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ON THE MATHEMATICAL STRUCTURE OF BALANCED CHEMICAL REACTION NETWORKS GOVERNED BY MASS ACTION KINETICS

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Abstract. Motivated by recent progress on the interplay between graph theory, dynamics, and systems theory, we revisit the analysis of chemical reaction networks described by mass action kinetics. For reaction networks possessing a thermodynamic equilibrium we derive a compact formulation exhibiting at the same time the structure of the complex graph and the stoichiometry of the network, and which admits a direct thermodynamical interpretation. This formulation allows us to easily characterize the set of positive equilibria and their stability properties. Furthermore, we develop a framework for interconnection of chemical reaction networks, and we discuss how the formulation leads to a new approach for model reduction.

Key words. chemical reaction networks, mass action kinetics, complex graph, weighted Laplacian matrix, equilibria, interconnection, model reduction

AMS subject classifications. 05C50, 34D05, 34D23, 80A30, 93A15, 93C15

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1. Introduction. Large-scale chemical reaction networks arise abundantly in systems biology and bioengineering. The most basic law prescribing the dynamics of the concentrations of the various species is the law of mass action, leading to polynomial differential equations for the evolution of each species. In order to handle the complexity of the resulting high-dimensional sets of nonlinear differential equations and to gain insight into their dynamical properties it is important to identify their underlying mathematical structure, and to express the equations in their most intrinsic way. In line with the recent surge of interest in network dynamics, at least two aspects should be fundamental in such a mathematical formulation: (1) a graph representation, and (2) a specific form of the differential equations.

The graph representation of chemical reaction networks is not immediate, since chemical reactions (the obvious candidates for identification with the edges of a graph) generally involve more than two chemical species (the simplest candidates for identification with the vertices). We will follow an approach that has been initiated and developed in the work of Horn and Jackson (see [15, 14]), and Feinberg (see, e.g., [11, 12]) by associating the complexes of the chemical reaction network, that is, the left- and right-hand sides of the reactions, with the vertices of a graph. The resulting directed graph, called the complex graph in this paper, is characterized by its incidence matrix. Furthermore, the expression of the complexes in the chemical species...
defines a matrix, called the complex stoichiometric matrix, while the standard stoichiometric matrix factorizes as the product of this complex stoichiometric matrix with the incidence matrix of the complex graph; see, e.g., [24, 3]. In order to derive a specific form of differential equations we will start with a formulation of mass action reaction network dynamics involving a nonsymmetric matrix defined by the complex graph and the chemical reaction constants, the basic form of which can be already found in the innovative paper by Sontag [26]. The main part of the paper, however, is devoted to a subclass of mass action reaction networks, called (detailed-)balanced reaction networks, where we assume the existence of a thermodynamical equilibrium, or, equivalently, where the detailed balance equations admit a solution. Balanced reaction networks are not only necessarily reversible but also involve, in cases in which the row rank of the stoichiometric matrix is smaller than the number of reactions, conditions on the forward and reverse reaction rate constants (usually referred to as the Wegscheider conditions; see [13]).

A basic contribution of the present paper is to derive for balanced chemical reaction networks a new formulation of the dynamics, involving a symmetric weighted Laplacian matrix of the complex graph. It will be shown how this form admits a natural thermodynamical interpretation, and in fact can be regarded as a full graph-theoretic version of the thermodynamical formulation for single reactions derived in the work of Katchalsky, Oster, and Perelson (see [22, 21]). As an immediate consequence we derive that all positive equilibria of balanced reaction networks are in fact thermodynamic equilibria. Furthermore, this new form of the equations of balanced chemical reaction networks enables us to give a very simple and insightful proof of some of the fundamental results obtained for a different class of mass action reaction networks (roughly speaking, weakly reversible networks with deficiency zero, or deficiency one under additional conditions) in the fundamental work of Horn and Jackson [15, 14] and Feinberg, e.g., [11, 12], which was an indispensable source of concepts and tools for the work reported in the present paper. In particular, we give a simple characterization of the set of positive equilibria and prove (under the assumption of persistence of the network) the asymptotic convergence to a unique equilibrium corresponding to the initial condition of the system. Subsequently we extend the formulation of the dynamics of chemical reaction networks to open reaction networks, i.e., involving an influx or efflux of some of their species, called boundary chemical species. It is shown how the chemical potentials of the boundary species define natural outputs for the system, resulting in a passive system, and how this leads to a theory of interconnection of open reaction networks, continuing the work of Oster and Perelson [21, 23].

The identification of an underlying weighted Laplacian matrix of the complex graph opens the way for the use of (algebraic) graph-theoretic methods, which seem essential for handling the complexity of large-scale reaction networks. In the current paper we present a new model reduction method, which is based on the fact that Schur complements of Laplacian matrices are again Laplacian. This reduction procedure draws inspiration from a similar technique in the theory of large-scale electrical circuits, sometimes referred to as Kron reduction, and leads to an approximating reduced model which is again a balanced mass action reaction network.

The paper is organized as follows. In section 2, we summarize the mathematical structure of chemical reaction networks described in, e.g., [15, 14, 11, 12, 24]; see also [3] for a clear account. In section 3, we recall the law of mass action kinetics, the Wegscheider conditions for existence of a thermodynamic equilibrium, and we derive...
for chemical reaction networks admitting a thermodynamic equilibrium an insightful formulation involving a symmetric weighted Laplacian matrix for the complex graph. Before providing the thermodynamical interpretation of this formulation, we discuss the decomposition of the complex graph into its connected components, largely following the exposition in [24], and its implications for the established formulation of balanced reaction networks. In section 4 we utilize the developed formulation to derive a simple characterization of the set of positive equilibria, and we give a Lyapunov analysis to show the convergence to a unique equilibrium depending on the initial concentration vector. In section 5 the framework is extended to reaction networks with inflows and outflows, and we discuss interconnection of such reaction networks through shared boundary chemical species. The application of the established formulation of balanced reaction networks to model reduction is discussed in section 6. Finally, section 7 contains the conclusions and topics of current and future research.

**Notation.** The space of \( m \)-dimensional real vectors is denoted by \( \mathbb{R}^m \), the space of \( m \)-dimensional real vectors consisting of all strictly positive entries by \( \mathbb{R}^m_+ \), and the space of \( m \)-dimensional real vectors consisting of all nonnegative entries by \( \mathbb{R}^m_{\geq 0} \). The rank of a real matrix is denoted by \( \text{rank} \), while its transpose is denoted as \( A^T \). Furthermore, \( \ker A \) and \( \text{im} A \) denote the kernel and image, respectively, of the matrix \( A \). Given \( a_1, \ldots, a_n \in \mathbb{R} \), \( \text{diag}(a_1, \ldots, a_n) \) denotes the diagonal matrix with diagonal entries \( a_1, \ldots, a_n \); this notation is extended to the block-diagonal case when \( a_1, \ldots, a_n \) are square matrices. If \( U \) is a linear subspace of \( \mathbb{R}^m \), then \( U^\perp \) denotes its orthogonal subspace (with respect to the standard Euclidean inner product). \( \mathbb{1}_n \) denotes the \( n \)-dimensional vector with all entries equal to 1. The time-derivative \( \frac{dx}{dt}(t) \) of a vector \( x \) depending on time \( t \) will be denoted by \( \dot{x}(t) \) or \( \dot{x} \). The mapping \( \text{Ln} : \mathbb{R}^m_+ \rightarrow \mathbb{R}^m, \ x \mapsto \text{Ln}(x) \), is defined as the mapping whose \( i \)-th component is given as \( (\text{Ln}(x))_i := \ln(x_i) \). Similarly, the mapping \( \text{Exp} : \mathbb{R}^m \rightarrow \mathbb{R}^m_+ \), \( x \mapsto \text{Exp}(x) \), is the mapping whose \( i \)-th component is given as \( (\text{Exp}(x))_i := \exp(x_i) \). Also, we define for any vectors \( x, z \in \mathbb{R}^m \) the vector \( x \cdot z \in \mathbb{R}^m \) as the elementwise product \( (x \cdot z)_i := x_i z_i, \ i = 1, \ldots, m \), and the vector \( \frac{x}{z} \in \mathbb{R}^m \) as the elementwise quotient \( \left( \frac{x}{z} \right)_i := \frac{x_i}{z_i}, \ i = 1, \ldots, m \). Note that with these notations \( \text{Exp}(x+z) = \text{Exp}(x) \cdot \text{Exp}(z) \) and \( \text{Ln}(x \cdot z) = \text{Ln}(x) + \text{Ln}(z) \), \( \text{Ln} \left( \frac{x}{z} \right) = \text{Ln}(x) - \text{Ln}(z) \).

2. Chemical reaction network structure. In this section we will survey the basic topological structure of chemical reaction networks. The first step is the stoichiometry expressing the conservation laws of chemical reactions. A next innovative step was taken in the work of Horn and Jackson and Feinberg (see [15, 14, 11, 12]) by defining the complexes of a reaction to be the vertices of a graph. We will summarize these achievements in a slightly more abstract manner, also making use of the expositions given in [24, 3].

