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Model Reduction in Bio-chemical Reaction Networks with Michaelis-Menten Kinetics

Katalin M. Hangos[1,2], Attila Gábor[3,1] and Gábor Szederkényi[1,4]
[1]Systems and Control Lab, Computer and Automation Research Institute of the Hungarian Academy of Sciences
[2]Department of Electrical Engineering and Information Systems, University of Pannonia, Hungary
[3]Bioprocess Engineering Group, IIM-CSIC, Spain
[4]Faculty of Information Technology, Péter Pázmány Catholic University, Budapest, Hungary
Emails: {hangos, gabora, szeder}@scl.sztaki.hu

***Abstract*— In this paper, a model reduction procedure is proposed for the simplification of biochemical reaction network models. The approach is capable of reducing ODE models where the right hand side of the equations contains polynomial and/or rational function terms. The method is based on a finite number of mixed integer quadratic programming (MIQP) steps where the objective function effectively measures the fit between the time functions of the selected concentrations of the original and the reduced models, and the integer variables keep track of the presence of individual reactions. The procedure also contains the re-estimation of rate coefficients in the reduced model to minimize the defined model error. Two examples taken from the literature illustrate the operation of the method.**

I. Introduction

The dynamic models of bio-chemical kinetic systems possess important distinctive properties within the class of non-linear state space models. They are smooth positive systems, where the right-hand side functions contain polynomial, quasi-polynomial and rational function type non-linearities in the deterministic isotherm case [1].

Model reduction in chemical and biological systems is a well studied field in system theory. Some well known techniques used for model reduction are *balanced truncation* for linear systems [2] and model *lumping* [3] methods. For biological and physical systems, where the state variables have physical meaning and the reduction should preserve this property, *singular perturbation* based reduction can be used. This approach takes advantage of the fact that different states can evolve on different time-scales. *Time scale separation* [4], [5] can divide the system into a fast and a slow part, then quasi steady state assumption can be used for the fast reactions in order to transform the corresponding differential equations into algebraic equations. If one considers the concentrations of the key important species as output variables, then the reaction kinetic model can be written in the form of a non-linear state-space model, for which recent extensions to balanced truncation are available for the reduction [6]. This approach, however, applies a non-linear coordinates transformation and thus both the physical meaning of the variables and the characteristic kinetic structure may be lost.

The simplest models within the class of reaction kinetic systems form the sub-class of reaction kinetic networks that obey the *mass action law* [7], [8]. Here one assumes constant reaction rate coefficients and polynomial dependence of the reaction rate on the species concentrations that corresponds to closed, isotherm and isobaric conditions.

The *model reduction methods applied to bio-chemical reaction systems* exhibit a few important specialities compared to the general case [9]. These reactions have also constant reaction rate coefficients, but one should assume complex nonlinear dependence of the reaction rates on the species concentration. The inherent relationship between model reduction and model parameter estimation has also been realized recently (see e.g. [10] and [11] in the area of bio-chemical reaction networks), where the need to re-estimate the parameters of the reduced model has arisen.

The general formulation of a model reduction problem for reaction kinetic systems leads to a mixed integer non-linear program (MINLP) problem, see e.g. [12], that present computational complexity challenges in realistic problem sizes. Therefore, the specialities of the system and/or the model reduction problem can be used to develop efficient solution heuristics. Therefore, the overall aim of our work was to propose a robust, numerically stable yet feasible method for reducing the number of reactions in a bio-chemical reaction network, that is also able to re-estimate the reaction rate coefficients and produce a sub-set of the original detailed reaction kinetic scheme as a result, but with suitably adjusted coefficients.

Instead of the general MINLP formulation of the problem, we use our approach developed for reaction kinetic systems with mass action kinetics (MAK) [13] that leads to a convex mixed integer quadratic problem (MIQP) formulation for which efficient solvers exist. A special embedding method is then applied for representing bio-chemical reaction systems in this form that enables efficient model reduction.

II. Model reduction

A. The studied model class

The parametric model class for which the model reduction technique is applied can generally be written as

$$\dot{x}(t) = f(x(t), k), \quad t \in [t_0, t_f], \tag{1}$$

$$x(t_0) = x_0, \tag{2}$$

where the right-hand side function $f : \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$, x_0 is the initial value, and t_0 and t_f determine the time

interval of interest. In this paper, we address the reduction of biochemical reaction models of the form (1) – (2). These models consist of three characteristic sets: the set of chemical *species*, the set of *complexes*, and the set of chemical *reactions*. Chemical species are formed into complexes (that are represented as the non-negative linear combinations of species), and complexes are transformed to each other via reactions. For example, the reaction network shown in Fig. 1 contains the species set $\{A, B, C, D, E\}$, the complex set (represented as the vertices of the directed graph of the reaction) $\{A, 2B, A + C, D, B + E\}$, and 20 elementary reactions depicted as directed edges on the reaction graph weighted by positive values k_{ij}, called the *reaction rate coefficients*. The state variables in such models are the species concentrations denoted by $[A], [B], [C], [D], [E]$ in the case of Fig. 1.

