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A guideline to model reduction by stoichiometric decomposition for biochemical network analysis

Steffen Waldherr

Abstract— **Many biochemical network models include quantities that are conserved in molarity. While important theoretical results rely on such conservation relations, they often pose a problem for numerical analyses. Several analysis routines that are very relevant for biochemical models, for example sensitivity or stability analysis, intrinsically cannot deal with networks where conservation relations are present. To apply these routines, one generally needs to construct an equivalent reduced model without the conservation relations.**

Here, a method to remove conservation relations from biochemical reaction network models is proposed. The method is based on an orthogonal decomposition for the stoichiometric matrix, which makes the approach numerically efficient even for very large networks. Based on this decomposition, a reduced differential equation which describes the dynamics within a specified stoichiometric class is derived. Finally, applications of the reduction approach for steady state computation and stability analysis are discussed.

I. Introduction

Biochemical network models describe the conversion of one set of biochemical reactants into another set via reactions. These reactions are subject to the conservation of matter, which gives rise to a structural property called conservation relations in biochemical networks. For networks modelled with an ordinary differential equation of the form

$$\dot{x} = Nv(x),$$

a conservation relation is represented by a vector g which satisfies the equation

$$g^{\mathrm{T}}\dot{x} = 0,$$

making $g^{\mathrm{T}}x$ a conserved quantity.

There is an extensive body of scientific literature on the interpretation and consequences of conservation relations in biochemical network models. In chemical reaction network theory, conservation relations determine stoichiometric subspaces of networks [5], which are quite useful in network analysis. In particular, the associated partitioning of the state space into stoichiometric compatibility classes provides strong results on the structure and stability of steady states in the network [4], [14].

While conservation relations are a relevant structural property, they usually pose problems for numerical analysis routines, especially in software for automated network analysis. Due to the structural eigenvalue equal to zero of the network's Jacobian at steady state, numerical analyses which rely on the Jacobian being invertible, such as local sensitivity analysis, cannot be applied directly. Also, even when the dynamics in each stoichiometric class are structurally stable, the differential equation for a network with conservation relations is not structurally stable for any choice of parameter values when looking at the full state space. This is problematic for stability and bifurcation analysis, which relies on the network's equations being structurally stable for almost all parameter values. Also, when computing equilibrium points of a network, numerical algorithms may select a solution in a stoichiometric class different from the considered initial conditions, if no special care for this situation is taken.

Conservation relations are also an important property of biochemical reaction networks studied in metabolic control theory [7]. Here, the construction of an equivalent reduced model without conservation relations is crucial in order to allow the computation of the various coefficients used in metabolic control theory [9]. Reder [11] has shown that for networks with conservation relations, after an appropriate reordering of the species, the stoichiometric matrix N can be decomposed as

$$N = LN_r, \tag{1}$$

where L is a tall rectangular matrix with the identity in the upper block, and an integer matrix in the lower block. Based on this decomposition, an equivalent reduced model without conservation relations is constructed. Commonly, the first r components of the reordered species vector are taken as "independent" species, and the remaining $n - r$ components as "dependent" species. The reduced model then contains only the concentrations of the independent species as state variables. While this approach to construct a reduced model maintains an intuitive relation between state variables in the original and reduced systems, the distinction between independent and dependent species is not unique. Also, the decomposition of the stoichiometric matrix is numerically challenging, since it requires to put the stoichiometric matrix into the reduced row echolon form. Software tools which are using this reduction approach, for example the Systems Biology Toolbox for Matlab [13] or the PySCeS library for Python [10], typically implement special code involving Gaussian elimination and careful pivoting to get this reduction correct for larger networks. A detailed discussion of computational issues related to conservation relations is also given in [12].