2.1. Stoichiometry. Consider a chemical reaction network involving \( m \) chemical species (metabolites), among which \( r \) chemical reactions take place. The basic structure underlying the dynamics of the vector \( x \in \mathbb{R}^m_+ \) of concentrations \( x_i, \ i = 1, \ldots, m \), of the chemical species is given by the balance laws

\[
\dot{x} = Sv,
\]

where \( S \) is an \( m \times r \) matrix, called the **stoichiometric matrix**. The stoichiometric matrix \( S \), which consists of (positive and negative) integer elements, captures the basic conservation laws of the reactions. For example, the stoichiometric matrix of
the two coupled reactions involving the chemical species $X_1, X_2, X_3$ given as
\begin{equation}
X_1 + 2X_2 \rightleftharpoons X_3 \rightleftharpoons 2X_1 + X_2
\end{equation}
is
\[
S = \begin{bmatrix}
-1 & 2 \\
-2 & 1 \\
1 & -1
\end{bmatrix}.
\]
The elements of the vector $v \in \mathbb{R}^r$ are commonly called the reaction fluxes. In section 3.1 we review how $v$ can be expressed as a function $v(x)$ using the law of mass action kinetics. In many cases of interest, especially in biochemical reaction networks, chemical reaction networks are intrinsically open, in the sense that there is a continuous exchange with the environment (in particular, flow of chemical species and connection to other reaction networks). This will be modeled by a vector $v_b \in \mathbb{R}^b$ consisting of $b$ boundary fluxes $v_b$, leading to an extended model
\begin{equation}
\dot{x} = Sv + Sbv_b.
\end{equation}
Here the matrix $S_b$ consists of mutually different columns whose elements are all 0 except for one element equal to 1 or $-1$. The nonzero elements correspond to boundary fluxes for part of the chemical species, called the boundary chemical species, with $+1$ denoting an uptake flux and $-1$ a demand flux.

The stoichiometry already contains useful information about the network dynamics, independent of the precise form of the reaction rate $v(x)$. In particular, if an $m$-dimensional row-vector $k$ satisfies $kS = 0$, then the quantity $kx$ is a conserved quantity for the dynamics $\dot{x} = Sv(x)$ for all possible reaction rates $v = v(x)$. Indeed, $\frac{d}{dt}kx = kSv(x) = 0$. If $k \in \mathbb{R}^m_+$, then the quantity $kx$ is commonly called a conserved moiety. Geometrically, for all possible fluxes the solutions of the differential equations $\dot{x} = Sv(x)$ starting from an initial state $x_0$ will always remain within the affine space $x_0 + imS$. In cases involving an open chemical reaction network, $\frac{d}{dt}kx = 0$ modifies into $\frac{d}{dt}kx = kS_bv_b$, expressing that the time evolution of the quantity $kx$ depends only on the boundary fluxes $v_b$.

2.2. The complex graph. The network structure of a chemical reaction network cannot be directly captured by a graph involving the chemical species (since generally there are more than two species involved in a reaction). Instead, we will follow an approach originating in the work of Horn and Jackson (see [15, 14]) and Feinberg [11, 12] introducing the space of complexes. The set of complexes of a chemical reaction network is simply defined as the union of all the different left- and right-hand sides (substrates and products) of the reactions in the network, where a product complex of one reaction may be the substrate complex of another and a complex may be the product/substrate complex of more than one reaction. Thus, the complexes corresponding to the network (2.2) are $X_1 + 2X_2, X_3$ and $2X_1 + X_2$.

Denoting the number of complexes by $c$, the expression of the complexes in terms of the chemical species is formalized by an $m \times c$ matrix $Z$, called here the complex stoichiometric matrix, whose $\rho$th column captures the expression of the $\rho$th complex in the $m$ chemical species. For example, for the network (2.2)
\[
Z = \begin{bmatrix}
1 & 0 & 2 \\
2 & 0 & 1 \\
0 & 1 & 0
\end{bmatrix}.
\]

\footnote{For an approach based on species-reaction graphs, see, e.g., [7, 8, 3].}
Note that by definition all elements of the matrix $Z$ are nonnegative integers.

Since the complexes are left- and right-hand sides of the reactions, they can be naturally associated with the vertices of a directed graph, with edges corresponding to the reactions. The complexes on the left-hand side of the reactions are called the substrate complexes, and those on the right-hand side of the reactions are called the product complexes. Formally, the reaction $\sigma = \pi$ between the $\sigma$th and the $\pi$th complex defines a directed edge with tail vertex being the $\sigma$th complex and head vertex being the $\pi$th complex. The resulting graph is called the complex graph.

Recall (see, e.g., [5]) that any directed graph is defined by its incidence matrix $B$. This is an $c \times r$ matrix, $c$ being the number of vertices (complexes) and $r$ being the number of edges (reactions), with $(\rho,j)$th element equal to $-1$ if vertex $\rho$ is the tail vertex of edge $j$ and 1 if vertex $\rho$ is the head vertex of edge $j$, while 0 otherwise. The relation between the complex stoichiometry matrix $Z$ and the standard stoichiometric matrix $S$ is expressed as

\begin{equation}
S = ZB.
\end{equation}

3. The dynamics of mass action kinetics chemical reaction networks.

In this section we will derive a compact form for the dynamics of a chemical reaction network, whose reactions are described by mass action kinetics. After deriving a general form in section 3.1 we will focus on balanced chemical reaction networks.

3.1. The general form of mass action kinetics. The dynamics of the concentration vector $x$ (or, equivalently, in case of a fixed volume, the vector $n$ of mole numbers) is given once the internal fluxes $v$ are specified as a function $v = v(x)$ of $x$, defining the reaction rates. The most basic model for specifying the reaction rates is mass action kinetics, defined as follows. Consider the first reaction in (2.2),

\begin{equation}
X_1 + 2X_2 \rightleftharpoons X_3,
\end{equation}

involving the three chemical species $X_1, X_2, X_3$ with concentrations $x_1, x_2, x_3$. In mass action kinetics the reaction is considered to be a combination of the forward reaction $X_1 + 2X_2 \rightarrow X_3$ with forward rate equation $v_{\text{forw}}(x_1, x_2) = k_{\text{forw}} x_1 x_2^2$ and the reverse reaction $X_1 + 2X_2 \leftarrow X_3$, with rate equation $v_{\text{rev}}(x_3) = k_{\text{rev}} x_3$. The constants $k_{\text{forw}}$, $k_{\text{rev}}$ are called, respectively, the forward and reverse reaction constants. The net reaction rate is thus

\begin{equation}
v(x_1, x_2, x_3) = v_{\text{forw}}(x_1, x_2) - v_{\text{rev}}(x_3) = k_{\text{forw}} x_1 x_2^2 - k_{\text{rev}} x_3.
\end{equation}

In general, the mass action reaction rate of the $j$th reaction of a chemical reaction network, from a substrate complex $S_j$ to a product complex $P_j$, is given as

\begin{equation}
v_j(x) = k_j^{\text{forw}} \prod_{i=1}^m x_i Z_{ij} - k_j^{\text{rev}} \prod_{i=1}^m x_i Z_{ij}^{\text{rev}},
\end{equation}

where $Z_{ij}$ is the $(i, \rho)$th element of the complex stoichiometric matrix $Z$, and $k_j^{\text{forw}}, k_j^{\text{rev}} \geq 0$ are the forward/reverse reaction constants of the $j$th reaction, respectively. Without loss of generality we will throughout assume that for every $j$ the constants $k_j^{\text{forw}}, k_j^{\text{rev}}$ are not both equal to zero (since otherwise the $j$th reaction is not active).

Equation (3.1) can be rewritten in the following way. Let $Z_{S_j}$ and $Z_{P_j}$ denote the columns of the complex stoichiometry matrix $Z$ corresponding to the substrate
complex $S_j$ and the product complex $P_j$ of the $j$th reaction. Using the mapping $\ln : \mathbb{R}_+^c \rightarrow \mathbb{R}^c$ as defined at the end of the introduction, the mass action reaction equation (3.1) for the $j$th reaction takes the form

$$v_j(x) = k_j^{\text{forw}} \exp \left( Z_{S_j}^T \ln(x) \right) - k_j^{\text{rev}} \exp \left( Z_{P_j}^T \ln(x) \right).$$

The complete reaction network dynamics is now described as follows. Denote the vector of reaction rates for the complete set of reactions by $v(x) = [v_1(x) \cdots v_r(x)]^T$. For every $\sigma, \pi \in \{1, \ldots, c\}$, denote by $a_{\sigma\pi} = \sum_j k_j^{\sigma\pi}$, $a_{\sigma\pi} = \sum_j k_j^{\pi\sigma}$ if $(\sigma, \pi) = (S_j, P_j)$, $j \in \{1, \ldots, r\}$, and $a_{\sigma\pi} = 0$ if there are no reactions between complexes indexed by $\sigma$ and $\pi$. Define the weighted adjacency matrix $A$ of the complex graph as the matrix with $(\sigma, \pi)$th element $a_{\sigma\pi}$, where $\sigma, \pi \in \{1, \ldots, c\}$. Furthermore, define the matrix $L$ as the $c \times c$ matrix

$$L := \Delta - A,$$

where $\Delta$ is the diagonal matrix whose $(\rho, \rho)$th element is equal to the sum of the elements of the $\rho$th column of $A$. Then it can be verified that the vector $Bv(x)$ for the mass action reaction rate vector $v(x)$ is equal to

$$Bv(x) = -Z \text{Exp} \left( Z^T \ln(x) \right),$$

where the mapping $\text{Exp} : \mathbb{R}^c \rightarrow \mathbb{R}_+^c$ has been defined at the end of the introduction. Hence the dynamics can be compactly written as

$$\dot{x} = -ZL \text{Exp} \left( Z^T \ln(x) \right).$$

A similar expression of the dynamics corresponding to mass action kinetics, in less explicit form, was already obtained in [26].

