2}\int_0^\infty ||y(t)||^2 dt, \quad x(0) = x_0, \quad u(t) = 0, \quad 0 \le t < \infty \tag{13}$$

.
In the following, we will give a theorem showing that the functions $L_c$ and $L_o$ are the solutions of the Hamilton–Jacobi equations.

**Theorem 1** [3]: Assume $h(0) = 0$ and $f$ is asymptotically stable on a neighborhood $W$ of 0 with $f(0) = 0$, and that $L_o(x)$ exists and is smooth on $W$. Then for all $x \in W$, $L_o(x)$ is the unique smooth solution of

$$\frac{\partial L_o}{\partial x}(x)f(x) + \frac{1}{2}h^T(x)h(x) = 0, \quad L_o(0) = 0, \tag{14}$$

Furthermore, assume that $L_c$ exists and is smooth on $W$. Then for all $x \in W, L_c(x)$ is the unique smooth solution of

$$\frac{\partial L_c}{\partial x}(x)f(x) + \frac{1}{2}\frac{\partial L_c}{\partial x}(x)g(x)g(x)^T\frac{\partial^T L_c}{\partial x}(x) = 0, \quad L_c(0) = 0, \tag{15}$$

such that $-(f(x) + g(x)g(x)^T\frac{\partial^T L_c}{\partial x}(x))$ is asymptotically stable on $W$.

It can be easily seen that $L_o$ and $L_c$ are nonnegative.

The above assumptions and implications can be summarized as following.

**Assumptions A1** The following assumptions must be fullfilled:

1. $f(x)$ is asymptotically stable on some neighborhood $W$ on 0.
2. The system is zero–state observable on $W$.
3. $L_o$ and $L_c$ exist and are smooth on $W$.
4. $\frac{\partial^2 L_c}{\partial x^2}(0) > 0$ and $\frac{\partial^2 L_o}{\partial x^2}(0) > 0$.

From the previous section as a condition of global asymptotic stability for the quadratic differential subsystem equation (10).

For our system, we obtain the following controllability and observability functions:

$$L_o(x) = \sum_{i=1}^{N}\frac{1}{4}x_i^2 \cdot \frac{1}{[a_{ii} - \sum_{i\neq j} b_{ij}x_j]} \tag{16}$$

and

$$\begin{aligned} L_c(x) =& 2\sum_{i=1}^{N}\frac{a_{ii} - \sum_{i\neq j} b_{ij}x_j}{(c_{ii} + \sum_{i\neq j} d_{ij}x_j)^2}\frac{\sum_{i=1}^{N} c_{ij}x_j}{[(c_{ii} + \sum_{i\neq j} d_{ij}x_j)x_i + \sum_{i\neq j} c_{ij}x_j]} + \\ & \ln\left((c_{ii} + \sum_{i\neq j} d_{ij}x_j)x_i + \sum_{i\neq j} c_{ij}x_j\right) \end{aligned}$$

We will make use of the following approximation

$$\frac{\sum_{i\neq j} c_{ij}x_j}{[(c_{ii}+\sum_{i\neq j} d_{ij}x_j)x_i+\sum_{i\neq j} c_{ij}x_j]}+\ln\left((c_{ii}+\sum_{i\neq j} d_{ij}x_j)x_i+\sum_{i\neq j} c_{ij}x_j\right)$$
$$\approx\left((c_{ii}+\sum_{i\neq j} d_{ij}x_j)x_i+\sum_{i\neq j} c_{ij}x_j\right)^{\frac{2}{3}}$$

**Lemma 1** [3]: There exists a coordinate transformation $x=\phi(\tilde{x}), \phi(0)=0$ defined on a neighborhood of 0, such that in the new coordinates $\tilde{x}=\phi^{-1}(x)$ the function $L_c(x)$ is of the form

$$L_c(\phi(\tilde{x}))=\frac{1}{2}\tilde{x}^T\tilde{x} \tag{17}$$

Furthermore in the new coordinates, $\tilde{x}=\phi^{-1}(x)$ we can rewrite $L_o(x)$ in the form

$$L_o(\phi(\tilde{x}))=\frac{1}{2}\tilde{x}^T M(\tilde{x})\tilde{x} \quad \text{where} \quad M(0)=\frac{\partial^2 L_o}{\partial x^2}(0), \tag{18}$$

where $M(\tilde{x})$ is an $N\times N$ symmetric matrix with elements being smooth functions of $\tilde{x}$.

The goal is to show that the symmetric matrix $M(\tilde{x})$ is diagonalizable: $M(\tilde{x})=T(\tilde{x})\Lambda(\tilde{x})T^T(\tilde{x})$ with $\lambda_i(\tilde{x}), i=1,\cdots,n$ are the eigenvalues of $M(\tilde{x})$ and $T(\tilde{x})$ is the corresponding orthogonal matrix of normalized eigenvectors, i. e. $T^T(\tilde{x})T(\tilde{x})=I, \tilde{x}\in V$.

