A Unified View on Bipartite Species-reaction Graphs and Their Relation to Interaction Graphs and Qualitative Dynamics of Chemical Reaction Networks

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Abstract

The Jacobian matrix of a dynamic system and its principal minors play a prominent role in the study of qualitative dynamics and bifurcation analysis. When interpreting the Jacobian as an adjacency matrix of an interaction graph, its principal minors reate to sets of disjoint cycles in this graph and conditions for qualitative dynamic behaviors can be inferred from its cycle structure. The Jacobian of chemical reaction systems decomposes into the product of two matrices, which allows more fine-grained analyses by studying a corresponding bipartite species-reaction graph. Several different bipartite graphs have been proposed and results on injectivity, multistationarity, and bifurcations have been derived. Here, we present a new definition of the species-reaction graph that directly connects the cycle structure with determinant expansion terms, principal minors, and the coefficients of the characteristic polynomial. It encompasses previous graph constructions as special cases. This graph has a direct relation to the interaction graph, and properties of cycles and sub-graphs can be translated in both directions. A simple equivalence relation enables simplified decomposition of determinant expansions and allows simpler and more direct proofs of previous results.

Keywords: chemical reaction network; determinant; bipartite graph; interaction graph; line-graph; qualitative dynamics

1 Introduction

The analysis of chemical reaction systems is hampered by the fact that parameters such as kinetic rate constants are inherently difficult to obtain from experimental data, and that *in-vitro* parameters might not translate to *in-vivo* experiments. In contrast to general dynamic systems, however, the dynamics of a chemical reaction system is constrained by the stoichiometry and topology of the reaction network. Moreover, while the exact algebraic form of chemical rate laws is often difficult

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to determine, they are typically monotone in the reactant's concentrations. Several approaches have been proposed that exploit these constraints and allow to determine—without knowledge of parameter values and with minimal conditions on the rate laws—if a reaction network is capable of specific *qualitative* dynamics such as oscillations and multiple equilibria, and to establish stability of equilibria.

While methods such as Chemical Reaction Network Theory [14,10,9], Stoichiometric Network Analysis [4], and Biochemical Systems Theory [17,18,19] exploit the particular algebraic structure of reaction systems, more recent methods focus on graphical representations of the Jacobian matrix of the dynamical system and its properties. Two main classes of graphs have been proposed: signed interaction graphs interpret the Jacobian as an adjacency matrix and relate chemical species that participate in the same reaction. Then, a positive cycle is necessary for multistationarity, whereas a negative cycle is necessary for oscillations [11,23,22,15]; other criteria have also been investigated [8]. The absence of negative undirected cycles implies monotonicity with respect to an orthant cone, ruling out chaotic and oscillatory dynamics [21,20,13].

On the other hand, the Jacobian of a reaction system can be written as the product of the stoichiometric matrix and the Jacobian of the reaction rate laws, giving rise to representations by bipartite species-reaction (SR) graphs with different vertices for species and reactions. Several SR graphs have been proposed in the context of qualitative dynamics, such as undirected [6,3] and directed [16] species-reaction graphs, and graphs with multiple edge-types [3]. Oriented versions of undirected SR-graphs also need to be considered in [6]. Criteria for the existence of multiple equilibria and oscillations [3,16,5,6] and for establishing monotonicity [21,1] have been derived. Exploiting the relation of principal minors of a matrix and cycles in its associated graph to coefficients in the characteristic polynomial allows inferring the possibility of saddle-point and Hopf bifurcations in a system [16].

In this work, we elucidate how the various interaction- and bipartite-graph-based methods are related and propose a new definition of the species-reaction graph, named *directed species-reaction graph (DSR-graph)*, that provides additional insight into several established results. We develop and emphasize the direct relation between determinant expansions, principal minors, the Jacobian matrix and its interaction graph, and our DSR-graph, making use of long-known relations [12]. We present refined criteria for sign-definiteness of the determinant of the Jacobian and its principal minors based on a simple equivalence relation of subgraphs of our DSR-graph and show the equivalence of two criteria developed independently in [16] and [6].

2   Chemical Reaction Networks

A *chemical reaction network* is given by its chemical *species* $S_1, \ldots, S_n$ and associated *reactions* $R_1, \ldots, R_r$. A reaction R_j describes how a set of species transforms into another set of species and is formally given by

$$R_j : y_{1,j} S_1 + \cdots + y_{n,j} S_n \longrightarrow y'_{1,j} S_1 + \cdots + y'_{n,j} S_n \,,$$
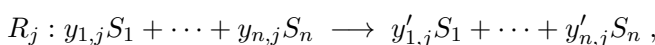
where $y_{i,j} \in \mathbb{N}$ is the molecularity of the *substrate* S_i and $y'_{i,j} \in \mathbb{N}$ that of the *product* S_i. Reversible reactions are modeled as two irreversible reactions: the *forward* and *backward* reaction. We require that no species is both substrate and product of a reaction, i.e., we exclude reactions such as $A + B \rightarrow 2A$; the *stoichiometric matrix* $\mathbf{N} \in \mathbb{Z}^{n \times r}$ is then the well-defined matrix with entries $N_{i,j} = y'_{i,j} - y_{i,j}$, where $N_{i,j} > 0$ (resp. $N_{i,j} < 0$) if species S_i is a product (resp. a substrate) of reaction R_j, and $N_{i,j} = 0$ if it does not participate in the reaction.

We denote by $x_i(t) \in \mathbb{R}_{\geq 0}$ the concentration of species S_i at time t and define the state vector $\mathbf{x} \equiv \mathbf{x}(t) = (x_1(t), \ldots, x_n(t))^T$. We adopt the usual convention of dropping the explicit dependence on t. The temporal dynamics of the reaction system is described by the nonlinear ordinary differential equations

$$\frac{d}{dt}\mathbf{x}(t) = \mathbf{f}(\mathbf{x}(t), \mathbf{k}) = \mathbf{N} \cdot \mathbf{v}(\mathbf{x}(t), \mathbf{k}) , \tag{1}$$

where $\mathbf{v}(\mathbf{x}(t), \mathbf{k}) = (v_1(\mathbf{x}(t), \mathbf{k}), \ldots, v_r(\mathbf{x}(t), \mathbf{k}))^T$ is the vector of reaction rates with positive rate parameters $\mathbf{k}$. The reaction rate $v_j(\mathbf{x}(t), \mathbf{k})$ describes the velocity of reaction R_j as a function of the current state $\mathbf{x}$ of the system. We restrict attention to non-autocatalytic rate laws, for which $\partial v_j / \partial x_i > 0$ if species S_i is a substrate of reaction R_j and all concentrations are positive, and $\partial v_j / \partial x_i \equiv 0$ if S_i is not a substrate of R_j. Thus an increase in a substrate concentration cannot decrease the reaction rate and species that are not substrates do not influence the reaction rate. Very similar conditions for reversible reactions were given in [3].