3.2. Balanced mass action kinetics. In the rest of this paper we will focus on an important subclass of mass action chemical reaction networks, characterized by the existence of a thermodynamic equilibrium.

**Definition 3.1.** A vector of concentrations $x^* \in \mathbb{R}_+^m$ is called an equilibrium for the dynamics $\dot{x} = Sv(x)$ if $Sv(x^*) = 0$, and a thermodynamic equilibrium if $v(x^*) = 0$. A chemical reaction network $\dot{x} = Sv(x)$ is called (detailed) balanced if it admits a thermodynamic equilibrium $x^* \in \mathbb{R}_+^m$.

Clearly, any thermodynamic equilibrium is an equilibrium, but not necessarily the other way around (since in general $S = ZB$ is not injective).

3.2.1. The existence of thermodynamic equilibria. Necessary and sufficient conditions for the existence of a thermodynamic equilibrium can be derived in the following linear-algebraic way following [13]. These conditions are usually referred to as the Wegscheider conditions, generalizing the classical results of [28].

Consider the $j$th reaction from substrate $S_j$ to product $P_j$, described by the mass action rate equation (3.2). Then $x^* \in \mathbb{R}_+^m$ is a thermodynamic equilibrium, i.e., $v(x^*) = 0$, if and only if

$$k_j^{\text{forw}} \exp \left( Z_{S_j}^T \ln(x^*) \right) = k_j^{\text{rev}} \exp \left( Z_{P_j}^T \ln(x^*) \right), \quad j = 1, \ldots, r.$$
Equations (3.5), referred to as the detailed balance equations, can be rewritten as follows. Define the equilibrium constant $K_j^{eq}$ of the $j$th reaction as (assuming $k_j^{rev} \neq 0$)

\begin{equation}
K_j^{eq} := \frac{k_j^{forw}}{k_j^{rev}}.
\end{equation}

Then the detailed balance equations (3.5) are seen to be equivalent to

\begin{equation}
K_j^{eq} = \exp \left( Z_0^j \log(x^*) - Z_j^j \log(x^*) \right), \quad j = 1, \ldots, r.
\end{equation}

Collecting all reactions, and making use of the incidence matrix $B$ of the complex graph, this amounts to the vector equation

\begin{equation}
K^{eq} = \text{Exp} \left( B^T Z^T \log(x^*) \right) = \text{Exp} \left( S^T \log(x^*) \right),
\end{equation}

where $K^{eq}$ is the $r$-dimensional vector with $j$th element $K_j^{eq}, j = 1, \ldots, r$.

**Proposition 3.2.** There exists a thermodynamic equilibrium $x^* \in \mathbb{R}_+^m$ if and only if $k_j^{forw} > 0, k_j^{rev} > 0$ for all $j = 1, \ldots, r$, and furthermore

\begin{equation}
\ln (K^{eq}) \in \text{im} \ S^T.
\end{equation}

**Proof.** Clearly $k_j^{forw} > 0, k_j^{rev} > 0, j = 1, \ldots, r$, is a necessary condition for the existence of a thermodynamic equilibrium. The existence of a vector $\log(x^*), x^* \in \mathbb{R}_+^m$, satisfying (3.8) is obviously equivalent to (3.9). □

It also follows that once a thermodynamic equilibrium $x^*$ is given, the set of all thermodynamic equilibria is described as follows.

**Proposition 3.3.** Let $x^* \in \mathbb{R}_+^m$ be a thermodynamic equilibrium. Then the set of all thermodynamic equilibria is given by

\begin{equation}
E := \{ x^{**} \in \mathbb{R}_+^m \mid S^T \log(x^{**}) = S^T \log(x^*) \}.
\end{equation}

**Remark 3.1.** Usually the conditions (3.9) are rewritten in the following more constructive form. By basic linear algebra (3.9) is satisfied if and only if for all row-vectors $\sigma$ satisfying $\sigma S^T = 0$ we have $\sum_{j=1}^r \sigma_j \ln K_j^{eq} = 0$. Putting back in the definition of the equilibrium constants (3.6), this is seen to be equivalent to the usual form of the Wegscheider conditions\(^4\)

\begin{equation}
\prod_{j=1}^r (k_j^{forw})^{\sigma_j} = \prod_{j=1}^r (k_j^{rev})^{\sigma_j}.
\end{equation}

**3.2.2. The standard form of balanced mass action reaction networks.** For balanced mass action chemical reaction networks we can further rewrite the dynamics (3.4) in the following useful way. Let $x^* \in \mathbb{R}_+^m$ be a thermodynamic equilibrium, i.e., $v(x^*) = 0$. Consider the rewritten form (3.7) of the “detailed balance” equations. These equations allow us to define [21, 22] the “conductance” $\kappa_j(x^*) > 0$

\(^4\)Note that (3.11) only needs to be checked for a maximally independent set of row-vectors $\sigma$ satisfying $\sigma S^T = 0$. By writing this as $\sigma B^T Z^T = 0$ this can be related to the topological structure of the complex graph and to the deficiency of the network; cf. [13]. Clearly, if the row rank of $S$ is equal to $r$, then the Wegscheider conditions are void. The Wegscheider conditions admit a thermodynamical interpretation, since they are intimately related to microscopic reversibility and the independence of the increase of Gibbs’ energy of the path in the reaction network; see also [21, 22].
of the \( j \)th reaction as the common value of the forward and reverse reaction rates at thermodynamic equilibrium \( x^* \), i.e.,

\[
\kappa_j(x^*) := k_{j}^{\text{forw}} \exp \left( \frac{Z_{S_j}^T \ln(x^*)}{\kappa} \right) = k_{j}^{\text{rev}} \exp \left( \frac{Z_{S_j}^T \ln(x^*)}{\kappa} \right), \quad j = 1, \ldots, r.
\]

Then the mass action reaction rate (3.2) of the \( j \)th reaction can be rewritten as

\[
u_j(x) = \kappa_j(x^*) \left[ \exp \left( \frac{Z_j^T \ln \left( \frac{x}{x^*} \right) \kappa \right) - \exp \left( \frac{Z_j^T \ln \left( \frac{x}{x^*} \right) \kappa \right) \right),
\]

where for any vectors \( x, z \in \mathbb{R}^m \) the quotient vector \( \frac{x}{z} \in \mathbb{R}^m \) is defined elementwise (see the end of the introduction).

Defining the \( r \times r \) diagonal matrix of conductances as

\[
\mathcal{K} := \text{diag}(\kappa_1(x^*), \ldots, \kappa_r(x^*)),
\]

it follows that the mass action reaction rate vector of a balanced reaction network can be written as

\[
v(x) = -\mathcal{K} B^T \text{Exp} \left( Z^T \ln \left( \frac{x}{x^*} \right) \kappa \right),
\]

and thus the dynamics of a balanced reaction network takes the form

\[
\dot{x} = -Z B K B^T \text{Exp} \left( Z^T \ln \left( \frac{x}{x^*} \right) \kappa \right), \quad \kappa > 0.
\]

This form will be the starting point for the analysis of balanced chemical reaction networks in the rest of this paper.

The matrix \( \mathcal{L} := B K B^T \) in (3.14) defines a \textit{weighted Laplacian matrix} \(^5\) for the complex graph, with weights given by the conductances \( \kappa_1(x^*), \ldots, \kappa_r(x^*) \). Note that \( \mathcal{L} \) is in general different from the matrix \( L \) obtained before; cf. (3.3). The symmetrization of \( L \) has been accomplished by the modification of \( \ln(x) \) into \( \ln \left( \frac{x}{x^*} \right) \), using the assumption that \( x^* \) is a thermodynamic equilibrium. A well-known [5] property of weighted Laplacian matrices \( B K B^T \) is that they are independent of the \textit{orientation} of the graph. Thus we may replace any reaction \( S = P \) by \( P = S \) without altering the Laplacian \( B K B^T \), in agreement with the usual understanding of a reversible reaction network.

Note that \( \mathcal{K} \), and therefore the Laplacian matrix \( \mathcal{L} = B K B^T \), is \textit{dependent} on the choice of the thermodynamic equilibrium \( x^* \). In section 3.3 we will see that actually this dependence is minor: for a connected complex graph the matrix \( \mathcal{K} \) is, up to a \textit{positive multiplicative factor}, independent of the choice of \( x^* \).

\subsection*{3.3. The linkage classes of the complex graph.}

The complex graph provides a number of tools for the analysis of reaction networks. Recall that for any directed graph \([5]\)

\[
\text{rank} B = \text{rank} \mathcal{L} = c - \ell,
\]

where \( c \) is the number of vertices of the graph, and \( \ell \) is equal to the number of \textit{components} \(^6\) of the complex graph, the \textit{linkage classes} in the terminology of [15],

\(^5\)A weighted Laplacian matrix [5] is a symmetric matrix with positive diagonal elements, non-positive off-diagonal elements, with zero column and row sums.

\(^6\)A directed graph is \textit{connected} if there is a path (a number of unoriented edges) between every two distinct vertices of the graph. The components of a directed graph are the maximal connected subgraphs.
Furthermore, if there is one linkage class in the network (i.e., the graph is connected and \( \text{rank } B = \text{rank } L = c - 1 \)), then

\[
(3.16) \quad \ker L = \ker B^T = \text{span } \mathbf{1}_c,
\]

where as before \( \mathbf{1}_c \) is the \( c \)-dimensional vector with elements all equal to 1.