This paper explores the construction of a reduced model with any stoichiometric decomposition, not necessarily in-

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Steffen Waldherr is with the Institute for Automation Engineering, Otto-von-Guericke-University, 39106 Magdeburg, Germany steffen.waldherr@ovgu.de

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teger, of the form (1), where the decomposed matrices are full rank. The main contribution is the development of a reduction method which does not rely on classifying species as "independent" or "dependent". Instead, the appropriate stoichiometric class is characterized by the factors obtained in the decomposition of the stoichiometric matrix. The method can be applied with singular value decomposition (SVD) [8] or the QR decomposition, making the construction of the reduced model numerically robust and efficient even for large-scale metabolic networks. The approach is particularly well suited for the numerical analysis of larger networks or in automated workflows, where numerical efficiency is important and a splitting of the species vector in dependent and independent variables is not required.

II. Methods and Theory

A. Network models with conservation relation

Consider a biochemical reaction network composed of n biochemical species S_i, $i = 1, \ldots, n$ and m reactions R_j, $j = 1, \ldots, m$ given by

$$R_j : \sum_{i=1}^{n} N_{ij}^s S_i \to \sum_{i=1}^{n} N_{ij}^p S_i, \tag{2}$$

where N_{ij}^s and N_{ij}^p are the substrate and product stoichiometric coefficients, respectively. Let us denote species concentrations by $x_i = [S_i]$, and summarize them with a species concentration vector $x \in \mathbb{R}^n$. The rate of reaction R_j is denoted by v_j, which yields the concentration dependent reaction rate vector $v(x) \in \mathbb{R}^m$. The components of the stoichiometric matrix $N \in \mathbb{Z}$ are given by $N_{ij} = N_{ij}^p - N_{ij}^s$. Balancing of the species then yields the differential equation

$$\dot{x} = Nv(x) \tag{3}$$

as a kinetic model for dynamics of the species concentrations, together with an initial condition $x(0) = x_0$.

Biochemical reaction networks are subject to the conservation of matter: the amount of entities which are neither added to nor removed from the system will not change over time. Mathematically, conservation relations in a biochemical reaction network are described by a vector $g \in \mathbb{R}^n$ such that

$$g^{\mathrm{T}}\dot{x} = g^{\mathrm{T}}Nv(x) = 0. \tag{4}$$

For a conservation relation, (4) is required to hold independent of the reaction rate vector $v(x)$. This is equivalent to

$$g \in \ker N^{\mathrm{T}}. \tag{5}$$

The number of linearly independent vectors g which satisfy condition (5) is $n - r$, where r is the rank of the stoichiometric matrix N [7]. All linear independent conservation relations are collected in the matrix $G \in \mathbb{R}^{n\times(n-r)}$, whose columns span the kernel of N^{T} and which satisfies

$$G^{\mathrm{T}}N = 0. \tag{6}$$

For each concentration vector x_0, chemical reaction theory defines the stoichiometric compatibility class [4] as the affine subspace

$$\mathcal{S} = x_0 + im\, N. \tag{7}$$

Regarding the conservation relations, it is then easy to see that $x \in \mathcal{S}$, if and only if

$$G^{\mathrm{T}}(x - x_0) = 0,$$

or

$$G^{\mathrm{T}}x = G^{\mathrm{T}}x_0. \tag{8}$$

In view of (4), one also sees that the solution $x(t)$ of the dynamic model (3) is restricted to the stoichiometric compatibility class of the initial condition $x(0)$.

In order to construct an equivalent model without conservation relations, a decomposition of the stoichiometric matrix into a link matrix $L \in \mathbb{R}^{n\times r}$ and a reduced stoichiometric matrix $N_r \in \mathbb{R}^{r\times m}$ was suggested in metabolic control theory [11]. By this decomposition,

$$PN = LN_r, \tag{9}$$

where $P \in \mathbb{R}^{n\times n}$ is a permutation matrix representing an appropriate reordering of the species vector, and both L and N_r are of full rank r. In metabolic control theory, L is commonly constructed to be of the special structure

$$L = \begin{pmatrix} I \\ L_0 \end{pmatrix}, \tag{10}$$

with the identity matrix of dimension r in the upper block, and an integer matrix L_0 in the lower block. For the reduced model, the permuted state vector Px can be partitioned accordingly as