We model mass transport over the boundaries of the system by *inflow* reactions of the form $R_j : \emptyset \rightarrow S_i$ with constant rate $v_j(\mathbf{x}, \mathbf{k}) = k_j > 0$ and *outflow* reactions $R_j : S_i \rightarrow \emptyset$ with rate $v_j(\mathbf{x}, \mathbf{k}) = k_j \cdot x_i$.

3 Jacobian Matrix and Qualitative Dynamics

The *Jacobian* of a reaction system (1) is the function

$$\mathbf{J} = \left(\frac{\partial f_i}{\partial x_j}\right)_{1 \leq i,j \leq n} = \mathbf{N} \cdot \left(\frac{\partial v_i}{\partial x_j}\right)_{1 \leq i \leq r, 1 \leq j \leq n} .$$

Evaluated at some state $\mathbf{x}_0$, the resulting matrix $\mathbf{J}(\mathbf{x}_0)$ allows to approximate the system's dynamics in the vicinity of $\mathbf{x}_0$.

A *multi-index* of size $|\alpha| := l$ is a tupel $\alpha = (\alpha_1, \ldots, \alpha_l) \subseteq \{1, \ldots, n\}$ with $\alpha_1 < \cdots < \alpha_l$. We denote by $\mathbf{J}_\alpha$ the submatrix of $\mathbf{J}$ obtained by selecting the rows and columns with index in α; its determinant $\det(\mathbf{J}_\alpha)$ is called a *principal minor* of order $|\alpha|$.

The characteristic polynomial of $\mathbf{J}$ depends on the system state $\mathbf{x}$ and is formally given by

$$P_{\mathbf{J}}(\lambda) = \det(\lambda \mathbf{I} - \mathbf{J}) = \lambda^n + c_{n-1}\lambda^{n-1} + \cdots + c_1\lambda + c_0 \quad \text{with} \quad c_i = (-1)^{n-i} \sum_{\substack{\alpha \subseteq \{1,\ldots,n\} \\ |\alpha| = n-i}} \det(\mathbf{J}_\alpha) .$$

The signs of the principal minors thus play a prominent role in determining the qualitative dynamics of a chemical reaction system: (i) *multistationarity* is excluded in fully open systems for non-autocatalytic reaction rates if all principal minors of $\det(-\boldsymbol{J}_\alpha)$ are positive for all $\boldsymbol{x} > \boldsymbol{0}$ [2]; this criterion simplifies to $\det(-\boldsymbol{J}) > 0$ for mass-action kinetics [7]. (ii) A necessary condition for a *saddle-node bifurcation* is a single zero eigenvalue, which only exists if $c_0 = 0$ and thus $\det(\boldsymbol{J}) = 0$. (iii) A *Hopf-Andronov bifurcation* requires a single pair of conjugate eigenvalues with zero real part. Under certain conditions, the vanishing of coefficients $c_i = 0$ for $i \neq 0$ implies that the Hurwitz determinant of order $(n-1)$ vanishes, which in turn is a necessary condition for a conjugate pair of imaginary eigenvalues [16].

4 Determinant Expansions and Interaction Graph

Recall that the determinant expansion of $\det(\boldsymbol{J})$ can be computed by

$$\det(\boldsymbol{J}) = \sum_{\pi} (-1)^{\mathrm{sign}(\pi)} \prod_{i=1}^{n} J_{i,\pi(i)} \;, \tag{2}$$

where π runs over the permutation group on $\{1, \ldots, n\}$ and $\mathrm{sign}(\pi)$ is its sign. Note that $J_{i,\pi(i)}$ depends on system state and parameter values. The expansion can equivalently be formulated in graphical terms by interpreting $\boldsymbol{J}$ as an adjacency matrix for the *interaction graph* G_I, whose vertex set are the species $S_1, \ldots, S_n$, and there is an edge $e = (S_i, S_j)$ with (formal) label $\gamma(e) = J_{ji}$ whenever $J_{ji} \not\equiv 0$. A *cycle* is a sequence of edges that starts and ends in the same vertex; it is *simple* if no vertex occurs more than once.

Definition 4.1 [line-graph [12]] Let $C_1, \ldots, C_q$ be a collection of disjoint simple cycles C_i covering each vertex of a graph G exactly once:

$$V(G) = V(C_1) \cup \cdots \cup V(C_q) \quad \text{and} \quad V(C_i) \cap V(C_j) = \emptyset \text{ if } i \neq j \;.$$

Their union

$$L := \bigcup_{i=1}^{q} C_i \subseteq G$$

is a sub-graph of G called a *line-graph*. The *label* of L is $\gamma(L) = \prod_{e \in L} \gamma(e)$. We denote by $\mathcal{L}(G)$ the collection of all line-graphs of G.

A line-graph is also called *Hamiltonian hooping* [22] or *nucleus* [8], and the special definition of a *subgraph* in [16] relates to the same concept.

Line-graphs correspond to permutations: for any permutation π, the term $\prod_{i=1}^{n} J_{i,\pi(i)}$ of the determinant expansion is nonzero if and only if all corresponding edges $(S_{\pi(i)}, S_i)$ exist in G_I. Since these edges form a line-graph L, the product is equal to the label of this line-graph: $\gamma(L) = \prod J_{i,\pi(i)}$. The sign of the permutation is also readily extracted from the graph:

Definition 4.2 [signum of a line-graph] Let $\epsilon(L)$ be the number of even-length cycles in a line-graph L. Then,

$$\omega(L) := (-1)^{\epsilon(L)} .$$

is called the *signum* of L and corresponds to the sign of the permutation given by L [12].

Note that $\omega(L)$ is independent of $\mathrm{sign}(\gamma(L))$. It is directly related to the signum $\xi(L)$ proposed in [22] via $\omega(L) = -\xi(-L)$, where $-L$ denotes the line-graph with edge-labels $-\gamma(\cdot)$. We can now formulate the determinant expansion of $\boldsymbol{J}$ in purely graphical terms:

Lemma 4.3 (Harary [12]) *The determinant expansion of $\boldsymbol{J}$ is given by*

$$\det(\boldsymbol{J}) = \sum_{L \in \mathcal{L}(G_I)} \omega(L)\,\gamma(L) = \sum_{L \in \mathcal{L}(G_I)} \prod_{C \subseteq L} \omega(C)\,\gamma(C) . \tag{3}$$

The problem of determining the sign of the determinant then involves determining the signs of the line-graphs, which in turn depend on the signs of their constituent edges. We call an edge *sign-definite* if the sign of its label is independent of the system state $\boldsymbol{x}$. The following lemma establishes sign-definiteness from properties of the reaction network.