In general, if the reaction network has \( \ell \) linkage classes, then the network can be decomposed as follows. Let the \( p \)th linkage class have \( r_p \) reactions between \( c_p \) complexes. Partition \( Z, B, \) and \( K \) matrices according to the various linkage classes as

\[
Z = [Z_1 \ Z_2 \ \ldots \ Z_\ell],
\]

\[
B = \begin{bmatrix}
B_1 & 0 & 0 & \ldots & 0 \\
0 & B_2 & 0 & \ldots & 0 \\
\vdots & \vdots & \ddots & \vdots & \vdots \\
0 & 0 & \ldots & 0 & B_{\ell-1} \\
0 & 0 & \ldots & 0 & B_{\ell}
\end{bmatrix},
\]

\[
K = \text{diag}(K_1, K_2, \ldots, K_\ell),
\]

where for \( p = 1, \ldots, \ell \), \( Z_p \in \mathbb{R}^{m \times c_p} \), \( B_p \in \mathbb{R}^{c_p \times r_p} \), and \( K_p \in \mathbb{R}^{r_p \times r_p} \) denote, respectively, the complex stoichiometric matrix, incidence matrix, and the diagonal matrix of balanced reaction constants for the \( p \)th linkage class. Furthermore, \( S_p = Z_pB_p \) is the stoichiometric matrix of the \( p \)th linkage class. It follows that (3.14) can be expanded as

\[
(3.18) \quad \dot{x} = - \sum_{p=1}^{\ell} Z_pB_pK_pB_p^T \text{Exp} \left( Z_p^T \text{Ln} \left( \frac{x}{x^*} \right) \right),
\]

expressing the contributions of each linkage class to the chemical reactions.

The above expressions also yield the following alternative characterization of the set of thermodynamic equilibria \( \mathcal{E} \) given in (3.10). In case of a connected complex graph we obtain, using \( S^T = B^TZ^T \) and \( \ker B^T = \text{span } \mathbf{1}_c \),

\[
(3.19) \quad \mathcal{E} = \{ x^{**} \in \mathbb{R}_+^m \mid Z^T \text{Ln} (x^{**}) - Z^T \text{Ln} (x^*) \in \text{span } \mathbf{1}_c \}.
\]

For disconnected complex graphs the same formula holds for every connected component. This observation has the following useful consequence.

**Proposition 3.4.** Consider two thermodynamic equilibria \( x^* \) and \( x^{**} \) with corresponding diagonal matrices \( K(x^*) \) and \( K(x^{**}) \) as defined in (3.13). Assume that the complex graph is connected. Then there exists a positive constant \( d \) such that

\[
K(x^{**}) = dK(x^*), \quad \text{Exp} \left( Z^T \text{Ln} \left( \frac{x}{x^{**}} \right) \right) = \frac{1}{d} \text{Exp} \left( Z^T \text{Ln} \left( \frac{x}{x^*} \right) \right).
\]

Furthermore, for a nonconnected complex graph there exist positive constants \( d_p, p = 1, \ldots, \ell \), such that for each \( p \)th linkage class the diagonal matrix \( K_p(x^*) \) given in (3.17) satisfies \( K_p(x^{**}) = d_pK_p(x^*), \) \( p = 1, \ldots, \ell \).
Proof. Assume that the complex graph is connected. Then by (3.19) there exists a constant $c$ such that $Z^T \ln(x^{**}) = Z^T \ln(x^*) + c1$. Hence by the definition of the conductances $\kappa_j$ in (3.12) we have

$$
\kappa_j(x^{**}) = k_j^{\text{form}} \exp \left( Z_{S_j}^T \ln(x^{**}) \right) = k_j^{\text{form}} \exp \left( Z_{S_j}^T \ln(x^*) + c \right) = d k_j^{\text{form}} \exp \left( Z_{S_j}^T \ln(x^*) \right) = dk_j(x^*),
$$

with $d := \exp(c) > 0$ for each $j = 1, \ldots, r$. The rest follows easily.

Hence the weighted Laplacian matrix $\mathcal{L} = B \mathbf{K} B^T$, is, up to a multiplicative factor, independent of the choice of the thermodynamic equilibrium $x^*$. The properties of this matrix (e.g., its eigenvalue distribution\footnote{Note that the set of eigenvalues of $B \mathbf{K} B^T$ consists of 0 (with multiplicity equal to the number of components of the graph) and strictly positive real numbers; cf. [5].}) serve as an important indicator of the network structure. In section 6 we will exploit the Laplacian matrix for model reduction purposes.

3.4. Deficiency. An important notion relating the structure of the complex graph to the stoichiometry, as introduced in the work of Feinberg [11], is the concept of deficiency.

Definition 3.5. The deficiency of a chemical reaction network with complex stoichiometric matrix $Z$ and incidence matrix $B$ is defined as

$$
\delta := \text{rank} B - \text{rank} ZB = \text{rank} B - \text{rank} S \geq 0.
$$

A reaction network is said to have zero-deficiency if $\delta = 0$.

Note that zero-deficiency is equivalent to $\ker Z \cap \text{im} B = 0$, or to the mapping $Z : \text{im} B \subset \mathbb{R}^c \to \mathbb{R}^m$ being injective. Hence in the zero-deficiency case there is a one-to-one correspondence between the rate vector $\dot{x} \in \text{im} S \subset \mathbb{R}^m$ of chemical species $x \in \mathbb{R}_+^n$ and the rate vector $\dot{y} \in \text{im} B \subset \mathbb{R}^c$ of complexes $y \in \mathbb{R}^c$. Many chemical reaction networks are zero-deficient, although with growing complexity (especially in biochemical networks), deficiency greater than zero is likely to occur. This is also expressed in the following proposition showing that for a reaction network with zero-deficiency all its linkage classes have zero-deficiency, but not necessarily the other way around.

Proposition 3.6 (see [24]). Consider a chemical reaction network with $\ell$ linkage classes as in (3.17). If the network has zero-deficiency, then necessarily the linkage classes have zero-deficiency. Zero-deficiency of the linkage classes implies zero-deficiency of the total network if and only if additionally

$$
\bigcap_{p=1}^\ell \text{im} \bar{Z}_p \bar{B}_p = 0,
$$

where $\bar{Z}_p$ and $\bar{B}_p$ denote the columns of $Z$, respectively, the rows of $B$, in (3.17) corresponding to $Z_p$, respectively, $B_p$.

3.5. Thermodynamical viewpoint. In this section we will indicate the thermodynamical interpretation of the quantities introduced before and show how this suggests a Lyapunov function which will be used in the next section. For more details regarding the thermodynamical approach to chemical reaction kinetics we refer the reader to [22, 21].
Recall that for an ideal dilute solution the chemical potential \( \mu_i \) of chemical species \( i \) with mole number \( n_i \) is given by

\[
\mu_i(x_i) = \mu_i^o + RT \ln \left( \frac{n_i}{V} \right) = \mu_i^o + RT \ln(x_i),
\]

with \( \mu_i^o \) a reference potential, \( R \) the universal gas constant, \( T \) the temperature, \( V \) the volume, and \( x_i = \frac{n_i}{V} \) the concentration. The \( m \)-dimensional vector \( \mu \) with components \( \mu_i \) is called the chemical potential vector, while the vector \( \mu^o \) with components \( \mu_i^o \) is called the reference chemical potential vector.

Starting instead from the formulation of a balanced chemical reaction network in (3.14), corresponding to a thermodynamic equilibrium \( x^* \), we may define the chemical potential vector \( \mu \) and the reference chemical potential vector \( \mu^o \) as

\[
\mu(x) = RT \ln \left( \frac{x}{x^*} \right), \quad \mu^o = -RT \ln(x^*).
\]

We conclude that \( \ln(x^*) = \ln(x) - \ln(x^*) \) is, up to the constant \( RT \), equal to the chemical potential vector, while \( -\ln(x^*) \) is, up to this same constant, equal to the reference chemical potential vector. An important role in (3.14) is formed by the quantity \( \gamma(x) := Z^T \mu(x) = (RT)Z^T \ln \left( \frac{x}{x^*} \right) \), which we will call the complex thermodynamical affinity. Correspondingly, we refer to \( \gamma^o := Z^T \mu^o \) as the reference complex thermodynamical affinity. Recalling from (3.8) the expression of the vector of equilibrium constants as \( K^eq = \exp \left( S^T \ln(x^*) \right) \), it follows that \( RT \ln(K^eq) = (RT)S^T \ln(x^*) = -S^T \mu^o = -B^T \gamma^o \). The dynamics of a balanced reaction network is determined by the complex thermodynamical affinity \( \gamma \), which acts as a “driving force” for the reactions.\(^8\)

In thermodynamics the vector of chemical potentials is derived as the vector of partial derivatives of the Gibbs’ free energy. This suggests defining the Gibbs’ free energy\(^9\) as

\[
G(x) = RT x^T \ln \left( \frac{x}{x^*} \right) + RT (x^* - x)^T 1_m,
\]

where \( 1_m \) denotes a vector of dimension \( m \) with all ones. Indeed, with this definition it is immediately checked that \( \frac{\partial G}{\partial x}(x) = RT \ln \left( \frac{x}{x^*} \right) = \mu(x) \).