For the dynamical description of biochemical reaction networks, we apply the classical structure using the stoichiometric matrix [14]. According to this notation, considering n species and m elementary reactions, the species concentrations $x_i = [X_i]$, for $i = 1, \ldots, n$ can be described as

$$\dot{x} = N \cdot r(x), \tag{3}$$

where $r \in \mathbb{R}^m$ is the vector of *reaction rates* and $N \in \mathbb{R}^{n \times m}$ is the *stoichiometric matrix*, the columns and rows of which correspond to reactions and species, respectively. N_{ij} is a real (most often integer) number denoting how many atoms/molecules of species X_i is produced or consumed in the jth elementary reaction, where a positive value corresponds to overall production and a negative value to overall consumption. To easily track the presence of individual reactions, we give the reaction rates in the form

$$r_i(x) = k_i \cdot q_i(x), \qquad i = 1 \ldots, m, \tag{4}$$

where $k = [k_1 \ \ldots \ k_m]^T$ is the vector of reaction rate coefficients and q_i-s are typically monomial or rational functions of x.

B. Model reduction approach

The ultimate goal of the model reduction is to eliminate as many reactions as possible from the original model (3) while maintaining a sufficiently good fit in a predefined time interval between (a subset of) the state variables of the original and the reduced model. When measuring the fit between the original and the reduced model, we only take into consideration a subset of the state variables (corresponding to the so-called *important* species). These variables are given by the set $\mathcal{I} := \{i_1, i_2, \ldots, i_{n_\mathcal{I}}\}$, where $i_j \in \{1, 2, \ldots, n\}$, $j = 1, 2, \ldots, n_\mathcal{I}$, and $n_\mathcal{I}$ is the number of important variables. Note that the choice of important variables is partially determined by physical considerations (e.g. measurability), but the observability/identifiability constraints should also be respected.

Let us denote the state variables and reaction rate coefficients of the reduced model by $\tilde{x} \in \mathbb{R}^n$ and $\tilde{k} \in \mathbb{R}^m$, respectively. Clearly, reaction no. i is eliminated from the reduced model if $\tilde{k}_i = 0$. Let us choose the same least-square functional as in [12] for quantifying the error between the original and the reduced model, namely

$$\Phi(\tilde{x}, x) := \sum_{l=0}^{N} \sum_{i \in \mathcal{I}} {w_{il}}^2 \left(\tilde{x}_i(t_l) - x_i(t_l)\right)^2, \tag{5}$$

where $t_0 < t_1 < \cdots < t_N$ are selected time instants, and w_{il}, $i \in \mathcal{I}$, $0 \le l \le N$ are appropriate weights, e.g. to take into account the magnitude of $x_i(t_l)$. For further information about time point selection and weighting factors see [13]. Moreover, in the case of the solution of (1) – (2) exists, the following nonlinear function is well-defined

$$\phi(\tilde{k}, k) := \Phi(\tilde{x}(\cdot, \tilde{k}), x(\cdot, k)). \tag{6}$$

Then, the model reduction objective can be written into the following general MINLP form in a straightforward way:

$$\min_{\tilde{k} \in [\underline{k}, \overline{k}]} \quad \mathrm{NNZ}(\tilde{k}) \tag{7}$$

$$\text{s.t.} \quad \phi(\tilde{k}, k) \le \delta, \tag{8}$$

where $\mathrm{NNZ}(\tilde{k})$ denotes the number of non-zero elements in $\tilde{k}$, k is the original fixed parameter vector, $\underline{k}, \overline{k} \in \mathbb{R}^m$ ($0 \le \underline{k} \le \overline{k}$) are the lower and upper bounds on $\tilde{k}$, and $\delta > 0$ is the user-specified tolerance for the model error. *It is important to emphasize, that – in contrast to many model reduction approaches – our primary aim is not the elimination of states form the system*, i.e. generally, $\dim(x) = \dim(\tilde{x})$.

