## POLITECNICO DI TORINO

Repository ISTITUZIONALE

## Reduction of Protein Networks Models by Passivity Preserving Projection

Original
Reduction of Protein Networks Models by Passivity Preserving Projection / Mesin, Luca; Canavero, Flavio; Rondoni, Lamberto. - In: COMMUNICATIONS IN THEORETICAL PHYSICS. - ISSN 0253-6102. - STAMPA. - 60:2(2013), pp. 247257. [10.1088/0253-6102/60/2/18]

Availability:
This version is available at: 11583/2511713 since: 2017-05-17T18:39:40Z

Publisher:
Institute of Physics, IOP

Published
DOI:10.1088/0253-6102/60/2/18

Terms of use:

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

Publisher copyright
(Article begins on next page)

# Reduction of Protein Networks Models by Passivity Preserving Projection 

Luca Mesin, ${ }^{1, *}$ Flavio Canavero, ${ }^{2, \dagger}$ and Lamberto Rondoni ${ }^{2}{ }^{\text {, }}$.<br>${ }^{1}$ Department of Electronics and Telecommunications, Politecnico di Torino, Torino, Italy<br>${ }^{2}$ Department of Mathematical Sciences, Politecnico di Torino, and INFN Sezione di Torino, Torino, Italy

(Received January 4, 2013; revised manuscript received March 29, 2013)


#### Abstract

Reduction of complex protein networks models is of great importance. The accuracy of a passivity preserving algorithm (PRIMA) for model order reduction (MOR) is here tested on protein networks, introducing innovative variations of the standard PRIMA method to fit the problem at hand. The reduction method does not require to solve the complete system, resulting in a promising tool for studying very large-scale models for which the full solution cannot be computed. The mathematical structure of the considered kinetic equations is preserved. Keeping constant the reduction factor, the approximation error is lower for larger systems.


PACS numbers: 82.20.Nk, 82.20.Wt
Key words: model order reduction, chemical kinetics

## 1 Introduction

Model Order Reduction (MOR) techniques are primary tools to study complex problems characterized by high dimensional systems. ${ }^{[1]}$ These problems can be simplified approximating them with a lower order model, which is capable of capturing the dynamical behavior preserving essential properties of the original system. Some methods allow us to build the reduced model even without requiring the solution of the complete system to be computed, representing the only possible solution in cases in which large-scale problems are considered.

MOR techniques found important applications to linear time-invariant systems, in particular those describing electronic systems with many interconnections. ${ }^{[2]}$ Moreover, some extensions to time varying ${ }^{[3-4]}$ and nonlinear problems ${ }^{[4-7]}$ have been proposed.

There are some popular classes of MOR algorithms: ${ }^{[8]}$ (i) Modal Analysis (or eigenmode truncation) techniques (which requires high computational costs, as the solution of the full system must first be computed); (ii) Proper Orthogonal Decomposition (computationally intensive, as the previous one); (iii) Moment Matching with Padé approximation via Asymptotic Waveform Evaluation (AWE; numerically ill-conditioned when the order of approximation is high); (iv) Truncated balance ${ }^{[9]}$ (which require to solve two large-scale Lyapunov matrix equations for the system Gramians); (v) MOR algorithms based on projection of the system onto a Krylov space ${ }^{[10-11]}$ of reduced order (allowing multi-point moment matching and numerically stable; this class can be considered as class number 3 , but with a more efficient implementation).

A projection technique is considered here, as it can be applied to large-scale problems. Different methods
have been proposed in the literature to choose the projection vectors: ${ }^{[8]}$ Arnoldi's algorithm ${ }^{[12]}$ is based on a generalized Gram-Schmidt orthonormalization of the Krylov subspace generated by the input vector; Padé Via Lanczos (PVL) method computes two matrices which are biorthonormal and have columns which span two different Krylov subspaces, one related to the input, the other to the output; ${ }^{[13]}$ the Passive Reduced-order Interconnect Macromodeling Algorithm (PRIMA) is an extension of the Arnoldi technique which guarantees passivity of the reduced system. ${ }^{[14]}$

In this paper, we consider a new application of projection based MOR: the order reduction of chemical kinetics equations describing protein networks. Chemical kinetics concerns the temporal dynamics of chemical reactions as they evolve, possibly towards equilibrium. The mathematical model of chemical reactions, under homogeneous conditions (i.e., neglecting spatial diffusion), is a set of ordinary differential equations. ${ }^{[15]}$ Considering only binary reactions, the equations have a quadratic nonlinearity. Similar equations are found in many different fields, such as the study of biochemical reactions, ${ }^{[16]}$ regulatory and signaling pathways in a cell, ${ }^{[17-18]}$ population dynamics in which only binary interactions are considered (e.g., in epidemiological models ${ }^{[19]}$ ). Complex networks of chemical reactions describe a variety of important industrial problems (e.g., fluid catalytic cracking, alkylation, fermentation, combustion, chemical vapor deposition, polymerization, petroleum refining ${ }^{[20-21]}$ ) and their analysis is important in the development, design, optimization and control of these processes.