For simplicity of notation we will assume in the rest of this paper that \( RT = 1 \), or, equivalently, we will redefine

\[
\mu(x) := \ln \left( \frac{x}{x^*} \right), \quad \gamma(x) := Z^T \mu(x) = Z^T \ln \left( \frac{x}{x^*} \right),
\]

\[
G(x) := x^T \ln \left( \frac{x}{x^*} \right) + (x^* - x)^T 1_m.
\]

Then the equation of a balanced reaction network (3.14) can be also written as

\[
\dot{x} = -Z B K B^T \exp \left( Z^T \frac{\partial G}{\partial x}(x) \right).
\]

\(^8\)Consider, on the other hand, the vector \( \alpha(x) := S^T \mu(x) \), known as (minus) the vector of thermodynamical affinities. In this case it is not possible (see, e.g., [22, 21]) to express the vector of mass action reaction rates \( v(x) \) as a function of \( \alpha(x) \). This is illustrated in [21] by considering the reaction \( X_1 = X_2 \) with reaction rate \( v(x_1, x_2) = k_{\text{forw}} x_1 - k_{\text{rev}} x_2 \). When the concentrations \( x_1 \) and \( x_2 \) are doubled, then so is the reaction rate \( v(x_1, x_2) \). However, \( -\alpha \) remains the same.

\(^9\)Note that this definition of \( G \), as before of \( \mu \) and \( \mu^o \), depends on the chosen thermodynamic equilibrium \( x^* \).
In the next section, we will employ $G(x)$ as a Lyapunov function.

A geometrical interpretation of (3.23) is as follows. Denote the dual space of the space of concentrations of chemical species $\mathcal{M} := \mathbb{R}^m$ by $\mathcal{M}^*$. Similarly, denote the dual space of $\mathcal{C} := \mathbb{C}^c$ by $\mathcal{C}^*$, and the dual of the space of reaction rates $\mathcal{R} = \mathbb{R}^r$ by $\mathcal{R}^*$. Define $v^* := B^T \text{Exp}(\gamma)$ and $\gamma := B v(x)$. All ingredients of (3.23) are then summarized in the following diagram, which expresses the duality relations between all the variables involved:

![Diagram](image)

The concentration vector $x$ and its time-derivative $\dot{x}$ are elements of the linear space $\mathcal{M}$ with conjugate vector being the chemical potential vector $\mu \in \mathcal{M}^*$. They are related by the Gibbs' function $G$ as $\mu(x) = G(x)$. Furthermore, the vector $\dot{y}$ is in the linear space $\mathcal{C}$, with conjugate vector the complex affinity $\gamma$. The relations between $\dot{y}$ and $\dot{x}$ and dually between $\mu$ and $\gamma$ are given by $\dot{x} = Z \dot{y}$, respectively, $\gamma = Z^T \mu$. Also note that $\dot{x} = Z \dot{y} = Z B v = S \dot{v}$, where the vector of fluxes $v$ is in the linear space $\mathcal{R}$, with conjugate vector $v^* := -K^{-1} v \in \mathcal{R}^*$. The added complication in the diagram is the map $\text{Exp} : \mathcal{C}^* \to \mathcal{C}^*$, which introduces a discrepancy between $v^*$ and $-\alpha := B^T \gamma = S^T \mu$.


4.1. Equilibria. Making use of the formulation of the dynamics of balanced reaction networks in (3.14), we start by giving a simple proof of the statement that all positive equilibria of a balanced reaction network are actually thermodynamic equilibria,\(^\text{10}\) and thus given by (3.10). A similar result was obtained in the classical papers \cite{14, 15, 12} for a different class of chemical reaction networks (roughly speaking, weakly reversible networks of deficiency zero or deficiency one under additional conditions).

**Theorem 4.1.** Consider a balanced chemical reaction network $\dot{x} = S v(x) = Z B v(x)$ governed by mass action kinetics, with thermodynamic equilibrium $x^* \in \mathbb{R}^m_+$. Then the set of all positive equilibria is equal to the set $\mathcal{E} = \{x^{**} \in \mathbb{R}^m_+ \mid S^T \ln(x^{**}) = S^T \ln(x^*)\}$ of thermodynamic equilibria given in (3.10).

**Proof.** Denote for the $j$th reaction the substrate complex by $S_j$ and the product complex by $P_j$. As before, let $Z_{S_j}$ and $Z_{P_j}$ denote the columns of the complex stoichiometric matrix $Z$ of the reaction network, corresponding, respectively, to substrate complex $S_j$ and product complex $P_j$. Define as before

$$\mu(x) = \ln \left( \frac{x}{y^*} \right), \quad \gamma(x) := Z^T \mu(x), \quad \gamma_{S_j}(x) = Z_{S_j}^T \mu(x), \quad \gamma_{P_j}(x) = Z_{P_j}^T \mu(x).$$

Suppose $x^{**} \in \mathbb{R}^m_+$ is an equilibrium, i.e., $Z B K B^T \text{Exp}(Z^T \ln(x^{**})) = 0$, or, equivalently, $Z B K B^T \text{Exp}(Z^T \mu(x^{**})) = 0$. Then also

$$\mu^T(x^{**}) Z B K B^T \text{Exp}(Z^T \mu(x^{**})) = 0.$$

\(^\text{10}\)Note, however, that the reaction network may have equilibria on the boundary of $\mathbb{R}^m_+$. Furthermore, these may not be in the closure of $\mathcal{E}$. 

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Denoting the columns of $B$ by $b_1, \ldots, b_r$, we have $BKB^T = \sum_{j=1}^r \kappa_j(x^*) b_j b_j^T$, while
\[
\mu^T(x^*) Z b_j = \mu^T(x^*) \left( Z_{P_j} - Z_{S_j} \right) = \gamma_{P_j}^T(x^*) - \gamma_{S_j}^T(x^*),
\]
\[
b_j^T \exp \left( Z^T \mu(x^*) \right) = \exp \left( \gamma_{P_j}^T(x^*) \right) - \exp \left( \gamma_{S_j}^T(x^*) \right).
\]
It follows that
\[
0 = \mu^T(x^*) Z BKB^T \exp \left( Z^T \mu(x^*) \right) = \gamma^T(x^*) BKB^T \exp \left( \gamma(x^*) \right)
\]
\[
= \sum_{j=1}^r \left[ \gamma_{P_j}(x^*) - \gamma_{S_j}(x^*) \right] \left[ \exp \left( \gamma_{P_j}(x^*) \right) - \exp \left( \gamma_{S_j}(x^*) \right) \right] \kappa_j(x^*).
\]
Since the exponential function is a strictly increasing function and $\kappa_j(x^*) > 0, j = 1, \ldots, r$, this implies that all terms in the summation are zero and thus
\[
\gamma_{P_j}(x^*) = \gamma_{S_j}(x^*), \quad \exp \left( \gamma_{P_j}(x^*) \right) = \exp \left( \gamma_{S_j}(x^*) \right), \quad j = 1, \ldots, r,
\]
which is equivalent to
\[
B^T \gamma(x^*) = B^T Z^T \mu(x^*) = 0, \quad B^T \exp \left( \gamma(x^*) \right) = B^T \exp \left( Z^T \mu(x^*) \right) = 0.
\]
The first equality tells us that $x^* \in \mathcal{E}$, and is thus a thermodynamical equilibrium (as also follows from the second equality).

**4.2. Asymptotic stability.** In the next theorem we show that $G$ serves as a Lyapunov function for (3.14).

**Theorem 4.2.** Consider a balanced mass action reaction network given by (3.14) or, equivalently, by (3.23), with $G : \mathbb{R}^m_+ \to \mathbb{R}$ given by (3.22). Then $G$ has a strict minimum at $x^*$, while $G(x) := \frac{\partial^2G}{\partial x^2}(x) S v(x), x \in \mathbb{R}^m_+$, satisfies
\[
G(x) \leq 0, \quad G(x) = 0 \text{ if and only if } x \in \mathcal{E}.
\]

**Proof.** In order to show that $G$ has a strict minimum at $x^*$ we note the following.

Let $x_i$ and $x_i^*$ denote the $i$th elements of $x$ and $x^*$, respectively. From the strict concavity of the logarithmic function, $z - 1 \geq \ln(z)$ for all $z \in \mathbb{R}_+$, with equality if and only if $z = 1$. Putting $z = \frac{x_i^*}{x_i}$ we get $x_i^* - x_i + x_i \ln(\frac{x_i}{x_i^*}) \geq 0$, with equality if and only if $x_i = x_i^*$. This implies that
\[
G(x) = \sum_{i=1}^m \left[ x_i^* - x_i + x_i \ln \left( \frac{x_i}{x_i^*} \right) \right] \geq 0,
\]
with equality if and only if $x_i = x_i^*, i = 1, \ldots, m$. Thus $G$ satisfies $G(x^*) = 0, G(x) > 0, x \neq x^*$.

