

BiRNe: Symbolic bifurcation analysis of reaction networks with Python

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Abstract

Computer algebra methods for analyzing reaction networks often rely on the assumption of mass-action kinetics, which transform the governing ODEs into polynomial systems amenable to techniques such as Gröbner basis computation and related algebraic tools. However, these methods face significant computational complexity, limiting their applicability to relatively small networks involving only a handful of species. In contrast, building on recent theoretical advances, we introduce here BiRNe (Bifurcations in Reaction NEtworks) Python module, which relies on a symbolic approach designed to detect bifurcations in larger reaction networks (up to 10-20 species, depending on the network’s connectivity) equipped with parameter-rich kinetics. This class includes enzymatic kinetics such as Michaelis–Menten, ligand-binding kinetics like Hill functions, and generalized mass-action kinetics. For a given network, the current algorithm identifies all minimal autocatalytic subnetworks and fully characterizes the presence of bifurcations associated with zero eigenvalues, thus determining whether the network admits multistationarity. It also detects oscillatory bifurcations arising from positive-feedback structures, capturing a significant class of possible oscillations.

1 Introduction

Reaction networks naturally arise as modeling structures in various fields, including biology, chemistry, ecology, economics, and epidemiology. A primary difficulty in analyzing such systems is the widespread lack of knowledge about the governing mathematical laws and, even more so, about the relevant quantities involved. For this reason, it is customary to consider classes of systems that depend on many parameters. Since realistic reaction

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networks are typically high-dimensional, the number of parameters is also large, and the computational complexity of even simple tasks quickly becomes intractable.

Historically, a large body of work has focused on mass-action kinetics, which models interactions as monomials in the concentrations of the reacting species. This assumption is particularly meaningful when considering elementary reactions in well-mixed reactors or, for example, in epidemiological models describing transition rates between compartmental classes. However, it may become less appropriate in other contexts, such as biochemical or cellular systems. Under mass-action kinetics, analyzing the fixed points of the concentration system amounts to solving for the roots of a system of polynomial equations, for which many tools from algebraic geometry are available. The main difficulty, however, is that analyzing fixed-point stability requires first obtaining a parametrization of the fixed-point variety, on which all subsequent analysis must then be performed. This unavoidable step comes with a great computational cost even for simple tasks, such as assessing the stability of fixed points, let alone more delicate bifurcation problems. For an illustration of the typical difficulties involved, see, among many others, Hernandez et al [13] for parametrization of fixed-points, Conradi et al. [9], Pérez Millán & Dickenstein [21], and Röst & Sadeghimanesh [22] for zero-eigenvalue bifurcations, and Gatermann et al. [11] and Banaji & Borosz [3] for purely imaginary-eigenvalue bifurcations.

In this contribution, we present an alternative computational tool that relies solely on the linearization of the system, without requiring explicit computation of fixed points. In particular, this method applies to any system for which the characteristic polynomial of the Jacobian can be obtained in symbolic form: typically covering networks of up to around 15 species. The central assumption is that the kinetics are *not* in mass-action form, but instead belong to a broad class of so-called *parameter-rich kinetics* [26], which includes widely used schemes such as Michaelis–Menten, Hill, and generalized mass-action kinetics.

This paper is organized as follows. Section 2 presents the standard literature ingredients concisely and refers to the appropriate sources. Section 3 introduces our newly developed Python module. An example of its applicability is presented in Section 4. The discussion in Section 5 closes the paper.

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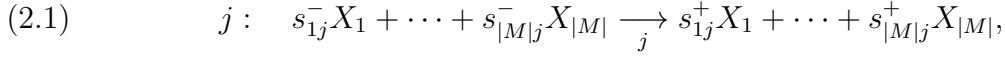
2 Preliminary theory

The content of this section has been presented in more detail in the publications [25, 26, 7].

2.1 Reaction networks and symbolic Jacobians

We consider reaction networks Γ as pairs of sets $\Gamma = (M, E)$, where M is the set of species X_m and E is the set of reactions j . Any reaction j is an ordered association

between nonnegative linear combinations of the species:



where the nonnegative coefficients $s_{mj}^-, s_{mj}^+ \geq 0$ are the *stoichiometric coefficients*. Species X_m appearing on the left-hand side (resp. right-hand side) of (2.1) with nonzero stoichiometric coefficients $s_{mj}^- > 0$ (resp. $s_{mj}^+ > 0$) are called *reactants* (resp. *products*). The stoichiometric coefficients of the reactant and product species are collected in two $|M| \times |E|$ matrices. The *reactant matrix* S^- is defined by

$$(2.2) \quad S_{mj}^- := s_{mj}^-,$$

and the *product matrix* S^+ by

$$S_{mj}^+ := s_{mj}^+.$$

The difference of the two matrices gives rise to the *stoichiometric matrix* $S := S^+ - S^-$ with entries

$$(2.3) \quad S_{mj} := s_{mj}^+ - s_{mj}^-.$$

Let $x(t) \in \mathbb{R}_{\geq 0}^{|M|}$ denote the time evolution of the nonnegative vector of species concentrations in a well-mixed, spatially homogeneous reactor. Its dynamics follow the system of Ordinary Differential Equations (ODEs)

$$(2.4) \quad \dot{x} = f(x) = S\mathbf{r}(x),$$

where S is the stoichiometric matrix defined in (2.3) and $\mathbf{r}(x) \in \mathbb{R}_{\geq 0}^{|E|}$ is the vector of *reaction rates*. In applications, the precise functional form of $r_j(x)$ is typically unknown. For this reason, the literature usually resorts to parametric families $\mathbf{r}(x, p)$, where p denotes positive parameters. Widely used reaction schemes in (bio)chemistry, ecology, and epidemiology include classic and generalized mass-action kinetics [28, 20], Michaelis–Menten kinetics [19], and Hill kinetics [15]. In ecology, these correspond respectively to Holling Functional Responses of type I, II, and III [16]. In line with this tradition, we restrict attention to reaction rates that are *monotone chemical functions* in the following sense.

Definition 2.1 (Monotone chemical function). A function r_j is a monotone chemical function if:

- i. $r_j(x) \geq 0$ for all $x \in \mathbb{R}_{\geq 0}^{|M|}$;
- ii. $r_j(x) > 0$ implies $x_m > 0$ for all species X_m with $s_{mj}^- > 0$;
- iii. $s_{mj}^- = 0$ implies $\partial r_j / \partial x_m \equiv 0$;
- iv. for $x > 0$ and $s_{mj}^- > 0$, it holds that $\partial r_j / \partial x_m > 0$.