Lemma 4.4 (sign-definite edges) *Let G_I be an interaction graph. An edge $(S, S') \in E(G_I)$ is sign-definite if and only if there are no two reactions R, R' such that S and S' are both substrates in R, and S is substrate and S' product in R', respectively.*

Proof. W.l.o.g., let $S = S_i$ and $S' = S_j$. The edge label is then

$$\gamma((S_i, S_j)) = J_{j,i} = \sum_{l=1}^{r} N_{j,l} \frac{\partial v_l}{\partial x_i} .$$

If S_i is not a substrate in R_l, then $\partial v_l / \partial x_i \equiv 0$, so assume S_i is a substrate for two reactions R_l and R_p. If S_j is also a substrate of R_l, then $N_{j,l} < 0$ and R_l provides a negative contribution to the sum. If S_j is a product of another reaction R_p, then $N_{j,p} > 0$ and R_p provides a positive contribution to the sum, making its sign dependent on $\boldsymbol{x}$. The overall sign of $\gamma((S_i, S_j))$ is thus indefinite if and only if S_j is a substrate in one and a product in another reaction, which can be established from the stoichiometric matrix alone. □

We remark that these considerations also hold for any principal minor by restricting attention to its induced subgraph of G_I. This allows computing each coefficient c_i of the characteristic polynomial by investigating the line-graphs of all sub-graphs $G(\boldsymbol{J}_\alpha)$ with $|\alpha| = n - i$.

5 The Directed Species-Reaction Graph

Analysis of qualitative dynamics via interaction graphs is considerably hampered by the fact that most networks contain sign-indefinite edges. Moreover, edge-labels are often sums of terms containing different rate-derivatives, making them hard to compare independently of a species concentration $\boldsymbol{x}$. These problems can be addressed by exploiting the particular structure of chemical reaction systems which naturally leads to a bipartite graph with vertices for species and reactions. Our proposed *directed species-reaction (DSR) graph* directly relates to previous definitions of bipartite graphs, but remedies several shortcomings. It also directly relates to the interaction graph, and we exploit this relation by formulating a corresponding determinant expansion in terms of appropriately defined line-graphs. A key observation is that line-graphs of a DSR naturally fall into equivalence classes and that arguments about the sign of principal minors can be resolved by looking at each equivalence class.

Definition 5.1 [directed species-reaction graph] The *directed species-reaction graph (DSR-graph)* $G = (V_S, V_R, E, \lambda)$ of a chemical reaction network is a bipartite, directed graph with edge-label function λ given by the sets of

$$\text{species vertices } V_S = \{S_1, \ldots, S_n\}; \quad \text{reaction vertices } V_R = \{R_1, \ldots, R_r\}$$

and the edge set $E = E_{SR} \cup E_{RS}$ consisting of

> *rate edges:*
> $$E_{SR} = \{(S_i, R_j) \in V_S \times V_R \,|\, \partial v_j / \partial x_i \not\equiv 0\} \text{ with labels } \lambda((S_i, R_j)) = \frac{\partial v_j}{\partial x_i}$$
> *stoichiometric edges:*
> $$E_{RS} = \{(R_j, S_i) \in V_R \times V_S \,|\, N_{i,j} \neq 0\} \text{ with labels } \lambda((R_j, S_i)) = N_{i,j}$$

The restriction of λ to E_{SR} and E_{RS} is denoted by λ_{SR} (a *rate label*) and λ_{RS} (a *stoichiometric label*), respectively, such that for a sub-graph H of G we have
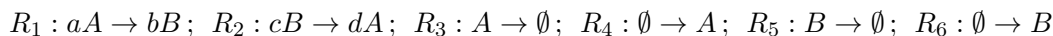
$$\lambda_{RS}(H) := \prod_{(S_i, R_j) \in E_{RS}(H)} N_{ij} \in \mathbb{R} \quad \text{and} \quad \lambda_{SR}(H) := \prod_{e \in E_{SR}(H)} \lambda(e) \,,$$

and $\lambda(H) = \lambda_{RS}(H) \cdot \lambda_{SR}(H)$. Importantly, $\lambda_{SR}(H)(\boldsymbol{x}) > 0$ for all $\boldsymbol{x} > \boldsymbol{0}$. Either label remains undefined if the respective edge-set is empty.

Our DSR-graph deviates in small but important aspects from previous definitions of bipartite species-reaction graphs: The *SR-graph* of [7] uses undirected edges and labels them by the *complex* in which the species occurs. Species on the same side of a reaction form a *c-pair*. All possible orientations of the graph are considered in proofs. In our DSR-graph, these information are encoded explicitly in the existence and direction of edges and two products do not form a c-pair. Instead of c-pairs, a similar undirected graph in [2] labels edges by $+1$ or -1 to the same

effect. The graph proposed in [16] uses directed edges, but does not contain edges from a reaction to its substrates. Directed edges from a substrate to its reaction can instead be traversed in opposite direction, while directed edges from a reaction to a product cannot, which also necessitates to allow semi-cycles and paths in a line-graph. In this graph, mass-action kinetics is also exploited by merging the corresponding factor from $\partial v_j / \partial x_i$ (which is the substrate molecularity of S_i in R_j) with the stoichiometric label and using relative concentrations.

Example 5.2 Consider a simple reaction network with two species A, B and reactions

$$R_1 : aA \to bB \, ; \quad R_2 : cB \to dA \, ; \quad R_3 : A \to \emptyset \, ; \quad R_4 : \emptyset \to A \, ; \quad R_5 : B \to \emptyset \, ; \quad R_6 : \emptyset \to B$$

The DSR-graph of this network is given in Figure 1 and has an intuitive interpretation: a reaction vertex represents the rate of the reaction, which is positively influenced only by its substrates. A change in the rate implies a positive change in the rate of the products, and a negative change in the rate of the substrates; this is reflected by the corresponding edges. The rate-edge labels λ_{SR} are positive functions, and the state-independent label λ_{RS} of a stoichiometric edge is positive for a product, and negative for a substrate.

