A Novel Technique for Model Reduction of Biochemical Reaction Networks

Manvel Gasparyan * **Arnout Van Messem** * **Shodhan Rao** *

* *Center for Biotech Data Science, Ghent University Global Campus, Incheon, South Korea (e-mail: [manvel.gasparyan],[arnout.vanmessem],[shodhan.rao]@ghent.ac.kr).*

Abstract: We illustrate a new technique for the model reduction of biochemical reaction networks governed by any kind of enzyme kinetics. Previously Rao et al. proposed a model reduction method for biochemical reaction networks governed by various reversible and irreversible enzyme kinetics. We extend the ideas of Rao et al. and show how the number of variables in the mathematical model of the chemical reaction network can be reduced by using the initial data from the network. Moreover, the outgoing reaction fluxes in the forward direction of the reduced reaction network remain unchanged compared to the original one. We then apply our new technique for model reduction to an example, for which the method proposed by Rao et al. encountered serious limitations.

Keywords: Chemical reaction networks, Enzyme kinetics, Graph theory, Model reduction, Linkage classes, Stoichiometry, Kron reduction method.

1. INTRODUCTION

A model of a biochemical reaction network contains a system of ordinary differential equations that explain the dynamics of the species concentrations of the network. Kinetic models of most biochemical reaction networks involve an extremely huge number of variables, which sometimes require huge computational efforts to analyze. Moreover since models of chemical reaction networks involve a huge number of parameters, the task of identifying these parameters for a particular setting is enormous and requires large experimental datasets, which is not easy since, often not all the species concentrations can be measured. Hence, there is a necessity of reducing kinetic models of biochemical reaction networks to simplified versions that possess the nature of the original model, but consist of fewer differential equations and variables.

Various model reduction tools are known in the literature related to biochemical reaction networks. Essential results of reducing enzyme kinetic reaction networks can, for example, be found in (Segel, 1975). See (Snowden et al., 2017) and (Radulescu et al., 2013) for a comprehensive review of certain notable model reduction methods. The rapid-equilibrium approximation (Segel, 1975), and the quasi-steady-state approximation (Segel and Slemrod, 1989), are some of the most natural techniques, as the reduced models obtained by any of these contain a subset of species concentrations of the original model.

The model proposed in (Rao et al., 2014) simplifies a given chemical reaction network by deleting complexes from the complex graph corresponding to the network. Here, complexes are defined as the left- (substrate) and right-hand (product) sides of the reactions in the network. We recall that the complexes can be naturally associated with the vertices of a complex graph with edges corresponding to the reactions. In this paper, we consider only reversible reaction networks, i.e., networks in which every reaction is reversible. Formally, the reversible reaction $\alpha \rightleftarrows \beta$ between the α^{th} and β^{th} complexes defines a directed edge with tail vertex being the α^{th} complex and head vertex being the β^{th} complex. The model proposed in (Rao et al., 2014) is based on the Kron reduction of the weighted Laplacian matrix, which describes the graph structure of the complexes and reactions in the network. The Kron reduction method described in (Kron, 1939) and (van der Schaft, 2010) is a popular method of model reduction for electrical networks and involves the computation of Schur complements of the balanced weighted Laplacian matrix. The method of (Rao et al., 2014) selects the complexes to be deleted in such a way that the behavior of important species in the reduced model is close to their original behavior.

As an example, we consider a biochemical reaction network with a single linkage class of reversible reactions given in Figure 1, where $\mathcal{C}_i$, $(i = 1, \cdots, n)$, are distinct complexes. We recall that a *linkage class* of a chemical reaction network is a connected component of the complex graph corresponding to the network.

$$\mathcal{C}_1 \rightleftarrows \mathcal{C}_2 \rightleftarrows \mathcal{C}_3 \rightleftarrows \cdots \rightleftarrows \mathcal{C}_n$$

Figure 1: Full network

The reduced network after deleting the complex $\mathcal{C}_2$ is given in Figure 2, where two reversible reactions, $\mathcal{C}_1 \rightleftarrows \mathcal{C}_2$ and $\mathcal{C}_2 \rightleftarrows \mathcal{C}_3$, of the full network are replaced by a reversible reaction $\mathcal{C}_1 \rightleftarrows \mathcal{C}_3$. The expressions of the reaction rate fluxes in the forward direction of all the remaining reactions of the reduced network are the same as those of the full network.