In order to show (4.3), consider, as in the proof of Theorem 4.1, the $j$th reaction between substrate complex $S_j$ and product complex $P_j$, and let $Z_{S_j}$ and $Z_{P_j}$ denote the columns of the complex stoichiometric matrix $Z$ corresponding to complexes $S_j$ and $P_j$. Using the notation (4.1) we compute, as in (4.2),
\[
\dot{G}(x) = \frac{\partial G}{\partial x}(x) \dot{x} = -\mu^T(x) Z BKB^T \exp(Z^T \mu(x))
\]
\[
= -\gamma^T(x) BKB^T \exp(\gamma(x))
\]
\[
= -\sum_{j=1}^r \left[ \gamma_{P_j}(x) - \gamma_{S_j}(x) \right] \left[ \exp \left( \gamma_{P_j}(x) \right) - \exp \left( \gamma_{S_j}(x) \right) \right] \kappa_j(x^*) \leq 0,
\]
since $\kappa_j(x^*) > 0$ for $j = 1, \ldots, r$, and the exponential function is strictly increasing. The “if” part of the second part of (4.3) is trivial. For the “only if” part, the summand in the third line of (4.4) is zero only if $\gamma_{S_j}(x) - \gamma_{P_j}(x) = 0$ for every $j$. This is equivalent to having $B^T \gamma(x) = 0$. Thus, $\dot{G}(x) = 0$ only if $B^T \gamma(x) = B^T Z^T \ln \left( \frac{x}{x^*} \right) = 0$. It follows that $G(x) = 0$ if and only if $x \in \mathcal{E}$. \hfill \Box

Remark 4.1. A similar reasoning for showing that $\dot{G} \leq 0$ was used in [3] (see also [14, 11, 12]), making use, however, of the convexity of the exponential function instead of the weaker property that the exponential function is increasing as in our proof. In this respect, it can be noted that Theorem 4.2 remains unaltered if we replace (3.14) by any equations of the form (not corresponding anymore to mass action kinetics)

$$\dot{x} = -Z B K B^T F \left( Z^T \ln \left( \frac{x}{x^*} \right) \right),$$

with $F : \mathbb{R}^c \to \mathbb{R}^c$ a mapping $F(y_1, \ldots, y_c) = \text{diag}(f_1(y_1), \ldots, f_c(y_c))$, where the functions $f_i, i = 1, \ldots, c$, are all monotonically increasing.

Since the function $G$ has a continuous extension to $\mathbb{R}^m_+$, on which it is proper, it directly follows from Theorem 4.2 that all solutions of (3.14) are bounded. In order to derive from Theorem 4.2 asymptotic stability towards the set of $\mathcal{E}$ of positive equilibria, we use a reasoning which is similar to the proof of the zero-deficiency theorem provided in [12], based on the following proposition in there. Recall from the introduction that $x \cdot z \in \mathbb{R}^m$ is defined as the elementwise product.

**Proposition 4.3.** Let $U$ be a linear subspace of $\mathbb{R}^m$, and let $x^*, x_0 \in \mathbb{R}^m_+$. Then there is a unique element $\mu \in U^\perp$, such that $(x^* \cdot \text{Exp}(\mu) - x_0) \in U$.

*Proof.* See the proof of [12, Proposition B.1, pp. 361–363]. \hfill \Box

Although it can be shown, using the same arguments as in [26], that the positive orthant $\mathbb{R}^m_+$ is forward invariant for (3.14), Theorem 4.2 does not directly prevent the solution trajectories of (3.14) to approach the boundary equilibria of (3.14) for $t \to \infty$. The reaction network is called persistent\footnote{It is generally believed that most reaction networks are persistent. However, up to now this persistence conjecture has been only partially proved (cf. [1, 4] and the references therein).} if for every $x_0 \in \mathbb{R}^m_+$ the $\omega$-limit set $\omega(x_0)$ does not intersect the boundary of $\mathbb{R}^m_+$. Define for every $x_0 \in \mathbb{R}^m_+$ the stoichiometric compatibility class [12] of $x_0$ as the invariant set $S(x_0) = \{x \in \mathbb{R}^m_+ \mid x - x_0 \in \text{im} S\}$.

**Theorem 4.4.** Consider the balanced chemical reaction network (3.14). Then for every $x_0 \in \mathbb{R}^m_+$, there exists a unique\footnote{Following an argument similar to that in [26, Theorem 6] (which basically deals with weakly reversible zero-deficiency chemical networks), one can show that the map which assigns $x_1$ to $x_0$ is real-analytic.} $x_1 \in \mathcal{E}$ with $x_1 \in S(x_0)$. The equilibrium $x_1$ is (locally) asymptotically stable with respect to all initial conditions in $S(x_0)$ near $x_1$. Furthermore, if the network is persistent, then $x_1$ is globally asymptotically stable with respect to all initial conditions in $S(x_0)$.

*Proof.* With reference to Proposition 4.3, define $U = \text{im} S$, and observe that $U^\perp = \ker S^T$. Let $x^*, x_0 \in \mathbb{R}^m_+$. Then by Proposition 4.3, there exists a unique $\mu \in \ker S^T$ such that $x^* \cdot \text{Exp}(\mu) - x_0 \in \text{span} S$. Define $x_1 := x^* \cdot \text{Exp}(\mu) \in \mathbb{R}^m_+$. It follows that $S^T \mu = S^T \ln \left( \frac{x}{x^*} \right) = 0$, that is, $x_1 \in \mathcal{E}$. Furthermore, $x_1 \in S(x_0)$. Together with Theorem 4.2 it follows that the equilibrium $x_1 \in \mathcal{E}$ is locally asymptotically stable with respect to nearby initial conditions in $S(x_0)$, and globally asymptotically stable with respect to all initial conditions in $S(x_0)$ if the network is persistent. \hfill \Box

Remark 4.2. Note that the convergence to $\mathcal{E}$ is equivalent to $B^T \gamma(x(t)) \to 0$ for $t \to \infty$. This means that the elements of the vector $\gamma$ of complex thermodynamical...
affinities belonging to the same connected component of the complex graph converge to the same value, similar to standard consensus algorithms [20].

5. Chemical reaction networks with boundary fluxes and interconnection of reaction networks. As discussed in section 2.1, the interaction of a chemical reaction network with the environment or another chemical reaction network can be modeled by identifying a vector of boundary chemical species \( x_b \in \mathbb{R}^b \), which is a subvector of the vector \( x \) of concentrations of all the chemical species in the network. These boundary chemical species are the species that are subject to inflow or outflow boundary fluxes \( v_b \).

The natural conjugate vector is (up to the constant \( RT \)) the vector of chemical potentials \( \mu_b = S^T_b \mu \in \mathbb{R}^b \) of boundary potentials. Indeed, up to the factor \( RT \), the product \( \mu_b^T v_b \) is equal to the power entering or leaving the chemical reaction network due to the influx or efflux of boundary chemical species.

By combining (2.3) and (3.14) this leads to the equations

\[
\dot{x} = -ZBK BT \text{Exp}
\left(Z^T \text{Ln} \left( \frac{x}{x^*} \right) \right) + S_b v_b,
\]

(5.1)

\[
\mu_b = S^T_b \text{Ln} \left( \frac{x}{x^*} \right),
\]

which define an input-state-output system with inputs \( v_b \) and outputs \( \mu_b \). Let \( G \) be defined by (3.22), and as before let \( \gamma(x) := Z^T \text{Ln} \left( \frac{x}{x^*} \right) \). It follows that the system satisfies the energy balance (passivity)

\[
\frac{d}{dt} G = -\gamma^T(x) BKB^T \text{Exp}(\gamma(x)) + \mu_b^T v_b \leq \mu_b^T v_b,
\]

(5.2)

where we have used the basic inequality \( \gamma^T BKB^T \text{Exp}(\gamma) \geq 0; \) see (4.4).

5.1. Interconnection of chemical reaction networks. Complexity of chemical reaction networks is further increased by the interconnection of reaction networks to each other. The most basic way of interconnecting chemical reaction networks is through shared boundary chemical species. Consider for simplicity of notation the interconnection of two chemical reaction networks which have all their boundary chemical species in common; the generalization to the general case is straightforward. Let \( B_i \) denote the incidence matrix of the complex graph, and \( Z_i \) the complex stoichiometry matrix of network \( i = 1, 2 \). The complex graph of the interconnected chemical reaction network is the direct union of the complex graphs of networks 1 and 2, with incidence matrix \( B \) given as the direct product \( B = \text{diag}(B_1, B_2) \). Note that the complex graph of such an interconnected network is not connected. In fact, if all the constituent networks are connected, then their complex graphs are linkage classes of the interconnected network; cf. section 3.4.

The complex stoichiometric matrix \( Z \) of the interconnected network is more involved. Permute the chemical species \( x_1, x_2 \) such that

\[
x_1 = \begin{bmatrix} \hat{x}_1 \\ \hat{x}_b \end{bmatrix}, \quad 
\quad \quad x_2 = \begin{bmatrix} x_{b2} \\ \hat{x}_2 \end{bmatrix}, \quad 
\quad \quad Z_1 = \begin{bmatrix} \hat{Z}_1 \\ Z_{b1} \end{bmatrix}, \quad \quad Z_2 = \begin{bmatrix} Z_{b2} \\ \hat{Z}_2 \end{bmatrix},
\]

where \( Z_{b1}, Z_{b2} \) are matrices with the same number of rows, equal to the number of shared boundary species \( x_b := x_{b1} = x_{b2} \in \mathbb{R}^b \). Then

\[
Z = \begin{bmatrix} \hat{Z}_1 & 0 \\ Z_{b1} & Z_{b2} \\ 0 & \hat{Z}_2 \end{bmatrix}.
\]

(5.3)
Note that in general the property of zero-deficiency is not maintained under interconnection. In fact, this was already discussed in Proposition 3.6 following [24].

Remark 5.1. The resulting matrix $Z$ in (5.3) may have equal columns, corresponding to the case that the two reaction networks have shared complexes (by definition consisting only of shared boundary chemical species, i.e., for which the corresponding columns of $Z_1$ and $Z_2$ are zero). Then one may identify the equal columns in the matrix $Z$ and thus obtain a reduced network with complex graph (possibly connected) consisting of the union of the complex graphs of the two networks with the vertices corresponding to the shared complexes being identified.

The existence of a thermodynamic equilibrium is not necessarily maintained under interconnection. Sufficient conditions for this to happen are given as follows.