A parametric vector $\mathbf{r}(x, p)$ of reaction rates for $\mathbf{\Gamma}$ such that $r_j(x, p)$ is a monotone chemical function for all j and for any choice of admissible parameters is called a *monotone kinetic model* for the network $\mathbf{\Gamma}$.

Let now $\bar{x}$ be a fixed point (steady state) of (2.4), i.e.

$$(2.5) \quad 0 = f(\bar{x}) = S\mathbf{r}(\bar{x}).$$

Its stability and possible bifurcations can be addressed at a linear approximation via the Jacobian matrix f_x of partial derivatives evaluated at $\bar{x}$:

$$(2.6) \quad f_x = \left. \frac{\partial f}{\partial x} \right|_{x=\bar{x}} = S \left. \frac{\partial \mathbf{r}}{\partial x} \right|_{x=\bar{x}},$$

where $\frac{\partial \mathbf{r}}{\partial x}$ is the $|E| \times |M|$ *reactivity matrix*. Assumptions (iii) and (iv) in Def. 2.1 imply that, at positive concentrations $x > 0$, the evaluated reactivity matrix is nonnegative:

$$(2.7) \quad \left(\frac{\partial \mathbf{r}}{\partial x} \right)_{jm} = \frac{\partial r_j}{\partial x_m} = \begin{cases} > 0 & \text{if } X_m \text{ is reactant to } j, \text{ i.e. } s_{mj}^- > 0; \\ = 0 & \text{otherwise.} \end{cases}$$

Inspired by (2.7), we define the $|E| \times |M|$ *symbolic reactivity matrix* R by

$$(2.8) \quad R_{jm} = \begin{cases} r'_{jm} > 0 & \text{if } X_m \text{ is reactant to } j, \text{ i.e. } s_{mj}^- > 0; \\ = 0 & \text{otherwise,} \end{cases}$$

where a positive symbol r'_{jm} represents a positive parameter. The reactivity matrix is thus a symbolic version of the transpose of the reactant matrix (2.2), as stated below.

Proposition 2.2. *For the symbolic reactivity matrix R , it holds that*

$$R_{jm} > 0 \quad \Leftrightarrow \quad s_{mj}^- > 0.$$

Proof. Directly by Eq. (2.8). □

Accordingly, we define the *symbolic Jacobian matrix* G as

$$(2.9) \quad G := SR.$$

In the theory presented here, we use the symbolic Jacobian to investigate two types of results: *exclusion results* and *existence results*.

1. **Exclusion results:** hold irrespective of the choice of symbols in the symbolic reactivity matrix R ;
2. **Existence results:** hold for specific choices of the symbols in R .

Exclusion results apply to any network endowed with a monotone kinetic model. Existence results, however, depend on the choice of kinetic model and require thus further specification.

To clarify, assume that for a certain network $\mathbf{\Gamma}$, the symbolic Jacobian $G = SR$ is invertible for all admissible R . Since any fixed-point Jacobian corresponds to a specific instantiation of R , we can *exclude* the possibility that any fixed-point in any monotone kinetic model has a singular Jacobian. Conversely, assume that $G = SR$ can be made singular for specific choices of R . The fact that such an R corresponds to an actual fixed-point reactivity matrix is not guaranteed *a priori*. First, the existence of any fixed-point requires a positive right kernel vector $v \in \mathbb{R}_{>0}^{|E|}$ of the stoichiometric matrix S :

$$(2.10) \quad Sv = 0.$$

Networks satisfying (2.10) are called *consistent* [1], and existence results based on fixed-point Jacobians require consistency: this is the case of fixed-point bifurcation results. Second, even for consistent networks, mapping the symbols r_{jm} in R to explicit parameters p in $\mathbf{r}(x, p)$ is not trivial. The notion of *parameter-rich kinetics* [26] identifies those monotone kinetic models for which this mapping is always possible.

Definition 2.3 (Parameter-rich kinetics). A monotone kinetic rate model $\mathbf{r}(x, p)$ is called *parameter-rich* if, for every positive fixed-point $\bar{x} > 0$ and every choice of an $|E| \times |M|$ symbolic reactivity matrix $\bar{R}$, there exists a choice of parameters $\bar{p} = p(\bar{x}, \bar{R})$ such that $\partial r_j / \partial x_m(\bar{x}, \bar{p}) = \bar{R}_{jm}$.

EXCLUSION RESULTS.	EXISTENCE RESULTS.
$\xrightarrow{1} X_1 \xrightarrow{2} X_2 \xrightarrow{3}$	$\begin{cases} X_1 \xrightarrow{1} X_2 \xrightarrow{2} 2X_1, \\ \xrightarrow{3} X_1 \xrightarrow{4} \end{cases}$
Equations:	Equations:
$\begin{cases} \dot{x}_1 = K_1 - r_2(x_1), \\ \dot{x}_2 = r_2(x_1) - r_3(x_2). \end{cases}$	$\begin{cases} \dot{x}_1 = K_3 - r_1(x_1) + 2r_2(x_2) - r_4(x_1), \\ \dot{x}_2 = r_1(x_1) - r_2(x_2). \end{cases}$
Symbolic Jacobian:	Symbolic Jacobian:
$\begin{pmatrix} -r'_{1x_1} & 0 \\ r'_{1x_1} & -r'_{2x_2} \end{pmatrix}.$	$\begin{pmatrix} -r'_{1x_1} - r'_{4x_1} & 2r'_{2x_2} \\ r'_{1x_1} & -r'_{2x_2} \end{pmatrix}.$
The eigenvalues are strictly negative irrespective of any parameter and concentration values. Fixed-point bifurcations are thus excluded for any choice of monotone kinetic model, and any fixed-point is locally stable.	As $\det = r'_{2x_2}(r'_{4x_1} - r'_{1x_1})$, a zero-eigenvalue bifurcation requires $r'_{4x_1} = r'_{1x_1}$. Definition 2.3 guarantees that this condition is always realizable at a fixed-point for parameter-rich kinetics. See [24] for an explicit realization of a saddle-node bifurcation for Michaelis–Menten kinetics.
<i>Exclusion results are always valid also for mass-action kinetics.</i>	<i>Existence results are not always valid for mass-action kinetics.</i>

2.2 Child-Selections and bifurcations

The previous subsection introduced the concepts of the *symbolic Jacobian* and *parameter-rich kinetics*. We now present the main tool for studying the spectra of symbolic Jacobians and possible bifurcations: *Child-Selections*.

