PROCEEDINGS OF
THE ROYAL SOCIETY A
MATHEMATICAL, PHYSICAL AND ENGINEERING SCIENCES

Unstable Cores are the source of instability in chemical reaction networks

Journal:	*Proceedings A*
Manuscript ID	RSPA-2023-0694.R1
Article Type:	Research
Date Submitted by the Author:	19-Dec-2023
Complete List of Authors:	Vassena, Nicola; Universitat Leipzig IZBI Stadler, Peter; Leipzig University, Computer Science; University of Vienna, Theoretical Chemistry; Universidad Nacional de Colombia Facultad de Ciencias; Santa Fe Institute
Subject:	Applied mathematics < MATHEMATICS, Differential equations < MATHEMATICS, Physical chemistry < CHEMISTRY
Keywords:	Autocatalysis, Stoichiometric Matrix, Parameter-rich kinetic model, Non-autocatalytic instabilities
Subject Category:	Mathematics
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.	
Unstable cores.zip	

Author-supplied statements

Relevant information will appear here if provided.

Ethics

Does your article include research that required ethical approval or permits?:
This article does not present research with ethical considerations

Statement (if applicable):
CUST_IF_YES_ETHICS :No data available.

Data

It is a condition of publication that data, code and materials supporting your paper are made publicly available. Does your paper present new data?:
My paper has no data

Statement (if applicable):
CUST_IF_YES_DATA :No data available.

Conflict of interest

I/We declare we have no competing interests

Statement (if applicable):
CUST_STATE_CONFLICT :No data available.

PROCEEDINGS A

royalsocietypublishing.org/journal/rspa

Research

Check for updates

Article submitted to journal

Subject Areas:
applied mathematics, theoretical chemistry

Keywords:
Autocatalysis, Stoichiometric Matrix, Parameter-rich kinetic model, Non-autocatalytic instabilities

Author for correspondence:
Nicola Vassena
e-mail: nicola.vassena@uni-leipzig.de

Unstable Cores are the source of instability in chemical reaction networks

Nicola Vassena[1] and Peter F. Stadler[1,2,3,4]

[1]Interdisciplinary Center for Bioinformatics, Universität Leipzig, Germany
[2]Bioinformatics Groups, Department of Computer Science; Competence Center for Scalable Data Services and Solutions Dresden/Leipzig (scaDS.AI); German Centre for Integrative Biodiversity Research (iDiv); Leipzig Research Center for Civilization Diseases; School of Embedded and Compositive Artificial Intelligence, Universität Leipzig, Germany
[3]Department of Theoretical Chemistry, University of Vienna, Austria
[4]Facultad de Ciencias, Universidad National de Colombia, Sede Bogotá, Colombia [5]Santa Fe Institute, Santa Fe, NM

In biochemical networks, complex dynamical features such as superlinear growth and oscillations are classically considered a consequence of autocatalysis. For the large class of parameter-rich kinetic models, which includes Generalized Mass Action kinetics and Michaelis-Menten kinetics, we show that certain submatrices of the stoichiometric matrix, so-called unstable cores, are sufficient for a reaction network to admit instability and potentially give rise to such complex dynamical behavior. The determinant of the submatrix distinguishes unstable-positive feedbacks, with a single real-positive eigenvalue, and unstable-negative feedbacks without real-positive eigenvalues. Autocatalytic cores turn out to be exactly the unstable-positive feedbacks that are Metzler matrices. Thus there are sources of dynamical instability in chemical networks that are unrelated to autocatalysis. We use such intuition to design non-autocatalytic biochemical networks with superlinear growth and oscillations.

THE ROYAL SOCIETY PUBLISHING

1. Introduction

Chemical Reaction Network theory has striven to elucidate the connection between the structure of a (bio)chemical reaction network and its dynamical behavior since Rutherford Aris' seminal work [1]. A question of particular interest for applications in biological systems is whether, for a given reaction network, there is a choice of kinetic parameters that renders an equilibrium dynamically unstable and thus may give rise to complex dynamical behavior.

Well-known examples of such instabilities, such as the famous Belusouv–Zhabotinsky reactions [2,3], typically involve autocatalysis, i.e., the presence of a species that catalyzes its own production. The concept of autocatalysis introduced by Wilhelm Ostwald [4] in the context of chemical kinetics refers to a temporary speed-up of the reaction before it settles down to reach equilibrium, see e.g. [5,6]. Autocatalysis plays a key role both in extant metabolic networks and in models of the origin of life. Autocatalytic pathways, such as glycolysis, contain reactions that consume some of the pathway's products and exhibit positive feedback [7,8]. In order to explain the emergence of self-replicating organisms, "collectively autocatalytic" networks of interacting molecules have been proposed [9]. In the setting of metabolic reaction networks, the importance of "network autocatalysis" has been emphasized [10,11]. In a more general setting, such structures have been studied as self-maintaining chemical organizations [12,13]. Despite the central role of autocatalysis, however, its formal, mathematical understanding is limited. Different concepts of autocatalysis have been proposed [14–18]; for a comparison see [19].

Even though autocatalysis has played a central role in investigations of complex dynamics, including deterministic chaos [20], dynamical systems theory does not seem to imply that autocatalysis has to be necessarily invoked to explain the existence of dynamic instabilities. In fact, the unstable manifold theorem [21] suggests superlinear divergence from an unstable equilibrium, while in a supercritical Hopf bifurcation [21,22] a stable equilibrium loses stability and generates a stable periodic orbit. Neither of these situations requires assumptions that even vaguely resemble autocatalysis. In both cases, the key property is the loss of stability of an equilibrium. This begs the question whether the existence of unstable equilibria can be explained in terms of the structure of the chemical reaction network, or more precisely, in terms of its stoichiometric matrix. Since autocatalytic cores are also characterized in terms of the stoichiometric matrix [17], we set out here to disentangle instability and autocatalysis in terms of a purely structural view on chemical reaction networks. On the one hand, we confirm that autocatalysis has always the potential to destabilize an equilibrium. Autocatalysis is thus a sufficient condition for instability in certain parameter regions. On the other hand, we establish that autocatalysis is not necessary for superlinear growth or oscillations.

In more detail, we shall see that small unstable subsystems are sufficient to imply that an entire reaction network admits instability in kinetic models that are sufficiently 'rich' in parameters (Def. 3.1), such as Michaelis-Menten [23], Hill [24], and Generalized Mass Action [25] kinetics. A key ingredient towards this result are the so-called Child-Selections (CS). Conceptually, a CS $\boldsymbol{\kappa}$ is a square submatrix of the stoichiometric matrix S comprising k species and k reactions such that there is a 1-1 association between species m and reactions $j(m)$ for which m is a reactant for $j(m)$. From this submatrix, we obtain the *Child-Selection matrix* $S[\boldsymbol{\kappa}]$ by reordering the columns so that species and their associated reactions correspond to the diagonal entries. The existence of an unstable Child-Selection matrix is sufficient for a network $\boldsymbol{\Gamma}$ with a parameter-rich kinetic model to admit instability (Cor. 5.1). Since Child-Selections can be "concatenated", minimal unstable Child-Selections are well defined, in the sense that the Child-Selection matrix $S[\boldsymbol{\kappa}]$ does not contain again a proper principal submatrix that is an unstable Child-Selection matrix, which leads to the main definition of this paper (Def. 5.1):

An unstable core *is a Hurwitz-unstable Child-Selection matrix for which no principal submatrix is unstable.*

Unstable cores come in two flavors: An unstable core is an *unstable-negative feedback* if $\operatorname{sign}\det S[\boldsymbol{\kappa}] = (-1)^k$ and *unstable-positive feedback* if $\operatorname{sign}\det S[\boldsymbol{\kappa}] = (-1)^{k-1}$. This terminology is inspired by positive and negative feedback cycles, where the sign of the feedback is typically defined as the sign of the product of the off-diagonal entries. The condition on the determinants translates into a structural difference in their spectra: Unstable-positive feedbacks have a single real-positive eigenvalue, while unstable-negative feedbacks have no real-positive eigenvalues at all (Lemma 6.1). The presence of related "positive feedbacks" is known to be *necessary* for multistationarity [26,27] (see also **EXAMPLE A**). Oscillations, on the other hand, can be induced both by unstable-positive and unstable-negative feedbacks (see **EXAMPLE B** and **EXAMPLE C**).

We then shall turn our attention to autocatalysis and autocatalytic cores in particular, and formally define an *autocatalytic matrix* (Def. 7.1), inspired by [17]. Autocatalytic cores are then autocatalytic submatrices of the stoichiometric matrix that do not contain any autocatalytic submatrix. Our main result (Thm. 7.1) characterizes autocatalytic cores in terms of unstable cores and Metzler matrices, i.e., matrices with nonnegative off-diagonal entries, and can be expressed as follows:

An autocatalytic core is an unstable-positive feedback that in addition is a Metzler matrix.

Recalling that autocatalytic networks must contain an autocatalytic core leads to a convenient characterization of general autocatalytic networks (Cor. 7.3):

A network is autocatalytic if and only if there is a Child-Selection matrix that is a Hurwitz-unstable Metzler matrix.

Our results show in particular that *every autocatalytic network admits instability*. The converse clearly is not true, i.e., *autocatalysis is not necessary for instability*: First, unstable-negative feedbacks are never autocatalytic (Cor. 7.2 and **EXAMPLE C**). Second, it is straightforward to construct unstable-positive feedbacks that are not Metzler matrices and thus not autocatalytic (see **EXAMPLES A, B**, and **EXAMPLE D** where we list non-autocatalytic unstable-positive feedbacks in the sequential and distributive double phosphorylation).

The paper is organized as follows. Section 2 presents the general setting of reaction networks and Section 3 the definition of parameter-rich models. Section 4 introduces Child-Selections and employs a Cauchy–Binet analysis to expand each coefficient of the characteristic polynomial via Child-Selections: this is used to connect the topology of the network to stability properties. Section 5 introduces the definition of *unstable cores* and its generalization, *D-unstable cores*. Section 6 addresses unstable-positive and unstable-negative feedbacks. In Section 7 we focus on autocatalytic cores and we show in Theorem 7.1 that they are a special case of unstable cores. Section 8 presents four examples of non-autocatalytic networks that shows either multistationarity (with superlinear growth) or oscillations. We refer to the Supplementary Material (SM) for a full analysis and explanation of such examples. Section 9 concerns the proof of Theorem 7.1. To this goal, we reduce first to the case of NC-networks where no reaction is explicitly catalytic, i.e., no reaction has a reactant that is also a product. Albeit our paper shows that autocatalysis is not necessary for complex behavior as oscillations or superlinear growth, in Section 10 we nevertheless provide an informal indication why autocatalysis has been the typical source of instability in well-known examples. Section 11 concludes the paper, discussing the results in a general context.

2. Chemical reaction networks, dynamics, and stability

A chemical reaction network $\boldsymbol{\Gamma}$ is a set M of *species* together with a set E of *reactions*. A reaction $j \in E$ is a pair of formal linear combinations

$$s^j_{m_1} m_1 + \ldots + s^j_{m_{|M|}} m_{|M|} \underset{j}{\to} \tilde{s}^j_{m_1} m_1 + \ldots + \tilde{s}^j_{m_{|M|}} m_{|M|}, \tag{2.1}$$

with *stoichiometric* coefficients $s_m^j \geq 0$ and $\tilde{s}_m^j \geq 0$. Usually, one assumes $s_m^j, \tilde{s}_m^j \in \mathbb{N}_0$, although this restriction is not relevant here. A species m is a *reactant* of j if $s_m^j > 0$ and a *product* of j if $\tilde{s}_m^j > 0$. Note that (2.1) assigns a fixed order to any reaction j, so that we treat all reactions as *irreversible*. However, reversible processes such as $j: A \rightleftharpoons B$ can be naturally taken into account by considering two opposite reactions $j_1: A \to B$ and $j_2: B \to A$. In biological systems, reaction networks are often *open*: they exchange chemicals with the outside environment. For this reason, we also consider reactions with no outputs (*outflow reactions*) or with no inputs (*inflow reactions*). These describe the exchange of material between the system and its environment.

A reaction j_C is *explicitly catalytic* if a species m is both a reactant and a product of the reaction j_C, i.e., $s_m^{j_C} \tilde{s}_m^{j_C} \neq 0$. The net change of chemical composition in a reaction network is described by the $|M| \times |E|$ *stoichiometric matrix* S defined as

$$S_{mj} := \tilde{s}_m^j - s_m^j, \tag{2.2}$$

Note that for explicit catalysts m with $s_m^{j_C} = \tilde{s}_m^{j_C}$, the stoichiometric coefficients cancel and thus do not appear in the entry S_{mj_C} of the stoichiometric matrix.