In contrast to the interaction graph, any subgraph of a DSR-graph is sign-definite:

Proposition 5.3 (sign-definite sub-graphs) *Let $H \subseteq G$ be any sub-graph of a DSR-graph G such that $E_{RS}(H) \neq \emptyset$. Then,*

$$\text{sign}(\lambda(H)) = \text{sign}(\lambda_{RS}(H)) \cdot \underbrace{\text{sign}(\lambda_{SR}(H))}_{\geq 0} \equiv \text{sign}(\lambda_{RS}(H))$$

is independent of the system state $\boldsymbol{x} > \boldsymbol{0}$.

The proposed DSR-graph directly relates to the interaction graph of the same network. Most results on injectivity and bifurcations rely on the fact that simple paths and simple cycles in G_I translate to simple paths and simple cycles in G, and we therefore emphasize this relation.

Proposition 5.4 (relation of DSR- and interaction graph) *Let $G = (V_S, V_R, E, \lambda)$ be the DSR-graph of a chemical reaction network. The interaction graph $G_I = (V(G_I), E(G_I), \gamma)$ of that network is then found as:*

$$V(G_I) = V_S$$
$$E(G_I) = \{(S, S') \in V_S \times V_S \,|\, \exists R \in V_R : (S, R), (R, S') \in E\}$$
$$\gamma((S, S')) = \sum_{R \in V_R} \lambda_{SR}((S, R)) \cdot \lambda_{RS}((R, S')) \, .$$

An edge in G_I may thus correspond to several 2-paths (S, R, S') from V_S to
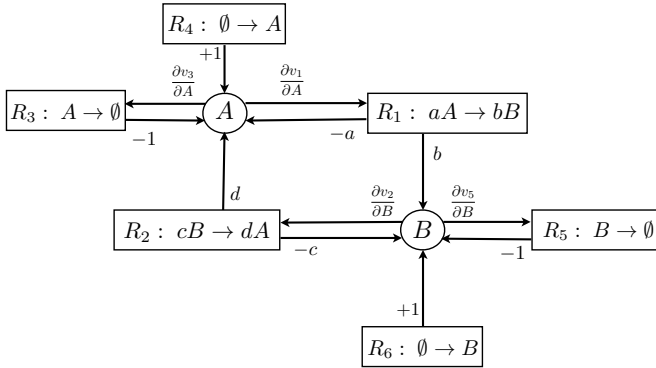
Fig. 1. Directed species-reaction graph for network of Example 5.2. Species vertices are given as circles, reaction vertices as rectangles. Production reactions R_4, R_6 are shown explicitly, but can be neglected for analyses. We use A, B instead of x_A, x_B for readability.

V_S in G via different reactions $R \in V_R$. Each summand of the edge-label in G_I corresponds exactly to one of the labels of a 2-path in G.

Example 5.5 In the network of Example 5.2, consider the upper-left entry

$$J_{1,1} = -a\frac{\partial v_1}{\partial x_A} - \frac{\partial v_3}{\partial x_B}$$

in the Jacobian matrix. The corresponding edge (A, A) in G_I corresponds to the 2-paths (A, R_1, A) with label $-a\frac{\partial v_1}{\partial x_A}$ and (A, R_3, A) with label $-\frac{\partial v_3}{\partial x_B}$ in the DSR-graph.

With $\boldsymbol{J} = \boldsymbol{N} \cdot (\partial \boldsymbol{v}/\partial \boldsymbol{x})$, the stoichiometric matrix is the incidence matrix describing stoichiometric edges and their labels in G, while $(\partial \boldsymbol{v}/\partial \boldsymbol{x})$ is the incidence matrix describing the rate edges and their labels. The adjacency matrix of G is

$$\boldsymbol{B} = \begin{pmatrix} \boldsymbol{0} & \boldsymbol{N} \\ (\partial \boldsymbol{v}/\partial \boldsymbol{x}) & \boldsymbol{0} \end{pmatrix}.$$

All 2-paths from V_S to V_S are described by the upper-left $n \times n$ sub-matrix of $\boldsymbol{B}^2$, which is just $\boldsymbol{J}$. By extension, an edge, a simple cycle or a line-graph in G_I typically correspond to several 2-paths, cycles or sub-graphs in G, respectively. This one-to-many mapping induces an equivalence relation on G.

Definition 5.6 [equivalence of 2-paths] Consider a reaction network with DSR-graph $G = (V_S, V_R, E, \lambda)$ and interaction graph $G_I = (V(G_I), E(G_I), \gamma)$. Let $e = (S, S') \in E(G_I)$ be an edge and denote by

$$\langle e \rangle := \{((S, R), (R, S')) \in E \times E \mid R \in V_R\}$$

the set of all corresponding 2-paths in G. Two 2-paths p, p' of G are *equivalent* if $p, p' \in \langle e \rangle$ for an $e \in E(G_I)$.

Definition 5.7 [species-cycle; species-line-graph] The equivalence relation is extended to cycles $C = (e_1, \ldots, e_q)$ and line-graphs $L = C_1 + \cdots + C_q$ of G_I by

$$\langle C \rangle := \{(p_1, \ldots, p_q) \mid p_i \in \langle e_i \rangle\} \qquad \text{and} \qquad \langle L \rangle := \{D_1 + \cdots + D_q \mid D_i \in \langle C_i \rangle\} \ .$$

An element of $\langle C \rangle$ or $\langle L \rangle$ is called a *species-cycle* or *species-line-graph* in G, respectively. Each species-cycle in $\langle C \rangle$ uses the same set of species-vertices in the same order, but different reaction-vertices. Each species-line-graph is a set of simple disjoint species-cycles covering each species-vertex exactly once. We again denote the set of all species-line-graphs in G by

$$\mathcal{L}(G) := \bigcup_{L \in \mathcal{L}(G_I)} \langle L \rangle \ .$$

Example 5.8 Consider a Michaelis-Menten type mechanism, given by the reactions

$$R_1 : E + S \rightarrow ES; \quad R_2 : ES \rightarrow E + S; \quad R_3 : ES \rightarrow E + P$$
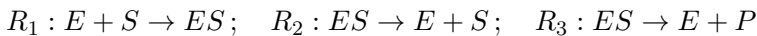
The DSR-graph for this mechanism is given in Figure 2. The edge $e = (ES, E) \in E(G_I)$ corresponds to the equivalence class $\langle e \rangle = \{(ES, R_2, E), (ES, R_3, E)\}$ in G. The cycle $C = (ES, S, ES)$ of G_I thus corresponds to two species-cycles in G, using either 2-path from $\langle e \rangle$ together with the 2-path (E, R_1, ES):

$$\langle C \rangle = \{(ES, R_2, E, R_1, ES), (ES, R_3, E, R_1, ES)\} \ .$$
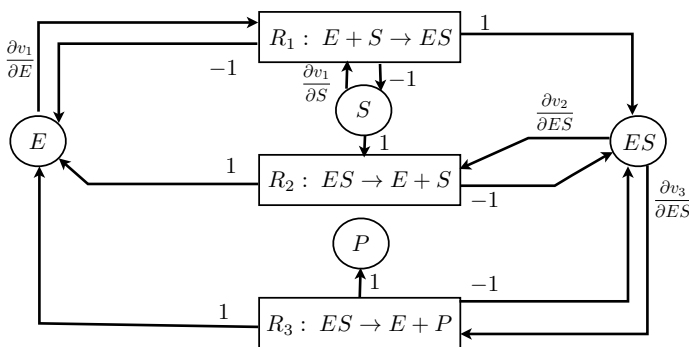