Definition 2.4 (Child Selection). A k -Child-Selection triple (or k -CS) is a triple $\kappa = (\kappa, E_\kappa, J)$ such that $|\kappa| = |E_\kappa| = k$, $\kappa \subseteq M$, $E_\kappa \subseteq E$, and $J : \kappa \rightarrow E_\kappa$ is a bijection satisfying $s_{mJ(X_m)}^- > 0$ for all $X_m \in \kappa$. The map J is called the *Child-Selection bijection*.

For each k -CS κ , we define the associated $k \times k$ *Child-Selection matrix* (or *CS-matrix*) as

$$(2.11) \quad S[\kappa]_{ml} := s_{mJ(l)}^+ - s_{mJ(l)}^-.$$

A CS-matrix is thus a square submatrix of the stoichiometric matrix S , up to a reshuffling of its columns according to the CS-bijection J . Rows follow the ordering of the species in M , while columns follow the order induced by J .

To analyze the spectrum of the symbolic Jacobian G , we consider its characteristic polynomial

$$(2.12) \quad g(\lambda) = \det(\lambda \text{Id} - G) = \sum_{k=1}^{|M|} a_k (-1)^k \lambda^{|M|-k},$$

and employ a central lemma from [25, 26], which expands each coefficient a_k in terms of Child-Selections.

Lemma 2.5. *Let $g(\lambda)$ be the characteristic polynomial of the symbolic Jacobian G of a network Γ . For each coefficient a_k in (2.12), it holds that*

$$(2.13) \quad a_k = \sum_{\kappa} \det S[\kappa] \prod_{X_m \in \kappa} R_{J(X_m)m},$$

where the sum runs over all k -CS triples κ .

The proof is based on the Cauchy–Binet formula and for this reason each summand $\det S[\kappa] \prod_{X_m \in \kappa}$ is called a *Cauchy–Binet summand* (or CB summand). Lemma 2.5 provides the foundation for deriving spectral properties of the Jacobian using Child-Selections alone. By selecting appropriate subsets κ , one can approximate or reconstruct the characteristic polynomial of G through the corresponding CS-matrices. In the following, we list the main implications of this approach, which can be automatically explored by our Python module.

Nondegenerate networks. Most stability and bifurcation results consider only *nondegenerate networks*, defined as follows. Consider an initial condition $x_0 \in \mathbb{R}_{>0}^{|M|}$ for (2.4). The sets

$$(2.14) \quad x_0 + \text{Im } S,$$

which are invariant under the flow, are called *stoichiometric compatibility classes*.

Left-kernel vectors w of the stoichiometric matrix S correspond to *linear conservation laws*, since

$$(2.15) \quad \frac{d(wx(t))}{dt} = w\dot{x} = wS\mathbf{r}(x) = 0.$$

Arbitrary but fixed values for these conservation laws, i.e. $C_i \in \mathbb{R}$ such that $w_i x(t) = C_i$, can be used to reduce the system to a specific stoichiometric compatibility class via a standard reduction procedure.

A network is *nondegenerate* if the dimension of its associated dynamical system equals the number of species $|M|$ minus the dimension n of the left kernel of S , i.e. the number of independent linear conservation laws. Equivalently:

Definition 2.6 (Nondegenerate networks). Let Γ be a reaction network with $|M| \times |E|$ stoichiometric matrix S , and let $n \geq 0$ denote the number of linearly independent conservation laws, i.e. $n = \dim \ker S^T$. Then Γ is *nondegenerate* if there exists a choice of the reactivity matrix R such that the symbolic Jacobian $G = SR$ possesses a nonzero $(|M| - n)$ -principal minor.

In terms of Child-Selections, the following characterization holds.

Proposition 2.7 ([7]). *In the setting of Def. 2.6, a network Γ is nondegenerate if and only if there exists an invertible $(|M| - n) \times (|M| - n)$ CS-matrix.*

Similarly, the spectrum of specific CS-matrices provides information about the possible spectral configurations of the symbolic Jacobian, as clarified below.

Instability and stability. Recall that a matrix A is *Hurwitz-stable* if all its eigenvalues have negative real part, and *Hurwitz-unstable* if at least one eigenvalue has positive real part. In dynamical systems theory [17], the Hurwitz-(in)stability of the Jacobian matrix sufficiently determines the local (in)stability of the corresponding fixed point. In our parameter-rich framework, this motivates the following definitions.

Definition 2.8 (Network admits stability). A nondegenerate network Γ *admits stability* if there exists a choice of the symbolic reactivity matrix $\bar{R}$ such that the symbolic Jacobian $S\bar{R}$ has $|M| - n$ eigenvalues with negative real part, counted with algebraic multiplicity. Here, n again denotes the number of independent conservation laws.

Definition 2.9 (Network admits instability). A network Γ *admits instability* if there exists a choice of the symbolic reactivity matrix $\bar{R}$ such that the corresponding symbolic Jacobian $S\bar{R}$ is Hurwitz-unstable.

Definition 2.8 can be interpreted as stating that there exists a choice of the symbolic reactivity matrix such that the symbolic Jacobian, when restricted to a stoichiometric compatibility class, is Hurwitz-stable. Consequently, if a consistent and nondegenerate network admits stability, then there exists a parameter choice for which (2.4) possesses a stable fixed point. Conversely, if a consistent network endowed with parameter-rich kinetics admits instability, then there exists a parameter choice for which system (2.4) possesses an unstable fixed point. Note that concluding directly on stability requires nondegeneracy, unlike the unstable case.

In terms of CS-matrices, the following propositions provide sufficient conditions.

Proposition 2.10 ([25]). *For a nondegenerate network, if there exists a $(|M| - n) \times (|M| - n)$ CS-matrix $S[\kappa]$ that is Hurwitz-stable, then the network admits stability.*

Proposition 2.11 ([26]). *If there exists a CS-matrix $S[\kappa]$ that is Hurwitz-unstable, then the network admits instability.*

Both Prop. 2.10 and Prop. 2.11 can be generalized by allowing the existence of a positive diagonal matrix D such that $S[\kappa]D$ is Hurwitz-(un)stable. The current version of our Python module, however, does not yet implement this generalization, and therefore we present the propositions in this restricted form.