To avoid the general MINLP solution of the problem and the integration of the dynamical equations required by the evaluation of the generally non-convex constraint (8), we will approximate (7) – (8) by a finite sequence of convex mixed integer quadratic programs (MIQPs) that are much more advantageous from a computational point of view. Using the fact that our kinetic models (3) are linear in the parameter vector k or $\tilde{k}$, the final form of the parametrized MIQP problem used for the approximation is the following:

$$\left\{ \begin{array}{ll} \min_{\tilde{k}, y} & \frac{1}{2}(\tilde{k} - k)^T H (\tilde{k} - k) \\ \text{s.t.} & y_i \in \{0, 1\}, \quad i = 1, \ldots, m \\ & \tilde{k}_i \ge 0, \quad i = 1, \ldots, m \\ & \tilde{k}_i - \overline{k}_i \, y_i \le 0, \quad i = 1, \ldots, m \\ & \tilde{k}_i - \underline{k}_i \, y_i \ge 0, \quad i = 1, \ldots, m \\ & \sum_{i=1}^{m} y_i \le \tilde{m}. \end{array} \right\}, \tag{MIQP($\tilde{m}$))}$$

where parameter $\tilde{m}$ gives the maximal number of non-zero reaction rate coefficients, and

$$H = \sum_{l=0}^{N} \sum_{i \in \mathcal{I}} \left(w_{il}^* \tilde{G}_i(t_l)\right)^T \left(w_{il}^* \tilde{G}_i(t_l)\right) \tag{9}$$

with weighting factors w_{il}^*, $i \in \mathcal{I}$, $0 \le l \le N$ depending on the original weights w_{il} and the length of the intervals $[t_{l-1}, t_l]$, and

$$\tilde{G}_i(t) = \frac{\partial f_i(x(t), k)}{\partial x} \frac{\partial x(t)}{\partial k} + \frac{\partial f_i(x(t), k)}{\partial k}. \tag{10}$$

It is easy to see that by solving MIQP($\tilde{m}$) for $\tilde{m} = 1, \ldots, m$, the associated objective function value is monotonically decreasing. Note that, some model properties e.g. stability, may be lost during the reduction, however one can check them in every reduction step $\tilde{m}$. More details about the derivation and properties of MIQP($\tilde{m}$) can be found in [13].

C. Embedding bio-chemical models into polynomial form

Bio-chemical reaction rate functions are usually in the form of a rational function, i.e. $r(x) = \frac{P_1(x)}{P_2(x)}$ where $P_1(x)$ and $P_2(x)$ are polynomials. One can embed $r(x)$ into a polynomial form by a new pseudo-state variable for the non-polynomial factor $\frac{1}{P_2(x)}$ in the rate function r and find an ODE, the solution of which is the new variable.

a) Michaelis-Menten kinetic rate function: A widely accepted rate function in the biochemical area is the so called Michaelis-Menten kinetics, that is in the form of a simple rational function

$$\frac{dx}{dt} = \frac{p_1 x}{p_2 + x} = p_1 r(x) \tag{11}$$

with two parameters p_1 and p_2. The following new variable z is introduced

$$z = \frac{1}{p_2 + x}. \tag{12}$$

Let us differentiate Eq. (12) to obtain

$$\frac{dx}{dt} = p_1 xz \quad \text{and} \quad \frac{dz}{dt} = -p_1 xz^3 \tag{13}$$

with initial conditions:

$$x(0) = x_0 \quad \text{and} \quad z(0) = \frac{1}{p_2 + x_0}. \tag{14}$$

Thus, the embedded polynomial ODE consists of Eqs. (13).

It is important to note that the parameter p_2 appears only in the initial values, therefore the model reduction will only consider to leave out p_1 as a reaction rate coefficient that corresponds to the rate function $r(x) = \frac{x}{p_2+x}$. *The new equation and variable is used only temporarily for the reduction procedure*, so the reduced model will have the original state equations possibly without the term $p_1 r(x)$.

III. Simple examples

The described procedure was implemented in MATLAB. The numerical sensitivities in Eq. (10) were computed by NIXE [15], while we used CPLEX to solve the MIQP optimization problem (MIQP($\tilde{m}$)).

A. An introductory example

The model reduction procedure is shown using an example model from [16]. The reaction network of the 5 species and 5 complexes, can be seen in Fig. 1. Assuming MAK the corresponding ODE model has the form:

$$\frac{dx_1}{dt} = (k_{21} + k_{23})x_2^2 + x_5(k_{51} + k_{53})x_2 + x_4(k_{41} + k_{43}) - x_1(k_{12} + k_{14} + k_{15}) - x_1 x_3(k_{32} + k_{34} + k_{35}) \tag{15}$$

$$\frac{dx_2}{dt} = (-2k_{21} - 2k_{23} - 2k_{24} - k_{25})x_2^2 - x_5 x_2(k_{51} - k_{52} + k_{53} + k_{54}) + x_1(2k_{12} + k_{15}) + x_4(2k_{42} + k_{45}) + x_1 x_3(2k_{32} + k_{35}) \tag{16}$$

$$\frac{dx_3}{dt} = k_{23}x_2^2 + k_{53}x_5 x_2 + k_{13}x_1 + k_{43}x_4 - x_1 x_3(k_{31} + k_{32} + k_{34} + k_{35}) \tag{17}$$

$$\frac{dx_4}{dt} = k_{24}x_2^2 + k_{54}x_5 x_2 + k_{14}x_1 - x_4(k_{41} + k_{42} + k_{43} + k_{45}) + k_{34}x_1 x_3 \tag{18}$$

$$\frac{dx_5}{dt} = k_{25}x_2^2 - x_5(k_{51} + k_{52} + k_{53} + k_{54})x_2 + k_{15}x_1 + k_{45}x_4 + k_{35}x_1 x_3 \tag{19}$$

where the concentrations of species A, B, C, D and E are denoted by x_1, x_2, $\ldots x_5$, respectively. For simplicity assume