Fig. 2. DSR-graph of Michaelis-Menten type mechanism of Example 5.8.

6   Determinant expansionss and DSR-Graph

We now turn our attention to the expansion of $\det(\boldsymbol{J})$ (and consequently $\det(\boldsymbol{J}_\alpha)$) in terms of the DSR-graph. We are particularly interested in conditions that guarantee that the determinant does not vanish for any positive system state $\boldsymbol{x} > \boldsymbol{0}$.

Lemma 6.1 (signum of sub-graph) *Let $L \subseteq G$ be a line-graph of G and define the* signum *of L as*

$$\sigma(L) := (-1)^{\epsilon(L)}$$

with $\epsilon(L)$ the number of cycles in L with even number of species-vertices. Then,

$$\omega(C) = \sigma(D)$$

for any cycle $C \subseteq G_I$ and $D \in \langle C \rangle$.

Proof. A species-cycle D in G with k species-vertices corresponds to a cycle C in G_I of length k. Thus, $\omega(C) = (-1)^k = \sigma(D)$. $\qquad\qquad\square$

A determinant expansion purely in terms of a DSR-graph is now easily found.

Lemma 6.2 (determinant expansion by DSR-graph) *Consider a chemical reaction network with Jacobian $\boldsymbol{J}$ and DSR-graph G. Then,*

$$\det(\boldsymbol{J}) = \sum_{L \in \mathcal{L}(G)} \sigma(L)\, \lambda(L) \ .$$

Proof. We reduce the expression to the one found for G_I in Lemma 4.3:

$$\sum_{L \in \mathcal{L}(G)} \sigma(L)\, \lambda(L) = \sum_{L \in \mathcal{L}(G_I)} \sum_{L' \in \langle L \rangle} \omega(L')\, \gamma(L') = \sum_{L' \in \mathcal{L}(G_I)} \omega(L')\, \gamma(L') \ ,$$

where ω and γ are again the signum and label function in G_I. $\qquad\qquad\square$

Example 6.3 Consider the DSR-graph of Example 5.2, given in Figure 1. Its species-line-graphs are

$$L_1 : (A, R_1, B, R_2, A)\,; \quad L_2 : (A, R_1, A) \cup (B, R_2, B)\,; \quad L_3 : (A, R_1, A) \cup (B, R_5, B)$$
$$L_4 : (A, R_3, A) \cup (B, R_2, B)\,; \quad L_5 : (A, R_3, A) \cup (B, R_5, B)$$

corresponding directly to the five expansion terms

$$\det(\boldsymbol{J}) = \underbrace{- bd\frac{\partial v_1}{\partial x_A}\frac{\partial v_2}{\partial x_B}}_{L_1} + \underbrace{ac\frac{\partial v_1}{\partial x_A}\frac{\partial v_2}{\partial x_B}}_{L_2} + \underbrace{a\frac{\partial v_1}{\partial x_A}\frac{\partial v_5}{\partial x_B}}_{L_3} + \underbrace{c\frac{\partial v_3}{\partial x_A}\frac{\partial v_2}{\partial x_B}}_{L_4} + \underbrace{\frac{\partial v_3}{\partial x_A}\frac{\partial v_5}{\partial x_B}}_{L_5} \ .$$

In contrast to the determinant expansion from G_I, the sum-of-products representation of labels of G yields a direct correspondence of species-line-graphs and expansion terms. Terms have the same partial derivatives if their species-line-graphs have identical substrate-reaction edges. This observation motivates to identify *compatible* line-graphs in G and determine their overall contribution to the expansion from their stoichiometric labels.

Proposition 6.4 (compatibility) *Let H, H' be two sub-graphs of G. The relation*

$$H, H' \text{ compatible} \ :\Longleftrightarrow\ E_{SR}(H) = E_{SR}(H')$$

defines an equivalence relation which we denote by $H \sim H'$. We further write

$$[H] := \{H \subseteq G \,|\, H' \sim H\}$$

for the equivalence class of a sub-graph H. In particular, $\sim$ partitions $\mathcal{L}(G)$ into equivalence classes in the quotient set $\mathcal{L}(G)/\sim$

Proof. Reflexivity, symmetry, and transitivity of $\sim$ are obvious.   □

As an example, L_1 and L_2 in Example 6.3 are the only non-trivially compatible species-line-graphs. The notion of compatibility suggests a strategy to determine if $\det(\boldsymbol{J})$ vanishes by summing over each individual compatibility class of $\mathcal{L}(G)$. If all classes are either non-negative or non-positive, the sign of the determinant is independent of the state $\boldsymbol{x}$.

Definition 6.5 [stoichiometric term of equivalence class] Let G be a DSR-graph and consider a compatibility class $[L] \in \mathcal{L}(G)/\sim$. The term

$$\Lambda([L]) := \sum_{L' \in [L]} \sigma(L')\lambda_{RS}(L')$$

is called the *stoichiometric term* of $[L]$. It is a constant independent of $\boldsymbol{x}$ and is computed from the stoichiometric matrix alone.

Lemma 6.6 (computing stoichiometric terms) *Fix a species-line-graph $L \in \mathcal{L}(G)$. Let r_j be the index of the unique reaction with substrate S_j in L. Define the $n \times n$ matrix $\boldsymbol{W}_L$ by*

$$W_{i,j} = \begin{cases} 1, & \text{if } (S_j, R_{r_j}) \in E_{SR}(L) \\ 0, & \text{else}, \end{cases}$$

and let $\boldsymbol{N}_L$ be the $n \times n$ stoichiometric matrix with columns not in $\{r_1, \ldots, r_n\}$ removed. Then,

$$\Lambda([L]) = \det(\boldsymbol{N}_L \cdot \boldsymbol{W}_L) = \pm \det(\boldsymbol{N}_L) \tag{4}$$

with the sign determined uniquely by $\boldsymbol{W}_L$.