The time-evolution $x(t) \geq 0$ of an $|M|$-vector of the concentrations under the assumption of spatial homogeneity, e.g. in a well-mixed reactor, obeys the system of ordinary differential equations

$$\dot{x} = f(x) := Sr(x), \tag{2.3}$$

where $r: \mathbb{R}_{\geq 0}^{|M|} \to \mathbb{R}_{\geq 0}^{|E|}$ is a vector of reaction rate functions. In this contribution, we will in particular be concerned with *equilibria* or *fixed points*, i.e., $|M|$-vectors $\bar{x}$ satisfying $f(\bar{x}) = 0$. Assuming that f is a continuously differentiable vector field, the stability of an equilibrium $\bar{x}$ is determined by the Jacobian matrix G evaluated at $\bar{x}$, which has entries $G_{hm}(\bar{x}) := \partial f_h(x)/\partial x_m|_{x=\bar{x}}$. A real square matrix A is *Hurwitz-stable* if all its eigenvalues λ satisfy $\operatorname{Re}\lambda < 0$. It is *Hurwitz-unstable* if there is at least one eigenvalue λ_u with $\operatorname{Re}\lambda_u > 0$. It is well known that an equilibrium $\bar{x}$ is dynamically stable if $G(\bar{x})$ is Hurwitz-stable, and unstable if $G(\bar{x})$ is Hurwitz unstable [21].

We consider all reactions to be directional. Thus the rate r_j of a reaction j is a non-negative function. We further assume that it depends only on the concentrations of its reactants, i.e., the molecular species m with stoichiometric coefficients $s_m^j > 0$. Finally, a reaction can only take place if all its reactants are present, in which case the rate increases with increasing reactant concentrations. We capture these conditions in the following formal definition of a kinetic model for a given chemical reaction network:

Definition 2.1. *Let $\Gamma = (M, E)$ be a chemical reaction network. A differentiable function $r: \mathbb{R}_{\geq 0}^M \to \mathbb{R}^E$ is a* kinetic model *for Γ if*

(i) $r_j(x) \geq 0$ for all x,
(ii) $r_j(x) > 0$ implies $x_m > 0$ for all m with $s_m^j > 0$,
(iii) $s_m^j = 0$ implies $\partial r_j/\partial x_m \equiv 0$,
(iv) if $x > 0$ and $s_m^j > 0$ then $\partial r_j/\partial x_m > 0$.

For $\bar{x} \in \mathbb{R}_{\geq 0}^M$ we write

$$r'_{jm}(\bar{x}) := \left.\frac{\partial r_j(x)}{\partial x_m}\right|_{x=\bar{x}}. \tag{2.4}$$

The $|E| \times |M|$ matrix $R(\bar{x})$ with entries $R_{jm} := r'_{jm}(\bar{x})$ is called the *reactivity matrix*. By construction, we have $r'_{jm}(\bar{x}) \geq 0$ for all $m \in M$ and $j \in E$, i.e., $R(\bar{x})$ is a non-negative matrix. For $\bar{x} > 0$, moreover, $r'_{jm}(\bar{x}) > 0$ if and only if $s_m^j > 0$. Thus, for any strictly positive equilibrium $\bar{x} > 0$, the signs of $R(\bar{x})$ are completely determined by the reactants in the network. Together, the stoichiometric matrix S and the reactivity matrix R determine the stability of an equilibrium, since

(2.3) implies that the Jacobian G is of the form

$$G(\bar{x}) = SR(\bar{x}). \tag{2.5}$$

Prominent examples of kinetic models include *Mass Action kinetics* [28]

$$r_j(x) := a_j \prod_{m\in M} x_m^{s_m^j} \tag{2.6}$$

and *Michaelis–Menten kinetics* [23]

$$r_j(x) := a_j \prod_{m\in M} \left(\frac{x_m}{(1+b_m^j x_m)} \right)^{s_m^j}. \tag{2.7}$$

Note that Mass Action kinetics appears as the limiting case of Michaelis–Menten kinetics with $b_m^j = 0$ for all j, m. Here, $r_j(x)$ depends on parameters (a_j and b_m^j). In general, we write $r(x; p)$ for a parametric kinetic model that depends on parameters p. In this contribution we are not interested in concrete choices of such parameters. Instead, we are interested in the existence of unstable equilibria given a suitable choice of parameters.

Definition 2.2. *A network $\boldsymbol{\Gamma} = (M, E)$ with a parametrized kinetic model $r(x; p)$* admits instability *if there exists a choice $\bar{p}$ of parameters such that there is a positive equilibrium $\bar{x}$ of $\dot{x} = Sr(x; \bar{p})$ with a Hurwitz-unstable Jacobian $G(\bar{x})$.*

3. Parameter-rich kinetic models

We are particularly interested in kinetic models $r(x; p)$ that have a sufficient number of free parameters p such that the equilibrium $\bar{x}$ and $R(\bar{x})$ can be chosen independently. We formalize this idea as follows:

Definition 3.1. *A kinetic rate model $r(x; p)$ is* parameter-rich *if, for every positive equilibrium $\bar{x} > 0$ and every $|E| \times |M|$ matrix R with entries satisfying $r'_{jm} > 0$ if $s_m^j > 0$ and $r'_{jm} = 0$ if $s_m^j = 0$, there are parameters $\bar{p} = p(\bar{x}, R)$ such that $\frac{\partial r_j(x;\bar{p})}{\partial x_m}\big|_{x=\bar{x}} = r'_{jm}$.*

For any choice of a positive vector $\bar{x}$ and matrix entries r'_{jm} with $s_m^j > 0$, in parameter-rich models it is possible to find parameter values $\bar{p}$ such that $\bar{x}$ is a fixed point and the r'_{jm} are the partial derivatives at the equilibrium $\bar{x}$. The only constraints on the Jacobian, therefore, derives from the stoichiometry of the network. In the following we write $\boldsymbol{r'}$ for an arbitrary non-zero choice of the r'_{jm} with $s_m^j > 0$. It is then convenient to think of the partial derivatives r'_{jm} themselves as *symbols* that can be specialized to particular positive values at our convenience. We write $R(\boldsymbol{r'})$ for the corresponding symbolic *reactivity matrix*. The Jacobian $G(\boldsymbol{r'}) = SR(\boldsymbol{r'})$ thus can also be viewed as a symbolic matrix. Combining this with Def. 2.2 and Def. 3.1 we immediately arrive at the following

Observation 3.1. *A network $\boldsymbol{\Gamma}$ with a parameter-rich kinetic model admits instability if and only if there is a choice of symbols $\mathbf{r}'$ such that the symbolic Jacobian $G(\mathbf{r}')$ is Hurwitz-unstable.*

Def. 3.1 requires parameter-rich kinetic models to have enough parameters to simultaneously satisfy constraints at two levels: at the level of the functions $r(x, p)$ and at the level of their first derivatives. The former comes from the equilibrium constraints, i.e. $S\boldsymbol{r}(x) = 0$, while the latter comes from the matrix R that – jointly with the stoichiometric matrix S – prescribes the Jacobian. This fact suggests that at least two parameters for each reaction rate r_j must be present in order to account for both levels of constraints. Mass action kinetics, Eq.(2.6), presents one single parameter for each reaction rate, while Michaelis–Menten kinetics, Eq.(2.7), at least two. This observation indicates that mass action kinetics is not parameter-rich, while Michaelis–Menten might be. Theorem 6.1 in [29] confirms this expectation regarding Michaelis–Menten kinetics:

royalsocietypublishing.org/journal/rspa Proc R Soc A 0000000

Lemma 3.1. *Michaelis–Menten kinetics, Eq.(2.7), is parameter-rich.*

In the SM, Section 2.1, we include a short proof of Lemma 3.1 to make this contribution self-contained. Clearly, any kinetic model that contains Michaelis–Menten kinetics as a special case is also parameter-rich, e.g. Hill kinetics [24]. In contrast, we formally confirm that mass action is *not* parameter-rich: the derivative of the reaction rate of j with respect to the concentration x_m of one of its reactants m reads

$$r'_{jm}(x) = s^j_m \, x_m^{(s^j_m - 1)} \, k_j \prod_{n \neq m} x_n^{s^j_n} = \frac{s^j_m}{x_m} r_j(x). \tag{3.1}$$

For a fixed equilibrium $\bar{x} > 0$, the relation $r'_{jm}(\bar{x}) = \frac{s^j_m}{\bar{x}_m} r_j(\bar{x})$ shows the absence of parameter freedom to harness the value of the derivatives $r'_{jm}(\bar{x})$ independently from the values of the fluxes $r_j(\bar{x})$ and the concentration $\bar{x}$. Thus, if the fluxes $\bar{r}_j = r_j(\bar{x})$ of a fixed concentration $\bar{x}$ solve the equilibrium constraints $S\bar{r} = 0$, the values of the derivatives $r'_{jm}(\bar{x})$ cannot be chosen independently and with freedom, contradicting Def. 3.1. In particular, the set of Jacobian matrices of an equilibrium of a mass-action system on a network $\boldsymbol{\Gamma}$ is a *subset* of the set of Jacobian matrices of an equilibrium of any parameter-rich models on $\boldsymbol{\Gamma}$. This has two important consequences: the fact that $\boldsymbol{\Gamma}$ endowed with parameter-rich kinetics admits instability does not imply that the same network $\boldsymbol{\Gamma}$ with mass-action kinetics admits instability. In contrast, the fact that $\boldsymbol{\Gamma}$ with parameter-rich kinetics does not admit instability implies that $\boldsymbol{\Gamma}$ does not admit instability with mass-action kinetics as well.

On the other hand, *Generalized Mass Action kinetics* considers the stoichiometric exponent s^j_m appearing in mass action to be an additional positive parameter itself. Such kinetics has been proposed to model intra-cellular reactions where the assumption of spatial homogeneity fits less. See [25] for more details. Let $c^j_m \in \mathbb{R}_{\geq 0}$ be the real parametric exponent of the species m in the reaction j and assume that $c^j_m > 0$ if and only if $s^j_m > 0$, and zero otherwise. Generalized Mass Action kinetics reads

$$r_j(x) := a_j \prod_{m \in M} x_m^{c^j_m}, \qquad \text{with } c^j_m \neq 0 \text{ if and only if } s^j_m \neq 0. \tag{3.2}$$

Analogously to Lemma 3.1, we have the following.

Lemma 3.2. *Generalized mass action, (3.2), is parameter-rich.*

Proof. The same computation as (3.1) leads to

$$r'_{jm}(x) = \frac{c^j_m}{x_m} r_j(x), \tag{3.3}$$

where now c^j_m is not a fixed integer value but a real-valued parameter. Thus, as in the proof of Lemma 3.1, we can fix any concentration $\bar{x} > 0$, equilibrium fluxes $\bar{r} \in \mathbb{R}^{|E|}_{>0}$ with $S\bar{r} = 0$ and any choice of symbols $\bar{\boldsymbol{r}}'$. For the positive choice of parameters

$$\begin{cases} c^j_m := \bar{x}_m \bar{r}'_{jm} (\bar{r}_j)^{-1}, \\ a_j := \bar{r}_j \left(\prod_{m \in M} \bar{x}_m \right)^{-\bar{x}_m \bar{r}'_{jm} (\bar{r}_j)^{-1}} \end{cases} \tag{3.4}$$

the generalized mass-action functions $r_j(x) := a_j \prod_{m \in M} x_m^{c^j_m}$ satisfy $Sr(\bar{x}) = 0$, i.e. $\bar{x}$ is an equilibrium, with prescribed partial derivatives $\bar{\boldsymbol{r}}'$. Thus Generalized Mass Action kinetics is parameter-rich. □

Finally, we point out that some parameter-rich kinetics can themselves be derived as a singular limit of mass-action systems: this should not create confusion. To clarify this in an explicit example, consider Michaelis–Menten kinetics. It is well known that a reaction $A \to B$ endowed with Michaelis-Menten kinetics can be seen as the singular limit of the three-reactions mass-action network $A+E \rightleftharpoons I \to B+E$. In this latter network, however, three reactions instead of one appear. Consequently, the associated mass-action system presents three parameters, not one. In contrast, the very network $A \to B$ presents only one parameter when endowed with mass action. In this viewpoint, the parameter-richness of Michaelis–Menten is inherited by such expanded slow-fast mechanism under mass-action constraints. Def. 3.1 treats nevertheless the structure of the network as given and fixed, and it does not consider expanded 'elementary' versions of the same network.

4. Child-Selections and Cauchy–Binet analysis

A central tool in this work are bijective associations between molecular species and reactions that give rise to square submatrices of S.

Definition 4.1. *Let $\boldsymbol{\Gamma} = (M, E)$ be a network with stoichiometric matrix S. A k-*Child-Selection triple*, or k-CS for short, is a triple $\boldsymbol{\kappa} = (\kappa, E_\kappa, J)$ such that $|\kappa| = |E_\kappa| = k$, $\kappa \subseteq M$, $E_\kappa \subseteq E$, and $J : \kappa \to E_\kappa$ is a bijection satisfying $s_m^{J(m)} > 0$ for all $m \in \kappa$. We call J a* Child-Selection bijection.