Different methods have been proposed to simplify large systems of equations describing chemical dynamics. ${ }^{[22]}$

[^0]Lumped models transform the unknown set of chemical concentrations into a smaller set of pseudospecies, but usually the extraction of information about specific chemicals is not easy. Sensitivity analysis examines the influence of different compounds on the chemicals of interest and neglects the equations of those with small impact; it requires that the complete reaction scheme and its full solution are known. Time scale analysis exploits the multiple time scales that usually characterize different reactions of a complex network and assumes that fast variables are in quasi-stationary equilibrium (i.e., they satisfy a simple algebraic equation); using a singular perturbation approach, fast dynamics are studied in a boundary layer and the outer solution within the so called inertial manifold, a low dimensional region in the phase space where the dynamics of the system (described by a reduced order model) develops after the initial transient.

In this study, a PRIMA approach is used to reduce the chemical kinetics equations describing a protein network model. We consider a generalization of the original PRIMA to nonlinear systems. Moreover, some innovative modifications of the standard method are introduced in order to fit better the specific application.

## 2 Methods

### 2.1 Chemical Kinetics of a Protein Network

In general, chemical kinetics equations (e.g., describing protein networks) under homogeneous conditions can be obtained applying the law of mass action. Considering only binary interactions, a system of equations with quadratic nonlinearity is obtained:

$$
\begin{equation*}
\dot{x}(t)=G x(t)+x^{T}(t) W x(t) . \tag{1}
\end{equation*}
$$

The square matrix $G$ in Eq. (1) represents the linear part, while $W$ is a three dimensional tensor describing binary interactions of the state variables, which are concentrations of chemical species forming the elements of the vector $x$.

A nonlinear system of Ref. [22] equations representing a protein network is considered as an example (see the Appendix A).

### 2.2 Reduction by Projection

Consider a linear system written as

$$
\begin{equation*}
\dot{x}(t)=G x(t), \quad x(0)=B \tag{2}
\end{equation*}
$$

where $x$ is a vector representing the state variables and $B$ is the vector of initial conditions. Taking the Laplace transform of Eq. (2) we obtain

$$
\begin{equation*}
s X(s)=G X(s)+B \tag{3}
\end{equation*}
$$

Inverting the matrix $G$, the following system is obtained

$$
\begin{equation*}
X(s)=s A X(s)+R \tag{4}
\end{equation*}
$$

where $A=G^{-1}$ and $R=-G^{-1} B$. The solution of the system is

$$
\begin{equation*}
X(s)=(I-s A)^{-1} R \tag{5}
\end{equation*}
$$

where $I$ is an identity matrix. Expanding Eq. (5) in terms of Taylor series, we have

$$
\begin{equation*}
X(s)=\left(I+s A+s^{2} A^{2}+\cdots\right) R=\sum_{k=0}^{\infty} s^{k} m_{k} \tag{6}
\end{equation*}
$$

where $m_{k}=A^{k} R$ represents the moment of order $k$. A reduced order model is obtained truncating the expansion after the first $q$ terms. The solution is then searched in the following Krylov subspace

$$
\begin{equation*}
\mathcal{K}(A, R, q)=\operatorname{span}\left\{R, A R, A^{2} R, \ldots, A^{q-1} R\right\} \tag{7}
\end{equation*}
$$

The original system is projected using a set of basis vectors obtained by the Arnoldi algorithm, which generates an orthonormal basis (constituting the columns of the projection matrix $V_{q}$ ) of the Krylov subspace (7) by the GramSchmidt procedure. Notice that only matrix products are needed here, avoiding the matrix inversion of Eq. (5), which has a high computational cost.

Using the PRIMA algorithm, the reduced system is obtained changing the matrix $G$ in system (2) by the congruence transformation

$$
\begin{equation*}
G_{q}=V_{q}^{T} G V_{q} \tag{8}
\end{equation*}
$$

which guarantees passivity and considering the following definition of the reduced state variables

$$
\begin{equation*}
x_{q}(t)=V_{q}^{T} x(t), \tag{9}
\end{equation*}
$$

associated with the following projection of the initial condition

$$
\begin{equation*}
B_{q}=V_{q}^{T} B \tag{10}
\end{equation*}
$$

In the case of a nonlinear system of equations including quadratic terms

$$
\begin{equation*}
\dot{x}=G x+x^{T} W x, \quad x(0)=B, \tag{11}
\end{equation*}
$$

the reduction method can be applied, finding the projection matrix $V_{q}$ based only on the linear part of the system. Then, the projection is performed obtaining the reduced problem

$$
\begin{equation*}
\dot{x}_{q}=G_{q} x_{q}+V_{q} x_{q}^{T} V_{q}^{T} W V_{q} x_{q}, \quad x_{q}(0)=B_{q} . \tag{12}
\end{equation*}
$$

Once solved the reduced order problem (12), an estimate of the solution of the full system can be obtained pseudoinverting the relation (9)

$$
\begin{equation*}
x^{\mathrm{est}}(t)=\left(V_{q}^{T}\right)^{\#} x_{q}(t), \tag{13}
\end{equation*}
$$

where $\left(V_{q}^{T}\right)^{\#}$ indicates the pseudo-inverse of the matrix $V_{q}^{T}$.

Note that, if the system (11) preserves positivity (as required in the case of chemical kinetics equations), as well system (12) does.