Cores. Let $\kappa = (\kappa, E_\kappa, J)$ be a k -CS. Child-Selections can be concatenated in the sense that any restriction κ' of κ , to subsets $\kappa' \subset \kappa$ and $E_{\kappa'} = J(\kappa') \subset E_\kappa$, is itself a k' -CS $\kappa' = (\kappa', E_{\kappa'}, J)$. From the perspective of CS-matrices, the CS-matrix associated with κ' appears as a principal submatrix of the CS-matrix associated with κ .

Therefore, it is natural to consider *minimal* CS-matrices $S[\kappa]$ with respect to a matrix property $\mathbb{P}$, meaning that $S[\kappa]$ satisfies $\mathbb{P}$ while no proper principal submatrix does. For examples, in [26] *unstable cores* are defined as Hurwitz-unstable CS-matrices such with no Hurwitz-unstable principal submatrix. For the purposes of this study, the main property of interest concerns specifically the sign of the determinant of unstable cores.

Definition 2.12 (Unstable-positive feedback, [26]). A $k \times k$ CS-matrix $S[\kappa]$ is an *unstable-positive feedback* if

$$(2.16) \quad \text{sign det } S[\kappa] = (-1)^{k-1},$$

and no $k' < k$ principal submatrix $S[\kappa']$ satisfies

$$(2.17) \quad \text{sign det } S[\kappa'] = (-1)^{k'-1}.$$

Unstable-positive feedbacks always possess a single real positive eigenvalue [26]. In [26], the definition was slightly more restrictive, requiring additionally that no principal submatrix of $S[\kappa]$ be Hurwitz-unstable. For the purposes of the present analysis, Def. 2.12 is the most appropriate.

For completeness, we also recall the definition of *unstable-negative feedback*, although the current version of our Python module BIRNE primarily focuses on unstable-positive feedbacks.

Definition 2.13 (Unstable-negative feedback, [26]). A $k \times k$ CS-matrix $S[\kappa]$ is an *unstable-negative feedback* if it is Hurwitz-unstable and

$$(2.18) \quad \text{sign det } S[\kappa] = (-1)^k,$$

and no $k' < k$ principal submatrix $S[\kappa']$ is Hurwitz-unstable.

Unstable-negative feedbacks always have one pair of complex-conjugate eigenvalues with positive real part and no real positive eigenvalue [26].

Autocatalysis. Autocatalysis is a fundamental concept in chemistry. Blokhuis et al. [6] provided a characterization of autocatalysis from a stoichiometric perspective, which has been then characterized in [26] in terms of CS-matrices. We recall the relevant definition.

Definition 2.14 (Stoichiometric Autocatalysis.). A network Γ with stoichiometric matrix S is *autocatalytic* if there exists a $|M'| \times |E'|$ submatrix S_A of S such that

1. for any reaction j appearing as a column of S_A , we have m_1 and m_2 , not necessarily distinct, with $s_{m_1 j}^- s_{m_2 j}^+ \neq 0$.
2. there exists a positive vector $v \in \mathbb{R}_{>0}^{|E'|}$ such that

$$(2.19) \quad Sv > 0.$$

We also recall that a square matrix A is called *Metzler* if all its nondiagonal entries are nonnegative, i.e. $A_{ij} \geq 0$, for all i, j [8]. We have the following result, which characterizes autocatalysis in terms of CS-matrices.

Theorem 2.15 ([26]). *A network is autocatalytic if and only if there exists a CS-matrix $S[\kappa]$ which is an unstable-positive feedback and a Metzler matrix.*

Real-zero eigenvalue: Multistationarity. Multistationarity refers to the coexistence of two or more fixed points under identical parameter values, and has been identified as a central mechanism underlying, for example, cell differentiation [23]. A network endowed with a parametric kinetic model is said to admit multistationarity if there exists a choice of parameters for which the system (2.4) has multiple fixed points. Building on the work of Banaji and Pantea, the capacity of a network to exhibit multistationarity under parameter-rich kinetics can be characterized in terms of CS-matrices.

Theorem 2.16 ([4], [25]). *A nondegenerate consistent network endowed with parameter-rich kinetics admits multistationarity if and only if there exist two $(|M| - n) \times (|M| - n)$ CS-matrices $S[\kappa_1]$ and $S[\kappa_2]$ such that*

$$(2.20) \quad \det S[\kappa_1] \det S[\kappa_2] < 0.$$

Proof. Banaji and Pantea [4, Theorem 3] proved that a nondegenerate consistent network admits multistationarity if the Jacobian of the system restricted to a stoichiometric compatibility class can be made singular for a certain choice of parameters. [25, Corollary 5.7] presents the straightforward translation of this condition in terms of Child-Selections as (2.20). $\square$

Purely-imaginary eigenvalues: Periodic Orbits. Periodic oscillations play a central role in many reaction networks. In biochemistry, they regulate metabolic processes, circadian rhythms, and other essential biological functions [14]. The following result [7] gives a sufficient condition in terms of CS-matrices for the system (2.4) to admit nonstationary periodic solutions.

Theorem 2.17 ([7]). *Let Γ be a consistent, nondegenerate network endowed with parameter-rich kinetics. Assume there exists a CS-matrix $S[\kappa]$ that is Hurwitz-stable and possesses a strict $k' \times k'$ principal submatrix $S[\kappa']$, which is an unstable-positive feedback. Then there exists a choice of parameters for which system (2.4) admits nonstationary periodic solutions.*

Minimal CS-matrices satisfying the assumption of the theorem are called *Oscillatory cores of Class A*. Other sufficient conditions, based e.g. on unstable-negative feedback are also provided in [7], which we state here for consistency.

Theorem 2.18 ([7]). *Let Γ be a consistent, nondegenerate network endowed with parameter-rich kinetics. Assume there exists an unstable-negative feedback $S[\kappa]$ which possesses a Hurwitz-stable $(k-1) \times (k-1)$ principal submatrix. Then there exists a choice of parameters for which system (2.4) admits nonstationary periodic solutions.*

Minimal CS-matrices satisfying the assumption of the theorem are called *Oscillatory cores of Class B*. The proof of both results relies on the theory of global Hopf bifurcation [10].