Note that since J is a bijection between two ordered sets, we can naturally consider the *signature* (or parity) $\operatorname{sgn} J$ of the map J, where J is seen as a permutation of a set of cardinality k. For an $|M| \times |E|$ matrix A, and subsets $\kappa \subseteq M$, $\iota \subseteq E$, the notation $A[\kappa, \iota]$ refers to the submatrix of A with rows in κ and columns in ι. For square matrices, principal submatrices with $\kappa = \iota$ are indicated as $A[\kappa]$. A k-CS $\boldsymbol{\kappa}$ identifies a $k \times k$ submatrix $S[\kappa, E_\kappa]$ of S. Its columns can be reordered such that the reactions $J(m)$ appear in the same order as their corresponding species m. This gives rise to a matrix $S[\boldsymbol{\kappa}]$ with entries

$$S[\boldsymbol{\kappa}]_{ml} := S[\kappa, E_\kappa]_{m,J(l)} = \tilde{s}_m^{J(l)} - s_m^{J(l)}, \tag{4.1}$$

where the permutation of the columns of $S[\boldsymbol{\kappa}]$ from $S[\kappa, E_\kappa]$ is described by the Child-Selection bijection J with signature $\operatorname{sgn} J$. In particular,

$$\det S[\boldsymbol{\kappa}] = \operatorname{sgn} J \det S[\kappa, E_\kappa], \tag{4.2}$$

since the determinant is a multilinear and alternating form of the columns of a matrix. We call a matrix $S[\boldsymbol{\kappa}]$ arising from a k-CS $\boldsymbol{\kappa}$ in $\boldsymbol{\Gamma}$ a *Child-Selection matrix*.

Let $\boldsymbol{\kappa} = (\kappa, E_\kappa, J)$ be a k-CS. Consider $\kappa' \subseteq \kappa$, $E_{\kappa'} = \{J(m) \mid m \in \kappa'\}$ and $J' : \kappa' \to E_{\kappa'}$ with $J'(m) = J(m)$. Clearly, $E_{\kappa'} \subseteq E_\kappa$ and $J' : \kappa' \to E_{\kappa'}$ is the restriction of J to κ', and thus bijective. In particular $\boldsymbol{\kappa'} = (\kappa', E_{\kappa'}, J')$ is a $|\kappa'|$-CS. We say that $\boldsymbol{\kappa'}$ is a *restriction* of $\boldsymbol{\kappa}$.

Observation 4.1. *Let $\boldsymbol{\kappa}$ be a k-CS and set $A := S[\boldsymbol{\kappa}]$. Then every principal submatrix of A satisfies $A[\kappa'] = S[\boldsymbol{\kappa'}]$, where $\boldsymbol{\kappa'}$ is the restriction of $\boldsymbol{\kappa}$ to $\kappa' \subseteq \kappa$.*

As a consequence, Child-Selections come with a natural notion of minimality w.r.t. some property $\mathbb{P}$.

Definition 4.2. *A k-CS $\boldsymbol{\kappa}$ is minimal w.r.t. $\mathbb{P}$ if there is no restriction $\boldsymbol{\kappa'}$ of $\boldsymbol{\kappa}$ with $\kappa' \subsetneq \kappa$ such that $\boldsymbol{\kappa'}$ has property $\mathbb{P}$.*

Observation 4.2. *Suppose $\mathbb{P}$ is a matrix property. A Child-Selection matrix $S[\boldsymbol{\kappa}]$ is minimal w.r.t. a matrix property $\mathbb{P}$ if no proper principal submatrix of $S[\boldsymbol{\kappa}]$ has the property $\mathbb{P}$.*

As addressed in [29], the k-CS triples and their associated matrices provide sufficient conditions for instability in a network with a parameter-rich kinetic model. We include the relevant arguments in the present setting. The instability of a matrix is characterized by the sign of the real part of its eigenvalues, i.e., of the roots of its characteristic polynomial. For matrices that are symbolic Jacobians of networks, the coefficients of the characteristic polynomial can be expanded along Child Selections: Let

$$g(\lambda) = \sum_{k=0}^{|M|} (-1)^k c_k \lambda^{|M|-k} \tag{4.3}$$

be the characteristic polynomial of the symbolic Jacobian matrix $G(\boldsymbol{r}') = SR(\boldsymbol{r}')$. The coefficients c_k are the sum of the principal minors $\det G[\kappa]$ for all sets $|\kappa| = k$. Applying the Cauchy–Binet formula to any principal submatrix $G[\kappa]$ of G we obtain

$$\det G[\kappa] = \det S[\kappa, E] R[E, \kappa] = \sum_{|\iota|=k} \det S[\kappa, \iota] \det R[\iota, \kappa]. \tag{4.4}$$

A central observation is that all nonzero summands are associated with Child-Selections:

Lemma 4.1. *Let $R[\iota, \kappa]$ be a submatrix of the reactivity matrix with $|\iota| = |\kappa| = k$. Then $\det R[\iota, \kappa] \neq 0$ only if $\iota = E_\kappa = J(\kappa)$ for some k-CS triple (κ, E_κ, J). In particular,*

$$\det R[\iota, \kappa] = \sum_{J:\kappa \mapsto \iota} \operatorname{sgn} J \prod_{m \in \kappa} r'_{J(m)m}, \tag{4.5}$$

where the sum runs on all Child-Selection bijections J between κ and $E_\kappa := \iota$.

Proof. The Child-Selection bijections $J : \kappa \to \iota$ identify permutations of the columns; thus (4.5) coincides with the Leibniz formula for the determinant. To prove that this is the case, consider the general form of the Leibniz formula $\det R[\iota, \kappa] = \sum_{\pi:\kappa \mapsto \iota} \operatorname{sgn} \pi \prod_{m \in \kappa} r'_{\pi(m)m}$, where π is now any bijection between κ and ι, not necessarily a Child-Selection bijection. The statement follows by noting that $\det R[\iota, \kappa] \neq 0$ requires the existence of at least one permutation $\bar{\pi} : \kappa \to \iota$ with $\prod_{m \in \kappa} r'_{\bar{\pi}(m)m} \neq 0$. Such a product is non-zero if and only if $r'_{\bar{\pi}(m)m} \neq 0$ for all $m \in \kappa$. By the definitions of R and k-Child-Selection, this is the case if and only if $\bar{\pi}$ is a Child-Selection bijection $J : \kappa \to \iota$. In fact, $r'_{\bar{\pi}(m)m} = R_{\bar{\pi}(m)m} \neq 0$ if and only if m is a reactant of $j = \bar{\pi}(m)$, i.e., $s_m^{\bar{\pi}(m)} \neq 0$. On the other hand, for a bijection $\bar{\pi} : \kappa \mapsto \iota$, the condition $s_m^{\bar{\pi}(m)} \neq 0$ for every $m \in \kappa$ precisely defines a Child-Selection bijection $J = \bar{\pi}$. □

Lemma 4.1 implies that we can rewrite the Cauchy–Binet expansion in the form

$$\det G[\kappa] = \sum_{E_\kappa} \det(S[\kappa, E_\kappa] R[E_\kappa, \kappa]), \tag{4.6}$$

where the sum runs precisely on all sets $E_\kappa \subseteq E$ for which there exists at least one Child-Selection bijection J with $E_\kappa = J(\kappa)$. We call the matrices

$$G[(\kappa, E_\kappa)] := S[\kappa, E_\kappa] R[E_\kappa, \kappa] \tag{4.7}$$

the *Cauchy–Binet (CB) summands* of G. We emphasize again that a pair of sets (κ, E_κ) does not uniquely identify a Child-Selection bijection, as there may be more than one bijection $J : \kappa \to \iota$ such that (κ, ι, J) is a k-CS. Applying Lemma 4.1, however, we can further expand the determinant of CB summands along k-CS:

$$\begin{aligned} \det G[(\kappa, E_\kappa)] &= \det S[\kappa, E_\kappa] \sum_{J:\kappa \mapsto E_\kappa} \operatorname{sgn} J \prod_{m \in \kappa} r'_{J(m)m} \\ &= \sum_{\boldsymbol{\kappa}} \det S[\boldsymbol{\kappa}] \prod_{m \in \kappa} r'_{J(m)m} = \sum_{\boldsymbol{\kappa}} \det(S[\boldsymbol{\kappa}] R[\boldsymbol{\kappa}]). \end{aligned} \tag{4.8}$$

Here, $R[\boldsymbol{\kappa}]$ is the diagonal matrix with entries $R[\boldsymbol{\kappa}]_{mm} = r'_{J(m)m}$. We call the matrices $G[\boldsymbol{\kappa}] := S[\boldsymbol{\kappa}]R[\boldsymbol{\kappa}]$ *elementary Cauchy–Binet (CB) components* of G.

Observation 4.3. *Putting together (4.6), (4.7), and (4.8), the k^{th} coefficient c_k of the characteristic polynomial $g(\lambda)$ of G can be expanded along CB summands and elementary CB components as*

$$c_k = \sum_{(\kappa, E_\kappa)} \det G[(\kappa, E_\kappa)] = \sum_{\boldsymbol{\kappa}} \det G[\boldsymbol{\kappa}], \tag{4.9}$$

where the first sum runs on all pairs of sets (κ, E_κ) with cardinality k for which there exists at least one Child-Selection bijection $J(\kappa) = E_\kappa$. The second sum runs on all k-CS triples $\boldsymbol{\kappa}$. This in particular proves that the characteristic polynomial is independent of the labeling of the network.

The following technical lemma shows that $\boldsymbol{\Gamma}$ admits instability for parameter-rich kinetic models whenever any CB summand admits instability.

Lemma 4.2. *Assume that $\boldsymbol{\Gamma} = (M, E)$ is a network with a parameter-rich kinetic model. Assume there exists a choice of positive symbols $\mathbf{r}'$ such that a CB summand $G[(\kappa, E_\kappa)]$ is Hurwitz-unstable. Then the network admits instability.*

Proof. Since the kinetic model is parameter rich, we can choose the non-zero symbolic entries $\mathbf{r}'$ of the reactivity matrix R as a function of a parameter ε as follows: For $m \in \kappa$ and $j \in E_\kappa$ choose $r'_{jm} > 0$ independent of ε and set $r'_{jm} = \varepsilon\rho_{jm}$ for all other j and m with $s^j_m > 0$, with $\rho_{jm} > 0$ any positive value. By construction, the square submatrix $R[E_\kappa, \kappa]$ of R comprising the rows $j \in E_\kappa$ and columns $m \in \kappa$ is independent of ε. Observation 4.3 guarantees that the stability does not depend on the labeling of the network. Therefore, without loss of generality, consider $\kappa = \{1, ..., k\}$: in the limit $\varepsilon \to 0$, the symbolic Jacobian of $\boldsymbol{\Gamma}$ becomes

$$G(\mathbf{r}'(0)) = \begin{pmatrix} G[\kappa, E_\kappa] & 0 \\ \dots & 0 \end{pmatrix}.$$

Thus $G(\mathbf{r}'(0))$ is Hurwitz-unstable whenever the CB summand $G[\kappa, E_\kappa]$ is Hurwitz-unstable. Appealing to the continuity of eigenvalues, Hurwitz-instability of $G(\mathbf{r}'(0))$ implies Hurwitz instability of $G(\mathbf{r}'(\varepsilon))$ for sufficiently small $\varepsilon > 0$. This in turn implies that $\boldsymbol{\Gamma}$ admits instability. □

Moreover, fix a k-CS $\boldsymbol{\kappa} = \{\kappa, E_\kappa, J\}$. We can further choose arbitrarily small symbols $r'_{jm} = \epsilon\rho_{jm}$ with $m \in \kappa$, $j \in E_\kappa$, and $j \neq J(m)$. The same argument as in the proof of Lemma 4.2 yields the following.

Corollary 4.1. *Assume that $\boldsymbol{\Gamma} = (M, E)$ is a network with a parameter-rich kinetic model. If there is a choice of positive symbols $\mathbf{r}'$ such that an elementary CB component $G[\boldsymbol{\kappa}]$ is Hurwitz-unstable, then there is also a choice of positive symbols such that the CB summand $G[(\kappa, E_\kappa)]$ is Hurwitz-unstable. Then, in particular, the network admits instability.*

5. Unstable cores and D-unstable cores

The results of Section 4 can now be used to obtain more convenient sufficient topological conditions for a network to admit instability. A matrix A is said to be *D-stable* if AD is Hurwitz-stable for every positive diagonal matrix D [30]. It is *D-unstable* if there is a positive diagonal matrix D such that AD is Hurwitz-unstable. Clearly, an elementary Cauchy–Binet component is Hurwitz-unstable for some choice of parameters if and only if $S[\boldsymbol{\kappa}]$ is D-unstable. In particular, D-unstable Child-Selection matrices $S[\boldsymbol{\kappa}]$ are sufficient for the network to admit instability. Unfortunately, D-stability is non-trivial to check algorithmically [31]. However, choosing D to be the identity matrix immediately shows that Hurwitz-instability implies D-instability. Thus Lemma 4.2 in particular recovers

Corollary 5.1 (Prop. 5.12 of [29]). *Let $\boldsymbol{\Gamma} = (M, E)$ be a network with a parameter-rich kinetic model and stoichiometric matrix S. If $\boldsymbol{\kappa}$ is a k-CS such that $S[\boldsymbol{\kappa}]$ is unstable then $\boldsymbol{\Gamma}$ admits instability.*

Since unstable Child-Selection matrices imply network instability, it is of interest to consider minimal unstable Child-Selection matrices.