### 2.3 Application to Protein Networks

In protein networks (and, more generally, in chemical kinetics), the matrix $G$ in Eq. (11), accounting for the
linear part, is usually sparse. In order to enrich the linear contribution, the equations were rewritten in terms of translated state variables

$$
\begin{equation*}
\hat{x}(t)=x(t)-x\left(t_{\text {fin }}\right)=x(t)-x_{f}, \tag{14}
\end{equation*}
$$

where $x\left(t_{\text {fin }}\right)=x_{f}$ is the solution at the final time of interest. For simplicity, in this paper $x\left(t_{\text {fin }}\right)$ was obtained by simulating the complete system. Nevertheless, differently from other approaches, such a simulation is not strictly needed (refer to the Discussion section). Translating the variables, the following system is obtained

$$
\begin{align*}
\dot{x}= & \dot{\hat{x}}=G\left(\hat{x}+x_{f}\right)+\left(\hat{x}+x_{f}\right)^{T} W\left(\hat{x}+x_{f}\right) \rightarrow \dot{\hat{x}} \\
= & G \hat{x}+\hat{x}^{T} W x_{f}+x_{f}^{T} W \hat{x} \\
& +\hat{x}^{T} W \hat{x}+x_{f}^{T} W x_{f}+G x_{f}, \tag{15}
\end{align*}
$$

where the first three terms on the right hand side are linear, the forth is quadratic and the last two are constant vectors. The linear term can be written as follows

$$
\begin{equation*}
\tilde{G}_{i j}=G_{i j}+\sum_{k} W_{i k j} x_{k}^{f}+\sum_{s} W_{i j s} x_{s}^{f} \tag{16}
\end{equation*}
$$

As stated in Subsec. 2.2, the initial condition $B$ is also projected. In order to fit the initial condition, referring to Eq. (7), the Krylov space was modified as

$$
\begin{equation*}
\mathcal{K}(A, R, q)=\operatorname{span}\left\{B, R, A R, A^{2} R, \ldots, A^{q-2} R\right\} \tag{17}
\end{equation*}
$$

where $A=\tilde{G}^{-1}$. The maximum order of moments which can be fitted is reduced by one with respect to the case in which the Krylov subspace (7) is used, but the initial condition is included in the space, so that it can be described by the reduced system.

A further modification of the standard method is proposed. We included in the linear term, determining the projection basis, a contribution obtained linearizing the quadratic term. As the trajectory in the phase space goes from the translated initial condition $\hat{x}_{0}=B-x_{f}$ to the zero vector (translated final condition $\hat{x}_{f}=x\left(t_{\text {fin }}\right)-x_{f}=$ 0 ), the linearization was done about a vector $\alpha \hat{x}_{0}$ (where $\alpha$ is a weight) considered to be a point around which the trajectory develops in the reduced phase space. The optimal weight $\alpha$ was estimated by minimizing the error of the estimated solution $x^{\text {est }}(t)$ in satisfying the complete system.

In summary, the following three methods were used for order reduction, after translating the biochemical concentrations vector:
(i) Standard PRIMA algorithm;
(ii) PRIMA algorithm applied using the subspace defined in Eq. (17), which is the union of a Krylov subspace (of lower order with respect to that used in (i) and the initial condition;
(iii) PRIMA algorithm applied on the subspace (17) generated using a matrix $A=G_{m}^{-1}$, where $G_{m}$ is given by
the sum of the linear part of the system and a weighted linearization of the quadratic operator

$$
\begin{equation*}
G_{m}=\tilde{G}+\alpha \hat{x}_{0}^{T} W \tag{18}
\end{equation*}
$$

### 2.4 Test of the Reduction Methods

Different sets of simulations were made to test the performance of the order reduction methods. The following definition of error was considered to check the accuracy of the solution $x^{\text {est }}=V_{q} x_{q}(t)$ estimated by the reduced system in approximating the solution $x(t)$ of the complete system

$$
\begin{equation*}
E=\sqrt{\frac{\sum_{i=1}^{N}\left\|x_{i}(t)-x_{i}^{\text {est }}(t)\right\|^{2}}{\sum_{i=1}^{N}\left\|x_{i}(t)\right\|^{2}}}, \tag{19}
\end{equation*}
$$

where $\|\cdot\|$ indicates the norm of the $L^{2}$ space.
As a specific example, the system of Ref. [22] kinetic equations given in Appendix A was first considered. It is a model of a mitogen-activated protein kinase pathway. Kinetic constants and initial conditions were chosen randomly (uniform distribution between 0 and 1 ). The system was reduced to order $5,10,15$ or 20 . One hundred tests were performed changing randomly the initial conditions (uniform distribution).

As shown in Appendix B, the system of equations described in Appendix A is dissipative. Moreover, it conserves many quantities, which are linear combinations of the state variables. The expressions of such linear combinations depend on the parameters of the model (i.e., on the kinetic constants). For simplicity, conserved quantities were estimated from the simulated solution of the complete system. Specifically, they were defined by the eigenvectors corresponding to the zero eigenvalue ${ }^{\S}$ of the autocorrelation matrix

$$
\begin{equation*}
R_{x x}=\int x(t) x^{T}(t) \mathrm{d} t \tag{20}
\end{equation*}
$$

The number of conserved quantities found with this approach was $N_{c}=11$. The error of the reduced system in conserving quantities which are constant for the complete system is investigated using the following definition

$$
\begin{equation*}
E_{c}=\sum_{i=1}^{N_{c}} \frac{\left\|S_{i}^{T} x^{\mathrm{est}}(t)\right\|}{\|x(t)\|} \tag{21}
\end{equation*}
$$

where $S_{i}$ is the $i$-th eigenvector associated to the zero eigenvalue.