$$Px = \begin{pmatrix} z \\ \tilde{z} \end{pmatrix}, \tag{11}$$

with $z \in \mathbb{R}^r$ the concentrations of the "independent" species and $\tilde{z} \in \mathbb{R}^{n-r}$ the concentrations of the "dependent" species. The reduced model is then commonly constructed as

$$\begin{aligned} \dot{z} &= N_r v(P^{\mathrm{T}}Lz) \\ x &= P^{\mathrm{T}}Lz \end{aligned} \tag{12}$$

with the initial condition z_0 taken from the first r components of Px_0 [11].

The classical reduction presented in this section is intuitive in that its state variables z are simply a subset of the original state variables x. However, this reduction has the significant drawback that the stoichiometric decomposition (9), with L as in (10), is numerically ill-conditioned and thus not very well suited for either large-scale networks or automated numerical analysis routines. Robust numerical routines to obtain L in the special form (10) use an orthogonal matrix decomposition followed by some carefully pivoted Gaussian elimination. As will be seen in Section III, a simpler reduction method can be devised by abandoning the separation into independent and dependent species, which is usually non-unique anyway.

B. Matrix decompositions

1) The singular value decomposition: The singular value decomposition (SVD) [8] is a matrix factorization where a matrix $M \in \mathbb{R}^{n\times m}$ is decomposed as a product of three matrices,

$$M = U\Sigma V^{\mathrm{T}} \tag{13}$$

with $U \in \mathbb{R}^{n\times n}$, $\Sigma \in \mathbb{R}^{n\times m}$, and $V \in \mathbb{R}^{m\times m}$. The three matrices U, Σ, and V have the special properties that U and V are orthogonal, that is $U^{\mathrm{T}}U = I_n$ and $V^{\mathrm{T}}V = I_m$, and Σ has all off-diagonal elements equal to zero.

The diagonal entries of Σ are called the singular values of M. These entries are sorted in descending order, that is $\Sigma_{11} \geq \Sigma_{22} \geq \ldots \geq \Sigma_{qq}$, with $q = \min(n, m)$. If r is the rank of M, then only the first r singular values are non-zero, and $\Sigma_{r+1,r+1} = \ldots = \Sigma_{qq} = 0$.

The singular value decomposition has been used previously on the stoichiometric matrix. In fact, Sauro and Ingalls [12] have suggested to determine the conservation relations by a SVD of the stoichiometric matrix, and also constructed an alternative link matrix L obeying the decomposition (9). The L constructed in this way will not be of the special structure (10) though, and they do not discuss how to derive a reduced model in this reference.

Doing a SVD of the stoichiometric matrix is also suggested in [3] as a method to determine the dominant modes of genome-scale metabolic networks. This allows to get a good overview picture of a large-scale network in terms of so called "eigen-reactions" and how individuals metabolites contribute to those.

2) The QR decompostion: In the QR decomposition with pivoting, a matrix $M \in \mathbb{R}^{n\times m}$ is decomposed as

$$MP = QR, \tag{14}$$

where $P \in \mathbb{R}^{m\times m}$ is a permutation matrix, $Q \in \mathbb{R}^{n\times n}$ an orthogonal matrix, i.e., $Q^{\mathrm{T}}Q = I_n$, and $R \in \mathbb{R}^{n\times m}$ an upper trapezoidal matrix [1]. The permutation matrix P captures column permutations in M that have been performed during the pivoting process. In the decomposition (14), R has the same rank as M. If $n \geq m$, R is upper triangular.

Pivoting has the effect that the diagonal elements of R are sorted by descending absolute value, i.e., $|R_{11}| \geq |R_{22}| \geq \cdots \geq |R_{\min(m,n),\min(m,n)}|$. Then, if M has rank $r \leq \min(m, n)$, the matrix R has the structure

$$R = \begin{pmatrix} R_1 \\ 0 \end{pmatrix}, \tag{15}$$

where $R_1 \in \mathbb{R}^{r\times m}$ is upper trapezoidal.