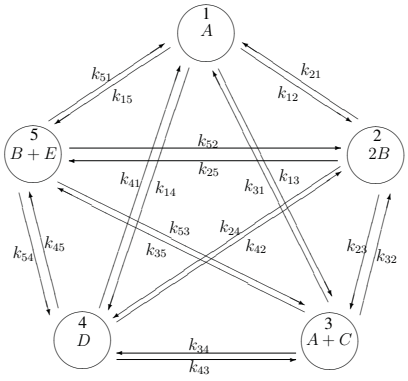

Fig. 1. Simple system [16]

that each initial concentration equals 1, i.e. $x_i(0) = 1$. The solution of the system can be seen in Fig. 2 denoted by continuous lines. Applying the reduction method the

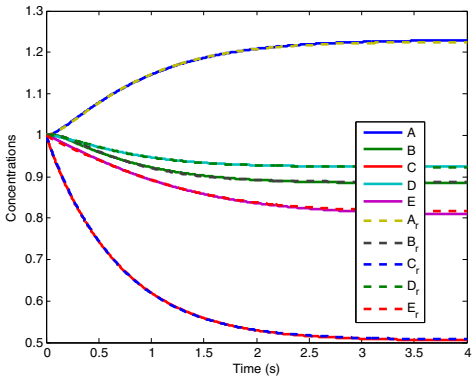

Fig. 2. Trajectories in the original and in the reduced systems

algorithm reduced the number of reactions to 7, that is the same as in [16], but with different parameter values. See the 3rd column of Table I for the parameters. Fig. 2 also contains the very good fitting reduced model with dashed lines.

B. Introductory example extended with Michaelis-Menten terms

For simplicity we consider the reaction network in Fig. 1, but assume that the reaction between $B + E$ (Complex 5) obeys the Michaelis-Menten kinetics (MMK) instead of MAK. This can be described using the term

$$k_{5i} x_2 \frac{x_5}{p + x_5} \quad \text{instead of} \quad k_{5i} x_2 x_5, \quad \text{for} \quad i \in \{1 \ldots 5\}$$

TABLE I

RATE COEFFICIENTS OF THE ORIGINAL SYSTEM AND THE RELATIVE RATE COEFFICIENTS IN THE REDUCED SYSTEMS.

Parameters	Original	MAK 7	MMK 10
k_1	0.1	0	0
k_2	1	1.1402	1.2323
k_3	0.1	0	0
k_4	1	0	1.2771
k_5	1	0	0.5773
k_6	0.8	2.2187	1.9894
k_7	0.2	0	0
k_8	1	1.1431	1.3625
k_9	1	1.1916	1.3169
k_{10}	0.6	0	0
k_{11}	1	0.7453	1.2105
k_{12}	0.9	1.7446	1.4564
k_{13}	0.1	0	0
k_{14}	0.8	2.4146	0.9158
k_{15}	0.9	0	1.1228
k_{16}	0	0	0
k_{17}	1	0	0
k_{18}	0.9	0	0
k_{19}	1	0	0
k_{20}	0.9	0	0

The reduced model parameters are in relative unit $(1/k)$, where k is the original parameter value.

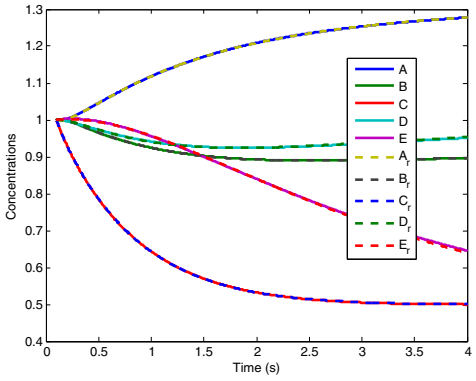

Fig. 3. Trajectories in the original and in the reduced systems assuming Michaelis-Menten Kinetics

First each $k_{5i}x_2x_5$ MAK terms are replaced in Equations (15)-(19) by MMK terms, which results in ODEs having rational polynomial terms in the right hand side.