In order to test the performance of the considered MOR techniques in reducing large systems of kinetic equations, a further test was considered on different systems with different dimensions $N$ between 20 and 100 . The linear term was chosen randomly, in order to include both real and complex conjugate eigenvalues (all with negative real parts for stability reasons). The quadratic term, modelled by the tensor $W$ in Eq. (1), was built choosing randomly $N$ rate constants $k$ and considering that if in

[^1]the reaction for the chemical species $C$ there is a nonlinear positive source term $k A B$, then in the equations for the species $A$ and $B$ there is the same source term, but with negative sign $(-k A B)$.

Each system (of dimension $N$ ) was reduced (to an order $q$ ) by a factor

$$
\begin{equation*}
F=\frac{N-q}{N} \tag{22}
\end{equation*}
$$

between $60 \%$ and $90 \%$, using each of the three reduction methods considered. Each case was repeated for 10 trials, choosing randomly the coefficients of the system and the initial conditions.

The approximation error was then considered for each trial as a function of the dimension of the system $N$, the reduction factor $F$ and the reduction method. A threeway analysis of variance (ANOVA) was performed to test whether these three factors had a statistically significant effect on the value of the approximation error. NewmanKeuls post hoc test was then performed to check the significance of pairwise differences. In the case in which the statistical significance was not obtained, a Wilcoxon signed rank test was performed on the difference between errors obtained by different methods when applied to the same system of equations (so that a paired statistical test was performed). The significance level was set to $p=0.05$. Highly significant differences are indicated if $p<0.001$.

## 3 Results

The errors in approximating a system of kinetic equations are estimated applying the three methods for order reduction listed in Subsec. 2.3.

Figure 1 shows an example of approximation of the solution of the system of Ref. [22] kinetic equations defined in Appendix A. The model was reduced to a system of order 5. The three order reduction methods are considered. Two concentrations are considered in Fig 1(a), where the solution of the complete system is compared with those obtained using the investigated reduction techniques. The root mean square (RMS) error in approximating the solution of the complete system with that obtained with the reduced one is shown in Fig. 1(b) as a function of time. Standard PRIMA algorithm makes a large mistake when approximating the initial condition. Including the initial condition in the approximation subspace allows to remove such an error, so that the initial condition of the reduced system becomes the same as that of the complete one. Increasing the weight of the linearization of the quadratic term, the error close to the initial condition is reduced, at the expense of enlarging the error for increasing time. An optimal weight can be chosen in order to get minimum average approximation error.


Fig. 1 Approximation of a system of Ref. [22] kinetic equations (defined in Appendix A) using a 5 order system. (a) Comparison between the solution of the complete system and those obtained using one of the 3 investigated methods (classical PRIMA technique, modified PRIMA fitting the initial condition, optimal reduction method obtained adding a weighted linearization of the quadratic term about the initial condition). Two examples of concentration dynamics (out of Ref. [22]) are considered. (b) Root mean square (RMS) error normalized with respect to the RMS of the solution of the complete system as a function of time.


Fig. 2 Average error in approximating a system of 22 kinetic equations (defined in Appendix A) using a reduced system of order (a) 5, (b) 10, (c) 15, or (d) 20. Three methods are considered: standard PRIMA algorithm, PRIMA algorithm applied to a modified Krylov space including the initial condition, optimal reduced method obtained adding a weighted linearization of the quadratic term about the initial condition. 100 choices of initial conditions are considered and the errors are shown versus the distance between the initial and final condition (at time $T=10$ ). Lines interpolating the errors are also shown.

Order of reduced system: 10


Order of reduced system: 15


Fig. 3 Approximation error $E$ (in (a) and (c), defined in Eq. (19), and error $E_{c}$ (in (b) and (d)), defined in Eq. (21) (measuring the error in satisfying conservation laws). One hundred simulations were considered, reducing the system of 22 kinetics equations (see Appendix A) to a reduced system of 10 (in (a) and (b)) or 15 equations (in (c) and (c)). Both individual errors and mean/standard deviation are shown.

Figure 2 shows the RMS error in approximating the solution of the system of 22 kinetic equations defined in the Appendix A using reduced systems of different orders and applying the three different reduction methods. One hundred simulations of different systems were obtained choosing randomly the initial conditions. The errors are provided as functions of the distance between the initial and final condition (at time $T=10$ ). Considering the projection subspace in which the initial condition is included, the error decreases. Further improvement could be obtained optimizing the choice of the factor weighting the linearization of the quadratic term considered as additional contribution to the linear part of the system of equations. Considering a reduced system with low order
( $q=5$ or $q=10$ ), the error increases for larger distances between initial and final conditions. This is an effect of the nonlinearity, which has a larger effect when the trajectory makes a longer path, hence it constitutes a difficulty with chaotic dynamics which may explore irregularly far away regions of the phase space. Therefore we do not treat chaotic dynamics in general. However, increasing the order of the approximation model, the error is reduced, with a lower rate for the standard PRIMA approach with respect to the other two methods. Indeed, the error of the solution obtained by the standard PRIMA approach is dominated by the mistake in fitting the initial conditions, whose approximation is marginally improved by increasing the order from 5 to 15 .