Definition 5.1. *An* unstable core *is an unstable Child-Selection matrix $S[\boldsymbol{\kappa}]$ for which no proper principal submatrix is unstable.*

By Obs. 4.2, an unstable core is an unstable Child-Selection matrix that has no unstable restriction. A straightforward observation yields the irreducibility of unstable cores.

Observation 5.1. *The eigenvalues of a reducible matrix are the union of the eigenvalues of its irreducible blocks. In particular, if a reducible matrix is Hurwitz-unstable, then one of the blocks is Hurwitz-unstable. Since a block is a proper principal submatrix, this implies that unstable cores are irreducible.*

Unstable cores are sufficient but not necessary causes of instability. A natural generalization arises from considering D-instability instead of Hurwitz-instability:

Definition 5.2. *A* D-unstable core *is a D-unstable Child-Selection matrix $S[\boldsymbol{\kappa}]$ for which no proper principal submatrix is D-unstable.*

An immediate consequence of the definition and the fact that Hurwitz-instability implies D-instability is that every unstable core contains a D-unstable core. Note that a D-unstable core may be Hurwitz-stable: in this case, it can be a proper submatrix of an unstable core. It remains an open question whether or under which network conditions the converse of Cor. 4.1 is also true:

Conjecture 5.1. *Suppose that the network does not possess any D-unstable core. Then $G(\boldsymbol{r}')$ cannot be Hurwitz-unstable and thus the network $\boldsymbol{\Gamma}$ does not admit instability.*

6. Unstable-positive and unstable-negative feedbacks

Definition 6.1. *Let $\boldsymbol{\Gamma}$ be a network with a parameter-rich kinetic model. An* unstable-positive feedback *is an unstable core satisfying* $\operatorname{sign}\det S[\boldsymbol{\kappa}] = (-1)^{k-1}$; *an* unstable-negative feedback *is an unstable core satisfying* $\operatorname{sign}\det S[\boldsymbol{\kappa}] = (-1)^{k}$.

Observation 6.1. *If $S[\boldsymbol{\kappa}]$ is an unstable-positive feedback then the associated elementary CB component $G[\boldsymbol{\kappa}] = S[\boldsymbol{\kappa}]R[\boldsymbol{\kappa}]$ satisfies $\operatorname{sign}\det G[\boldsymbol{\kappa}] = \operatorname{sign}\det S[\boldsymbol{\kappa}] = (-1)^{k-1}$ and thus $G[\boldsymbol{\kappa}]$ is unstable for any choice of symbols in $R[\boldsymbol{\kappa}]$.*

As an example, consider two networks with the following stoichiometric matrices

$$S^+ = \begin{pmatrix} -1 & 0 & 0 & 0 & 2 \\ 2 & -1 & 0 & 0 & 0 \\ 0 & 2 & -1 & 0 & 0 \\ 0 & 0 & 2 & -1 & 0 \\ 0 & 0 & 0 & 2 & -1 \end{pmatrix} \qquad S^- = \begin{pmatrix} -1 & 0 & 0 & 0 & -2 \\ 2 & -1 & 0 & 0 & 0 \\ 0 & 2 & -1 & 0 & 0 \\ 0 & 0 & 2 & -1 & 0 \\ 0 & 0 & 0 & 2 & -1 \end{pmatrix}, \tag{6.1}$$

where $\det S^+ = 31$ and $\det S^- = -33$, corresponding to unstable-positive and unstable-negative feedbacks, respectively. In fact: the Hurwitz-instability of S^+ is clear from the sign of its determinant, while the instability of S^- can be checked by computing its eigenvalues $(\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5) \approx (-3, -1.63 \pm 1.90i, 0.62 \pm 1.18i)$, where λ_4, λ_5 have positive-real part. Any proper principal submatrix of both S^+ and S^- is triangular with negative diagonal; thus

Hurwitz-stable. This concludes that both matrices are unstable cores: S^+ an unstable-positive feedback, S^- an unstable-negative feedback.

Lemma 6.1. *Unstable-positive feedbacks have a single real-positive eigenvalue, unstable-negative feedbacks have no real-positive eigenvalues.*

Proof. The characteristic polynomial of a real $|M| \times |M|$ matrix A can be written as $p(\lambda) = \sum_{k=0}^{|M|}(-1)^k c_k \lambda^{|M|-k}$ where c_k is the sum of the principal minors of size k. If A is an unstable core, then no proper principal submatrix of A has one single positive eigenvalue, and thus the sign of every principal minor of size $k < |M|$ is either $(-1)^k$ or 0. Thus $(-1)^k c_k \geq 0$. The coefficients of the characteristic polynomial p therefore exhibit at most one sign change. All coefficients have the same sign if $(-1)^{|M|} \det A > 0$ and thus $\operatorname{sign} \det A = (-1)^{|M|}$, i.e., if A is an unstable-negative feedback. Otherwise, $(-1)^{|M|} \det A < 0$ and thus $\operatorname{sign} \det A = (-1)^{|M|-1}$ and A is an unstable-positive feedback. Descartes' Rule of Sign, see e.g. [32], states that the number of positive roots of a polynomial is either the number of sign-changes between consecutive coefficients, ignoring vanishing coefficients, or is less than it by an even number. Thus an unstable core has a single real-positive eigenvalue if it is an unstable-positive feedback and no real-positive eigenvalues if it is an unstable-negative feedback. □

We emphasize that Lemma 6.1 does not exclude additional unstable pairs of complex conjugated eigenvalues. In particular, the unstable dimension of an unstable-positive feedback may be greater than one. For an example, see SM Section 3.1. It is necessarily odd, comprising one real eigenvalue and pairs of complex conjugated eigenvalues. Let now $\mathbb{P}_{\mathrm{Re}}$ be the matrix property of having one real-positive eigenvalue. We refer to Child-Selection matrices $S[\boldsymbol{\kappa}]$ that are minimal w.r.t. $\mathbb{P}_{\mathrm{Re}}$ as *generalized-unstable-positive feedbacks*. It is worthwhile noting that a matrix may be a generalized-unstable-positive feedback and not be an unstable core as it may contain an unstable-negative feedback as a proper submatrix; see SM Section 3.2 for an example. Using Cor. 4.1, the presence of a generalized-positive-unstable feedback in the stoichiometry of the network implies that the network admits instability. Moreover, minimality w.r.t. $\mathbb{P}_{\mathrm{Re}}$ can be checked based on the sign of the principal minors, alone. As a consequence, finding generalized-unstable-positive feedbacks present computational advantages compared to finding unstable-positive feedbacks. Finally, following the arguments in Lemma 4.2 and Lemma 6.1, the presence of a generalized-unstable-positive feedback characterizes the existence of a choice of parameters such that at least one coefficient c_k of the characteristic polynomial of the Jacobian $p(\lambda) = \sum_{k=0}^{|M|}(-1)^k c_k \lambda^{|M|-k}$ satisfies $c_k(-1)^k < 0$, which is in turn a necessary condition for multistationarity [33]. We will return to generalized-positive-feedbacks in Section 7, where we show that autocatalytic generalized-unstable-positive are always unstable-positive feedbacks. We will then provide a simple sufficient criterion that implies that a generalized-unstable-positive feedback is an unstable-positive feedback, by considering a related autocatalytic 'twin' matrix.

7. Autocatalytic cores as unstable cores and Metzler matrices

A reaction j_A is *explicitly autocatalytic* if it is explicitly catalytic and $0 < s_m^{j_A} < \tilde{s}_m^{j_A}$, for a species m. Autocatalysis can also be distributed over a sequence of reactions that collectively exhibit "network autocatalysis" [11,34]. The literature does not provide a single, widely accepted definition of "network autocatalysis", see [19]. Here we are inspired by the approach by Blokhuis, Lacoste, and Nghe [17], albeit with some adjustments in formalism and terminology.

Definition 7.1. *Let $\kappa \subseteq M$, $\iota \subseteq E$. A $|\kappa| \times |\iota|$ submatrix S' of the stoichiometric matrix S is an* autocatalytic matrix *if the following two conditions are satisfied:*

(i) there exists a positive vector $v \in \mathbb{R}^{|\iota|}_{>0}$ such that $S'v > 0$,

(ii) for every reaction column j there exist entries $m, \tilde{m}$, not necessarily distinct, such that m is a reactant of j, i.e., $s^j_m > 0$ and $\tilde{m}$ is a product of j, i.e. $\tilde{s}^j_{\tilde{m}} > 0$.

For the case $m = \tilde{m}$, Def. 7.1 recovers the definition of an explicitly-autocatalytic reaction j_A, where S' is a 1×1 matrix $S' = S_{mj_A} = \tilde{s}^{j_A}_m - s^{j_A}_m > 0$. Analogously to Def. 5.1 we can consider 'core' matrices that are minimal with the property of being autocatalytic.

Definition 7.2. *A stoichiometric submatrix A is an* autocatalytic core *if it is autocatalytic and it does not contain a proper submatrix that is autocatalytic.*

We recall that a square matrix with non-negative off-diagonal elements is known as a Metzler matrix (see e.g. [35]). We are now ready to state the main theorem.

Theorem 7.1. *A submatrix $\tilde{A}$ of the stoichiometric matrix S is an autocatalytic core if and only if $\tilde{A}$ is a $k \times k$ matrix with a reordering A of its columns such that $A = S[\boldsymbol{\kappa}]$ is a Metzler matrix and an unstable-positive feedback.*

We postpone the lengthy proof to Section 9. Thm. 7.1 directly implies the following observation and few important corollaries.

Observation 7.1. *A reaction j_{aut}, explicitly autocatalytic in a species m, is thus a 1×1 autocatalytic core $A := \tilde{s}^{j_{aut}}_m - s^{j_{aut}}_m > 0$. Also the converse is true: if $S[\boldsymbol{\kappa}]$ has a positive diagonal entry $S[\boldsymbol{\kappa}]_{mm} > 0$, then $J(m)$ is an explicitly-autocatalytic reaction in m. Minimality then implies that a $k \times k$ autocatalytic core A with $k > 1$ always identifies a Metzler matrix with non-positive diagonal.*

Corollary 7.1. *Every autocatalytic generalized-unstable-positive feedback is an autocatalytic core, i.e., it is an unstable-positive feedback.*

Proof. Every unstable Metzler matrix has at least one real-positive eigenvalue, thus if an autocatalytic matrix A is a generalized-unstable-positive feedback, i.e., A is minimal with the property $\mathbb{P}_{\mathrm{Re}}$ of having a real-positive eigenvalue, then A is minimal with the property of being unstable, and thus it is an unstable-positive feedback. □

Corollary 7.2. *No unstable-negative feedback is an autocatalytic matrix.*

Proof. By Lemma 6.1, unstable-negative feedbacks have no real-positive eigenvalues; thus they are never Metzler matrices and in particular, therefore, they are never autocatalytic. □

We call a network $\boldsymbol{\Gamma}$ *autocatalytic* if its stoichiometric matrix S contains a submatrix that is an autocatalytic core. This can also be expressed as a corollary from Thm. 7.1.

Corollary 7.3. *A network is autocatalytic if and only if there exists a k-CS $\boldsymbol{\kappa}$ such that the associated Child-Selection matrix $S[\boldsymbol{\kappa}]$ is an unstable Metzler matrix.*

Proof. If a network is autocatalytic, Thm. 7.1 implies the existence of a matrix $S[\boldsymbol{\kappa}]$ that is both a Metzler matrix and unstable. Conversely, reasoning as in the proof of Thm. 7.1, if $S[\boldsymbol{\kappa}]$ is an unstable Metzler matrix, it contains an irreducible Metzler matrix that is also unstable, i.e. autocatalytic, and thus S contains an autocatalytic core and the network is autocatalytic. □

We now draw the final dynamical conclusion from Cor. 7.3 together with Cor. 4.1:

Corollary 7.4. *Every autocatalytic network admits instability.*

Clearly, the converse is not true: autocatalysis is not necessary for instability. Both the presence of an unstable-positive and an unstable-negative feedback are sufficient conditions for the network to admit instability, again as a consequence of Cor. 4.1. By Cor. 7.2, furthermore, unstable-negative feedbacks are never autocatalytic. Moreover, it is easy to construct unstable-positive feedbacks that are not Metzler matrices and thus not autocatalytic. Consider for instance the following three examples:

$$S_1 = \begin{pmatrix} -1 & -2 \\ -1 & -1 \end{pmatrix}; \qquad S_2 = \begin{pmatrix} -1 & 0 & 1 \\ -1 & -1 & 0 \\ 1 & -1 & -1 \end{pmatrix}; \qquad S_3 = \begin{pmatrix} -1 & 1 & 1 & 0 \\ -1 & -1 & 0 & 1 \\ 1 & 1 & -1 & 0 \\ 1 & 0 & 1 & -1 \end{pmatrix}. \tag{7.1}$$

All three matrices are unstable with a real-positive eigenvalue, since $\det S_1 = -1$, $\det S_2 = 1$, and $\det S_3 = -2$. They do not contain proper unstable submatrices. This is straightforward to see for S_1 and S_2, since all the proper principal submatrices are weakly diagonally dominant with negative diagonal, and thus by Gershgorin's circle theorem [36] no proper principal submatrix can have an eigenvalue with a positive-real part. The same argument applies to the principal submatrices of S_3 with sizes 1 and 2. A direct computation (omitted here for brevity) shows that none of the four principal submatrices of S_3 with size 3 is Hurwitz-unstable. Hence S_3 does not contain an unstable proper submatrix. Then, considering $S_1 = S[\boldsymbol{\kappa}_1]$, $S_2 = S[\boldsymbol{\kappa}_2]$, $S_3 = S[\boldsymbol{\kappa}_3]$, for k-Child-Selections $\boldsymbol{\kappa}_1$, $\boldsymbol{\kappa}_2$, $\boldsymbol{\kappa}_3$, we conclude that S_1, S_2, and S_3 are unstable-positive feedbacks. On the other hand, they are not autocatalytic because they are not Metzler matrices.