$$\frac{dx_1}{dt} = (k_{21}+k_{23})x_2^2 + (k_{51}+k_{53})x_2\frac{x_5}{p+x_5} + x_4(k_{41}+k_{43}) - x_1(k_{12}+k_{14}+k_{15}) - x_1x_3(k_{32}+k_{34}+k_{35})$$

$$\frac{dx_2}{dt} = (-2k_{21}-2k_{23}-2k_{24}-k_{25})x_2^2 + x_1x_3(2k_{32}+k_{35}) - (k_{51}- k_{52}+k_{53}+k_{54})x_2\frac{x_5}{p+x_5} + x_1(2k_{12}+k_{15}) + x_4(2k_{42}+k_{45})$$

$$\frac{dx_3}{dt} = k_{23}x_2^2 + k_{53}x_2\frac{x_5}{p+x_5} + k_{13}x_1 + k_{43}x_4 - x_1x_3(k_{31}+k_{32}+k_{34}+k_{35})$$

$$\frac{dx_4}{dt} = k_{24}x_2^2 + k_{54}x_2\frac{x_5}{p+x_5} + k_{14}x_1 - x_4(k_{41}+k_{42}+k_{43}+k_{45}) + k_{34}x_1x_3$$

$$\frac{dx_5}{dt} = k_{25}x_2^2 - (k_{51}+k_{52}+k_{53}+k_{54})x_2\frac{x_5}{p+x_5} + k_{15}x_1 + k_{45}x_4 + k_{35}x_1x_3$$

Applying the embedding method we obtain the following ODEs which are linear in their parameters:

$$\frac{dx_1}{dt} = (k_{21}+k_{23})x_2^2 + x_5(k_{51}+k_{53})x_2z_1 + x_4(k_{41}+k_{43}) - x_1(k_{12}+k_{14}+k_{15}) - x_1x_3(k_{32}+k_{34}+k_{35})$$

$$\frac{dx_2}{dt} = (-2k_{21}-2k_{23}-2k_{24}-k_{25})x_2^2 + x_1x_3(2k_{32}+k_{35}) - x_5(k_{51}-k_{52}+k_{53}+k_{54})x_2z_1 + x_1(2k_{12}+k_{15}) + x_4(2k_{42}+k_{45})$$

$$\frac{dx_3}{dt} = k_{23}x_2^2 + k_{53}x_5x_2z_1 + k_{13}x_1 + k_{43}x_4 - x_1x_3(k_{31}+k_{32}+k_{34}+k_{35})$$

$$\frac{dx_4}{dt} = k_{24}x_2^2 + k_{54}x_5x_2z_1 + k_{14}x_1 - x_4(k_{41}+k_{42}+k_{43}+k_{45}) + k_{34}x_1x_3$$

$$\frac{dx_5}{dt} = k_{25}x_2^2 - x_5(k_{51}+k_{52}+k_{53}+k_{54})x_2z_1 + k_{15}x_1 + k_{45}x_4 + k_{35}x_1x_3$$

$$\frac{dz_1}{dt} = -z_1^2\frac{dx_5}{dt}$$

Note that parameter p is transformed to the initial condition of the ODE of the z_1 state variable: $z_1(0) = \frac{1}{p+x_5(0)}$. However, this has no effect on the reduction method because a Michaelis-Menten term is omitted if the corresponding k_{5i} parameter is 0.

Using the model reduction method we were able to reduce this reaction network by 10 parameters. The obtained parameters can be found in the 4th column of Table I and the concentration trajectories in Fig. 3. The trajectories of the original and reduced models are in very good agreement. Finally, the embedded Michaelis-Menten functions have to be transformed into the original form, by inverting the embedding procedure. This results the original number of state variables but much simpler right hand side functions in the ODEs.

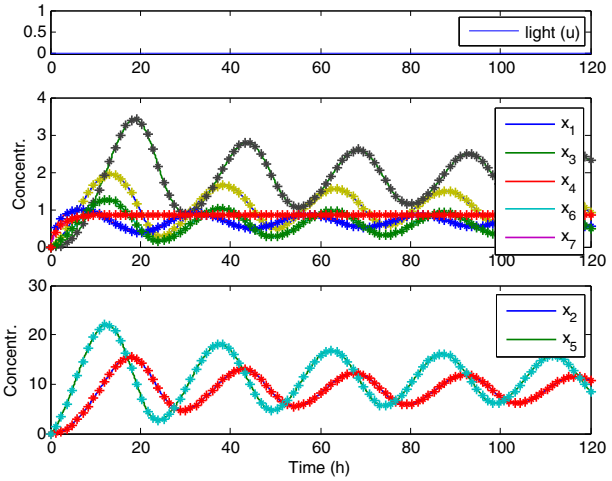

Fig. 4. Trajectories in the original and in the reduced systems (16 parameters) assuming zero input.

IV. CASE STUDY

A. Model reduction of Arabidopsis circadian

Arabidopsis circadian is a well known example of systems biology [17]. This model is often used in the literature for testing parameter identification methods. In [18] the author showed that, if the system is not well excited, then some parameters are not identifiable. This usually ruins the parameter estimation of the system i.e. results in infinite variances of some parameters. We will show that our method can find the reactions which should be removed in case of the poorly excited system. However, there are other approaches which can be used for the same purpose, e.g. in [19].