**Proposition 5.1.** The interconnection of two balanced reaction networks with vectors of equilibrium constants $K_{1,eq}^i, K_{2,eq}^i$ is again balanced if and only if there exists $(\hat{x}_1^*, \hat{x}_2^*, \hat{x}_b^*)$ such that

\begin{equation}
\begin{aligned}
\text{Ln} \begin{bmatrix}
K_{1,eq}^1 \\
K_{2,eq}^1 
\end{bmatrix}
= \begin{bmatrix}
B_1^T Z_1^T \\
0 
\end{bmatrix}
\begin{bmatrix}
\hat{x}_1^* \\
\hat{x}_b^*
\end{bmatrix}
\text{Ln} \begin{bmatrix}
K_{1,eq}^2 \\
K_{2,eq}^2 
\end{bmatrix}
= \begin{bmatrix}
B_2^T Z_2^T \\
0 
\end{bmatrix}
\begin{bmatrix}
\hat{x}_2^* \\
\hat{x}_b^*
\end{bmatrix}
\end{aligned}
\end{equation}

There exists such a thermodynamic equilibrium for the interconnected network if there is a partition $\{1, \ldots, b\} = I_1 \cup I_2$ such that all columns of $B_1^T Z_{b1}^T$ corresponding to the index set $I_1$ are contained in the image of $B_1^T Z_1^T$, while all columns of $B_2^T Z_{b2}^T$ corresponding to the complementary index set $I_2$ are contained in the image of $B_2^T Z_2^T$.

Proof. By assumption there exist thermodynamic equilibrium points $(\hat{x}_1^*, x_{b1}^*)$ and $(\hat{x}_2^*, x_{b2}^*)$ of the two individual networks. That means (cf. (3.8)) that

\begin{equation}
\text{Ln}(K_{1,eq}^i) = B_1 \begin{bmatrix}
\hat{x}_1^* \\
\hat{x}_b^*
\end{bmatrix}
\text{Ln}(K_{2,eq}^i) = B_2 \begin{bmatrix}
\hat{x}_2^* \\
\hat{x}_b^*
\end{bmatrix}
\end{equation}

Now define $x_{b*}^i \in \mathbb{R}^b$ by taking its $i$th component for $i \in I_1$ equal to the $i$th component of $x_{b1}^*$, and for $i \in I_2$ equal to the $i$th component of $x_{b2}^*$. Then there exist corresponding $\hat{x}_1^*, \hat{x}_2^*$ such that (5.4) is satisfied.

Under the assumptions of Proposition 5.1 it follows that the balanced interconnected network is given as

\begin{equation}
\begin{bmatrix}
\dot{x}_1 \\
\dot{x}_2
\end{bmatrix}
= -ZB \begin{bmatrix}
K_1(\hat{x}_1^{**}, x_{b1}^*) \\
K_2(\hat{x}_2^{**}, x_{b2}^*)
\end{bmatrix}
B^T \text{Exp} \begin{bmatrix}
\text{Ln}(\frac{\hat{x}_1^{**}}{x_{b1}^*}) \\
\text{Ln}(\frac{\hat{x}_2^{**}}{x_{b2}^*})
\end{bmatrix}
\end{equation}

where $\hat{x}_1^{**}, \hat{x}_2^{**}, x_{b*}^i$ satisfy (5.4), and $K_1(\hat{x}_1^{**}, x_{b1}^*)$ and $K_2(\hat{x}_2^{**}, x_{b2}^*)$ are proportionally related to $K_1(\hat{x}_1^*, x_{b1}^*)$ and $K_2(\hat{x}_2^*, x_{b2}^*)$, respectively, as in Proposition 3.4.

**5.2. Interconnection arising from port interconnection.** The above procedure for interconnection of chemical reaction networks can be also interpreted as arising from power-port interconnection at the boundary chemical species. Recall the formulation (5.1) of an open chemical reaction network with inputs $v_b$ being the influx/efflux of the boundary chemical species and $\mu_b$ their chemical potentials. Then the interconnection of two chemical reaction networks (as above under the simplifying assumption that all boundary chemical species are shared) can be seen to result from the power-port interconnection constraints

\begin{equation}
\begin{aligned}
\mu_{b1} &= \mu_{b2}, \\
v_{b1} + v_{b2} &= 0,
\end{aligned}
\end{equation}
expressing that the chemical potentials of the boundary chemical species are equal, while the boundary fluxes of the two networks add up to zero (conservation of boundary chemical species). Indeed, the resulting interconnected dynamics is given by the differential-algebraic equations

\[
\begin{bmatrix}
\dot{x}_1 \\
\dot{x}_2
\end{bmatrix} = - \begin{bmatrix}
Z_1 B_1 K_1 (x_1^*) B_1^T \exp(Z_1^T \mu_1(x_1)) \\
Z_2 B_2 K_2 (x_2^*) B_2^T \exp(Z_2^T \mu_2(x_2))
\end{bmatrix} + \begin{bmatrix}
S_{b1} \\
-S_{b2}
\end{bmatrix} v,
\]

\[
0 = \begin{bmatrix}
S_{b1}^T & -S_{b2}^T
\end{bmatrix} \begin{bmatrix}
\mu_{b1}(x_1) \\
\mu_{b2}(x_2)
\end{bmatrix},
\]

with \( v = v_{b1} = -v_{b2} \) acting as a vector of Lagrange multipliers. After elimination of the algebraic constraint \( \mu_{b1}(x_1) = \mu_{b2}(x_2) \) and the Lagrangian multipliers \( v \), this can be seen to result in the dynamics (5.5).

Recalling that \( \mu_b^T v_b \) is (modulo the constant \( RT \)) the power provided to the chemical reaction network, this implies that the interconnection (5.6) is power-preserving, that is, \( \mu_{b1}^T v_{b1} + \mu_{b2}^T v_{b2} = 0 \), in line with the standard way of interconnecting physical networks [22, 21, 23].

6. Model reduction of chemical reaction networks. For many purposes one may wish to reduce the complexity of a large-scale chemical reaction network, while retaining the structure of a chemical reaction network. In fact, most of the approaches to model reduction of large-scale chemical reaction networks simplify the pathways of the chemical reaction network by leaving out intermediate species or complexes (see, e.g., [10, 2]), or by reduction of mass action enzymatic reactions to their Michaelis–Menten description [18].

In the following we will propose a new model reduction approach which is directly based on the formulation (3.14), in particular on the weighted Laplacian matrix \( \mathcal{L} \). First we recall from [27] the following result regarding Schur complements of weighted Laplacian matrices.\(^{13}\)

**Proposition 6.1.** Consider a directed graph with vertex set \( \mathcal{V} \) and with weighted Laplacian matrix \( \mathcal{L} = B K B^T \). Then for any subset of vertices \( \mathcal{V}_r \subset \mathcal{V} \) the Schur complement of \( \mathcal{L} \) with respect to the indices corresponding to \( \mathcal{V}_r \) is well-defined and is the weighted Laplacian matrix \( \hat{\mathcal{L}} = B \hat{K} B^T \) of another directed graph with incidence matrix \( \hat{B} \), whose vertex set is equal to \( \mathcal{V} - \mathcal{V}_r \).

Consider a balanced reaction network described in the standard form (3.14):

\[
\Sigma: \quad \dot{x} = -Z BK B^T \exp \left( Z^T \ln \left( \frac{x}{x^*} \right) \right).
\]

Reduction will be performed by deleting certain complexes in the complex graph, resulting in a reduced complex graph with weighted Laplacian \( \hat{\mathcal{L}} = B \hat{K} B^T \). Furthermore, by leaving out the corresponding columns of the complex stoichiometric matrix \( Z \) one obtains a reduced complex stoichiometric matrix \( \hat{Z} \) (with as many columns as the remaining number of complexes in the complex graph), leading to the reduced reaction network

\[
\hat{\Sigma}: \quad \dot{\hat{x}} = -\hat{Z} B \hat{K} B^T \exp \left( \hat{Z}^T \ln \left( \frac{\hat{x}}{x^*} \right) \right), \quad \hat{K} > 0.
\]

\(^{13}\) In electrical circuit theory the process of reduction of a resistive network to a resistive network with fewer vertices, but an equivalent resistance, is referred to as *Kron reduction*; cf. [19, 9].

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Note that \( \hat{\Sigma} \) is again a balanced chemical reaction network governed by mass action kinetics, with a reduced number of complexes and stoichiometric matrix \( \hat{S} := \hat{Z} \hat{B} \). The next proposition shows that also other properties of \( \Sigma \) are inherited by \( \hat{\Sigma} \).

**Proposition 6.2.** Consider the balanced reaction network \( \Sigma \) and its reduced order model \( \hat{\Sigma} \) given by (6.1). Denote their sets of equilibria by \( \mathcal{E} \), respectively, \( \hat{\mathcal{E}} \). Then \( \mathcal{E} \subseteq \hat{\mathcal{E}} \). Furthermore, if \( \Sigma \) has deficiency zero, then so does \( \hat{\Sigma} \).