3 The BiRNe module

BiRNe is an easy-to-use, open-source, Python-based module designed to identify stability changes of fixed points in reaction networks and to determine whether they are (i) of autocatalytic or non-autocatalytic nature, and (ii) whether they induce multistationarity or periodic oscillations. The module targets reaction networks of medium size (around 15 species or reactions). BiRNe is built on SYMPY, a computer algebra system for symbolic mathematical computations that provides a wide variety of tools and solvers ranging from calculus to linear algebra [18]. BiRNe accepts a list of reactions as **input**. See Algorithm 1 for the pseudocode. In plain terms, its workflow proceeds as follows:

1. **Build the stoichiometric matrices.** The input list of reactions is translated into *reactant* and *product* matrices, S^- and S^+ , respectively. The *stoichiometric matrix* S is then obtained as $S = S^+ - S^-$. See (2.2), (2.1), (2.3) for a definition of such matrices.
2. **Check the network’s consistency.** The existence of a strictly positive right kernel vector of S , and hence the consistency of the network (2.10), is determined by solving the linear programming problem using SciPy’s linear optimizer [27]:

$$(3.1) \quad \begin{array}{ll} \min & v \\ \text{s.t.} & Sv = 0 \\ & v > 0 \end{array}$$

In certain modeling contexts, such as metabolic networks, the lack of consistency may simply reflect the omission of obvious production or degradation reactions, or the deliberate focus on a specific subnetwork structure. Moreover, results such as Thm. 2.17 naturally extend to any larger consistent network that contains the same motifs. For these reasons, if the network is not consistent, a warning is issued, but the algorithm continues its execution.

3. **Generate the symbolic reactivity and Jacobian matrices.** The symbolic reactivity matrix R is generated from the reactant matrix and has entries R_{jm} of the form

$$(3.2) \quad R_{jm} = \begin{cases} \mathbf{r}(\mathbf{j}, \mathbf{m}), & \text{if } S_{mj}^- > 0, \\ 0, & \text{otherwise.} \end{cases}$$

Here, $\mathbf{r}(\mathbf{j}, \mathbf{m})$ is a SYMPY symbol instantiated with the string representation ' $\mathbf{r}(\mathbf{j}, \mathbf{m})$ ', allowing instantaneous identification of its position in R . The symbolic Jacobian G is then computed as

$$(3.3) \quad G = SR.$$

4. **Compute and organize the characteristic polynomial of G .** The characteristic polynomial of G is computed using SYMPY's CHARPOLY function, which implements the Samuelson–Berkowitz algorithm [5]. Coefficients c_k are extracted by size. Relating to (2.12) and Lemma 2.5, they correspond to

$$(3.4) \quad c_k = (-1)^k a_k = \sum_{\kappa} (-1)^k \det S[\kappa] \prod_{X_m \in \kappa} \mathbf{r}(\mathbf{j}, \mathbf{m}),$$

where each $\mathbf{r}(\mathbf{j}, \mathbf{m})$ satisfies $\mathbf{r}(\mathbf{j}, \mathbf{m}) = R_{J(X_m)m}$ for some CS bijection J . In particular, CB-summands associated with κ whose CS-matrix $S[\kappa]$ is Hurwitz-unstable and satisfies

$$(3.5) \quad \text{sign } \det S[\kappa] = (-1)^{k-1}$$

are readily identified in c_k as those carrying negative coefficients.

Moreover, particular emphasis is given to *minimal* negative CB-summands, that is, summands

$$(3.6) \quad (-1)^k \det S[\kappa] \prod_{X_m \in \kappa} \mathbf{r}(\mathbf{j}, \mathbf{m}) < 0$$

in c_k such that in *no* coefficient $c_{k'}$ with $k' < k$ there exists a negative summand

$$(3.7) \quad (-1)^{k'} \det S[\kappa'] \prod_{X_m \in \kappa'} \mathbf{r}(\mathbf{j}, \mathbf{m}) < 0,$$

where κ' is a restriction of κ , i.e.

$$(3.8) \quad \{\mathbf{r}(\mathbf{j}, \mathbf{m}) \mid X_m \in \kappa'\} \subset \{\mathbf{r}(\mathbf{j}, \mathbf{m}) \mid X_m \in \kappa\}.$$

The CS-matrix associated with such minimal negative CB-summands identifies the *unstable cores*, which are *unstable positive feedbacks* (see Def. 2.12). In parallel, a Hasse diagram [2] is constructed with the root vertex $c_0 = 1$. The direct descendants of the root vertex are the minimal negative CB-summands representing unstable-positive feedbacks. From each such vertex, identified by a CS-triple κ' , further descendants are identified in coefficients c_k , $k > k'$, for CB-summands associated to CS-triples κ whenever the relation (3.8) holds, that is, when κ' is a restriction of κ .

5. **Check nondegeneracy of the network.** According to Prop. 2.7 and Lemma 2.5, nondegeneracy is verified by ensuring that the largest $(|M| - \dim(\text{Ker } S^T))^{\text{th}}$ coefficient is not identically zero as a function of the symbolic entries of R . If the network is found to be degenerate, a warning is issued: most of the known results hold for nondegenerate networks. For analogous modeling reasons as exposed in the consistency check above, the algorithm continues nevertheless its execution.
6. **Check if the network admits stability.** Likewise, the same largest $(|M| - \dim(\text{Ker } S^T))^{\text{th}}$ coefficient is examined to determine if the network admits stability. For any CB-summand with positive sign, the corresponding CS-matrix is extracted and its eigenvalues computed. If any such CS-matrix is Hurwitz-stable, the network is declared stable and further testing is omitted.
7. **Test for multistationarity.** We check whether the same coefficient contains CB-summands with both positive and negative signs. If this is the case, for nondegenerate networks, multistationarity is implied by Thm. 2.16.
8. **Testing autocatalysis.** Negative CB-summands are further examined for autocatalysis: the associated CS-matrix is extracted and tested for the Metzler property. If the matrix is Metzler, the corresponding feedback is autocatalytic. Autocatalytic unstable-positive feedbacks identify *autocatalytic cores* in the sense of [6]. A network is certified as *autocatalytic* if at least one negative CB-summand is associated with a Metzler CS-matrix, and as *non-autocatalytic* otherwise.
9. **Testing oscillations.** For any *negative* CB-summand in a coefficient c_k ,

$$(3.9) \quad (-1)^k \det S[\kappa] \prod_{X_m \in \kappa} r(j, m) < 0,$$

we test whether there exists a CB-summand with *positive* sign in a coefficient $c_{\tilde{k}}$ with $\tilde{k} > k$,

$$(3.10) \quad (-1)^{\tilde{k}} \det S[\tilde{\kappa}] \prod_{X_m \in \tilde{\kappa}} r(j, m) > 0,$$

such that κ is a restriction of $\tilde{\kappa}$, i.e.