The reaction network of Arabidopsis circadian [17] consists of 7 species, 27 parameters and 1 input variable. The corresponding system of equations is

$$\frac{dx_1}{dt} = q_1 x_7 u + n_1 \frac{x_6}{g_1 + x_6} - m_1 \frac{x_1}{k_1 + x_1} \quad (20)$$

$$\frac{dx_2}{dt} = p_1 x_1 - r_1 x_2 + r_2 x_3 - m_2 \frac{x_2}{k_2 + x_2} \quad (21)$$

$$\frac{dx_3}{dt} = r_1 x_2 - r_2 x_3 - m_3 \frac{x_3}{k_3 + x_3} \quad (22)$$

$$\frac{dx_4}{dt} = n_2 \frac{g_2^2}{g_2^2 + x_3^2} - m_4 \frac{x_4}{k_4 + x_4} \quad (23)$$

$$\frac{dx_5}{dt} = p_2 x_4 - r_3 x_5 + r_4 x_6 - m_5 \frac{x_5}{k_5 + x_5} \quad (24)$$

$$\frac{dx_6}{dt} = r_3 x_5 - r_4 x_6 - m_6 \frac{x_6}{k_6 + x_6} \quad (25)$$

$$\frac{dx_7}{dt} = (1 - u) p_3 - m_7 \frac{x_7}{k_7 + x_7} - q_2 u x_7. \quad (26)$$

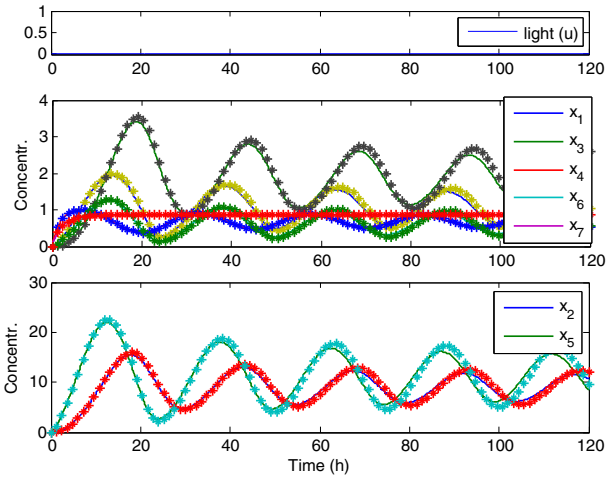

Fig. 5. Trajectories in the original and in the reduced systems (15 parameters) assuming zero input

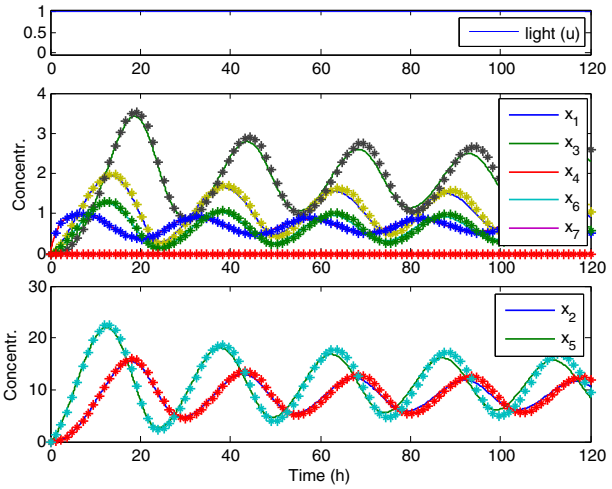

Fig. 6. Trajectories in the original and in the reduced systems assuming (13 parameters) constant light.

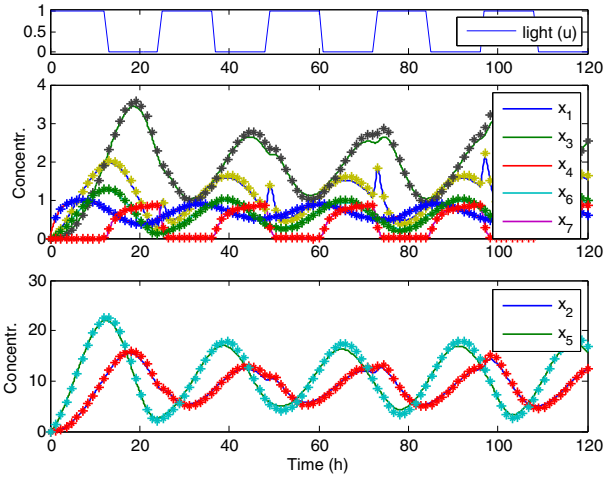

Fig. 7. Trajectories in the original and in the reduced systems (17 parameters) assuming pulsed light.