Proof. The matrix $\boldsymbol{N}_L \cdot \boldsymbol{W}_L$ corresponds to a graph containing only rate edges corresponding to substrate-reaction pairs of $[L]$; its determinant sums the contributions of all remaining species-line-graphs in that graph. Moreover, $\boldsymbol{W}_L$ is simply a permutation matrix whose determinant is thus ± 1.   □

Theorem 6.7 (determinant expansion by compatibility classes) *Consider a reaction network and let $\boldsymbol{J}$ be its Jacobian matrix and G its DSR-graph. Then,*

$$\det(\boldsymbol{J}) = \sum_{[L] \in \mathcal{L}(G)/\sim} \Lambda([L]) \cdot \lambda_{SR}(L) . \tag{5}$$

The determinant is non-negative for all $\boldsymbol{x} > \boldsymbol{0}$ if

$$\Lambda([L]) \geq 0 \text{ for all } [L] \in \mathcal{L}(G)/\sim$$

and positive if in addition $\Lambda([L]) > 0$ for at least one compatibility class. Similar conditions hold for non-positivity (negativity) of the determinant.

Proof. Because $\sim$ is an equivalence relation on $\mathcal{L}(G)$, we can partition the sum of Lemma 6.2 by each equivalence class. Note that the rate label is identical and non-negative for all members of a class. If all stoichiometric terms are non-negative, then so is the sum.   □

Note that (5) together with (4) is a graphical version of the Cauchy-Binet formula for $\det(\boldsymbol{N} \cdot \partial \boldsymbol{v}/\partial \boldsymbol{x})$. We can now restrict our attention to establishing non-negativity (or non-positivity) of the stoichiometric term for each compatibility class. For convenience we focus on $\det(\boldsymbol{J}) = (-1)^n \det(-\boldsymbol{J})$, which is found by inverting signs of stoichiometric edges in G. The determinant expansion is obviously non-zero if and only if the expansion of $\det(\boldsymbol{J})$ is. We start by giving a sufficient condition to find a positive expansion term in open networks.

Lemma 6.8 (existence of positive term in open networks) *Consider a reaction network and assume that there is an inflow reaction $\emptyset \to S_i$ and an outflow reaction $R_i : S_i \to \emptyset$ for each species S_i, $1 \leq i \leq n$. Consider the DSR-graph $G(-\boldsymbol{J})$ and let L_{out} be the species-line-graph*

$$L_{out} := \bigcup_{i=1}^{n} (S_i, R_i, S_i) \,,$$

of 2-paths from each species to itself via its outflow reaction. Then,

  (i) $[L_{out}] = \{L_{out}\}$

  (ii) $\Lambda([L_{out}]) > 0$

  (iii) $\Lambda([L_{out}]) \cdot \lambda_{SR}(L_{out}) > 0$ *for all $\boldsymbol{x} > \boldsymbol{0}$*

Proof. First note that S_i is a substrate to R_i, so $((S_i, R_i), (R_i, S_i)) \in E \times E$ for each species S_i. Thus, L_{out} is indeed a species-line-graph. Since there is no other edge out of an outflow reaction, no other species-line-graph can use the same substrate-reaction pairs and thus the compatibility class has a single element. Each cycle in L_{out} has exactly one species-vertex and thus $\sigma(L_{\text{out}}) = +1$. Further, its stoichiometric edge is positive in $G(-\boldsymbol{J})$ and thus the stoichiometric term of $[L_{\text{out}}]$ is also. For positive concentrations, the outflow rate changes are positive, proving the last claim.   □

Next, we show that species-line-graphs that contain both the forward- and backward reaction of a reversible reaction always lead to a zero stoichiometric term for their compatibility class. This result also gives a retrospective justification for splitting reversible reactions.

Lemma 6.9 (zero-contribution of reversible reaction) *Let $L \in \mathcal{L}(G)$ be a species-line-graph. Let R_f, R_b be the forward and backward reaction of a reversible*

reaction and assume $R_f, R_b \in V_R(L)$. Then,

$$\Lambda([L]) \equiv 0 \ .$$

Proof. The construction in this proof is illustrated in Fig. 3. Denote by $S_f, S_r \in V_S(L)$ the species with $(R_f, S_f), (R_b, S_b) \in E_{RS}(L)$. Because R_f, R_b constitute one reversible reaction, the edges $(R_f, S_b), (R_b, S_f)$ exist in the graph G. Construct a sub-graph L' by replacing $(R_f, S_f), (R_b, S_b)$ by $(R_f, S_b), (R_b, S_f)$. If R_f, R_b are contained in one species-cycle $C_3 \in L$, they are now contained in two different cycles $C_1, C_2 \in L'$ (or vice-versa). Thus, L' is a species-line-graph and $L' \sim L$. Moreover, $\lambda((R_f, S_f)) = -\lambda((R_b, S_f))$ and $\lambda((R_b, S_b)) = -\lambda((R_f, S_b))$ and thus $\lambda(L) = \lambda(L')$. However, let $n_i := |E(C_i)|$, then

$$\sigma(C_1)\sigma(C_2) = (-1)^{n_1-1} (-1)^{n_2-1} = (-1)^{n_3-2} = -\sigma(C_3)$$

and thus $\sigma(L')\lambda(L') = -\sigma(L)\lambda(L)$. This construction gives a bijection between species-line-graphs L and L' and thus $\Lambda([L]) \equiv 0$. □
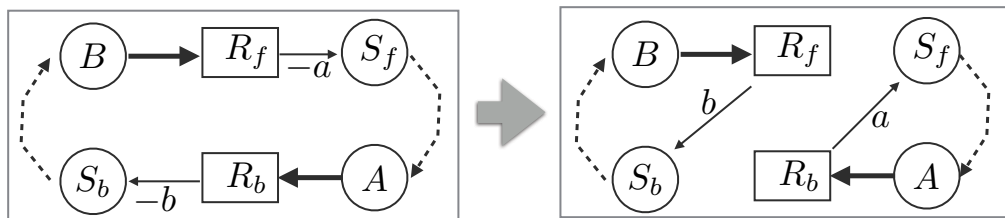