The matrices S_1 and S_2 have "twin" autocatalytic cores

$$A_1 = \begin{pmatrix} -1 & 2 \\ 1 & -1 \end{pmatrix}; \qquad A_2 = \begin{pmatrix} -1 & 0 & 1 \\ 1 & -1 & 0 \\ 1 & 1 & -1 \end{pmatrix}, \tag{7.2}$$

in the following sense:

Definition 7.3. *A pair (A, B) of $k \times k$ matrices is a called a* twin-pair *if* $\prod_{m \in \kappa'} A_{m\gamma(m)} = \prod_{m \in \kappa'} B_{m\gamma(m)}$ *holds for every cyclic permutation γ on a set κ' of size $k' = 1, \dots, k$.*

Twin matrices are in particular similar as they share the same characteristic polynomial and thus the same eigenvalues, but even more is true.

Lemma 7.1. *Let (A, B) be a twin-pair of matrices and D be any diagonal matrix D. Then (AD, BD) is a twin pair of matrices.*

Proof. We have

$$\prod_{m \in \kappa'} A_{m\gamma(m)} d_{mm} = \prod_{m \in \kappa'} A_{m\gamma(m)} \prod_{m \in \kappa'} d_{mm} = \prod_{m \in \kappa'} B_{m\gamma(m)} \prod_{m \in \kappa'} d_{mm} = \prod_{m \in \kappa'} B_{m\gamma(m)} d_{mm}$$

whenever γ is a cyclic permutation on κ'. □

Another valuable observation is that generalized-unstable-positive feedbacks that possess an autocatalytic twin are unstable-positive feedbacks, as the next lemma formally states.

Lemma 7.2. *Let S be a generalized-unstable-positive feedback, i.e., minimal with the property $\mathbb{P}$ of having a real-positive eigenvalue. If S possesses an autocatalytic twin A, then S is an unstable-positive feedback.*

Proof. A is a generalized-unstable-positive feedback and autocatalytic; thus it is an unstable-positive feedback via Cor. 7.1. S is a twin-matrix of A, which implies that any principal submatrix of S shares the same Leibniz expansion as the respective principal submatrix of A. In particular, then, S contains a proper unstable principal submatrix if and only if A does. From the fact that A is an unstable-core, i.e., A does not contain any proper unstable principal submatrix, it follows that S is an unstable-positive feedback. □

The unstable positive feedback S_3, on the other hand, has no twin autocatalytic core. Since only a single off-diagonal entry is negative, (7.3) can never hold for a pair (S_3, A_3) where A_3 is a Metzler matrix because the parity of the negative signs can never match. See SM, Section 1.1 and 1.2, for examples of pairs of networks that contain twins unstable core (S_1, A_1) and (S_2, A_2). The definition of twins does not seem to offer a clear chemical interpretation behind sharing the stability features. This underlines that similarities in the global dynamics of networks possessing twin cores are not to be expected, a priori.

8. Examples

EXAMPLE A: Superlinear growth with unstable-positive feedback.

$$A + B \underset{1}{\to} C \qquad D \underset{4}{\to}$$

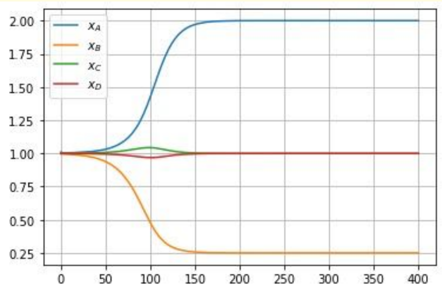
$$2A + B \underset{2}{\to} D \qquad \underset{F_A}{\to} A$$

$$C \underset{3}{\to} \qquad \underset{F_B}{\to} B$$

The unique unstable core

$$\begin{array}{c c} & \begin{array}{cc} 1 & 2 \end{array} \\ \begin{array}{c} A \\ B \end{array} & \begin{pmatrix} -1 & -2 \\ -1 & -1 \end{pmatrix}. \end{array} \tag{8.1}$$

is an unstable-positive feedback. It is not a Metzler matrix, thus the network is non-autocatalytic. The associated parameter-rich system admits multistationarity in the form of two equilibria, one stable and one unstable. On the heteroclinic orbit connecting the two equilibria, we see superlinear growth of the concentration x_A.



See SM, Section 1.1.

EXAMPLE B: Oscillations with unstable-positive feedback.

$$A + B \underset{1}{\to} C + E \qquad E \underset{5}{\to}$$

$$B + C \underset{2}{\to} E \qquad \underset{F_A}{\to} A$$

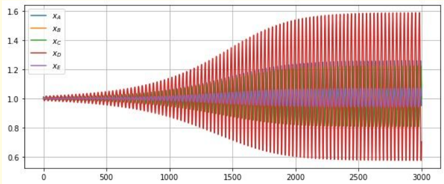
$$C + D \underset{3}{\to} A + E \qquad \underset{F_B}{\to} B$$

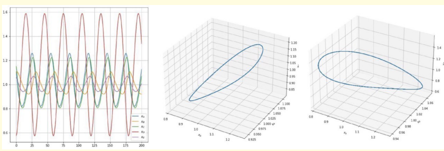
$$2B + D \underset{4}{\to} E \qquad \underset{F_D}{\to} D$$

The unique unstable core

$$\begin{array}{c c} & \begin{array}{ccc} 1 & 2 & 3 \end{array} \\ \begin{array}{c} A \\ B \\ C \end{array} & \begin{pmatrix} -1 & 0 & 1 \\ -1 & -1 & 0 \\ 1 & -1 & -1 \end{pmatrix} \end{array} \tag{8.2}$$

is an unstable-positive feedback. It is not a Metzler matrix and thus the network is non-autocatalytic. The associated parameter-rich system admits oscillations.





See SM, Section 1.2.

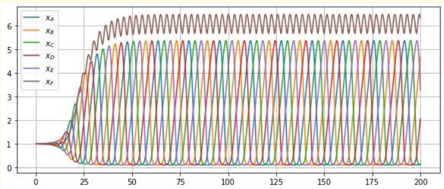
EXAMPLE C: Oscillations with unstable-negative feedback.

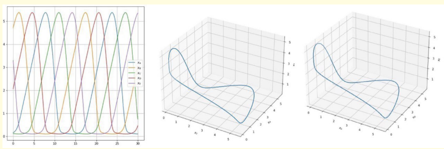
$$\begin{aligned}
&\xrightarrow[F_A]{} A\\
A+B &\xrightarrow[1]{} A+F \qquad \xrightarrow[F_B]{} B\\
B+C &\xrightarrow[2]{} B+F \qquad \xrightarrow[F_C]{} C\\
C+D &\xrightarrow[3]{} C+F \qquad \xrightarrow[F_D]{} D\\
D+E &\xrightarrow[4]{} D+F \qquad \xrightarrow[F_E]{} E\\
E+A &\xrightarrow[5]{} E+F\\
&F \xrightarrow[6]{}
\end{aligned}$$

The unique unstable core

$$\begin{array}{c c}
 & \begin{array}{ccccc} 1 & 2 & 3 & 4 & 5 \end{array}\\
\begin{array}{c} A\\ B\\ C\\ D\\ E \end{array} & \begin{pmatrix} 0 & 0 & 0 & 0 & -1\\ -1 & 0 & 0 & 0 & 0\\ 0 & -1 & 0 & 0 & 0\\ 0 & 0 & -1 & 0 & 0\\ 0 & 0 & 0 & -1 & 0 \end{pmatrix}
\end{array}$$

is an unstable-negative feedback, hence non-autocatalytic. The associated parameter-rich system admits oscillations.





See SM, Section 1.3, where we also present a mass-action variation of the same example.

EXAMPLE D: Non-autocatalytic unstable-positive feedbacks in the dual futile cycle.

$$\begin{cases}
A+E_1 \underset{2}{\overset{1}{\rightleftharpoons}} I_1 \xrightarrow[3]{} B+E_1 \underset{8}{\overset{7}{\rightleftharpoons}} I_3 \xrightarrow[9]{} C+E_1;\\
A+E_2 \xleftarrow[6]{} I_2 \underset{4}{\overset{5}{\rightleftharpoons}} B+E_2 \xleftarrow[12]{} I_4 \underset{10}{\overset{11}{\rightleftharpoons}} C+E_2.
\end{cases}$$

The network has only three unstable-positive feedbacks.

$$\begin{array}{c c}
 & \begin{array}{ccccc} 1 & 7 & 9 & 4 & 6 \end{array}\\
\begin{array}{c} A\\ E_1\\ I_3\\ B\\ I_2 \end{array} & \begin{pmatrix} -1 & 0 & 0 & 0 & 1\\ -1 & -1 & 1 & 0 & 0\\ 0 & 1 & -1 & 0 & 0\\ 0 & -1 & 0 & -1 & 0\\ 0 & 0 & 0 & 1 & -1 \end{pmatrix}
\end{array}$$

$$\begin{array}{c c}
 & \begin{array}{ccccc} 10 & 4 & 6 & 7 & 9 \end{array}\\
\begin{array}{c} C\\ E_2\\ I_2\\ B\\ I_3 \end{array} & \begin{pmatrix} -1 & 0 & 0 & 0 & 1\\ -1 & -1 & 1 & 0 & 0\\ 0 & 1 & -1 & 0 & 0\\ 0 & -1 & 0 & -1 & 0\\ 0 & 0 & 0 & 1 & -1 \end{pmatrix}
\end{array}$$

$$\begin{array}{c c}
 & \begin{array}{cccccc} 1 & 7 & 9 & 10 & 4 & 6 \end{array}\\
\begin{array}{c} A\\ E_1\\ I_3\\ C\\ E_2\\ I_2 \end{array} & \begin{pmatrix} -1 & 0 & 0 & 0 & 0 & 1\\ -1 & -1 & 1 & 0 & 0 & 0\\ 0 & 1 & -1 & 0 & 0 & 0\\ 0 & 0 & 1 & -1 & 0 & 0\\ 0 & 0 & 0 & -1 & -1 & 1\\ 0 & 0 & 0 & 0 & 1 & -1 \end{pmatrix}
\end{array}$$

They are all non-autocatalytic since they are not Metzer-matrices, but they all admit an autocatalytic twin (see SM, Section 1.4). Even when endowed with a kinetics that is not parametric-rich, as Mass Action kinetics, the network is indeed known to admit instability in the form of two stable and one unstable equilibria [37]. See SM, Section 1.4.

9. NC-networks and Proof of Theorem 7.1

For a characterization of autocatalytic cores in network terms, it is convenient to remove momentarily explicit catalysis from the network. This has the advantage that the definition of autocatalysis then relies on the sign structure of the matrix alone and does not require a reference to the numerical values of the stoichiometric coefficients. To this end, we split every explicitly-catalytic reaction j_C, with $s_m^{j_C}\tilde{s}_m^{j_C} \neq 0$ for at least one species m, into two reactions j_{C1}, j_{C2} such that $s_m^{j_{C1}} = s_m^{j_C}$, and $\tilde{s}_m^{j_{C2}} = \tilde{s}_m^{j_C}$, for every m. That is, the reactants of j_C coincide with the reactants of j_{1C} and the products of j_C coincide with the products of j_{2C}. An *intermediate species* m_I is added, so that m_I is the single product of reaction j_{1C} and the single reactant of reaction j_{2C}. For instance, the explicitly-catalytic reaction j_C

$$m_1 + m_2 \xrightarrow{j_C} m_1 + m_3 \tag{9.1}$$

is split into j_{C1}, j_{C2} as

$$m_1 + m_2 \xrightarrow{j_{C1}} m_I \xrightarrow{j_{C2}} m_1 + m_3 \tag{9.2}$$

with the addition of the intermediate species m_I. We call the replacement of an explicitly-catalytic reaction j_C with the *non-explicitly-catalytic triple* (m_I, j_{C1}, j_{C2}) a *non-explicitly-catalytic extension* of j_C. Clearly, we can generalize this procedure to all explicitly-catalytic reactions in the network.

