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Model reduction of detailed-balanced reaction networks by clustering linkage classes

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Abstract: We propose a model reduction method that involves sequential application of clustering of linkage classes and Kron reduction. This approach is specifically useful for chemical reaction networks with each linkage class having less number of reactions. In case of detailed balanced chemical reaction networks that are governed by general enzyme kinetics, we show that our procedure ensures that the space of equilibria corresponding to the original model is a subspace of the space of equilibria of the reduced model.

Keywords: Biochemical reaction networks, Model reduction, Graph theory, Network dynamics.

1. INTRODUCTION

An important topic in systems biology is the study of large-scale models of biochemical reaction networks that describe the dynamics of metabolism, signaling, gene expression, etc. in living cells. Biochemical reaction networks usually involve many enzyme-catalyzed processes governed by nonlinear enzyme-kinetic rate laws. Owing to intricate stoichiometry and regulatory mechanisms, the enzyme-catalyzed processes of a network are highly interdependent. Consequently, the complexity of the models describing their dynamics is daunting, even if we make simplifying assumptions of uniform spatial distribution and constant system temperature and pressure. A deterministic model of such a reaction network may contain high-dimensional sets (typically of the order of 100) of coupled polynomial or rational ordinary differential equations, which sometimes require huge computational effort to analyze.

There is a growing need of mathematical tools for analyzing complex models of reaction networks and for obtaining biological insights from the analysis. The computational effort required to analyze a mathematical model of biochemical reaction network is considerably reduced if we can obtain a reduced model that mimics the behaviour of the original model satisfactorily, but contains less differential equations and parameters as compared to the original model.

Model reduction of biochemical reaction networks has been a very active area of research in the past few years and a lot of complementary approaches have been devised for the purpose. The reader is referred to [14] for a detailed exposition of some well known model reduction procedures. Here we list only a few of the known methods. The most commonly used techniques are the singular perturbation method, the time-scale separation technique [6,12,15,17,20], the rapid-equilibrium approximation, also known as the quasi-equilibrium approximation (see [18]) and the quasi steady-state approximation (QSSA) (see for e.g., [19]). Model reduction can also be carried out by reducing the number of parameters (e.g. [2,10–12]) or the number of reactions (e.g. [1,3,5,13]). Some of these model reduction methods are based on a priori experimental information and/or biological knowledge and hence are only locally effective.

The authors of the current paper have previously proposed a model reduction method [16] that overcomes most of the limitations of the other well known model reduction approaches. The method proposed in [16] proceeds by a simple stepwise reduction in the number of 'complexes', which are the combinations of species on the left and right-hand sides of the various reactions in the network. The method is based on the reduction of the underlying weighted Laplacian (see [4] for a definition) describing the structure of the graph of complexes which is a graph with vertices corresponding to the complexes and edges corresponding to the reactions in the network. The effect of this stepwise reduction is monitored by an error integral, which quantifies how much the behaviour of the reduced model deviates from the original. The procedure ensures that the set of complexes that are deleted is in some sense the optimal set for which the desired level of closeness between the transient behaviors of the original and the reduced model is obtained. This method is inspired by Kron reduction method [9] which is a popular method of reduction of resistive electrical network models.

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Listed below are the advantages of the method proposed in [16] that cannot all be found in one particular model reduction method that was listed earlier. The model reduction technique of [16] is easy to implement and can be automated. It does not rely on a priori knowledge about the experimental conditions or biological function of the network. Furthermore, the reduced model largely retains the kinetics and structure of the original model. This enables a direct biochemical interpretation and yields insight into which parts of the network have the highest influence on its behaviour. It also accelerates computations by reducing computational effort, especially when we deal with models of huge biochemical reaction networks. For networks governed by mass action kinetics, an improvement of the model reduction approach [16] in terms of the computational effort involved has been proposed recently (see [7]).