**Lemma 2** [3]: Assume that there exists a neighborhood $V$ of 0 where the number of distinct eigenvalues of $M(\tilde{x})$ is constant for $\tilde{x}\in V$. Then the eigenvalues $\lambda_i(\tilde{x}), i=1,\cdots,N$ on $V$ are smooth functions of $\tilde{x}$, as well as the associated normalized eigenvectors.

For our system (1), we will make further approximations.

**Assumptions A2** The following assumptions must be fullfilled:

1. $\sum_{i\neq j} d_{ij}x_j\approx 0$.
2. $\sum_{i\neq j} c_{ij}x_j\approx 0$.
3. $\sum_{i\neq j} a_{ij}x_j\approx 0$.

By choosing the following coordinate transformation

$$x_i=\frac{1}{c_{ii}}\left(\frac{c_{ii}^2}{a_{ii}}\right)^{\frac{3}{2}}(\tilde{x}_i)^3 \tag{19}$$

we obtain for the transformed controllability function $L_c(\tilde{x})$:

$$L_c(\tilde{x})=\frac{1}{2}\tilde{x}^T\tilde{x} \tag{20}$$

As a transformed observability function $L_o(\tilde{x})$ we have:

$$L_o(\tilde{x})=\frac{1}{2}\tilde{x}M(\tilde{x})\tilde{x}^T \tag{21}$$

where $M(\tilde{x})$ is a diagonal matrix given as

$$M(\tilde{x}) = \mathrm{diag}\{\frac{1}{2^7}\left(\frac{c_{ii}\tilde{x}_i}{a_{ii}}\right)^4\} \tag{22}$$

In general, for diagonalizing $M(x)$, the following Theorem [3] is needed:

**Theorem 2** [3]: Consider the system given by (11) and assume Lemma 2 holds. On a neighborhood $U$ of 0 there exists a coordinate transformation $x = \psi(z), \psi(0) = 0$, such that in the new coordinates $z \in W := \psi^{-1}(U)$ the function $L_c$ is of the form

$$\tilde{L}_c(z) = L_c(\psi(z)) = \frac{1}{2}z^T z \tag{23}$$

and the function $L_o$ is of the form

$$\tilde{L}_o(z) = L_o(\psi(z)) = \frac{1}{2}z^T \begin{pmatrix} \tau_1(z) & \cdots & 0 \\ \cdots & \cdots & 0\cdots \\ 0 & \cdots & \tau_N(z) \end{pmatrix} z \tag{24}$$

where $\tau_1(z) \geq \cdots \geq \tau_N(z)$ are smooth functions of $z$, called the singular value functions of the system.

It is important to remark that for a linear system the singular value functions $\tau_i, i = 1, \cdots, N$ are constant and equal to the squared Hankel singular values.

In our case, since $M(\tilde{x})$ is already a diagonal matrix, it means that we choose $\tilde{x} = z$.

To obtain a balanced form of the controllability and observability functions, we will need an additional coordinate transformation: $\tilde{z}_i = \eta_i(z_i) = \tau_1(0, \cdots, 0, z_i, 0, \cdots, 0)^{\frac{1}{4}} z_i, i = 1, \cdots, N$ and thus we have $\tilde{z} = \eta(z) = (\eta_1(z_1), \cdots, \eta_n(z_N))$ on $\tilde{z} \in \tilde{W} = \eta(W)$. By defining $\breve{L}_c(\tilde{z}) = \tilde{L}_c(\eta^{-1}(\tilde{z}))$ and $\breve{L}_o(\tilde{z}) = \tilde{L}_o(\eta^{-1}(\tilde{z}))$, we obtain instead of the equations (23) and (24)

$$\breve{L}_c(\tilde{z}) = \frac{1}{2}\tilde{z}^T \begin{pmatrix} \sigma_1(\tilde{z}_1)^{-1} & \cdots & 0 \\ \cdots & \cdots & 0\cdots \\ 0 & \cdots & \sigma_N(\tilde{z_N})^{-1} \end{pmatrix} \tilde{z} \tag{25}$$

and

$$\breve{L}_0(\tilde{z}) = \frac{1}{2}\tilde{z}^T \begin{pmatrix} \sigma_1(\tilde{z}_1)^{-1}\tau_1(\eta^{-1}(\tilde{z})) & \cdots & 0 \\ \cdots & \cdots & 0\cdots \\ 0 & \cdots & \sigma_N(\tilde{z_N})^{-1}\tau_N(\eta^{-1}(\tilde{z})) \end{pmatrix} \tilde{z} \tag{26}$$

where $\sigma_i(\tilde{z}_i) = \tau_i(0, \cdots, 0, \eta_i^{-1}(\tilde{z}_i), 0, \cdots, 0)^{\frac{1}{2}}$ for $i = 1, \cdots, N$. It follows that at the coordinate axes, we have

$$\breve{L}_c(0, \cdots, 0, \tilde{z}_i, 0, \cdots, 0) = \frac{1}{2}\tilde{z}_i^2 \sigma_i(\tilde{z}_i)^{-1} \tag{27}$$

$$\breve{L}_0(0, \cdots, 0, \tilde{z}_i, 0, \cdots, 0) = \frac{1}{2}\tilde{z}_i^2 \sigma_i(\tilde{z}_i) \tag{28}$$

for $i = 1, \cdots, N$. The correspondence to linear theory becomes obvious: there the $\sigma_i$ are the Hankel singular values and the interpretation of equations (25) and (26) is that the $\tilde{z}_1, \cdots, \tilde{z}_n$ are increasingly less important in terms of the input and output energy.