Fig. 4 Average error in approximating a system of 50 equations using a reduced system of order 10. The equations were obtained choosing randomly the eigenvalues of the matrix defining the linear term including both real and complex conjugate eigenvalues (shown on the left, together with the eigenvalues of the matrix obtained after projection on the reduced space). The quadratic term was built choosing randomly 50 rate constants and including both generation and loss terms, as required in chemical reactions. Three methods are considered (from top to bottom): standard PRIMA algorithm, PRIMA algorithm applied to a projection subspace including the initial condition, optimal reduced method obtained adding a weighted linearization of the quadratic term about the initial condition.

Figure 3 shows the approximation error $E$ (defined in Eq. (19)) and the error $E_{c}$ (defined in Eq. (21)) in preserving the 11 quantities which are conserved by the complete system. The error $E$ in approximating the solution reflects the error $E_{c}$ in satisfying the conservation laws, as shown by their similar behavior.

Figure 4 shows the application of the three reduction
methods to approximate the solution of a system of 50 equations using a reduced model of order 10 . The equations were obtained as described in Subsec. 2.4, choosing randomly the eigenvalues of the matrix defining the linear part and building the quadratic term including both generation and loss contributions, as required in chemical reactions. The eigenvalues of the complete system and of
the reduced ones are shown on the left. The solution of the complete and reduced systems are shown on the right. The reduced model obtained using PRIMA algorithm cannot fit the initial conditions and fails in reproducing correctly
the largest oscillation modes. The other two methods fit correctly the initial condition and approximate better the most important eigenvalues. As a result, the approximation error is much lower.


Fig. 5 Average error in approximating different systems of equations, using different methods (standard PRIMA, PRIMA fitting initial conditions, optimal reduction including additional weighted linearization of quadratic term) and with different reduction factors. The order of the complete systems are (a) 20, (b) 40, (c) 60, and (d) 100 . Mean and standard deviation of errors over 10 repetitions are shown.

Figure 5 shows the results of the application of the three reduction methods to a set of simulations of systems modelling kinetic networks of different orders (between 20 and 100). The equations were generated randomly as in the case of Fig. 4. Each system was reduced by different reduction factors between $90 \%$ and $60 \%$. Four cases are considered in Fig. 5. Keeping constant the reduction factor $F$, the errors are lower in the case in which the complete model to be reduced is larger. In the case of low order systems, standard PRIMA provides lower errors than the other two methods, if the reduced system has 2 or 4 equations (as in Figs. 5(a) and (5b), with $F=$ $90 \%$ ). Notice that with 2 equations the matrix defining the system is even neglected in the projection subspace including the initial condition vector (17). In all other cases, the average error of the two innovative methods is lower than that associated with the standard PRIMA algorithm. The errors decrease with lower reduction factors and, keeping $F$ constant, when increasing the number of equations in the system.

Figure 6 shows the statistical analysis of the approxi-
mation errors versus the following three factors: reduction method, dimension of the system, reduction factor. Most of the differences are highly significant $(p<0.001)$. In particular, the performances of the reduction methods improve when the system under consideration is larger and when the reduction factor is lower (as indicated also in Fig. 5). Moreover, the method with optimal weighted linearization allows us to obtain the best performances. Notice that the error obtained using the reduction method which fits the initial condition is lower in the average, but not statistically lower than that obtained using standard PRIMA. In order to check if this is only due to the large spread of data (reflecting the large differences in the simulated systems of equations), paired comparisons were considered studying the sign of the difference between the errors obtained by the two methods when applied to the same problems. Wilcoxon signed rank test indicated that the performances were significantly higher (with $p<0.05$ ) when the initial condition was fitted in the following cases: $N$ equal to $40,60,80,100 ; F$ equal to $80 \%$ and $70 \%$. Higher performances were obtained in the average by the
standard PRIMA algorithm when the number of equations is very low (lower or equal to 4 ): in such a case, the lower order of moments matched using the approximation subspace (17) determines a larger error with respect to that made by the standard PRIMA algorithm in matching
the initial condition. Moreover, equivalent performances were obtained by the two methods when the order of the reduced model is sufficiently high, so that the approximation of the initial condition is good also for the standard PRIMA algorithm.


Fig. 6 Statistical analysis of the average error as a function of three factors: (a) Reduction method (standard PRIMA, PRIMA fitting initial conditions, optimal reduction including additional weighted linearization of quadratic term), (b) Dimension $N$ of the system to be reduced and (c) Reduction factor $F$. Asterisks indicate highly significant differences $(p<0.001)$.