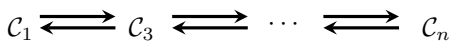

Figure 2: Reduced network

The method is effective in deleting intermediate complexes from the linkage classes that have more than two complexes. It is most efficient in bringing down the number of complexes in every linkage classes to two. However, when every linkage class has just two complexes, the method fails as explained in the example below.

Suppose that each connected component of the complex graph corresponding to a network has only two complexes. For example, let $X_i, i = 1, \cdots, 10$ be distinct chemical species and consider the reaction network with three linkage classes described in Figure 3.

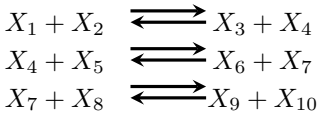

Figure 3: Reaction network with three linkage classes

The complexes corresponding to the network in Figure 3 are:

$$\begin{aligned} \mathcal{C}_1 &= X_1 + X_2 & \qquad \mathcal{C}_4 &= X_6 + X_7 \\ \mathcal{C}_2 &= X_3 + X_4 & \qquad \mathcal{C}_5 &= X_7 + X_8 \\ \mathcal{C}_3 &= X_4 + X_5 & \qquad \mathcal{C}_6 &= X_9 + X_{10}. \end{aligned}$$

In this case, deletion of any complex by the approach of (Rao et al., 2014) ends up deleting the corresponding linkage class. The reduced model will then have the remaining reactions occurring independently, therefore possessing a behavior which is totally different from the original one.

Since most biochemical networks in real life have a reaction network structure in which each linkage class consists of only two complexes, novel techniques for model reduction of biochemical reaction networks are necessary. In this paper we introduce a new approach for model reduction of biochemical reaction networks like the one characterized by Figure 3 and which in conjunction with the method proposed by (Rao et al., 2014) results in a meaningful model reduction of networks. We use the conserved quantities of the network to rewrite the model of the chemical reaction network in a form for which the reduction method described in (Rao et al., 2014) is applicable. This rewriting effectively leads to clustering of linkage classes that share common species, thereby leading to bigger linkage classes in the complex graph of the network. It enables the method of (Rao et al., 2014) to be then applied in order to delete intermediate complexes from the newly obtained bigger linkage classes. Finally, as an example, we apply our reduction method to delete certain complexes from a simple chemical reaction network governed by enzyme kinetics.

2. PRELIMINARIES

The space of n dimensional real vectors is denoted by $\mathbb{R}^n$ and the space of n dimensional real vectors consisting of only strictly positive entries is denoted by $\mathbb{R}^n_+$.

We follow the general description of chemical reaction networks as in (Rao et al., 2014). We consider reversible chemical reaction networks for which there are no inflows from and outflows to the exterior environment. Suppose r reversible chemical reactions are occurring among m chemical species (metabolites). The *reaction vector* corresponding to the reversible reaction $\mathcal{S} \rightleftarrows \mathcal{P}$ is the vector $y \in \mathbb{R}^m$ whose i^{th} $(i = 1, \cdots, m)$ member is the number of moles of the i^{th} species in $\mathcal{P} - \mathcal{S}$. We define as in (Rao et al., 2013) the *stoichiometric matrix* S as the $m \times r$ matrix whose j^{th} $(j = 1, \cdots, r)$ column is the reaction vector corresponding to the j^{th} reaction of the chemical reaction network. For example, consider the reversible reaction network illustrated in Figure 4.

Figure 4: Example of a reaction network

For the above reaction network there are three species X_1, X_2 and X_3 (i.e., $m = 3$) and three complexes (i.e., $c = 3$), namely, $X_1 + 3X_2, X_3$ and $2X_1 + 2X_2$. In this case, the reaction vectors corresponding to the network are given by

$$y_1 = \begin{bmatrix} -1 \\ -3 \\ 1 \end{bmatrix} \qquad y_2 = \begin{bmatrix} 2 \\ 2 \\ -1 \end{bmatrix}.$$

Thus, the 3×2 stoichiometric matrix S of the network described in Figure 1 is given by

$$S = \begin{bmatrix} -1 & 2 \\ -3 & 2 \\ 1 & -1 \end{bmatrix}.$$

We denote by $x \in \mathbb{R}^m_+$ and $\nu \in \mathbb{R}^r$ the *concentration vector* of the chemical species and the *vector of overall reaction fluxes (rates)* in the forward direction of the given reaction network respectively. The basic structure underlying the dynamics of the concentration vector x is given by the *balance laws*

$$\dot{x} = S\nu(x), \tag{1}$$

where ν depends on the governing laws of the reactions in the network.