Definition 9.1 (Non-explicitly-catalytic extension). *A network $\boldsymbol{\Gamma}^{NC}$ is a* non-explicitly-catalytic extension *(in short, NC-extension) of $\boldsymbol{\Gamma}$ if $\boldsymbol{\Gamma}^{NC}$ is obtained from $\boldsymbol{\Gamma}$ by substituting all explicitly-catalytic reactions j_C with triples (m_I, j_{C1}, j_{C2}). Let S be the stoichiometric matrix of $\boldsymbol{\Gamma}$. Then S^{NC} indicates the stoichiometric matrix of $\boldsymbol{\Gamma}^{NC}$.*

Observation 9.1. *Let $\boldsymbol{\Gamma}$ be a network with $|M|$ species and $|E|$ reactions, of which n are explicitly-catalytic. Then $\boldsymbol{\Gamma}^{NC}$ is a network with $(|M|+n)$ species and $(|E|+n)$ reactions. Moreover, if S is the $|M| \times |E|$ stoichiometric matrix of $\boldsymbol{\Gamma}$, the stoichiometric matrix S^{NC} of $\boldsymbol{\Gamma}^{NC}$ is an $(|M|+n) \times (|E|+n)$ matrix. In particular, if S is a square matrix, so it is S^{NC}.*

The notion of NC-extension is consistent with the definition of autocatalytic core. Let A be an autocatalytic core in $\boldsymbol{\Gamma}$ and call A^{NC} the NC-extension of A in $\boldsymbol{\Gamma}^{NC}$. We have the following lemma.

Lemma 9.1. *A is an autocatalytic core of $\boldsymbol{\Gamma}$ if and only if A^{NC} is an autocatalytic core of $\boldsymbol{\Gamma}^{NC}$.*

Proof. Let A be a $|\kappa| \times |\iota|$ stoichiometric submatrix of $\boldsymbol{\Gamma}$. Without loss of generality, we can consider that $\boldsymbol{\Gamma}$ has one single explicitly-catalytic reaction j_C in ι, since we can inductively iterate the argument for any explicitly-catalytic reaction. Then, let (m_I, j_{1C}, j_{2C}) be its associated non-explicitly-catalytic triple. A^{NC} is a $(|\kappa|+1) \times (|\iota|+1)$ matrix.

Assume first that A is an autocatalytic matrix of $\boldsymbol{\Gamma}$. Consider the positive vector $v \in \mathbb{R}^{|\iota|}_{>0}$ such that $Av > 0$ and define $\tilde{v}(\varepsilon) \in \mathbb{R}^{|\iota|+1}_{>0}$ as

$$\tilde{v}_j(\varepsilon) := \begin{cases} v_j & \text{for } j \neq j_{1C}, j \neq j_{2C} \\ v_{j_C} + \varepsilon & \text{for } j = j_{1C} \\ v_{j_C} & \text{for } j = j_{2C} \end{cases}, \tag{9.3}$$

for positive $\varepsilon > 0$. This implies that $(A^{NC}\tilde{v})_m = (Av)_m - \varepsilon$ for $m \neq m_I$ with $s_m^{j_C} = s_m^{j_{1C}} > 0$, $(A^{NC}\tilde{v})_m = (Av)_m$ for $m \neq m_I$ with $s_m^{j_C} = s_m^{j_{1C}} = 0$, and $(A^{NC}\tilde{v})_{m_I} = \varepsilon$. In particular, for small enough $\varepsilon > 0$, we have that $A^{NC}\tilde{v} > 0$. Moreover, the column j_C of A has an entry m with $s_m^{j_C} > 0$. This implies that the entry m of the column j_{1C} of A^{NC} satisfies $s_m^{j_{1C}} > 0$. On the other hand the entry m_I of the column j_{1C} satisfies $\tilde{s}_{m_I}^{j_{1C}} > 0$. Similarly, the column j_C has an entry $\tilde{m}$ with

17

$\tilde{s}^{j_C}_{\tilde{m}} > 0$; thus the entry $\tilde{m}$ of the column j_{2C} of A^{NC} satisfies $\tilde{s}^{j_{2C}}_{\tilde{m}} > 0$. On the other hand the entry m_I of the column j_{2C} satisfies $s^{j_{2C}}_{m_I} > 0$, concluding that A^{NC} is an autocatalytic matrix of $\boldsymbol{\Gamma}^{NC}$.

Assume now that A^{NC} is an autocatalytic matrix of $\boldsymbol{\Gamma}^{NC}$. There exists a positive vector $\tilde{u} \in \mathbb{R}^{|\iota|+1}_{>0}$ with $A^{NC}\tilde{u} > 0$. Consider the positive vector $\tilde{v} \in \mathbb{R}^{|\iota|+1}_{>0}$ defined as $\tilde{v}_j := \tilde{u}_j$ for all $j \neq j_{1C}$ and $\tilde{v}_{j_{1C}} := \tilde{v}_{j_{2C}} = \tilde{u}_{j_{2C}}$. We show that $(A^{NC}\tilde{v})_m \geq (A^{NC}\tilde{u})_m > 0$ for all $m \neq m_I$. In fact, note that $\tilde{u}_{j_{1C}} > \tilde{u}_{j_{2C}}$, otherwise $(A^{NC}\tilde{u})_{m_I} \leq 0$ would contradict $A^{NC}\tilde{u} > 0$. On the other hand, the column j_{1C} of A^{NC} has only negative entries, with the single exception of the entry m_I with $A^{NC}_{m_I j_{1C}} = 1$. This yields $\tilde{v}_{j_{2C}}(A^{NC}_{mj_{1C}} + A^{NC}_{mj_{1C}}) \geq \tilde{u}_{j_{1C}}A^{NC}_{mj_{1C}} + \tilde{u}_{j_{2C}}A^{NC}_{mj_{2C}}$ and thus $(A^{NC}\tilde{v})_m \geq (A^{NC}\tilde{u})_m > 0$ for all $m \neq m_I$. Since m_I is not a species in $\boldsymbol{\Gamma}$, it does not appear as a row in A. Thus we conclude that for the positive vector $v \in \mathbb{R}^{|\iota|}_{>0}$ defined as $v_j := \tilde{v}_j$ for $j \neq j_C$ and $v_{j_C} := \tilde{v}_{j_{1C}} = \tilde{v}_{j_{2C}}$ we obtain $Av > 0$. Moreover, the column j_{1C} of A^{NC} contains an entry $m \neq m_I$ with $s^{j_{1C}}_m > 0$ and the column j_{2C} contains an entry $\tilde{m} \neq m_I$ with $\tilde{s}^{j_{2C}}_m > 0$. This implies that the column j_C of A has as well the entry m with $s^{j_C}_m > 0$ and the entry $\tilde{m}$ with $\tilde{s}^{j_C}_{\tilde{m}} > 0$, and concludes that A is an autocatalytic matrix of $\boldsymbol{\Gamma}$.

The above proves that a matrix A is autocatalytic in $\boldsymbol{\Gamma}$ if and only if A^{NC} is autocatalytic in $\boldsymbol{\Gamma}^{NC}$. The preservation of minimality follows from a straightforward observation. B is a submatrix of A in $\boldsymbol{\Gamma}$ if and only if B^{NC} is a submatrix of A^{NC} in $\boldsymbol{\Gamma}^{NC}$. Thus, A does not contain any autocatalytic proper submatrix if and only if A^{NC} does not contain any autocatalytic proper submatrix. □

We call a *non-explicitly-catalytic network* (in short: *NC-network*) a network that does not possess any explicitly-catalytic reaction. Since the autocatalytic cores of a network $\boldsymbol{\Gamma}$ can be studied in its NC-extension $\boldsymbol{\Gamma}^{NC}$ as a consequence of Lemma 9.1, we proceed now by considering NC-networks. The advantage is that in NC-networks the stoichiometric matrix S fully determines the reactivity matrix R, $R_{jm} \neq 0$ if and only if $S_{mj} < 0$. We will come back to general explicitly-catalytic networks in the next section. A first consequence of this approach is that autocatalytic matrices and cores can be defined puerly at the matrix level, without reference to the stoichiometric coefficients. We have indeed the following proposition.

Proposition 9.1. *Consider a NC-network $\boldsymbol{\Gamma}^{NC}$. Let $\kappa \subseteq M$, $\iota \subseteq E$. Then a $|\kappa| \times |\iota|$ submatrix A of the stoichiometric matrix S is an* autocatalytic core *if the following three conditions are satisfied:*

(i) there exists a positive vector $v \in \mathbb{R}^{|\iota|}_{>0}$ such that $Av > 0$,
(ii) for every column j there exist both positive and negative entries, i.e., there is $m, \tilde{m}$ such that $A_{mj} > 0$ and $A_{\tilde{m}j} < 0$,
(iii) A does not contain any proper submatrix satisfying conditions (i) and (ii).

Proof. For NC-networks, a reactant m of a reaction j always appears as a strictly negative entry $A_{mj} < 0$, whereas a product $\tilde{m}$ of reaction j always appears as a strictly positive entry $A_{\tilde{m}j} > 0$. The rest follows from the definition of autocatalytic cores. □

Prop. 9.1 is clearly equivalent to Def. 7.2 for the case of NC-networks. In [17] the analysis focused on NC-networks, and the conditions in Prop. 9.1 were indeed given as the definition of autocatalytic cores. We further note that in NC-networks autocatalysis requires at least two species and two reactions, since explicit (auto)catalysis is excluded.

Lemma 9.2. *If S is a $|\kappa| \times |\iota|$ autocatalytic matrix of a NC-network, then $|\kappa| \geq 2$ and $|\iota| \geq 2$.*

Proof. Condition 2 in Prop. 9.1 implies that there are at least 2 rows: $|\kappa| \geq 2$. Then $|\iota| = 1$ is impossible since we would have $S_{m1} < 0$, and thus condition 1 could not be satisfied; hence $|\iota| \geq 2$. □

For NC-networks, [17] proves that autocatalytic cores necessarily satisfy relevant conditions, as stated in the following Lemma:

Lemma 9.3 (Blokhuis et al. [17]). *Let $\tilde{A}$ be an autocatalytic core of a NC-network. Then $\tilde{A}$ is square, invertible, and irreducible. Moreover, there exists an autocatalytic core A, obtained by re-ordering the columns of $\tilde{A}$, such that A is a Metzler matrix with negative diagonal.*

For completeness, we prove Lemma 9.3 in our own setting and notation in the SM, Section 2.2. A straightforward corollary follows.

Corollary 9.1. *Let $\tilde{A}$ be an autocatalytic core of a NC-network. Then, there exists a* unique *autocatalytic core A with negative diagonal obtained by reordering the columns of $\tilde{A}$.*

Proof. Since A is a Metzler matrix, each column and row has a unique negative entry. Thus each column and each row of $\tilde{A}$ has a unique negative entry, and the permutation of the columns with negative diagonal is uniquely defined. □

In summary, an autocatalytic core of a NC-network uniquely identifies an invertible, irreducible Metzler matrix A with negative diagonal. Hurwitz-stability of Metzler matrices has been extensively studied in the literature, see e.g. [38] and the references therein. The notorious Frobenius–Perron theorem is typically stated for non-negative matrices N, i.e., with $N_{mj} \geq 0$ for all m and j. By considering $\alpha \geq \max_m |A_{mm}|$ and the non-negative matrix $N := A + \alpha\,\mathrm{Id}$, some important consequences of the theorem generalize to Metzler matrices. In particular, the Frobenius–Perron theorem guarantees that any Metzler matrix A has one real eigenvalue λ^* such that $\lambda^* > \mathrm{Re}\,\lambda$ for all other eigenvalues λ. Moreover, if A is irreducible, then the eigenvector v of λ^* can be chosen positive. Another straightforward consequence is that $Av \geq av$ for some $a > 0$ implies $\lambda \geq a$. See e.g. [39], where also the following consequent statement can be found.

Lemma 9.4. *Let A be an invertible, irreducible, Metzler matrix. Then A is Hurwitz-unstable if and only if there exists a positive $v > 0$ such that $Av > 0$.*

To make this document self-contained, we include a short proof in the SM, Section 2.3. Lemma 9.4 implies that within the set of invertible and irreducible Metzler matrices with negative diagonal, Hurwitz-instability characterizes autocatalytic matrices. We expand on such an idea in the last lemma of this section, where we characterize autocatalytic cores among the Metzler matrices with negative diagonal.