## 4 Discussion

Krylov spaces have been originally proposed to find approximate solutions of large linear systems without requiring matrix inversion or to estimate eigenvalues of large matrices without solving directly the characteristic polynomial equation. Thus, they allow a reduction of the computational cost when studying large linear systems, as those obtained, for example, when solving numerically mathematical models written in terms of partial differential equations ${ }^{[23]}$ or when studying a device with a complex network of interconnections. ${ }^{[2,24]}$

Krylov subspaces were used to reduce linear systems as it was noticed that the approximation of eigenvalues, transfer function and solution in time of a problem were accurate even considering only the first few vectors. Thus, an approximate solution could be obtained without solving the complete system.

In protein networks (and, more generally, in chemical kinetics), the equations are not linear, and the linear part is related to a sparse matrix with most vanishing eigenvalues. As there is a strong interest in producing models of
reduced order, ${ }^{[22]}$ we applied the classical MOR algorithm PRIMA to check its feasibility in extracting some essential features of protein networks models. The unknowns were translated to match the solution at the final time of interest, in order to enrich the linear part of the system. For simplicity, this solution was computed numerically, but in real situations in which large-scale problems are considered, this could be unfeasible and is not required by our method. Indeed, in such cases, the final concentrations could be either measured or estimated iteratively using reduced models. Not shown preliminary results indicate that a good estimate of the concentration of the chemicals at the final simulation time can be obtained with about 5 iterations of the reduced method (large systems with 500 equations were considered with a reduction factor of $90 \%$ ). For the first estimate, a linear approximation of the nonlinear term was computed about the initial condition and included in the matrix defining the projection subspace. Then, the solution at the end of the simulation was considered as an estimate of $x_{f}$ in Eq. (14) and the method was iterated to convergence.

Notice that the same stationary condition can be reached starting from different properly chosen initial conditions, depending on the conserved quantities and on the corresponding basins of attraction. ${ }^{[15,25]}$ The same reduced model could be applied for all these problems, using the initial conditions of interest.

We considered a time range in which most of the variables reached their stable state, but not much larger than the time constants of fast variables, so that even a raw approximation in the boundary layer provided an important percentage contribution to the total error. The projection on the Krylov subspace determined a gross approximation in the boundary layer, as the initial condition was not fit (it was approximated by its projection onto the Krylov subspace). The average error in approximating the solution of the complete system decays approximately exponentially in time (see Fig. 1(d)).

In order to be fitted by the approximate solution, the initial condition was included in the Krylov subspace (removing the last vector, in order to keep the same dimension of the subspace). Even if the model thus obtained considered a lower power of the matrix defining the system, the average error was usually lower than using the standard method, as the initial condition was correctly fitted. On the other hand, a larger (but still small) error was obtained close to the slow manifold toward which the dynamics of the system settles after the initial transient. Nevertheless, the most of the contribution to the error is still in the boundary layer (see Fig. 1(d)).

A further improvement in representing the overall dynamics of the system could be obtained by distributing better the error in time. In order to obtain such a result, it is here proposed to use an additional contribution to the linear part of the system, which is considered to define the subspace onto which the system must be projected: the linearization of the quadratic term of the system about an optimal vector, which is a scaled version of the translated initial condition. Indeed, the system could be approximated linearly in a neighbor of the average position of the trajectory in the phase space. Such a point could be approximated by a vector which is between the initial and the final condition (i.e., a scaled version of the translated initial condition, as the final condition of the translated system is zero). Sometimes, the trajectory of the system in the phase space goes far from the initial condition performing a large transient before stabilizing around the final position. For this reason, it is possible that the optimal amplitude scaling (providing minimum approximation error) is larger than 1, as shown in Fig. 1(c).

When applied on a set of different systems of equations, the considered MOR techniques provided good approximations of the solution of the full system (of the order of $10 \%$ ), even considering high reduction of large systems (reduction factor of the order of $70-80 \%$, for systems of at least 60 equations). The application to large systems is
needed, as such methods were specifically introduced for the reduction of large-scale systems, for which the computation of the solution is computationally intensive.

The resulting reduced model is of the same type of the complete one: it has a nonlinearity of polynomial type, with a quadratic term, as the full system. This is a great difference between our approach and the popular methods based on the quasi-steady state assumption, in which the concentrations of chemicals with fast dynamics (assumed to be instantaneously in equilibrium) are given as rational functions solving algebraic equations (involving slow variables) and substituted into the equations of slow variables. This manipulation could generate approximate equations which do not satisfy specific properties of chemical kinetics equations. ${ }^{[15,25]}$ On the other hand, the reduced model generated using our approach has still polynomial nonlinearities of the same type as that of the complete system. A further property which was conserved by our simulations is the positivity of the solutions. We notice also that the quantities conserved by the complete system are also approximately conserved by the solution obtained using the reduced system, with a precision which is in line with the accuracy in representing the solution in time.

PRIMA algorithm was used on dissipative chemical reactions (see Appendix B) satisfying passivity. Many other approaches have been proposed, ${ }^{[8]}$ even within the field of methods based on projection into a Krylov subspace. The extension of this work to the application of other techniques is an interesting future perspective.