QR decomposition with pivoting using the Householder method was suggested in [15] as a numerically efficient and robust way to determine conservation relations in a stoichiometric network.

III. Results

A. Removing conservation relations via stoichiometric matrix decomposition

1) Decomposition of the stoichiometric matrix and model reduction: This section describes the removal of conservation relations from the biochemical network model (3) based on an orthogonal decomposition like SVD or QR. First, either SVD or QR decomposition is applied to the stoichiometric matrix. From this decomposition, an appropriate coordinate transformation for the state variables is constructed. The reduced model is then formulated easily in the transformed coordinates.

Both QR and SVD decomposition can be applied to yield a decomposition of the stoichiometrix matrix N as

$$N = UM, \tag{16}$$

where $U \in \mathbb{R}^{n\times n}$ is an orthogonal matrix. For the QR decomposition with pivoting, one has $U = Q$ and $M = RP^{\mathrm{T}}$. For the SVD decomposition, U is as in (13) and $M = \Sigma V^{\mathrm{T}}$. Recall from Section II-A that N is of rank $r \leq \min(n, m)$. Consider the following splitting of the matrix U in (16):

$$U = (L, G), \tag{17}$$

where $L \in \mathbb{R}^{n\times r}$ and $G \in \mathbb{R}^{n\times(n-r)}$. Since U is orthogonal, L and G have the properties that

- $L^{\mathrm{T}}L = I_r$,
- $G^{\mathrm{T}}G = I_{n-r}$,
- $G^{\mathrm{T}}L = 0$ and $L^{\mathrm{T}}G = 0$.

These properties will be essential to the following derivations.

From the properties of the matrix M in the decomposition (16), one can now find a matrix $N_r \in \mathbb{R}^{r\times m}$ such that

$$N = LN_r, \tag{18}$$

which is formally a decomposition as in the classical case (9), but with the special properties of L listed above, due to U being orthogonal. For the SVD decomposition, one has

$$\Sigma = \begin{pmatrix} \Sigma_1 \\ \Sigma_2 \end{pmatrix}, \tag{19}$$

with $\Sigma_1 \in \mathbb{R}^{r\times m}$ and $\Sigma_2 \in \mathbb{R}^{(n-r)\times m}$, $\Sigma_2 = 0$. With the splitting of U as in (17), one finds that

$$N = L\Sigma_1 V^{\mathrm{T}} + G\Sigma_2 V^{\mathrm{T}} = L\Sigma_1 V^{\mathrm{T}}, \tag{20}$$

and thus

$$N_r = \Sigma_1 V^{\mathrm{T}}. \tag{21}$$

For the QR decomposition, R is structured according to (15), and thus $N = LR_1P^{\mathrm{T}}$ and

$$N_r = R_1 P^{\mathrm{T}}. \tag{22}$$

Moreover, since $G^{\mathrm{T}}N = G^{\mathrm{T}}LN_r = 0$, the columns of G describe all conservation relations of the form (5) present in the network (3), but again with the special properties of G due to U being orthogonal.

2) The reduced kinetic equations: In this section, a reduced differential equation of order r is derived for the reaction network. The reduced model describes the dynamics of the reaction network within a fixed stoichiometric class. Also the formulas for transforming from the original to the reduced model and vice versa are provided. The state variable of the reduced kinetic system is $z \in \mathbb{R}^r$, and is defined by the equation

$$z = L^{\mathrm{T}} x. \tag{23}$$

The differential equation for z is derived as

$$\begin{aligned} \dot{z} &= L^{\mathrm{T}} \dot{x} \\ &= L^{\mathrm{T}} N v(x) \\ &= N_r v(x). \end{aligned} \tag{24}$$