By choosing as a new transformation function

$$z_i = \sqrt{2^{\frac{7}{8}} \frac{a_{ii}}{c_{ii}} \tilde{z}_i} \tag{29}$$

we obtain as the new controllability and observability functions

$$\breve{L}_c(\tilde{z}) = \frac{1}{2} \tilde{z}^T \begin{pmatrix} 2^{\frac{7}{4}} \frac{a_{11}}{c_{11}\tilde{z}_1} & \cdots & 0 \\ \cdots & \cdots & 0 \cdots \\ 0 & \cdots & 2^{\frac{7}{4}} \frac{a_{NN}}{c_{NN}\tilde{z}_N} \end{pmatrix} \tilde{z} \tag{30}$$

and also

$$\breve{L}_0(\tilde{z}) = \frac{1}{2} \tilde{z}^T \begin{pmatrix} 2^{\frac{7}{4}} \frac{a_{11}}{c_{11}} & \cdots & 0 \\ \cdots & \cdots & 0 \cdots \\ 0 & \cdots & 2^{\frac{7}{4}} \frac{a_{NN}}{c_{NN}} \end{pmatrix} \tilde{z} \tag{31}$$

We consider now system (11) after we perform the coordinate transformation $x = \chi(\tilde{z}) := \Phi(\eta^{-1}(\tilde{z}))$

$$\dot{\tilde{z}} = \tilde{f}(\tilde{z}) + \tilde{g}(\tilde{z})u \tag{32}$$

$$y = \tilde{h}(\tilde{z}) \tag{33}$$

For our gener regulatory network, we obatin the following transformation:

$$x_i = \frac{2^{\frac{21}{16}}}{c_{ii}} \left( \frac{a_{ii}}{c_{ii}} \right)^{\frac{3}{2}} \tilde{z}_i^{\frac{3}{2}} \tag{34}$$

Thus, similar to linear systems, we can come up with a definition for nonlinear systems:

**Definition 2:** A nonlinear system is in *balanced form* if its controllability and observability functions are of the form of (25) and (26).

# 4 Example: Linear Gene Regulatory Network

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, $f(x_i) = x_i$.

$$\dot{x}_j = -l_j x_j + \sum_{i=1}^{N} D_{ij} x_i + \sum_{i=1}^{p} m_{ij} u_i \tag{35}$$

Thus, the system has a linear representation of the form

$$\begin{aligned} \dot{x}(t) &= Ax(t) + Bu(t)) \\ y(t) &= Cx(t) \end{aligned} \tag{36}$$

with $C = I$ and

$$A = D - L \quad \text{and} \quad B = M \tag{37}$$

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

The following results are well–known [2]:

**Theorem 1**: Consider the system (36). The matrix $X = \int_0^\infty \exp^{A^T t} C^T C \exp^{At} dt$ is the **controllability gramian** and $Y = \int_0^\infty \exp^{A^T t} B^T B \exp^{At} dt$ the **observability gramian**. Furthermore, $X$ and $Y$ are symmetric and positive definite, and solutions of the Lyapunov equations

$$\begin{aligned} A^T X + XA + C^T C &= 0 \\ AY + YA^T + BB^T &= 0 \end{aligned} \tag{38}$$

In addition, we have the following result.

**Theorem 2**: The eigenvalues of $XY$ are similarity invariants, i.e., they do not depend on the choice of the state space coordinates. There exists a state space representation where

$$\Sigma := W = M = \begin{pmatrix} \sigma_1 & \cdots & 0 \\ \cdots & \sigma_i & 0 \\ 0 & \cdots & \sigma_n \end{pmatrix} \tag{39}$$

with $\sigma_1 \geq \sigma_2 \geq \cdots \geq \sigma_n > 0$ the square roots of the eigenvalues of $XY$. Such representations are called *balanced*, and the system is in *balanced form*. In addition, the $\sigma_i, i = 1, \cdots, n$, equal the Hankel singular values, i.e., the singular values of the Hankel operator of the system.

The Hankel operator of a linear system is the operator which maps (the reflection of) past inputs to future outputs, assuming the future input is zero.

We obtain based on both Theorem 1 and 2 for $XY$:

$$XY = \frac{1}{4}(D - L)^{-1}(D - L)^{-T} M M^T \tag{40}$$

By further assuming both matrices $D$ and $M$ have almost vanishing off-diagonal values $m_{ij} \approx 0$ and $d_{ij} \approx 0$, $\Sigma$ is a diagonal matrix where the diagonal elements are equal to $\frac{1}{2}\frac{m_{ii}}{d_{ii} - l_i}$ ordered as decreasing values.

# 5 Conclusions

We present a nonlinear model reduction of gene regulatory networks based on balanced truncation. The method is based on solving Hamilton-Jacobi equations and several matrix transformations. 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.

## References


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