## 5 Conclusion

MOR techniques based on the projection into a Krylov subspace are applied to protein network models. The solution of the complete system is not required and the approximation error is reduced as the system is larger so that our projection methods are of interest for large-scale systems for which a numerical solution is very intensive. Two innovative methods are proposed, to fit initial condition and to optimize the performances considering an additional linear operator which is used to select the projection vectors. Good fit of the solution of the full system is obtained approximating the complete system of equations with a reduced model preserving passivity and the same mathematical structure of protein network equations. As our method is based on a proper projection of the phase space, based on the linear part of the flux around a specific point, its effectiveness requires the steady state dynamics not to be chaotic. Chaos may indeed take the evolution far away from the region of the chosen point. However, this is not a problem in reaction networks such as the one discussed in Appendix A. Indeed, reaction networks in which all reactions are reversible are expected to eventually converge to a fixed point, possibly after very long and complex evolutions. ${ }^{[15,25-26]}$

## Appendix A

The specific model of 22 equations used to test the MOR techniques describes a biochemical reaction process (a mitogen-activated protein kinase pathway) with the following reaction equations: $x_{0}+x_{1} \underset{k_{1}}{\stackrel{k_{0}}{\rightleftarrows}} x_{2}, x_{2} \underset{k_{3}}{\stackrel{k_{2}}{\rightleftarrows}} x_{3}+x_{1}$, $x_{3}+x_{4} \underset{k_{5}}{\stackrel{k_{4}}{\rightleftarrows}} x_{5}, x_{5} \underset{k_{7}}{\stackrel{k_{6}}{\rightleftarrows}} x_{0}+x_{4}, x_{6}+x_{3} \underset{k_{9}}{\stackrel{k_{8}}{\rightleftarrows}} x_{7}, x_{7} \underset{k_{11}}{\stackrel{k_{10}}{\rightleftarrows}}$ $x_{8}+x_{3}, x_{8}+x_{9} \underset{k_{13}}{\stackrel{k_{12}}{\rightleftarrows}} x_{10}, x_{10} \underset{k_{15}}{\stackrel{k_{14}}{\rightleftarrows}} x_{6}+x_{9}, x_{8}+x_{3} \underset{k_{17}}{\stackrel{k_{16}}{\rightleftarrows}} x_{11}$,
$x_{11} \underset{k_{19}}{\stackrel{k_{18}}{\rightleftarrows}} x_{12}+x_{13}, x_{12}+x_{9} \underset{k_{21}}{\stackrel{k_{20}}{\rightleftarrows}} x_{13}, x_{13} \underset{k_{23}}{\stackrel{k_{22}}{\rightleftarrows}} x_{8}+x_{9}$, $x_{14}+x_{12} \underset{k_{25}}{\stackrel{k_{24}}{\rightleftarrows}} x_{15}, x_{15} \underset{k_{27}}{\stackrel{k_{26}}{\rightleftarrows}} x_{16}+x_{12}, x_{16}+x_{17} \underset{k_{29}}{\stackrel{k_{28}}{\rightleftarrows}} x_{18}$ $x_{18} \underset{k_{31}}{\stackrel{k_{30}}{\rightleftarrows}} x_{14}+x_{17}, x_{16}+x_{12} \underset{k_{33}}{\stackrel{k_{32}}{\rightleftarrows}} x_{19}, x_{19} \underset{k_{35}}{\stackrel{k_{34}}{\rightleftarrows}} x_{20}+x_{12}$, $x_{20}+x_{17} \underset{k_{37}}{\stackrel{k_{36}}{\rightleftarrows}} x_{21}, x_{21} \underset{k_{39}}{\stackrel{k_{38}}{\rightleftarrows}} x_{16}+x_{17}$, which are portrayed in Fig. 7.


Fig. 7 Graphical representation of the biochemical reaction described in Appendix A. The nodes represent the different chemicals; the dotted line links connect reacting chemicals (e.g. they connect $A$ and $B$ in the reaction $A+B \rightarrow C$ ); the solid line links connect reaction products to the reacting chemicals (e.g. they connect $A$ to $C$ and $B$ to $C$ in the reaction $A+B \rightarrow C)$.

## Appendix B

Consider a set of trajectories starting from different initial conditions chosen within a volume $V_{0}$ in the phase space. A dynamical system is called dissipative if the phase space volumes $V(t)$ on average contract. This property is satisfied if the divergence of the flux is negative. ${ }^{[27]}$

The divergence is a linear operator, so that the divergence of the flux of our system of equations (described in Appendix A) is the sum of the divergences of the linear and the quadratic terms. The linear part is defined by a matrix with non-positive trace (which is equal to the divergence). Indeed, possible non-zero terms in the diagonal of such a matrix correspond, by the law of mass action, to a loss of compounds proportional to their own

## concentrations.

Consider now the quadratic terms: if in the $i$-th reaction there is the source (positive) term $k_{k l} x_{k} x_{l}$ (where $i, k$ and $l$ are different, so that this term does not contribute to the divergence) then there are the loss terms $-k_{k l} x_{k} x_{l}$ in the dynamic equations for $x_{l}$ and $x_{k}$, which give a negative contribution to the divergence.

## Acknowledgments

We are grateful to the anonymous referees for useful remarks and to Irene Donato for producing the graphical representation of the biochemical reaction of Appendix A. Moreoever, we are indebted to Chiara Frola, who performed preliminary tests.