Let $x_0 \in \mathbb{R}^m_+$ denote the vector of initial concentrations, i.e., $x|_{t=0} = x_0$. Consider a vector $k \in \ker(S^\top)$. This vector obeys the equation $k^\top \dot{x} = 0$, consequently $k^\top x$ is a constant, meaning that $k^\top x = k^\top x_0$. The equation

$$k^\top x = \text{constant} \tag{2}$$

is called a *conservation law* of the network. For example, with reference to the network illustrated in Figure 4, the vector $k = [1 \quad 1 \quad 4]^\top$ satisfies equation (2) and hence leads to a conservation law. In general the number of linearly independent conservation laws is equal to the dimension of $\ker(S^\top)$. Thus, irrespective of the governing laws of a reaction network we can find all the conservation laws by computing $\ker(S^\top)$.

3. DESCRIPTION OF THE REDUCTION METHOD

In this section we provide the main idea of the reduction method of biochemical reaction networks, which extends the model reduction method described in (Rao et al., 2014). Their method is based on the Kron reduction of the weighted Laplacian matrix of the complex graph corresponding to the biochemical reaction networks. However, as explained in the introduction , we cannot always delete complexes immediately from the reaction network using the Kron reduction method. Therefore, we propose a new approach for model reduction, which allows to enable the model reduction approach in (Rao et al., 2014) to be applicable for any kind of chemical reaction network. This new reduction method is based on rewriting the mathematical model of reaction networks in a preferred form before applying the method proposed by (Rao et al., 2014).

Consider again the chemical reaction network described in Figure 3 governed by enzyme kinetics. We denote the species concentration vector of this network by $x = [x_i]_{i=1}^{10} \in \mathbb{R}_+^{10}$. Moreover, we denote by $\nu = [\nu_i(x)]_{i=1}^{3} \in \mathbb{R}^3$ the vector of outgoing reaction fluxes in the forward direction corresponding to the reversible reactions shown in Figure 3. It is easy to see, that we can extend the balance laws (1) to obtain the ten differential equations describing the basic structure of species concentrations of the network as follows:

$$\begin{cases} \dot{x}_1 = -\nu_1(x), & \dot{x}_2 = -\nu_1(x) \\ \dot{x}_3 = \nu_1(x), & \dot{x}_4 = \nu_1(x) - \nu_2(x) \\ \dot{x}_5 = -\nu_2(x), & \dot{x}_6 = \nu_2(x) \\ \dot{x}_7 = \nu_2(x) - \nu_3(x), & \dot{x}_8 = -\nu_3(x) \\ \dot{x}_9 = \nu_3(x), & \dot{x}_{10} = \nu_3(x) \end{cases} . \tag{3}$$

In this case the dimension of $\ker(S^\top)$ is four, hence the chemical reaction network given by Figure 3 has exactly four conservation laws. We can easily derive these conservation laws from the system (3) of differential equations. Thus, we have the following system:

$$\begin{cases} x_3 &= C_1 - x_1 \\ x_5 &= C_2 + x_2 + x_4 \\ x_6 &= C_3 + x_7 + x_9 \\ x_8 &= C_4 - x_{10} \end{cases}, \tag{4}$$

where C_k, $(k = 1, \cdots 4)$, are certain constants (not necessarily positive). The idea of our new technique is to use the conserved quantities C_k, $(k = 1, \cdots 4)$, to rewrite the mathematical model of the chemical reaction network that we want to reduce in a preferred form for which we can apply the Kron model reduction method without limitations. We use conserved quantities to cluster the three linkage classes of the original network into one linkage class as shown in Figure 5. It can be done by substituting x_3, x_5, x_6 and x_8, as in equations (4), in the expression of the vector ν of the reaction fluxes, which is a function of the species concentration vector. We rewrite the chemical reaction network as a network with a single linkage class of reversible reactions (cfr., Figure 1).

$$X_1 + X_2 \underset{}{\overset{\nu_1}{\rightleftharpoons}} X_4 \overset{\nu_2}{\rightleftharpoons} X_7 \overset{\nu_3}{\rightleftharpoons} X_9 + X_{10}$$