Fig. 3. Illustration of construction for Lemma 6.9. A cycle containing the forward- and backward reaction is split into two cycles, leading to a compatible line-graph with same absolute label, but opposite sign. Dashed line: arbitrary path through the graph; bold line: substrate-reaction edges defining the compatibility class.
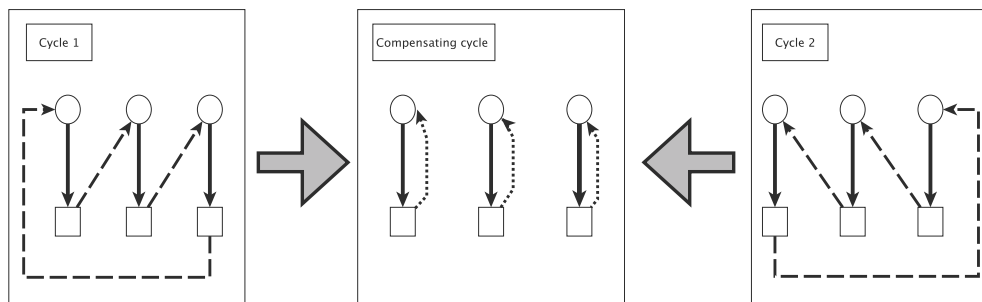

Fig. 4. Illustration of compensating cycles. For a cycle Cycle 1 (C), a compatible compensating cycle (center, L_C) always exists, whose stoichiometries might dominate. A second compatible cycle Cycle 2 may however yield the same compensating cycle. Round (rectangular) nodes denote species (reaction) vertices.

Lemma 6.10 (existence of positive compatible species-line-graphs) *Let $G(-\boldsymbol{J})$ be a DSR-graph and consider a species-line-graph L containing a cycle C. Construct a sub-graph $L_C \subseteq G$ by replacing each 2-path $((S, R), (R, S'))$ in C by $((S, R), (R, S))$. Then,*

(i) $\sigma(L_C)\lambda(L_C) > 0$ *for all* $\boldsymbol{x} > \boldsymbol{0}$

(ii) $L_C \sim C$

(iii) $(L\backslash C) \cup L_C \sim L$.

Proof. The construction is illustrated in Fig. 4. With $(S, R) \in E(C)$, species S is a substrate of R. Then, also $(R, S) \in E(G)$ and thus L_C is a proper sub-graph of G with exactly one odd-length cycle D_i from each species-vertex $S_i \in V_S(C)$ to itself. Thus, $\sigma(D_i) = +1$ and $\lambda(D_i) > 0$ for all $\boldsymbol{x} > \boldsymbol{0}$ and $i = 1, \ldots, n$. These cycles use the same substrate-reaction pairs as C and thus $C \sim L_C$. They also cover each species-vertex in C exactly once, so $L \sim (L\backslash C) \cup L_C$. As a special case, $L_C = C$ if $|V_S(C)| = 1$. $\qquad\square$

The sign of the contribution of a species-line-graph depends on its constituent species-cycles. Since each sub-graph of a DSR-graph is sign-definite, we can give simple conditions for a species-cycle to be positive or negative by determining the number of substrate-to-substrate 2-paths in the cycle.

Lemma 6.11 (condition for sign of species-cycles) *Consider a species-cycle* C *in a DSR-graph* $G(-\boldsymbol{J})$. *Let* s *be the number of* substrate-pairs, *that is, of 2-paths* (S, R, S') *in* C, *such that* S, S' *are both a substrate of* R. *We call* C *a* p-cycle *(an* n-cycle*) if* $\sigma(C)\lambda(C) > 0)$ *(resp.* < 0*). Then,*

$$C \text{ is p-cycle} \iff s \text{ is even}$$
$$C \text{ is n-cycle} \iff s \text{ is odd}.$$

Proof. We consider the four possible combinations of $V_S(C)$ even/odd and s even/odd. For $V_S(C)$ even and s odd, the number of negative 2-paths is also odd, thus $\sigma(C) = +1$ and $\lambda(C) < 0$, as $E(C)$ contains an odd number of negative stoichiometric edges. Thus, the overall contribution of C is negative. The other three cases follow the same reasoning. $\qquad\square$

In [7,2] p-cycles (n-cycles) were called e-cycles (o-cycles). As a consequence of Lemma 6.10, we can give a simple condition when a negative contribution to the determinant expansion is cancelled (see also [7,2]).

Proposition 6.12 (dominating term) *Let* $G(-\boldsymbol{J})$ *be a DSR-graph and consider a species-line-graph* L *containing an n-cycle* C. *Let* $L' = (L\backslash C) \cup L_C$. *Then,*

$$\sigma(L)\lambda(L) + \sigma(L')\lambda(L') \geq 0 \iff \lambda_{RS}(L_C) \geq |\lambda_{RS}(C)|.$$

We then say that L_C *dominates* C. *We call* C *a* stoichiometric *or* s-cycle, *if* $\lambda_{RS}(L_C) = |\lambda_{RS}(C)|$.

The previous Lemma 6.10 and Proposition 6.12 hold the key to determine, for all $\boldsymbol{x} > \boldsymbol{0}$, if a determinant vanishes or not. Clearly, for a species-line-graph L to give a negative contribution to the stoichiometric term $\Lambda([L])$ of its compatibility class, it contains an odd number of n-cycles. Replacing one of these n-cycles C

by L_C leads to a new compatible species-line-graph with positive contribution that compensates the negative. However, there might be a second species-line-graph in the same class, also with negative contribution that contains another negative cycle that leads to the same compensating species-line-graph. Thus, the compensating species-line-graph needs to dominate *the sum* of all these contributions. Next, we give conditions when such situation arises and provide a simple sufficient condition that excludes it.

Theorem 6.13 (species-reaction intersection of species-cycles) *Consider a species-line-graphs L in $G(-\boldsymbol{J})$ and assume that in every compatible species-line-graph, each n-cycle C is dominated by L_C. Further assume that*

$$\Lambda([L]) < 0 .$$

Then, there are $L_1, L_2 \in [L]$ and two non-disjoint n-cycles $C_1 \subseteq L_1$, $C_2 \subseteq L_2$ such that all paths in $C_1 \cap C_2$ start in V_S and end in V_R.