Lemma 9.5. *Let A be a $k \times k$ Metzler matrix with negative diagonal. Then the following two statements are equivalent:*

(i) *A is an autocatalytic core;*
(ii) $\mathrm{sign}\det A = (-1)^{k-1}$ *and for every* $\emptyset \neq \kappa' \subsetneq \{1, \dots, k\}$ *we have* $\mathrm{sign}\det A[\kappa'] = (-1)^{|\kappa'|}$ *or* $\det A[\kappa'] = 0$.

Proof. Suppose A is an autocatalytic core. The proof of Lemma 9.4 shows that A is Hurwitz-unstable with at least one real-positive eigenvalue λ^*. Descartes' rule of sign therefore implies that the coefficients c_n of the characteristic polynomial $p(\lambda) = \sum_{n=0}^{k} (-1)^n c_n \lambda^{k-n}$ of A do not all have the same sign. Since $c_1 = \mathrm{tr}\,A < 0$, there exists a smallest n, $1 < n \leq k$ and $\kappa' \subset \{1, 2, \dots, n\}$ with $|\kappa'| = n$ such that the submatrix $A[\kappa']$ satisfies $\mathrm{sign}\det A[\kappa'] = (-1)^{|\kappa'|-1}$ and $\mathrm{sign}\det A[\kappa''] = (-1)^{|\kappa''|}$ or $\mathrm{sign}\det A[\kappa''] = 0$ for all non-empty $\kappa'' \subsetneq \kappa'$. We proceed by showing that $A[\kappa']$ is an autocatalytic core. If $A[\kappa']$ is not irreducible, the rows and columns can be simultaneously reordered such that $A[\kappa']$ has a block-triangular form. Thus there is $\kappa'' \subsetneq \kappa'$ such that $\mathrm{sign}\det A[\kappa''] = (-1)^{|\kappa''|-1}$, contradicting minimality of κ'. Thus $A[\kappa']$ is irreducible and thus every column contains a non-zero off-diagonal entry. Since A is a Metzler matrix with negative diagonal, every column in particular contains both a positive and a negative entry. Since $\mathrm{sign}\det A[\kappa'] = (-1)^{|\kappa'|-1} \neq 0$, $A[\kappa']$ is invertible. It is unstable, since by construction its characteristic polynomial has exactly one sign change. Lemma 9.4 now implies the existence of a positive vector $v \in \mathbb{R}^{|\kappa|'}_{>0}$ such that $A[\kappa']v > 0$. Thus $A[\kappa']$ is an autocatalytic core and cannot be a proper submatrix of the network autocatalytic core A. Hence $A[\kappa'] = A$ and $|\kappa'| = k$.

Conversely, assume that condition 2 holds. We first show that A is invertible and irreducible. Invertibility trivially follows from $\det A \neq 0$. Indirectly assume now that A is reducible; then the determinant of A can be expressed as a product of determinants of principal submatrices, which would imply the existence of a proper principal submatrix $A[\kappa']$ with $\operatorname{sign}\det A[\kappa'] = (-1)^{|\kappa'|-1}$, contradicting the assumption; thus A is irreducible. The sign of its determinant further implies that A is unstable and thus Lemma 9.4 implies the existence of a positive vector $v \in \mathbb{R}^k_{>0}$ such that $Av > 0$. Moreover, the irreducibility of A again guarantees that every column of A has one negative diagonal entry and at least one positive off-diagonal entry. Thus A is autocatalytic. It remains to show that there are no autocatalytic submatrices. The only submatrices that could be autocatalytic cores are the principal ones since an autocatalytic core uniquely identifies a square matrix with one negative entry in each column by Cor. 9.1. Moreover, we can restrict to the irreducible ones, via Lemma 9.3. Again, all invertible and irreducible principal $|\kappa'|$-submatrices $A[\kappa']$ with $|\kappa'| < k$ satisfy $\operatorname{sign}\det A[\kappa'] = (-1)^{|\kappa'|}$ by assumption. By Lemma 6.1, none of them has any positive real eigenvalue. Following the arguments in the proof of Lemma 9.4, $A[\kappa']$ is Hurwitz-stable and thus there is no positive vector $v \in \mathbb{R}^{|\kappa'|}_{>0}$ such that $A[\kappa']v > 0$. Therefore, A does not contain a proper submatrix that is autocatalytic and hence it is an autocatalytic core. □

We are now in the position to state the main result for NC-networks.

Lemma 9.6. *Let S be a stoichiometric matrix of a NC-network. Then a submatrix $\tilde{A}$ of S is an autocatalytic core if and only if $\tilde{A}$ is a $k \times k$ submatrix of S whose columns can be rearranged in a matrix A that satisfies the following conditions:*

(i) A is a Metzler matrix with negative diagonal;
(ii) $\operatorname{sign}\det A = (-1)^{k-1}$;
(iii) no principal submatrix $A[\kappa']$ with $|\kappa'| < k$ is Hurwitz-unstable.

Proof. By Cor. 9.1, an autocatalytic core $\tilde{A}$ uniquely identifies a matrix A that is a Metzler matrix with negative diagonal. Lemma 9.5 implies that among the Metzler matrices with negative diagonal, the autocatalytic cores are exactly those that satisfy $\operatorname{sign}\det A = (-1)^{k-1}$ and for every $\emptyset \neq \kappa' \subsetneq \{1, \dots, k\}$ we have $\operatorname{sign}\det A[\kappa'] = (-1)^{|\kappa'|}$ or $\det A[\kappa'] = 0$. From Descartes' rule of sign an identical argument as in the proof of Lemma 9.5 implies that no proper principal submatrix $A[\kappa']$ with $|\kappa'| < k$ is Hurwitz-unstable.

Conversely, assume that A satisfies conditions 1-3. Condition 3 implies that for all principal submatrices $A[\kappa']$ we have $\operatorname{sign}\det A[\kappa'] = (-1)^{|\kappa'|}$ or $\det A[\kappa'] = 0$. Lemma 9.5 concludes that A is an autocatalytic core. □

We focus on the relationship between autocatalytic cores and unstable cores. We first note a straightforward corollary of Lemma 9.3.

Corollary 9.2. *Let A be a $k \times k$ autocatalytic core of an NC-network, with rows in $\kappa \subseteq M$ and columns in $\iota \subseteq E$. For any $m \in \kappa$, let $J(m) \in \iota$ indicate the unique reaction such that $A_{m\,J(m)} < 0$. Then $\boldsymbol{\kappa} := (\kappa, \iota, J)$ is a k-CS.*

Proof. It is sufficient to notice that $A_{mJ(m)} < 0$ implies $s_m^{J(m)} > 0$. The statement follows from the definition of k-Child-Selection triples. □

Thus the notion of autocatalytic cores in [17] is consistent with our notion of cores as minimal Child-Selections, even though the definition of autocatalytic cores does not require a fixed order of the columns: any $\tilde{A}$ obtained by reordering the columns of an autocatalytic core A is also an autocatalytic core. In turn, the ordering of the columns in the Child-Selection perspective plays a crucial role to draw dynamical conclusions. In fact, as an immediate consequence of Cor. 9.2 we get that $A := S[\boldsymbol{\kappa}]$ is the unique matrix with negative diagonal obtained by reordering the columns of an autocatalytic core $\tilde{A}$. In particular, A is a Metzler matrix.

We are finally ready to prove Theorem 7.1

Proof of Theorem 7.1. Assume firstly $A = S[\boldsymbol{\kappa}]$ is a Metzler matrix and an unstable-positive feedback; thus A is irreducible, via Obs. 5.1. Lemma 9.4 implies that there exists a positive vector $v \in \mathbb{R}^k_{>0}$ such that $Av > 0$. Via construction of $S[\boldsymbol{\kappa}]$, the diagonal entries correspond to positive stoichiometric coefficients $s_m^{J(m)} > 0$. If $k = 1$, the instability of the 1×1 matrix $S[\boldsymbol{\kappa}]$ simply implies that $S[\boldsymbol{\kappa}] > 0$, and thus $\tilde{s}_m^{J(m)} > 0$. This concludes that $J(m)$ is an explicitly-autocatalytic reaction in m, and in particular $S[\boldsymbol{\kappa}]$ is an autocatalytic core. Consider now $k \geq 2$: A is irreducible and thus every column j as at least a positive non-diagonal entry m. In particular $\tilde{s}_m^j \geq A_m^j > 0$; thus A is autocatalytic. Finally, any proper principal submatrix of A is also a Metzler matrix. Via minimality of unstable-positive feedbacks, it does not contain any other unstable proper principal submatrix, i.e., for all κ' there is no positive v' such that $A[\kappa']v' > 0$, again via Lemma 9.4. This implies that A does not contain any autocatalytic submatrix, which concludes that A is an autocatalytic core.

Conversely assume that $A = S[\boldsymbol{\kappa}]$ is an autocatalytic core. We have to show that A is a Metzler matrix. Lemma 9.1 states that A is an autocatalytic core if and only if its NC-extension A^{NC} is an autocatalytic core. Using Lemma 9.6, A^{NC} is a Metzler matrix with negative diagonal. Consider a column j_C in A associated to an explicitly-catalytic reaction j_C and its associated non-explicitly-catalytic triple (m_I, j_{C1}, j_{C2}) in A^{NC}. The column j_{C1} has a single negative entry, i.e., a single reactant m^* (via Lemma 9.3) and a single product m_I, via the construction of NC-extension. Moreover, the single reactant m^* corresponds to the diagonal entry $A_{m^*m^*} = S[\boldsymbol{\kappa}]_{m^*m^*} = S_{m^*J(m^*)}$, since $J(m^*) = j_C$. The column j_{C2} has a single negative entry, i.e., a single reactant m_I, again via the construction of NC-extension. The column j_C in A, then, has entries $A_{mj_C} = A^{NC}_{mj_{C1}} + A^{NC}_{mj_{C2}}$, for $m \neq m_I$ since m_I is not a species in A. Such sum has always non-negative summands, except for $m = m^*$, and $m = m_I$. The first corresponds to a diagonal entry in A, the second does not appear in A at all, therefore $A_{mj_C} \geq 0$ for all $m \neq m^*$. Repeating such argument for all explicitly-catalytic reactions yields that A_{mj} is non-negative for all non-diagonal entries $j \neq m$; thus A is a Metzler matrix. Finally, since A is autocatalytic, there exists $v \in \mathbb{R}^k_{>0}$ such that $Av > 0$. Applying Lemma 9.4 yields instability of A with $\operatorname{sign}\det A = (-1)^{k-1}$ and the minimality of A as an autocatalytic matrix translates into the minimality of A as an unstable matrix, just as discussed above in this same proof. Hence, A is an unstable-positive feedback and a Metzler matrix. □

10. Further observations on NC-networks: what is special about autocatalysis

Lemma 7.1 together with Cor. 4.1 suggests that an autocatalytic unstable-core is indistinguishable from a non-autocatalytic unstable-core, as far as its (in)stability properties are concerned. What is special about autocatalysis thus is not captured by spectral properties. The following two corollaries of Lemma 9.6 point at the peculiarity of autocatalysis among unstable cores, at least for NC-networks.

Corollary 10.1. *Let $\boldsymbol{\Gamma}^{NC}$ be a NC-network. Consider a CB-summand $G([\kappa, E_\kappa]) = S[\kappa, E_\kappa]R[\kappa, E_\kappa]$. If $S[\kappa, E_\kappa]$ is an autocatalytic core, then*

$$\det R[\kappa, E_\kappa] = \operatorname{sgn}(J) \prod_{m \in \kappa} r'_{J(m)m} \quad \textit{and} \quad \operatorname{sign}(\det S[\kappa, E_\kappa]) = \operatorname{sgn}(J)(-1)^{k-1}, \tag{10.1}$$

for a unique Child-Selection bijection J.

Proof. Corollary 9.1 implies that the Child-Selection bijection J from κ to E_κ is unique. Thus, Lemma 4.1 implies $\det R[\kappa, E_\kappa] = \text{sgn}(J) \prod_{m \in \kappa} r'_{J(m)m}$. On the other hand, condition 2 of Lemma 9.6 yields sign det $S[\kappa, E_\kappa]\, \text{sgn}(J) = (-1)^{k-1}$. □

Corollary 10.1 implies that the stability of the CB-summand associated with the stoichiometry of an autocatalytic core corresponds to the stability of a single elementary CB component. An interesting consequence of Cor. 10.1 is the following.