In order to arrive at an equation in z only, one needs to substitute the variable x by a function of z. However, inverting (23) is not possible, since x is underdetermined in this equation. At this point, one needs to choose the stoichiometric class within which the reduced dynamics of the network are to be constructed. As was seen in (8), a stoichiometric class is defined by the equation $G^{\mathrm{T}} x = G^{\mathrm{T}} x_0$. Thus, for the stoichiometric class determined by $G^{\mathrm{T}} x_0$, the full characterization of x is given by

$$\begin{pmatrix} z \\ G^{\mathrm{T}} x_0 \end{pmatrix} = \begin{pmatrix} L^{\mathrm{T}} \\ G^{\mathrm{T}} \end{pmatrix} x = U^{\mathrm{T}} x \tag{25}$$

Since U is orthogonal, $U^{\mathrm{T}} = U^{-1}$, and one gets

$$x = U \begin{pmatrix} z \\ G^{\mathrm{T}} x_0 \end{pmatrix} = Lz + GG^{\mathrm{T}} x_0. \tag{26}$$

In conclusion, the reduced dynamics of the reaction network (3) within the stoichiometric class determined by $G^{\mathrm{T}} x_0$ are given by the ordinary differential equation

$$\dot{z} = N_r v(Lz + GG^{\mathrm{T}} x_0) \tag{27}$$

with the initial condition

$$z(0) = L^{\mathrm{T}} x_0. \tag{28}$$

For any $z(t)$ which is a solution of (27), the corresponding concentration vector $x(t)$ is obtained via equation (26). One can also check that this $x(t)$ is guaranteed to be in the stoichiometric class determined by $G^{\mathrm{T}} x_0$ for any $z \in \mathbb{R}^r$:

$$G^{\mathrm{T}} x = G^{\mathrm{T}}(Lz + GG^{\mathrm{T}} x_0) = G^{\mathrm{T}} x_0. \tag{29}$$

B. Applications

As discussed in the introduction, computational algorithms for the analysis of the reaction network (3) will often not respect the condition that the concentration vector x must stay within a stoichiometric class, usually defined from the initial condition of the network's differential equation as $G^{\mathrm{T}} x_0 = G^{\mathrm{T}} x(0)$. This section explores the benefits of using the suggested model reduction approach for steady state computation and stability analysis of steady states in the network.

Conservation relations within a network are in particular a problem for algorithms which compute a steady state of (3), that is a concentration vector x_s for which $Nv(x_s) = 0$. The iterative solvers which are commonly applied for steady state computation typically require a starting point x_0 to be defined, which would in principle be ideal for determining the stoichiometric class that is being considered. However, if the implementation of the solver does not consider conservation relations, for example a generic root finding algorithm, it is not guaranteed that the result x_s of the solver is in the same stoichiometric class as x_0. In fact, the stoichiometric class that the result x_s happens to fall in must be considered random and not under control of the algorithm's user.

An approach which does not suffer from this problem is to have a generic algorithm compute a steady state z_s of the reduced model (27), which satisfies $0 = N_r v(Lz_s + GG^{\mathrm{T}} x_0)$, where x_0 also specifies the stoichiometric class within which a steady state is to be computed, using $z_0 = L^{\mathrm{T}} x_0$ as starting point. Then, a steady state of the original model is given via the transformation rule (26) as $x_s = Lz_s + GG^{\mathrm{T}} x_0$. This steady state is indeed in the stoichiometric class specified by x_0, since $G^{\mathrm{T}} x_s = G^{\mathrm{T}} x_0$.