$$(3.11) \quad \{r(j, m) \mid X_m \in \kappa\} \subset \{r(j, m) \mid X_m \in \tilde{\kappa}\}.$$

This corresponds to the existence of an edge in the constructed Hasse diagram that connects vertex with negative coefficient to a descendant vertex with positive coefficient. Once such a pair is found, the Hurwitz-stability of $S[\tilde{\kappa}]$ is checked. If stability is confirmed, $S[\tilde{\kappa}]$ satisfies the assumptions of Thm. 2.17, and the network is certified to admit nonstationary periodic solutions.

Algorithm 1 BIRNE

Require: L : List of reactions

Ensure: $\mathcal{U}_a, \mathcal{U}_n, \mathcal{O}$: map of unstable (non-)autocatalytic cores and oscillatory cores

$\mathcal{U}_a, \mathcal{U}_n, \mathcal{O} \leftarrow \langle \text{CB-summand, CS-matrix} \rangle, \langle \text{CB-summand, CS-matrix} \rangle, \langle \text{CB-summand, []} \rangle$

$S^+, S^-, M, R \leftarrow \text{STOICHIOMETRICMATRICES}(L)$ $\triangleright M$: metabolites, R : reactions

$S \leftarrow S^+ - S^-$

$\text{admitsStability}, \text{multiStationarity} \leftarrow \text{False}, \text{False}$

if $\exists v \in \mathbb{R}_{>0} : Sv = 0$ **then** $\triangleright$ Consistency check