The model reduction approach of [16] has one serious limitation which we explain below. Assume that every connected component (*linkage class* in chemical reaction network (CRN) terminology) of the graph of complexes corresponding to a network has only two complexes. In this case, deletion of any complex by the approach of [16] simply results in the deletion of the corresponding linkage class. For example assuming that $X_1, \ldots, X_{10}$ are distinct chemical species, consider the following reaction network with 3 linkage classes.

$$\left.\begin{array}{l} X_1 + X_2 \rightleftharpoons X_3 + X_4 \\ X_4 + X_5 \rightleftharpoons X_6 + X_7 \\ X_7 + X_8 \rightleftharpoons X_9 + X_{10} \end{array}\right\} \tag{1}$$

Deletion of the complex $X_4 + X_5$ results in elimination of the second linkage class. Thus the reduced model will have the first reaction occuring independently of the third reaction and consequently the reduced model will exhibit a dynamic behaviour which is far from that of the original model. Most biochemical networks in real life fall under the category of reaction networks with each linkage class having only two complexes and therefore there is a need to develop a more effective graph-theory based approach for model reduction of biochemical reaction networks. In this paper, we propose a method to overcome this particular limitation. Each step of this method involves clustering two linkage classes and deletion of complexes in the clustered linkage class. The clustering of linkage classes at every step ensures that the resulting linkage class has at least three complexes, so that deletion of a single complex from it does not result in the elimination of the linkage class.

We further consider the application of our model reduction procedure for detailed balanced networks governed by general enzyme-kinetic rate laws. The reader is referred to [8] for a description of properties of such networks. Thermodynamically the assumption of detailed-balancedness for any network without interactions with the external environment is well justified as it corresponds to microscopic reversibility. We show that for such networks, the clustering procedure described in this paper ensures that the space of equilibria of the original network is equivalent to that of the clustered network. As a consequence to this, the sequential application of clustering of complexes and Kron reduction will result into a reduced model where the space of equilibria of the original network is a subspace of that corresponding to the reduced network. This set inclusion property is due to the property of Kron reduction method applied to detailed-balanced networks [21].

Notation: The space of n dimensional real vectors is denoted by $\mathbb{R}^n$ and the space of n dimensional real vectors consisting of all strictly positive entries is denoted by $\mathbb{R}^n_+$. Define the mapping $\mathrm{Ln} : \mathbb{R}^m_+ \to \mathbb{R}^m, \quad x \mapsto \mathrm{Ln}(x)$, as the mapping whose i-th component is given as $(\mathrm{Ln}(x))_i := \ln(x_i)$.

2. PRELIMINARIES

Let us recall the general description of (bio)chemical reaction networks as recently reviewed in [22]. In this paper, we consider reversible (bio)chemical reaction networks that do not interact with the external environment, meaning that there are no inflows from and no outflows to the external environment. Assume that there are m species, c complexes and r reversible reactions in such a network. Define the *complex composition matrix* Z as the $m \times c$ matrix whose α-th column captures the expression of the α-th complex in the m chemical species. For example consider the reversible reaction network given by

$$X_1 + 3X_2 \rightleftharpoons X_3 \rightleftharpoons 2X_1 + 2X_2 \tag{2}$$

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, $\{X_1 + 3X_2,\ X_3,\ 2X_1 + 2X_2\}$. In this case, the complex composition matrix is given by

$$Z = \begin{bmatrix} 1 & 0 & 2 \\ 3 & 0 & 2 \\ 0 & 1 & 0 \end{bmatrix}$$

Note that all the entries of the complex composition matrix are nonnegative integers. We define as in [21] the *graph of complexes* as a directed graph whose nodes are the complexes and whose edges correspond to the reversible reactions of the network. The direction of each edge is arbitrary, usually given by the direction of the forward reaction of the network. Note that the direction of each edge of the graph of complexes does not affect the modelling or the model reduction procedure described in this paper. One can associate an *incidence matrix* B with the graph of complexes. This is a matrix of dimension $c \times r$. The j^{th} column of B corresponds to the j^{th} edge of the graph of complexes and has entries -1 corresponding to the tail vertex, $+1$ corresponding the head vertex and the remaining entries are all 0. Observe that an incidence matrix B corresponding to the reaction network (2), which has two reversible reactions (i.e., $r = 2$), is

$$B = \begin{bmatrix} -1 & 0 \\ 1 & -1 \\ 0 & 1 \end{bmatrix}$$

The first column describes the first reversible reaction $X_1 + 3X_2 \rightleftharpoons X_3$ while the second one describes the second reaction $X_3 \rightleftharpoons 2X_1 + 2X_2$.

For simplifying the description of our approach later, let us introduce further the following notations. For a given reaction edge i, we denote a substrate complex (which is assumed to be the tail vertex of i-th edge) by $\mathcal{S}_i$ and a product complex (which corresponds to the head vertex) by $\mathcal{P}_i$. Correspondingly, $Z_{\mathcal{S}_i}$ and $Z_{\mathcal{P}_i}$ denote the column of Z that is related to the complex $\mathcal{S}_i$ and $\mathcal{P}_i$, respectively.