As an example to illustrate the problem with steady state computations, let us study a simple biochemical network describing a covalent modification cycle [6]. The covalent cycle is a frequent reaction motif in biochemical signal transduction and is formed by a signaling protein and two enzymes. One of the enzymes covalently adds a small chemical group, e.g. a phospate group, to the protein, and the other enzyme removes this group. In this way, the protein may cycle back and forth between the modified and unmodified state. The reaction network is given by

$$\begin{aligned} x_1 + x_2 &\leftrightharpoons x_5 \to x_3 + x_2 \\ x_3 + x_4 &\leftrightharpoons x_6 \to x_1 + x_4, \end{aligned} \tag{30}$$

where x_1 (x_3) is the unmodified (modified) protein, x_2 is the enzyme adding the modification, and x_4 is the enzyme undoing the modification. The network has $n = 6$ species and $m = 4$ reactions, and the rank of the stoichiometric matrix N is 3. Thus there are three conserved quantities

$$\begin{aligned} &x_1 + x_3 + x_5 + x_6 \\ &x_2 + x_5 \\ &x_4 + x_6. \end{aligned} \tag{31}$$

When solving for a steady state from a given initial point, it is usually desired that the values for the conserved quantities in steady state are the same as for the initial point.

To highlight the relevance of the reduction to the correct stoichiometric class, steady state computation for network (30) is performed. Reaction rate kinetics are assumed to be given by the law of mass action, with parameter values all equal to 1. The initial conditions which will determine the stoichiometric class are given in Table I, where x_1 and x_4 are varied to obtain different stoichiometric classes.

Figure 1 shows steady states of the network (30) computed from these five different initial conditions. Two approaches are compared: solving directly the equations resulting from the mass action model of the network, or solving the equations for the reduced model according to the previous section.

TABLE I

INITIAL CONDITIONS FOR THE COVALENT CYCLE

Variable	x_1	x_2	x_3	x_4	x_5	x_6
Value	$1, 2, \ldots, 5$	1	0	$0.2, 0.4, \ldots, 1$	0.1	0.1

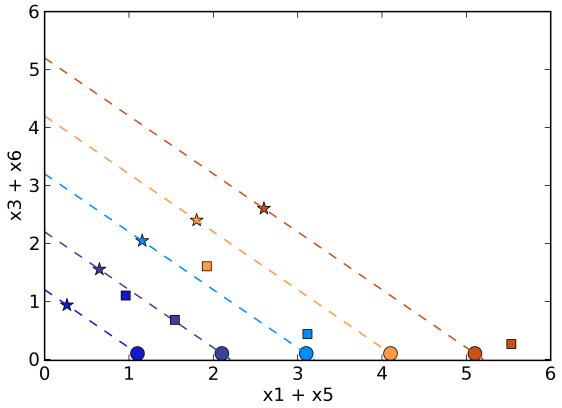

Fig. 1. Steady states in the covalent modification cycle, computed from the reduced model (stars) or the full model (squares). Different colors indicate steady states computed from different initial conditions (circles) with their stoichiometric classes (dashed lines).

While the latter correctly returns the steady state in the same stoichiometric class as the initial condition, the direct approach with the original network does not guarantee this property.

A naive approach to make sure that the solver's output x_s is in the same stoichiometric class as the provided starting point x_0 would be to add the constraints

$$G^{\mathrm{T}} x_s = G^{\mathrm{T}} x_0 \tag{32}$$

to the steady state equation $Nv(x_s) = 0$. However, there are two disadvantages with this naive approach compared to computing the steady state via the suggested model reduction approach. The naive approach yields a system of $2n - r$ equations in n variables. First, this is an overdetermined equation system, and solvers may run into numerical problems where due to floating-point approximation errors it may seem that the equations are infeasible. Second, even if the first problem does not occur, the method proposed here is still computationally more efficient, since only r equations in r variables have to be solved.

As a second case where the removal of conservation relations via the proposed method helps with a typical analysis task, let us consider the stability analysis of a reaction network in the proximity of a steady state. This analysis is typically based on the Jacobian of the right hand side of (3) evaluated at the steady state. By Lyapunov's stability theorem, small perturbations of the network away from the steady state x_s decay exponentially if and only if the Jacobian

$$J(x_s) = N \frac{\partial v}{\partial x}(x_s) \tag{33}$$

has all its eigenvalues in the left half complex plane, with real part less than zero.