Proof. An illustration for this proof is given in Fig. 5. First note that the non-empty intersection of two cycles is always a collection of paths. Let P be one of the paths in the intersection of C_1, C_2. If P ends in V_S, there are two substrate-reaction pairs involving the same substrate species. Hence, L_1, L_2 cannot be compatible. If P begins in V_R, there are two different species-reaction vertices leading into it, one from C_1, one from C_2. These edges are contained in all compatible sub-graphs leading to non-simple cycles. The sub-graphs are hence not species-line-graphs. The only remaining case is a path from V_S to V_R which yields both unique substrate-reaction pairs and (potentially) the same number of reactions and species. $\qquad\square$
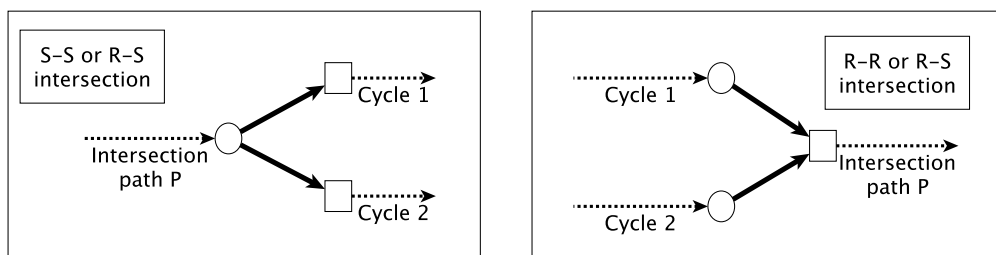

Fig. 5. Illustration of non-feasible intersection of cycles in compatible line-graphs. Left: Both possible intersections ending in V_S require two substrate-reaction pairs with the same species and cannot occur in compatible sub-graphs. Right: An intersection from V_R to V_S uses a reaction vertex twice and leads to a zero overall contribution. Round (rectangular) nodes denote species (reaction) vertices. Dotted edges denote arbitrary paths through the graph, bold edges denote substrate-reaction pairs.

As a corollary of the theorem, we get a simple condition of the cycle-structure of a DSR-graph that allows to test if the determinant of the network does not vanishes anywhere. An equivalent condition was first formulated in [7].

Corollary 6.14 (necessary condition for positive determinant) *Consider a DSR-graph $G(-\boldsymbol{J})$. The determinant $\det(-\boldsymbol{J})$ is positive if*

(i) *there is at least one positive stoichiometric term*

(ii) *every cycle C in G is either a p-cycle or dominated by L_C*

(iii) *no two n-cycles have an intersection from V_S to V_R*

The existence of a positive term is guaranteed for open networks by Lemma 6.8.

7 Extensions

The idea of decomposing the determinant expansion using equivalence classes can be extended if a partial order on the rate derivatives $\partial v_i / \partial x_j$ is established. Since $\lambda_{SR}(L)$ is a product of rate derivatives, this order induces a partial order on some compatibility classes L, L' such that $\lambda_{SR}(L) \geq \lambda_{SR}(L')$ for all $\boldsymbol{x} > \boldsymbol{0}$. This order of classes consequently implies that

$$\Lambda([L]) > \Lambda([L']) \implies \Lambda([L]) \cdot \lambda_{SR}(L) > \Lambda([L']) \cdot \lambda_{SR}(L') \,,$$

allowing comparison of two equivalence classes by their stoichiometric term alone such that a negative contribution of $[L']$ can be compensated by a larger positive one of $[L]$, independently of $\boldsymbol{x}$.

For mass-action kinetics, such a partial order is given for all species-line-graphs that use the same set of reaction vertices. The rate derivatives for mass-action rate laws are of the simple form

$$\frac{\partial v_i}{\partial x_j}(\boldsymbol{x}^*) = -N_{j,i} \cdot v_i(\boldsymbol{x}^*) \cdot \frac{1}{x_j^*} \,.$$

Consider now two species-line-graphs L, L' in $G(-\boldsymbol{J})$ with $V_R(L) = V_R(L')$. Then,

$$\lambda_{SR}(L) = \prod_{(S_j, R_i) \in E(L)} -N_{j,i} \cdot v_i(\boldsymbol{x}^*) \cdot \frac{1}{x_j^*} \quad \text{and} \quad \lambda_{SR}(L') = \prod_{(S_j, R_i) \in E(L')} -N_{j,i} \cdot v_i(\boldsymbol{x}^*) \cdot \frac{1}{x_j^*} \,,$$

and thus

$$\frac{\lambda_{SR}(L)}{\lambda_{SR}(L')} = \frac{\prod_{(S_j, R_i) \in E(L)} -N_{j,i}}{\prod_{(S_j, R_i) \in E(L')} -N_{j,i}} \text{ independently of } \boldsymbol{x} > \boldsymbol{0} \,.$$

This allows combining the results for all compatibility classes with the same reaction-vertices, a strategy employed in [7,16]: Let V_R^* be the specific set of n reactions, and let $G^* \subseteq G(-\boldsymbol{J})$ be the DSR-graph with $V_R(G^*) = V_R^*$. Then, all species-line-graphs in G^* give a combined non-negative contribution to the determinant if

$$\sum_{[L] \in \mathcal{L}(G^*)/\sim} \Lambda([L]) \cdot \left(\prod_{(S_i, R_j) \in E(L)} -N_{i,j} \right) \geq 0 \,. \tag{6}$$

This term can be computed similar to Lemma 6.6 by replacing $\boldsymbol{W}_L$ by a suitable $n \times n$ matrix extracted from $\boldsymbol{N}$. The term (6) was called a *critical fragment* (of size n) if it is negative [16] and the question of the relation between critical fragments

and conditions on Corollary 6.14 was raised. Since the products $\prod(-N_{i,j})$ are all positive, Corollary 6.14 gives a sufficient condition to exclude a critical fragment, as it establishes non-negativity for each summand in (6).

8   Discussion

The particular structure of dynamic chemical reaction network models allows to derive conditions for establishing or excluding specific qualitative dynamics. These conditions enable a first analysis and model selection independently of numerical values for rate constants and for all members of a large class of rate laws.

Here, we proposed a new definition of a bipartite species-reaction graph, termed DSR-graph. In contrast to previous definitions, all relevant features of cycles, such as feasible directions to traverse edges and substrate/product relations of species and reactions are directly encoded in the graph. Our DSR-graph contains previous definitions as special cases. We elucidated the direct connection of the DSR-graph to the systems' interaction graph and demonstrated how cycle features can be mapped by simple equivalences of edges and 2-paths. For calculating terms of the determinant expansions of the Jacobian matrix, both graphs yield structurally similar formulas, but the DSR-graph allows a more fine-grained analysis of the terms. As a new result for bipartite graphs of chemical reaction systems, we proposed a simple equivalence relation on the species-line-graphs of the DSR-graph that allows to collect comparable terms in the expansion and subsequently enabled simpler and more direct proofs of conditions for the non-vanishing of principal minors of the Jacobian matrix. We finally addressed a question raised in [16] on the relation of their conditions to the ones developed by Craciun et al in [7].

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