$m \leftarrow |M|$

$d \leftarrow \dim(\text{Ker} S^T)$

$\mathbf{R} \leftarrow \text{GENERATEACTIVITYMATRIX}(S^-)$

$\mathbf{G} \leftarrow S \cdot \mathbf{R}$

$p \leftarrow \text{CHARPOLY}(\mathbf{G})$

$\triangleright p = \mathbf{G}.\text{charpoly}(\lambda)$

$C \leftarrow \text{COEFFICIENTS}(p)$

$\triangleright C = \langle \text{int}, \text{list} \rangle$

if $C[m - d] \neq \emptyset$ **then** $\triangleright$ Non-degeneracy check

$C_n, C_p \leftarrow \text{DIVIDECOEFFICIENTSBYSIGN}(C)$

$\triangleright C_{n/p} = \langle \text{int}, \text{list} \rangle$

if $C_n[m] \neq \emptyset$ and $C_p[m] \neq \emptyset$ **then**

$\triangleright$ Multistationarity check

$\text{multistationarity} \leftarrow \text{True}$

end if

for $c \in C_p[m]$ **do** $\triangleright$ Stability check

$S_c \leftarrow \text{CSMATRIX}(S, c)$

if S_c is Hurwitz-stable **then**

$\text{admitsStability} \leftarrow \text{True}$

 Break

end if

end for

for $i \in \{1, \dots, k - 1\}$ **do**

for $c \in C_n[i]$ **do**

if $\text{MINIMALITYCHECK}(c) == \text{True}$ **then**

$S_c \leftarrow \text{CSMATRIX}(S, c)$

$k \leftarrow |S_c|$

if S_c is Metzler **then**

$\triangleright$ Autocatalysis check

$\text{autocatalytic} \leftarrow \text{True}$

$\mathcal{U}_a[c] \leftarrow S_c$

else

$\mathcal{U}_n[c] \leftarrow S_c$

end if

for $\ell \in \{i + 1, \dots, m\}$ **do**

for $c' \in C_p[\ell]$ **do**

$S_{c'} \leftarrow \text{CSMATRIX}(S, c')$

if $c \subseteq c'$ and $S_{c'}$ is Hurwitz-stable **then**

$\triangleright$ Oscillatory Check

if $\text{MINIMALITYCHECK}(c') == \text{True}$ **then**

$\mathcal{O}[c] \leftarrow [S_c, c', S_{c'}]$

end if

end if

end for

end for

end if

end for

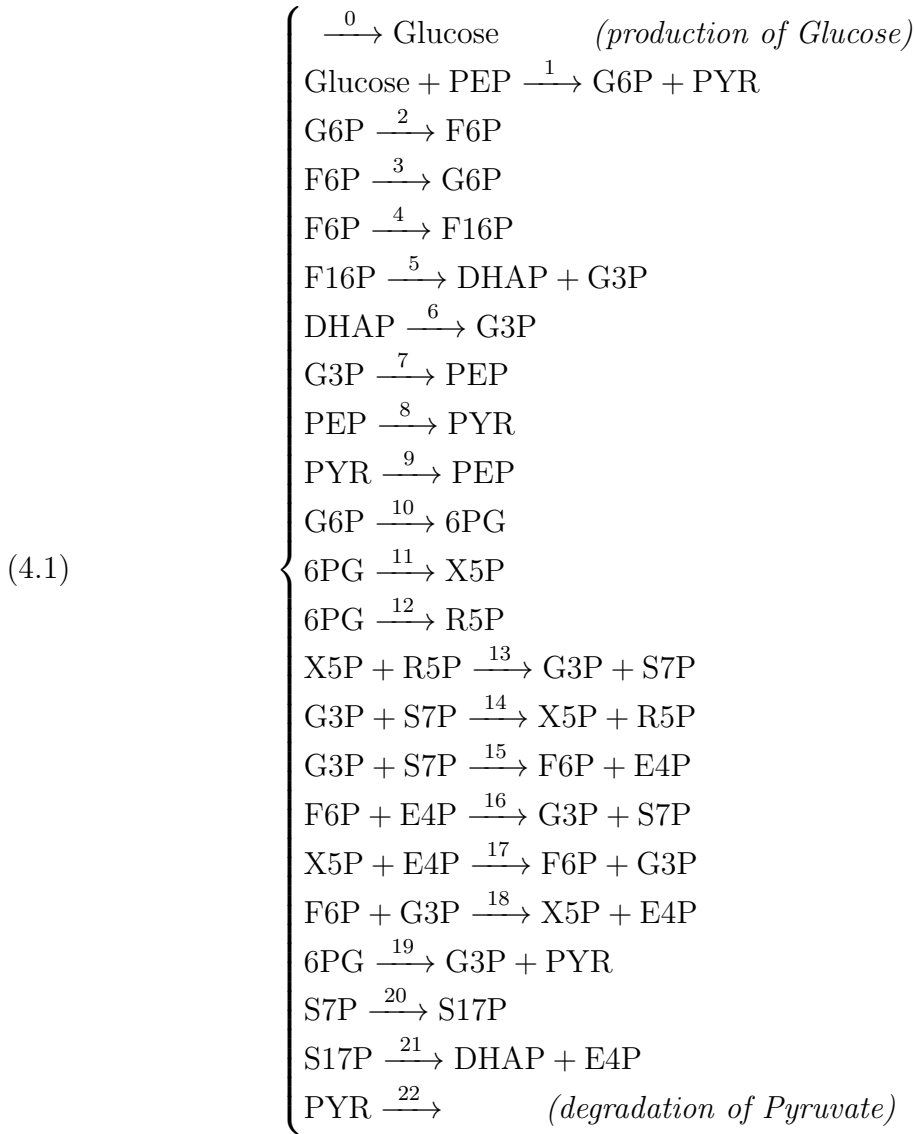
end if

end if

return $\mathcal{U}_a, \mathcal{U}_n, \mathcal{O}, \text{admitsStability}$

4 An example

To show the effectiveness of BiRNE, we study a simplified model of glycolysis and the pentose phosphate pathway in the central metabolism of *E. coli*. As the purpose of this example is here only to demonstrate the capabilities of our module, we do not discuss any biological implication. The network consists of 14 metabolites: Glucose, Glucose-6-Phosphate (G6P), 6-Phosphogluconolactone (6PG), Fructose-6-Phosphate (F6P), Fructose-1,6-Bisphosphate (F16P), Dihydroxyacetonephosphate (DHAP), Glyceraldehyde-3-Phosphate (G3P), Xylulose-5-Phosphate (X5P), Ribose-5-Phosphate (R5P), Erythrose-4-Phosphate (E4P), Sedoheptulose-7-Phosphate (S7P), Sedoheptulose-1,7-Bisphosphate (S17P), Phosphoenolpyruvate (PEP), and Pyruvate (PYR); together with the following 23 reactions among them.



The size and connectivity of this metabolic network seats at the upper end of the applicability of BiRNE. The module computed the characteristic polynomial in 18,651 s and constructed the Hasse diagram and determined all unstable cores in further 8,037 s. The network was found to be consistent, non-degenerate, and to admit both stability and

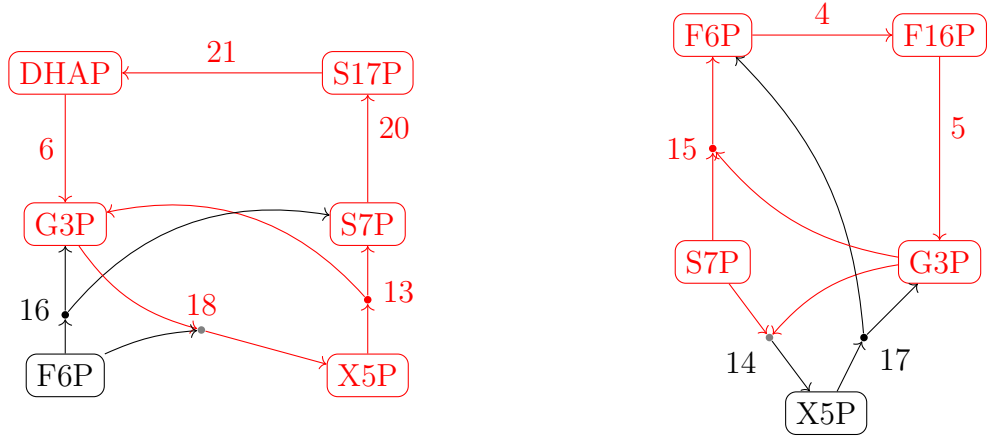


Figure 1: Depiction of two oscillatory cores of class A based on an autocatalytic (left) and a non-autocatalytic (right) unstable-positive feedback within the Glycolysis and Pentose Phosphate Pathway. Both unstable-positive feedbacks are shown in red. For clarity, hyperarrows involving multiple reactants or products are represented here in bipartite form. The associated CS-matrices are, respectively, (4.3) and (4.7).

multistationarity. In total, 33,820 negative CB-summands were identified, comprising 49 unstable cores: 29 autocatalytic and 20 non-autocatalytic. Among these unstable cores, 8 (5 autocatalytic and 3 non-autocatalytic) gave rise to 11 oscillatory motifs.

We refer to <https://github.com/hollyritch/Bi.R.Ne> for the complete output. Here we present two oscillatory cores of class A to exemplify: one based on autocatalytic unstable-positive feedback and one on non-autocatalytic unstable-positive feedback (see Figure 1, left and right, respectively). The first example, left in Fig. 1, concerns the following CS-triple:

$$(4.2) \quad \kappa_1 = (\kappa_1 = \{F6P, DHAP, G3P, X5P, S7P, S17P\}, E_{\kappa_1} = \{6, 13, 16, 18, 20, 21\}, J(\kappa) = \{16, 6, 18, 13, 20, 21\}),$$

with associated Hurwitz-stable CS-matrix:

$$(4.3) \quad S[\kappa_1] = \begin{matrix} & 16 & 6 & 18 & 13 & 20 & 21 \\ \begin{matrix} F6P \\ DHAP \\ G3P \\ X5P \\ S7P \\ S17P \end{matrix} & \begin{pmatrix} -1 & 0 & -1 & 0 & 0 & 0 \\ 0 & -1 & 0 & 0 & 0 & 1 \\ 1 & 1 & -1 & 1 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 \\ 1 & 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 \end{pmatrix} \end{matrix}$$

with eigenvalues all $\lambda_i = -1$. On the other hand, marked in red in Fig. 1, the restriction κ'_1 defined on $\kappa_1 \setminus \{F6P\}$:

$$(4.4) \quad \kappa'_1 = (\kappa'_1 = \{DHAP, G3P, X5P, S7P, S17P\}, E_{\kappa_1} = \{6, 13, 18, 20, 21\}, J(\kappa_1) = \{6, 18, 13, 20, 21\}),$$

identifies a Hurwitz-unstable CS-matrix, which is in particular an unstable-positive feed-

back and Metzler. This yields autocatalysis via Thm. 2.15.

$$(4.5) \quad S[\kappa'_1] = \begin{array}{c} \text{DHAP} \\ \text{G3P} \\ \text{X5P} \\ \text{S7P} \\ \text{S17P} \end{array} \begin{pmatrix} 6 & 18 & 13 & 20 & 21 \\ -1 & 0 & 0 & 0 & 1 \\ 1 & -1 & 1 & 0 & 0 \\ 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 1 & -1 \end{pmatrix},$$

with $\det S[\kappa'_1] = (-1)^{5-1} = 1$. The CS-matrix $S[\kappa'_1]$ corresponds to an autocatalytic core sensu [6], precisely of type II. In conclusion, $S[\kappa_1]$ is an oscillatory core of class A.