Figure 5: Reduced network

Moreover, although the species concentrations x_3, x_5, x_6 and x_8 are no longer participating in the expressions of the reaction fluxes of the reduced reaction network, the values of the reaction fluxes in the forward direction remain identical to the values of the original reaction fluxes. Since, we now have a chemical reaction network with a single linkage class of reversible reactions, we can apply the model reduction approach proposed by (Rao et al., 2014) to the reduced network to delete the intermediate complexes X_4 and X_7 from the network. In other words, the final version of the reduced reaction network can be expressed as in Figure 6, and we can rewrite the expression of the overall reaction flux ν in the forward direction of the chemical reaction network given by Figure 3 in a form depending only on the concentrations x_1, x_2, x_9 and x_{10}.

$$X_1 + X_2 \rightleftharpoons X_9 + X_{10}$$

Figure 6: Final reduced network

4. EXAMPLE OF THE LAW OF ENZYME KINETICS

In this section we apply our method to reduce the reaction network described in Figure 3 governed by general enzyme kinetics, see, (Segel and Slemrod, 1989). For simplicity we consider a reaction network of two linkage classes as illustrated in Figure 7, where X_i, $(i = 1, \cdots, 7)$ are distinct biochemical species.

$$\begin{aligned} X_1 + X_2 &\rightleftharpoons X_3 + X_4 \\ X_4 + X_5 &\rightleftharpoons X_6 + X_7 \end{aligned}$$

Figure 7: Reaction network with two linkage classes

We denote the species concentration vector of the network by $x = [x_i]_{i=1}^{7} \in \mathbb{R}_+^7$. For $i = 1, \cdots, 7$, let K_i denote the Michaelis constant of X_i.

In this case, from the balance laws (1), we obtain the following conservation laws

$$\begin{cases} x_3 &= C_1 - x_1 \\ x_5 &= C_2 - x_6 \end{cases}, \tag{5}$$

where C_1 and C_2 are positive constants. For $j = I, II$, let $V_{m,f}^j$ and $V_{m,r}^j$ denote the maximum rates in the forward and the reverse directions of the j^{th} reversible reaction respectively. Let $\nu_1(x)$ and $\nu_2(x)$ denote the outgoing reaction fluxes in the forward direction of the two reversible reactions, which are given by the following formulas:

$$\begin{cases} \nu_1(x) &= \dfrac{V_{m,f}^I \frac{x_1 x_2}{K_1 K_2} - V_{m,r}^I \frac{x_3 x_4}{K_3 K_4}}{1 + \frac{x_1}{K_1} + \frac{x_2}{K_2} + \frac{x_3}{K_3} + \frac{x_4}{K_4}} \\ \nu_2(x) &= \dfrac{V_{m,f}^{II} \frac{x_4 x_5}{K_4 K_5} - V_{m,r}^{II} \frac{x_6 x_7}{K_6 K_7}}{1 + \frac{x_4}{K_4} + \frac{x_5}{K_5} + \frac{x_6}{K_6} + \frac{x_7}{K_7}} \end{cases} . \tag{6}$$

By substituting the values of x_3 and x_5 given by (5) in the expressions of the reaction fluxes (6), we can rewrite the reaction network as in Figure 8, which is a chemical reaction network with a single linkage class.

$$X_1 + X_2 \underset{}{\overset{\overline{\nu}_1}{\rightleftharpoons}} X_4 \overset{\overline{\nu}_2}{\rightleftharpoons} X_6 + X_7$$

Figure 8: Reduced reaction

For $j = I, II$, let $\overline{V}^j_{m,f}$ and $\overline{V}^j_{m,r}$ denote the maximum reaction fluxes in the forward and the reverse directions of the two reversible reactions respectively, as they appear in the reduced reaction network given by Figure 8. For the expressions of $\overline{\nu}_1$ and $\overline{\nu}_2$ we then obtain:

$$\begin{cases} \overline{\nu}_1(x) & = \dfrac{\overline{V}^I_{m,f}\frac{x_1x_2}{\overline{K}_1\overline{K}_2} - \overline{V}^I_{m,r}\frac{x_1x_4}{\overline{K}_1\overline{K}_4} - M_1x_4}{1 + \frac{x_1}{\overline{K}_1} + \frac{x_2}{\overline{K}_2} + \frac{x_4}{\overline{K}_4}} \\ \overline{\nu}_2(x) & = \dfrac{\overline{V}^I_{m,f}\frac{x_4x_6}{\overline{K}_4\overline{K}_6} - \overline{V}^{II}_{m,r}\frac{x_6x_7}{\overline{K}_6\overline{K}_7} + M_2x_4}{1 + \frac{x_4}{\overline{K}_4} + \frac{x_6}{\overline{K}_6} + \frac{x_7}{\overline{K}_7}} \end{cases}, \quad (7)$$

where $M_i, i = 1, 2$ are positive constants, and $\overline{K}_j, j = 1, 2, 4, 6, 7$ are constants depending on the Michaelis constants of the chemical species of the original reaction network.