Here the state variable x_i denotes the concentrations of the species, the input variable u represents the light and it is a time dependent, binary valued (light is on or off) function. After embedding the rational functions as showed above the system has 16 state variables (the 7 original states: $x_1 - x_7$, and an additional 9 because of the embedding). The parameters $k_1, \ldots, k_7$ occur only in the initial conditions. In Eq. (23) the parameter g_2^2 appears both in the nominator and in the denominator. It is clear, after the transformation the g_2^2 will be transformed from the denominator to the initial condition and the first term in Eq. (23) will depend only on the product of n_2 and g_2^2, so the value of g_2^2 can be fixed to the original value and excluded from the estimation without the loss of generality.

In the model reduction we considered 3 different cases. In Case I we assume no light i.e. $u(t) = 0$, in Case II the light is turned on ($u(t) = 1$), while in Case III the input follows a pulse-like profile. The original (continuous lines) and the reduced model (denoted by stars) trajectories can be seen in Figures 4, 5, 6 and 7, while the resulted parameters can be found in Table II. In the lower part of Table II one can find the relative error of the reductions i.e. the average deviation of the reduced model trajectories. The results are as follows

Case I.: from the reduction error in 3rd and 4th columns of Table II, it is clear that the model can be reduced by 2 parameters (q_1 and q_2) without any error and one more parameter (m_6) can be omitted if we tolerate less than 10 % error for each species or 6% in average. The former result is obvious from the structure of the system because q_1 and q_2 are multiplied by the input u which is 0. However the latter result cannot be obtained so easily. The trajectories are in Fig. 4 and 5, the fitting is very good in both cases.

Case II.: the 5th and 6th columns of Table II tell that in case of constant light, 4 parameters (m_7, p_3, q_1 and q_2) can be omitted without any error. To see this from structural information one has to find out that each term in Eq. (26) depends either on x_7 or on $(1 - u) = 0$. As the initial condition for x_7 is 0, the right hand side will be zero, thus p_3, m_7 and q_2 can be omitted. q_1 appears only in (20) multiplied

by x_7, which is zero. This is not obvious without the results of the algorithm. The parameter m_6 can be omitted from the model for almost the same cost as in Case I.

Case III.: the pulsed input signal excites the system well, which results in more informative dynamics (see the small peaks in Fig. 7 appearing in almost every concentrations triggered by the switching of the input). In this case our algorithm can omit only one parameter if we tolerate some error (4.5% in average).

Note that, after the model reduction one can transform the system back to the original ODE form and omit the reactions found in the reduction procedure.

TABLE II

RATE COEFFICIENTS OF THE ORIGINAL AND OF THE REDUCED SYSTEMS TOGETHER WITH THE RELATIVE, AVERAGE DEVIATION OF THE STATES.

Param.	Original values	Case1 (16)*	Case1 (15)*	Case2 (14)*	Case2 (13)*	Case3 (17)*
n_1	7.5038	1.0000	1.0000	1.0000	1.0000	1.0000
n_2	0.6801	1.0000	1.0000	1.0000	1.0000	1.0000
m_1	10.0980	1.0000	1.0000	1.0000	1.0000	1.0000
m_2	1.9685	1.0000	1.0000	1.0000	1.0000	1.0000
m_3	3.7511	1.0000	1.0000	1.0000	1.0000	1.0000
m_4	2.3422	1.0000	1.0000	1.0000	1.0000	1.0000
m_5	7.2482	1.0000	1.0415	1.0000	1.0415	1.0399
m_6	1.8981	1.0000	0	1.0000	0	0
m_7	1.2000	1.0000	1.0000	0	0	1.0000
p_1	2.1994	1.0000	1.0000	1.0000	1.0000	1.0000
p_2	9.4440	1.0000	1.0046	1.0000	1.0046	1.0039
p_3	0.5000	1.0000	1.0000	0	0	1.0000
r_1	0.2817	1.0000	1.0000	1.0000	1.0000	1.0000
r_2	0.7676	1.0000	1.0000	1.0000	1.0000	1.0000
r_3	0.4364	1.0000	0.9732	1.0000	0.9732	0.9729
r_4	7.3021	1.0000	1.0167	1.0000	1.0167	1.0165
q_1	4.5703	0	0	0	0	1.0000
q_2	1.0000	0	0	0	0	1.0000
States		Deviation per specie (%)				
x_1		0	7.6024	0	7.6024	6.2025
x_2		0	5.1350	0	5.1350	3.9287
x_3		0	5.6781	0	5.6781	4.3989
x_4		0	3.1621	0	3.1621	2.5787
x_5		0	8.5746	0	8.5746	7.2411
x_6		0	8.4928	0	8.4928	7.0963
x_7		0	0.0007	0	0.0000	0.0023
Average deviation:		0	5.52	0.0	5.52	4.49

*The values in the second line shows the number of non-zero parameters. The reduced model parameters are in relative unit $(1/k)$, where k is the original parameter value.