Corollary 10.2. *Let $\boldsymbol{\Gamma}^{NC}$ be a NC-network. Consider a CB-summand $G([\kappa, E_\kappa]) = S[\kappa, E_\kappa]R[\kappa, E_\kappa]$, where $S[\kappa, E_\kappa]$ is an autocatalytic core. Then, $G([\kappa, E_\kappa])$ is unstable for any choice of symbols r'_{jm} with $m \in \kappa$, $j \in E_\kappa$.*

Proof. From Cor. 10.1 we compute the sign of the determinant of the Cauchy–Binet summand $G([\kappa, E_\kappa])$,

$$\text{sign}\det G([\kappa, E_\kappa]) = \text{sign}(\det S[\kappa, E_\kappa] \det R[\kappa, E_\kappa]) = \text{sgn}(J)\,\text{sgn}(J)(-1)^{k-1} = (-1)^{k-1}, \quad (10.2)$$

and thus $G([\kappa, E_\kappa])$ is always unstable, independently of the choice of symbols r'_{jm}. □

In essence, autocatalysis provides an "always-unstable" subnetwork, independent of any parameter choice. This has relevant consequences for the dynamical analysis, in particular when dealing with realistic parameter values or with kinetic models that are not parameter-rich, such as mass action. We remark, however, that the converse of Cor. 10.2 is not true: there are also non-autocatalytic subnetworks whose associated Jacobian is unstable for every choice of parameters. To see this, consider the stoichiometric matrix S_3, already discussed in the previous section, and associated reactivity matrix R_3

$$S_3 = \begin{pmatrix} -1 & 1 & 1 & 0 \\ -1 & -1 & 0 & 1 \\ 1 & 1 & -1 & 0 \\ 1 & 0 & 1 & -1 \end{pmatrix} \qquad R_3 = \begin{pmatrix} r'_{1A} & r'_{1B} & 0 & 0 \\ 0 & r'_{2B} & 0 & 0 \\ 0 & 0 & r'_{3C} & 0 \\ 0 & 0 & 0 & r'_{4D} \end{pmatrix}. \quad (10.3)$$

Since $\det S_3 = -1$ and $\det R_3 = r'_{1A} r'_{2B} r'_{3C} r'_{4D} > 0$, we have that sign det $G_3 = \text{sign}(\det S_3 \det R_3) = -1$, and thus G_3 is unstable irrespective of the choices of symbols.

As a final caveat, we caution the reader about exchanging statements between a network $\boldsymbol{\Gamma}$ and its NC-extension $\boldsymbol{\Gamma}^{NC}$. Such exchanges may work well for the stoichiometric matrix S, as shown in Lemma 9.1. In general, however, the exchanges fail for the reactivity matrix R and consequently for the dynamics. In particular, both Cor. 10.1 and Cor. 10.2 do not hold for general networks with explicitly-catalytic reactions. Still, they offer a qualitative hint and explanation of the special nature of autocatalysis and a possible reason for the omnipresence of autocatalysis in networks that have been of interest in the literature.

11. Conclusion

For a broad class of kinetic models, which includes Michaelis–Menten and Generalized Mass Action kinetics (but not classical Mass Action kinetics), we have shown here that an inspection of the topology of a chemical reaction network may be conclusive on whether the network admits dynamical instability. More precisely, we found that unstable cores, characterized as certain minimal submatrices of the stoichiometric matrix that are Hurwitz unstable, provide a sufficient condition for network instability via Cor 5.1. Moreover, we conjecture that the slightly more general D-unstable cores are even necessary; Conjecture 5.1.

The present study thus complements investigations into sufficient conditions for universal stability as *deficiency zero* [40], or exclusion of multiple equilibria as *injectivity* [27,41] and *concordance* [42]. See [33,43] for two comprehensive overviews on such topics. Note, however, that injectivity and concordance only concern the uniqueness of equilibria, but not their stability, while the conditions for the deficiency-zero theorem are quite restrictive and they only hold for weakly-reversible mass-action networks. See [25] for generalizations and failures of the deficiency statements for a parameter-rich model such as Generalized Mass Action kinetics.

We observed that there are two classes of unstable cores, unstable-positive and unstable-negative feedbacks, distinguished by the sign of their determinant as well as the presence of real-valued positive eigenvalue. Autocatalytic cores, as defined in [17], turn out to be exactly (after a suitable permutation of the columns) unstable-positive feedbacks that are Metzler matrices. This simple characterization lends support to this particular definition of autocatalysis, which also has been adapted e.g. in [44,45].

While positive and negative feedbacks are distinguished by spectral properties, this is not the case for autocatalytic versus non-autocatalytic unstable cores. The existence of twins shows that there are both types of cores sharing the same characteristic polynomial. Nevertheless, autocatalysis is the source of instability in well-known examples of chemical networks with "interesting" dynamics. This is probably a consequence of the fact that an autocatalytic core is dynamically unstable irrespective of the parameter choices (Cor. 10.1 and Cor. 10.2). In order to design an example of dynamic instability, it therefore suffices to pick an autocatalytic core and complement it with feed and waste product to achieve a modicum of chemical realism. This, together with chemists' intuition on the importance of autocatalysis, may explain why non-autocatalytic examples do not appear to be widely known.

References

1. Aris R. 1965 Prolegomena to the rational analysis of systems of chemical reactions. *Arch. Rational Mech. An.* **19**, 81–99. (10.1007/BF00282276)
2. Zhabotinsky AM. 1964 Periodical oxidation of malonic acid in solution (a study of the Belousov reaction kinetics). *Biofizika* **9**, 306–311. (russian).
3. Cassani A, Monteverde A, Piumetti M. 2021 Belousov–Zhabotinsky type reactions: the non-linear behavior of chemical systems. *J. Math. Chem.* **59**, 792–826. (10.1007/s10910-021-01223-9)
4. Ostwald W. 1890 Über Autokatalyse. *Ber Verh Kgl Sächs Ges Wiss Leipzig, Math Phys Class* **42**, 189–191.
5. Bissette AJ, Fletcher SP. 2013 Mechanisms of Autocatalysis. *Angew. Chem. Int. Ed.* **52**, 12800–12826. (10.1002/anie.201303822)
6. Schuster P. 2019 What is special about autocatalysis?. *Monatsh. Chem.* **150**, 763–775. (10.1007/s00706-019-02437-z)
7. Kun Á, Papp B, Szathmáry E. 2008 Computational identification of obligatorily autocatalytic replicators embedded in metabolic networks. *Genome Biology* **9**, R51. (10.1186/gb-2008-9-3-r51)
8. Siami M, Motee N, Buzi G, Bamieh B, Khammash M, Doyle JC. 2020 Fundamental Limits and Tradeoffs in Autocatalytic Pathways. *IEEE Trans. Automat. Contr.* **65**, 733–740. (10.1109/TAC.2019.2921671)
9. Kauffman SA. 1986 Autocatalytic Sets of Proteins. *J. Theor. Biol.* **119**, 1–24. (10.1016/S0022-5193(86)80047-9)
10. Smith E, Morowitz HJ. 2004 Universality in intermediary metabolism. *Proc. Natl. Acad. Sci. USA* **101**, 13168–13173. (10.1073/pnas.0404922101)
11. Braakman R, Smith E. 2013 The compositional and evolutionary logic of metabolism. *Physical Biology* **10**, 011001. (10.1088/1478-3975/10/1/011001)
12. Kaleta C, Centler F, Dittrich P. 2006 Analyzing molecular reaction networks: from pathways to chemical organizations. *Mol Biotechnol* **34**, 117–123. (10.1385/MB:34:2:117)
13. Benkö G, Centler F, Dittrich P, Flamm C, Stadler BMR, Stadler PF. 2009 A Topological Approach to Chemical Organizations. *Alife* **15**, 71–88. (10.1162/artl.2009.15.1.15105)
14. Andersen JL, Flamm C, Merkle D, Stadler PF. 2012 Maximizing output and recognizing autocatalysis in chemical reaction networks is NP-complete. *J. Syst. Chem.* **3**, 1. (10.1186/1759-2208-3-1)
15. Deshpande A, Gopalkrishnan M. 2014 Autocatalysis in reaction networks. *Bull. Math. Biol.* **76**, 2570–2595.
16. Barenholz U, Davidi D, Reznik E, Bar-On Y, Antonovsky N, Noor E, Milo R. 2017 Design

principles of autocatalytic cycles constrain enzyme kinetics and force low substrate saturation at flux branch points. *eLife* **6**, e20667. (10.7554/eLife.20667)
17. Blokhuis A, Lacoste D, Nghe P. 2020 Universal motifs and the diversity of autocatalytic systems. *Proc. Natl. Acad. Sci.* **117**, 25230–25236. (10.1073/pnas.201352711)
18. Unterberger J, Nghe P. 2022 Stoechiometric and dynamical autocatalysis for diluted chemical reaction networks. *Journal of Mathematical Biology* **85**, 26.
19. Andersen JL, Flamm C, Merkle D, Stadler PF. 2020 Defining Autocatalysis in Chemical Reaction Networks. *J. Systems Chem.* **8**, 121–133.
20. Gyorgyi L, Field RJ. 1991 Simple models of deterministic chaos in the Belousov-Zhabotinskii reaction. *J. Phys. Chem.* **95**, 6594–6602. (10.1021/j100170a041)
21. Hsu SB, Chen KC. 2022 *Ordinary differential equations with applications* vol. 23. World scientific.
22. Guckenheimer J, Holmes P. 1984 *Nonlinear oscillations, dynamical systems and bifurcations of vector fields*. Springer.
23. Michaelis L, Menten ML. 1913 Die Kinetik der Invertinwirkung. *Biochem. Z.* **49**, 333–369.
24. Hill AV. 1910 The possible effects of the aggregation of the molecules of haemoglobin on its dissociation curves. *J. Physiol.* **40**, 4–7.
25. Müller S, Regensburger G. 2012 Generalized mass action systems: Complex balancing equilibria and sign vectors of the stoichiometric and kinetic-order subspaces. *SIAM J. Appl. Math.* **72**, 1926–1947. (10.1137/1108470)
26. Soulé C. 2003 Graphic requirements for multistationarity. *ComPlexUs* **1**, 123–133.
27. Banaji M, Donnell P, Baigent S. 2007 P matrix properties, injectivity, and stability in chemical reaction systems. *SIAM Journal on Applied Mathematics* **67**, 1523–1547.
28. Guldberg CM, Waage P. 1867 *Etudes sur les affinités chimiques*. Imprimerie de Brøgger & Christie.
29. Vassena N. 2023 Symbolic hunt of instabilities and bifurcations in reaction networks. *Discrete and Continuous Dynamical Systems B*. (10.3934/dcdsb.2023190)
30. Arrow KJ, McManus M. 1958 A note on dynamical stability. *Econometrica* **26**, 448–454. (10.21236/ad0134947)
31. Kushel OY. 2019 Unifying matrix stability concepts with a view to applications. *SIAM Review* **61**, 643–729. (10.1137/18M119241X)
32. Wang X. 2004 A Simple Proof of Descartes's Rule of Signs. *American Mathematical Monthly* **111**, 525–526. (10.2307/4145072)
33. Banaji M, Pantea C. 2016 Some results on injectivity and multistationarity in chemical reaction networks. *SIAM Journal on Applied Dynamical Systems* **15**, 807–869.
34. Smith E, Morowitz HJ, Copley SD. 2008 Core Metabolism as a Self-Organized System. In Rasmussen S, Bedau MA, Chen L, Deamer D, Krakauer DC, Packard NH, Stadler PF, editors, *Protocells: Bridging Nonliving and Living Matter* , pp. 432–460. MIT Press. (10.7551/mitpress/9780262182683.003.0020)
35. Duan X, Jafarpour S, Bullo F. 2021 Graph-Theoretic Stability Conditions for Metzler Matrices and Monotone Systems. *SIAM J. Control Opt.* **59**, 3447–3471. (10.1137/20m131802x)
36. Gershgorin SA. 1931 Über die Abgrenzung der Eigenwerte einer Matrix. *Bulletin de l'Académie des Sciences de l'URSS. Classe des sciences mathématiques et naturelles* **6**, 749–754.
37. Hell J, Rendall AD. 2015 A proof of bistability for the dual futile cycle. *Nonlinear Analysis: Real World Applications* **24**, 175–189. (10.1016/j.nonrwa.2015.02.004)
38. Narendra KS, Shorten R. 2010 Hurwitz Stability of Metzler Matrices. *IEEE Trans. Automatic Control* **55**, 1484–1487. (10.1109/TAC.2010.2045694)
39. Bullo F. 2020 *Lectures on network systems* vol. 1. Kindle Direct Publishing.
40. Feinberg M. 1987 Chemical reaction network structure and the stability of complex isothermal reactors—I. The deficiency zero and deficiency one theorems. *Chemical Engineering Science* **42**, 2229–2268.
41. Banaji M, Craciun G. 2010 Graph-theoretic criteria for injectivity and unique equilibria in general chemical reaction systems. *Advances in Applied Mathematics* **44**, 168–184.
42. Shinar G, Feinberg M. 2012 Concordant chemical reaction networks. *Mathematical Biosciences* **240**, 92–113.
43. Feinberg M. 2019 *Foundations of Chemical Reaction Network Theory*. Springer.
44. Despons A, De Decker Y, Lacoste D. 2023 Structural constraints limit the regime of optimal flux in autocatalytic reaction networks. Technical report arXiv. (10.48550/arXiv.2306.02366)
45. Gagrani P, Blanco V, Smith E, Baum D. 2023 The geometry and combinatorics of an autocatalytic ecology in chemical and cluster chemical reaction networks. Technical report arXiv. (10.48550/arXiv.2303.14238)