Clearly, the expressions of the overall reaction fluxes in the forward direction of the reactions in the network shown in Figure 8 can be expressed as (7). We remark, that the kinetics of the first and the second reversible reactions of the reduced reaction network are different from the original kinetics. We can now apply the model reduction method described in (Rao et al., 2014) to delete the intermediate complexes X_4 and obtain the model of a network as shown in Figure 9.

$$X_1 + X_2 \rightleftharpoons X_6 + X_7$$

Figure 9: Final reduced network

We like to emphasize that, for this example, our newly proposed technique for model reduction of biochemical reaction networks allows us to apply the method proposed by (Rao et al., 2014), whereas this was previously impossible. The procedure results in a reduced model with less variables compared to the original reaction network with reaction fluxes remaining unchanged.

5. CONCLUSION

In this paper we presented an extended version of the model reduction method of chemical reaction networks proposed by (Rao et al., 2014). The idea behind our model reduction method is to rewrite a given chemical reaction network in a preferred form using the conserved quantities of the network. Once we have the preferred form of the original reaction network, we apply the Kron reduction method introduced in (Rao et al., 2014), which results in a gradual reduction in the number of complexes of the chemical reaction network. Our model reduction method assures that the expression of the vector of outgoing reaction fluxes of the reduced network remains unchanged after reducing the network. It also leads to less number of species, but more parameters added due to the introduction of conserved quantities in the model of the reduced network.

Our method is effective in clustering two linkage classes that have two complexes each and share some common species. It looks at the complexes with the shared species and rewrites the expression for the concentrations of the remaining species of such complexes using the conserved quantities of the network. This leads to clustering of linkage classes with common species, thus enabling the method of (Rao et al., 2014) to be applied in order to delete the intermediate complexes from the complex graph corresponding to the resulting network.

We have applied our model reduction method to a simple example of a chemical reaction network governed by general enzyme kinetics, for which the model reduction method described in (Rao et al., 2014) had serious limitations. We used the conserved quantities of the reaction network to rewrite the given reaction network in a form of a reaction network with a single linkage class, for which the model reduction method given in (Rao et al., 2014) based on the Kron reduction method was applicable.

Currently, we are working on generalizing our model reduction method. We are also planning to use mathematical programs in order to write a program that will use our new reduction technique for biochemical reaction networks to reduce the number of complexes automatically.

REFERENCES

Kron, G. (1939). Tensor analysis of networks. *Wiley, New York*.

Radulescu, O., Gorban, A., Zinovyev, A., and Novel, V. (2013). Glycolytic ascillations in a model of a lactic acid bacterium metabolism. *Biophys Chem*, 172, 53–60.

Rao, S., van der Schaft, A., Eunen, K.V., Bakker, B., and Jayawardhana, B. (2013). On the mathematical structure of balanced chemical reaction networks governed by mass action kinetics. *Siam J. Appl. Math.,*, 73, 953–973.

Rao, S., van der Schaft, A., Eunen, K.V., Bakker, B., and Jayawardhana, B. (2014). A model reduction method for biochemical reaction networks. *BMC Systems Biology*, 8, 1–17.

Segel, I.H. (1975). *Biochemical calculations*. Davis, California.

Segel, L. and Slemrod, M. (1989). The quasi-steady-state assumption: a case study in perturbation. *SIAM Rev Soc Ind Appl Math*, 31, 446–477.

Snowden, T.J., van der Graaf, P.H., and Tindall, M.J. (2017). Methods of model reduction for large-scale biological systems: A survey of current methods and trends. *Society for Mathematical Biology*, 79, 1449–1486.

van der Schaft, A. (2010). Characterization and partial synthesis of the behavior of resistive circuits at their terminals. *Syst. Control Lett*, 59, 423–428.