## References

[1] F. Canavero, S. Grivet-Talorcia, I.A. Maio, and I.S. Stievano, Linear and Nonlinear Macromodels for SystemLevel Signal Integrity and EMC Assessment, IEICE Trans. Commun. E88-B (2005) 1121.
[2] R. Achar and M.S. Nakhla, Simulation of High-Speed Interconnects, Proceedings of IEEE 89 (2001).
[3] J. Roychowdhury, Reduced-Order Modeling of TimeVarying Systems, IEEE Trans on Circuits and Systems-II (Analog and Digital Signal Proc3essing) 46 (1999) 1273.
[4] J.R. Phillips, Projection-Based Approaches for Model Order Reduction of Weakly Nonlinear, Time-Varying Systems, IEEE Trans. on Computer-Aided Design of Int. Circuits and Systems 22 (2003) 171.
[5] Y. Chen and J. White, A Quadratic Method for Nonlinear Model Order Reduction, MSM 2000, Technical Proceedings of the 2000 International Conference on Modeling and Simulation of Microsystems, (2000) 477.
[6] Y. Chen, Model Order Reduction for Nonlinear Systems, MIT MS thesis (1999).
[7] S. Chaturantabut and D.C. Sorensen, SIAM Journal on Numerical Analysis 50 (2012) 46.
[8] Zhaojun Bai, Krylov Subspace Techniques for Reducedorder Modeling of Large-Scale Dynamical Systems, Applied Numerical Mathematics, IMACS 43 (2002) 9.
[9] S. Gugercin and A.C. Antoulas, Int. J. Control 77 (2004) 748.
[10] M.H. Gutknecht, A Brief Introduction to Krylov Space Methods for Solving Linear Systems, Frontiers of Computational Science, Proceedings of the International Symposium on Frontiers of Computational Science 2005 eds. Y. Kaneda, H. Kawamura, and M. Sasai, Springer-Verlag, Berlin Heidelberg, Mar. (2007) 53.
[11] I.C.F. Ipsen and C.D. Meyer, Amer. Math. Monthly 105 (1998) 889.
[12] W.E. Arnoldi, Quarrt. Appl. Math. 9 (1951) 17.
[13] P. Feldmann and R.W. Freund, Efficient Linear Circuit Analysis by Padè Approximation via the Lanczos Process, IEEE Trans. on Computer-Aided Design of Int. Circuits and Systems 14 (1995) 639.
[14] A. Odabasioglu, M. Celik, and L.T. Pileggi, PRIMA:Passive Reduced-order Interconnect Macromodeling Algorithm, IEEE Trans. on Computer-Aided Design of Int. Circuits and Systems 17 (1998) 645.
[15] A. Picco and L. Rondoni, Boltzmann Maps for Networks of Chemical Reactions and the Multi-Stability Problem, Networks and Heterogeneous Media 4 (?) 501.
[16] M. Ullah, H. Schmidt, K.H. Cho, and O. Wolkenhauer, Deterministic Modelling and Stochastic Simulation of Biochemical Pathways Using MATLAB, IEE Proc.-Syst. Biol. 153 (2006) 53.
[17] J.P. Keener and J. Sneyd, Mathematical Physilogy, ? , Springer (1998).
[18] J.J. Tyson, K.C. Chen, and B. Novak, Sniffers, Buzzers, Toggles and Blinkers: Dynamics of Regulatory and Signaling Pathways in the Cell, Current Opinion in Cell Biology 15 (2003) 221.
[19] M. Barthélemya, A. Barratb, R. Pastor-Satorrasc, and A. Vespignani, Journal of Theoretical Biology 235 (2005) 275.
[20] S.E. Prickett and M.L. Mavrovouniotis, Comput. Chem. Eng. 21 (1997) 1219.
[21] S.E. Prickett and M.L. Mavrovouniotis, Comput. Chem. Eng. 21 (1997) 1325.
[22] M.S. Okino and M.L. Mavrovouniotis, Chemical Reviews 98 (1998) 391.
[23] P. Astrid, Fast Reduced Order Modeling Technique for Large Scale LTV Systems, Proceeding of the American Control Conference, Boston, Massachusetts 2 (2004) 762.
[24] R.A. Rutenbar, Georges G.E. Gielen, and J. Roychowdhury, Hierarchical Modeling, Optimization, and Synthesis for System-Level Analog and RF Designs, Proceedings of IEEE 95 (2007).
[25] L. Rondoni, Math. Mod. Meth. Appl. Sci. 6 (1996) 245.
[26] L. Rondoni, Patterns in a Reaction-Diffusion System, and Statistical Dynamics, NONLINEARITY 9 (1996) 819.
[27] O.G. Jepps and L. Rondoni, Deterministic Thermostats, Theories of Nonequilibrium Systems and Parallels with the Ergodic Condition, J. Phys. A: Math. Theor. 43 (2010) 1.


[^0]:    *E-mail: luca.mesin@polito.it
    ${ }^{\dagger}$ E-mail: flavio.canavero@polito.it
    $\ddagger$ E-mail: lamberto.rondoni@polito.it

[^1]:    ${ }^{\text {§}}$ To allow for numerical approximation, eigenvalues lower than $10^{-8}$ were considered.