In case the reaction network has conservation relations, i.e. the rank of N is less than n, the Jacobian $J(x_s)$ has a zero eigenvalue with multiplicity at least $n - r$, independent of the steady state x_s and the reaction rate law v: from (4), one gets

$$g^{\mathrm{T}} N \frac{\partial v}{\partial x}(x_s) = g^{\mathrm{T}} J(x_s) = 0. \tag{34}$$

Thus $J(x_s)$ has a zero eigenvalue with multiplicity at least equal to the number of linearly independent vectors g such that (4) holds, which is exactly $n - r$.

While the zero eigenvalue appears at first sight to exclude the possibility of exponential convergence to steady state, this is in fact not necessarily the case. When the multiplicity is equal to $n-r$, all perturbations related to the zero eigenvalue change the stoichiometric class of the concentration vector, and are thus not consistent with the network's intrinsic dynamics close to the considered steady state. In this case, the zero eigenvalue should be discarded for a dynamical stability analysis. However, it is not possible to just neglect the zero eigenvalue without doing a full conservation analysis. In case the multiplicity of the zero eigenvalue is larger than $n-r$, it is not only due to a conservation relation, and is then quite relevant for a stability analysis.

Instead of considering the original ODE (3) of the network, a better approach is to study the stability of the corresponding steady state $z_s = L^{\mathrm{T}} x_s$ in the reduced equations (27). The Jacobian of the reduced equations is given by

$$J_r(z_s) = N_r \frac{\partial v}{\partial x}(L z_s + G G^{\mathrm{T}} x_0) L, \tag{35}$$

and does not have a structurally zero eigenvalue related to conservation relations, since both N_r and L are of maximal rank. Therefore, it can be ascertained that solutions of both the reduced network (27) and of the original network (3), within the considered stoichiometric class specified by $G^{\mathrm{T}} x_0$, converge exponentially to the steady state z_s or x_s, respectively, if and only if the Jacobian $J_r(z_s)$ of the reduced model has all its eigenvalues in the left half complex plane.

In the covalent modification cycle (30), the existence of three linearly independent conservation relations corresponds to a zero eigenvalue with multiplicity 3. In fact, a numerical computation yields the eigenvalues (with multiplicity) $\{0, 0, 0, -0.45, -2.7, -3.1\}$ for the full Jacobian $J(x_s)$ at the steady state within the stoichiometric class defined by the initial conditions in Table I with $x_1 = 1$ and $x_4 = 0.2$. The reduced Jacobian $J_r(z_s)$ at this steady state has the eigenvalues $\{-0.45, -2.7, -3.1\}$.

C. Implementation and Availability

The proposed algorithm for the removal of conservation relations from biochemical reaction network in the SVD variant has been implemented in the Python package `pybrn`, available as open source from `http://pybrn.sourceforge.net`. The `pybrn` package uses the SVD implementation available in the Python Numpy package for matrix computations (`http://www.numpy.org`).

IV. Conclusions

This paper gives an approach to remove conservation relations from biochemical reaction network models, based on numerically robust matrix decompositions like the SVD or QR decomposition. These decompositions factor a given matrix into the product of orthogonal matrices and a matrix structured according to the rank of the decomposed matrix, and the here proposed method exploits this general structure. It is a simple, computationally efficient method to determine a reduced network model, which can be used for common analysis tasks such as computation of steady states, numerical simulation, or stability analysis.

Since the stoichiometric matrix is usually sparse, it would be particularly beneficial to employ a matrix decomposition tailored for sparse matrices, which are available for the QR decomposition [2].

The proposed approach is particularly appropriate for automated network analysis in software tools. In this case, there is no disadvantage from the property that coordinates of the reduced model can not be interpreted directly as species, since the software tools can handle this transparently, and communicate to the user only the original coordinates from the back-transformation $x = Lz + GG^{\mathrm{T}}x_0$. It is also useful for large networks, where a removal of conservation relations can not be done in the classical approach by hand or with numerically ill-conditioned methods.

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