The second example, right in Fig. 1, is based on the following CS-triple:

$$(4.6) \quad \begin{aligned} \kappa_2 &= (\kappa_2 = \{\text{F6P}, \text{F16P}, \text{G3P}, \text{X5P}, \text{S7P}\}, E_{\kappa_2} = \{4, 5, 14, 15, 17\}, \\ J(\kappa_2) &= \{4, 5, 15, 17, 14\}) \end{aligned}$$

with associated Hurwitz-stable CS-matrix:

$$(4.7) \quad S[\kappa_2] = \begin{array}{c} \text{F6P} \\ \text{F16P} \\ \text{G3P} \\ \text{X5P} \\ \text{S7P} \end{array} \begin{pmatrix} 4 & 5 & 15 & 17 & 14 \\ -1 & 0 & 1 & 1 & 0 \\ 1 & -1 & 0 & 0 & 0 \\ 0 & 1 & -1 & 1 & -1 \\ 0 & 0 & 0 & -1 & 1 \\ 0 & 0 & -1 & 0 & -1 \end{pmatrix},$$

with eigenvalues $(\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5) \approx (-2.24, -1.34 \pm 0.8i, -0.04 \pm 0.43)$. On the other hand, marked in red in Fig. 1, the restriction κ'_2 defined on $\kappa_2 \setminus \{\text{X5P}\}$:

$$(4.8) \quad \begin{aligned} \kappa'_2 &= (\kappa'_2 = \{\text{F6P}, \text{F16P}, \text{G3P}, \text{S7P}\}, E_{\kappa_2} = \{4, 5, 14, 15\}, \\ J(\kappa_2) &= \{4, 5, 15, 14\}) \end{aligned}$$

identifies a Hurwitz-unstable CS-matrix $S[\kappa'_2]$, which is in particular an unstable-positive feedback but not a Metzler matrix; thus, there is no autocatalysis:

$$(4.9) \quad S[\kappa'_2] = \begin{array}{c} \text{F6P} \\ \text{F16P} \\ \text{G3P} \\ \text{S7P} \end{array} \begin{pmatrix} 4 & 5 & 15 & 14 \\ -1 & 0 & 1 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & -1 \\ 0 & 0 & -1 & -1 \end{pmatrix},$$

with $\det S[\kappa'_2] = (-1)^{4-1} = -1$. Finally, we point out that the same set κ_2 and E_{κ_2} , but with different bijection $J(\kappa_2) = \{4, 5, 17, 15, 14\}$, gives rise to a Hurwitz-unstable CS-matrix:

$$(4.10) \quad S[\tilde{\kappa}_2] = \begin{array}{c} \text{F6P} \\ \text{F16P} \\ \text{G3P} \\ \text{X5P} \\ \text{S7P} \end{array} \begin{pmatrix} 4 & 5 & 14 & 17 & 15 \\ -1 & 0 & 0 & 1 & 1 \\ 1 & -1 & 0 & 0 & 0 \\ 0 & 1 & -1 & 1 & -1 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & -1 & 0 & -1 \end{pmatrix},$$

obtainable from $S[\kappa_2]$ with a single swap of columns (14,15). In particular, $S[\tilde{\kappa}_2]$ is unstable and does not give rise to oscillations. For simplicity, we have not marked such subtlety in Fig. 1.

5 Discussion

We have presented BIRNE, a Python-based computer algebra module designed to identify motifs associated with stability changes of fixed points in reaction networks and the resulting bifurcations, classified as either leading to multistationarity (zero-eigenvalue bifurcations) or to periodic oscillations (purely imaginary eigenvalue bifurcations).

In contrast to commercial symbolic computing environments with restrictive licensing and recurring fees, Python is developed under an OSI-approved open-source license, making it freely accessible. In addition, SYMPY provides a powerful computer algebra system within Python for symbolic computations, offering a broad range of algorithms and solvers for calculus and linear algebra. For networks of moderate size (typically up to 15 species and reactions, depending on the network’s connectivity) our implementation can determine multistationarity and identify all unstable-positive feedbacks, classifying them as autocatalytic or non-autocatalytic, and further detecting whether they give rise to periodic oscillations. The presented algorithm relies solely on basic functionality common to most symbolic computation platforms. Consequently, it could be adapted to more efficient symbolic programming environments with minimal effort. On the other hand, substantial performance gains, such as those needed to apply the method to large-scale networks, appear unlikely: the approach relies on computing the characteristic polynomial of a symbolic matrix, an operation whose computational complexity grows exponentially with the matrix size, i.e., with the number of species in the network. Thus, at best, only minor gains would be expected, i.e. size limitations could be raised only by a handful of additional species and reactions within reasonable computation times. The analysis of large reaction networks, such as metabolic systems in bacteria or eukaryotes involving hundreds to thousands of species and reactions, requires a fundamentally different methodological approach. In this regard, we refer to our forthcoming framework for detecting autocatalytic cycles in chemical reaction networks [12], based on graph-theory tools.

The current version (November 2025) of the module evaluates multistationarity based on Thm. 2.16 without specifying the bifurcation type and scans only for one mechanism of oscillations (Thm. 2.17). Future developments aim to extend these capabilities by certifying specific zero-eigenvalue bifurcations, such as *saddle-node bifurcations* (cf. [24]), and incorporating additional oscillatory motifs, for example those described as Recipe 0 in [7] or addressed in Thm. 2.18, thereby broadening the module’s analytical scope and applicability.

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