V. CONCLUSION

An optimization based model reduction procedure has been presented in this paper for biochemical reaction network models. The original MINLP problem with a non-convex constraint set was approximated by a series of MIQP steps using the fact that the reaction network models are linear in the reaction rate coefficients that can be used to keep track of the presence of individual reactions. This way, a significant improvement of computational efficacy has been achieved. The novel technical contribution of the approach compared to [13] is the handling of rational functions in the ODEs through the embedding of rational function terms into polynomial form. Two examples taken from the related literature illustrate the operation of the method: a purely polynomial mass-action model, and a more complex circadian clock model with Michaelis-Menten kinetics.

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REFERENCES

[1] J. Anderson, Y.-C. Chang, and A. Papachristodoulou, "Model decomposition and reduction tools for large-scale networks in systems biology," *Automatica*, vol. 47(6), pp. 1165–1174, 2011.

[2] K. Glover, "All optimal hankel-norm approximations of linear multivariable systems and their l-infinity-error bounds," *International Journal of Control,*, vol. 39, p. 1115ďž˝1193., 1984.

[3] J. C. W. Kuo and J. Wei, "Lumping analysis in monomolecular reaction systems. analysis of approximately lumpable system," *Industrial and Engineering Chemistry Fundamentals*, vol. 8, pp. 124–133, 1969.

[4] Z. P. Gerdtzen, P. Daoutidis, and W.-S. Hu, "Non-linear reduction for kinetic models of metabolic reaction networks." *Metabolic Engineering*, vol. 6(2), pp. 140–154, 2004.

[5] P. Kokotovic, H. K. Khalil, and J. OReilly, "Singular perturbation methods in control: analysis and design." *Philadelphia, PA, USA: Society for Industrial and Applied Mathematics*, 1999.

[6] S. Lall, J. Marsden, and S. Glavaski, "A subspace approach to balanced truncation for model reduction of nonlinear control systems," *International Journal of Robust and Nonlinear Control*, vol. 12, no. 6, pp. 519–535, 2002.

[7] P. Érdi and J. Tóth, *Mathematical Models of Chemical Reactions. Theory and Applications of Deterministic and Stochastic Models*. Manchester, Princeton: Manchester University Press, Princeton University Press, 1989.

[8] M. Feinberg, "On chemical kinetics of a certain class," *Arch. Rational Mech. Anal.*, vol. 46, pp. 1–41, 1972.

[9] O. Radulescu, A. Gorban, A. Zinovyev, and A. Lilienbaum, "Robust simplifications of multiscale biochemical networks," *BMC Systems Biology*, vol. 2, no. 1, p. 86, 2008.

[10] M. R. Maurya, S. Katare, P. R. Patkar, A. E. Rundell, and V. Venkatasubramanian, "A systematic framework for the design of reduced-order models for signal transduction pathways from a control theoretic perspective," *Computers and Chemical Engineering*, vol. 30, pp. 437–452, 2006.

[11] M. Apri, M. de Gee, and J. Molenaar, "Complexity reduction preserving dynamical behavior of biochemical networks," *Journal of Theoretical Biology*, vol. 304, pp. 16–26, 2012.

[12] I. P. Androulakis, "Kinetic mechanism reduction based on an integer programming approach," *AIChE Journal*, vol. 46, pp. 361–371, 2000.

[13] R. Hannemann-Tamás, A. Gábor, G. Szederkényi, and K. M. Hangos, "Model complexity reduction of chemical reaction networks using mixed-integer quadratic programming," *Computers & Mathematics with Applications*, 2012, In Press.

[14] A. N. Gorban, I. Karlin, and A. Zinovyev, "Invariant grids for reaction kinetics," *Physica A*, vol. 33, pp. 106–154, 2004.

[15] R. Hannemann, W. Marquardt, B. Gendler, and U. Naumann, "Discrete first- and second-order adjoints and automatic differentiation for the sensitivity analysis of dynamic models," in *Procedia Computer Science*, vol. 1, 2010, pp. 297–305.

[16] A. Papachristodoulou and B. Recht, "Determining interconnections in chemical reaction networks," in *American Control Conference*, 2007.

[17] J. Locke, A. Millarb, and M. Turner, "Modelling genetic networks with noisy and varied experimental data: the circadian clock in arabidopsis thaliana," *Journal of Theoretical Biology*, vol. 234, pp. 383–393, 2005.

[18] O.-T. Chis, J. R. Banga, and E. Balsa-canto, "Structural identifiability of systems biology models: a critical comparison of methods." *PloS One*, vol. 6(11), 2011.

[19] E. Balsa-Canto and J. R. Banga, "Amigo, a toolbox for advanced model identification in systems biology using global optimization," *Bioinformatics*, vol. 27(16), pp. 2311–2313, 2011.