**Proof.** Assume that the complex graph is connected; otherwise the same argument can be repeated for every component (linkage class). Recall from (3.10) that the set of equilibria \( \mathcal{E} \) is given as \( \{ x^{**} \mid \text{Ln}^T(\frac{x^{**}}{x^*})S = 0 \} \), where \( S = ZB \). It follows that \( \mathcal{E} \) is equivalently represented as \( \mathcal{E} = \{ x^{**} \mid \text{Ln}^T(\frac{x^{**}}{x^*})Z\mathcal{L} = 0 \} \), where \( \mathcal{L} := BK^T \) is the weighted Laplacian matrix of the complex graph. Let \( \mathcal{V}_r \) be the set of complexes to be left out in the reduced network. After permutation of the complexes we partition \( \mathcal{L} = BK^T \) and \( Z \) as

\[
\mathcal{L} = \begin{bmatrix}
L_{11} & L_{12} \\
L_{21} & L_{22}
\end{bmatrix}, \quad Z = \begin{bmatrix} Z_1 & Z_2 \end{bmatrix},
\]

where \( \mathcal{V}_r \) corresponds to the last part of the indices (denoted by 2). Then post-multiply \( \text{Ln}^T(\frac{x^{**}}{x^*})Z\mathcal{L} = 0 \) by the invertible matrix

\[
\begin{bmatrix}
I \\
-L_{22}^{-1}L_{21} & I
\end{bmatrix},
\]

not changing the solution set \( \mathcal{E} \). It follows that

\[
\mathcal{E} = \left\{ x^{**} \mid \text{Ln}^T(\frac{x^{**}}{x^*}) \begin{bmatrix} Z_1 & Z_2 \end{bmatrix} \begin{bmatrix} L_{11} & -L_{12}L_{22}^{-1}L_{21} & L_{12} \\
0 & L_{22} \end{bmatrix} = 0 \right\}
\subset \left\{ x^{**} \mid \text{Ln}^T(\frac{x^{**}}{x^*}) \hat{Z}\hat{\mathcal{L}} = 0 \right\} = \hat{\mathcal{E}}.
\]

For the second statement assume that the full-order network has deficiency zero, i.e., \( \ker Z \cap \text{im} B = 0 \), or, equivalently, \( \ker Z \cap \text{im} \mathcal{L} = 0 \). Postmultiplication of \( \mathcal{L} \) with the matrix in (6.3) yields

\[
\ker \begin{bmatrix} Z_1 & Z_2 \end{bmatrix} \cap \text{im} \begin{bmatrix} L_{11} - L_{12}L_{22}^{-1}L_{21} & L_{12} \\
0 & L_{22} \end{bmatrix} = 0,
\]

which implies \( \ker \hat{Z} \cap \text{im} \hat{\mathcal{L}} = 0 \), i.e., zero-deficiency of \( \hat{\Sigma} \).

A dynamical interpretation of the reduction procedure can be given as follows. Let \( \mathcal{V}_r \) again be the set of complexes which we leave out in the reduced network, and partition \( \mathcal{L} \) and \( Z \) as in (6.2). Write out \( \Sigma \) as

\[
\dot{x} = -\begin{bmatrix} Z_1 & Z_2 \end{bmatrix} \begin{bmatrix} L_{11} & L_{12} \\
L_{21} & L_{22} \end{bmatrix} \begin{bmatrix} \text{Exp}(Z_2^T\text{Ln}(\frac{Z_1}{Z_2})) \\
\text{Exp}(Z_2^T\text{Ln}(\frac{Z_1}{Z_2})) \end{bmatrix} w_1.
\]

Consider now the auxiliary dynamical system

\[
\begin{bmatrix} \dot{y}_1 \\
\dot{y}_2 \end{bmatrix} = -\begin{bmatrix} L_{11} & L_{12} \\
L_{21} & L_{22} \end{bmatrix} \begin{bmatrix} w_1 \\
w_2 \end{bmatrix},
\]

where we impose the constraint \( \dot{y}_2 = 0 \). It follows that \( w_2 = -L_{22}^{-1}L_{21}w_1 \), leading to the reduced dynamics \( \dot{y}_1 = -(L_{11} - L_{12}L_{22}^{-1}L_{21})w_1 = -\hat{\mathcal{L}}w_1 \). Putting back in
A subnetwork of the phosphorylation EGFReceptor network in [17]. The concentrations of [Grb], [RP], [R-G], [R-G-S], [G-S], and [SOS] are given in nM, and all reaction rates have the unit of nM·s⁻¹.

<table>
<thead>
<tr>
<th>Reactions</th>
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<th>Rate constants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grb + RP ⇌ R-G</td>
<td>( v_1 = k_1^{\text{forw}} \text{[Grb][RP]} - k_1^{\text{rev}} \text{[R-G]} )</td>
<td>( \hat{k}_1^{\text{forw}} = 0.003 \text{ nM}^{-1} \text{s}^{-1} )</td>
</tr>
<tr>
<td>SOS + R-G ⇌ R-G-S</td>
<td>( v_2 = k_2^{\text{forw}} \text{[SOS][R-G]} - k_2^{\text{rev}} \text{[R-G-S]} )</td>
<td>( \hat{k}_2^{\text{forw}} = 0.01 \text{ nM}^{-1} \text{s}^{-1} )</td>
</tr>
<tr>
<td>R-G-S ⇌ RP + G-S</td>
<td>( v_3 = k_3^{\text{forw}} \text{[R-G-S]} - k_3^{\text{rev}} \text{[RP][G-S]} )</td>
<td>( \hat{k}_3^{\text{rev}} = 0.03 \text{ s}^{-1} )</td>
</tr>
<tr>
<td>G-S ⇌ SOS + Grb</td>
<td>( v_4 = k_4^{\text{forw}} \text{[G-S]} - k_4^{\text{rev}} \text{[SOS][Grb]} )</td>
<td>( \hat{k}_4^{\text{rev}} = 0.0045 \text{ nM}^{-1} \text{s}^{-1} )</td>
</tr>
</tbody>
</table>

The reduced subnetwork obtained from the subnetwork in Table 6.1. The unit of concentration is nM and the unit of reaction rate is nM·s⁻¹.

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<tr>
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<td>( \hat{v}_2 = \hat{k}_2^{\text{forw}} \text{[SOS][R-G]} - \hat{k}_2^{\text{rev}} \text{[RP][G-S]} )</td>
<td>( \hat{k}_2^{\text{forw}} = k_2^{\text{forw}} )</td>
</tr>
</tbody>
</table>

\( w_1 = \text{Exp}(\hat{Z}^T \text{Ln}(\hat{Z})) \), making use of \( \hat{x} = Z_1 \hat{y}_1 + Z_2 \hat{y}_2 = Z_1 \hat{y}_1 + \hat{Z} \hat{y}_1 \), we then obtain the reduced network \( \hat{\Sigma} \) given by (6.1).

We conclude that the reduction of \( \Sigma \) to \( \hat{\Sigma} \) rests on the assumption that the deleted complexes are approximately constant in time (compared to the other complexes). When perturbed from equilibrium we assume that certain species in the chemical reaction network reach their equilibrium much faster than the remaining ones. The principle behind our model reduction method is to impose the condition that complexes entirely made up of such species remain at constant concentrations. It is thus important to determine the right set of complexes to be deleted in order to ensure that the resulting reduced model approximates the full model well.

Example 6.1. As an example, we consider the network of the phosphorylation of the epidermal growth factor receptor (EGFR) as discussed in [17]. The complete model consists of 25 reactions, where 22 of them are described by mass action kinetics. We focus on the detailed-balanced subnetwork of the model as listed in Table 6.1. The subnetwork in Table 6.1 consists of 7 complexes which are made out of 6 species. Removal of the R-G-S and G-S complexes by an application of our model reduction method results, after a straightforward computation, in the reduced subnetwork given in Table 6.2. We note that the reaction rates in the reduced subnetwork are independent of the choice of thermodynamic equilibrium point \( x^* \), while their rate constants are easily related to those of the original network. A numerical comparison of the original subnetwork and the reduced one is shown in Figure 6.1, where the concentrations of the 5 species of the reduced subnetwork are seen to behave similarly as in the original subnetwork.
7. Conclusions. In this paper we have provided a compact, geometric formulation of the dynamics of mass action chemical reaction networks possessing a thermodynamic equilibrium. This formulation clearly exhibits both the structure of the complex graph and the stoichiometry, and furthermore admits a direct thermodynamical interpretation. Exploiting this formulation, we were able to recover, for this class of mass action kinetics chemical reaction networks, some of the results in the fundamental work [15, 14, 11, 12] in a simple and insightful way, without having to rely on the properties of deficiency zero or one. Drawing inspiration from [22, 21, 23], we have shown how the framework leads to an input-state-output formulation of open chemical reaction networks, and how this may be used for interconnection. Furthermore, we have indicated how this formulation, in particular the Laplacian matrix of the complex graph, may be used for a systematic model reduction procedure based on the elimination of certain intermediate complexes.

Current research is taking place in a number of directions. In [16] we have shown how the formulation (3.14) extends to reversible Michaelis–Menten reaction rates. The use of our formulation for the analysis of steady states corresponding to nonzero (constant) boundary fluxes or clamped boundary species concentrations is under study, taking into account the possibility of multiple steady states [7]. For an application of our new model reduction procedure to a model of yeast glycolysis, we refer the reader to [25]. Further ramifications of the model reduction method are currently being investigated, in particular its properties for systems with boundary fluxes or clamped boundary species. Another promising application of the weighted Laplacian matrix for large-scale reaction networks is its use for decomposition purposes; see [2]. A challenging question is the extension of our framework to biochemical reaction networks, where the reactions are enzymatic, and the amount of enzymes, through the activity of the gene and protein networks, will depend on, for example, the concentrations of a number of chemical species (metabolites). This will lead to the introduction of an additional network structure (on top of the complex graph of the metabolic reaction network) originating from the regulatory, and possibly competing, feedback loops.

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REFERENCES


