Mass action systems: two criteria for Hopf bifurcation without Hurwitz

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Abstract

We state two sufficient criteria for periodic oscillations in mass action systems. Neither criterion requires a computation of the Hurwitz determinants. Instead, both criteria exploit the linear algebra concepts of D-stability and P-matrices. The criteria are complementary: the first is based on a stable matrix that is not a P^- matrix, while the second is based on a P^- matrix that is not stable. In analogy, a qualitatively different interpretation follows: the first criterion relates to positive feedback in the network, while the second concerns negative feedback. We present examples that showcase the applicability of both criteria.

As a final independent remark, we prove that for the special case of fully-open networks, the capacity for Hopf bifurcation is just equivalent to the capacity for a steady-state with a complex pair of eigenvalues with positive-real part.

Keywords: mass action systems, periodic oscillations, D-stability, P^- matrices, global Hopf bifurcation

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1 Introduction

The quest of finding periodic orbits in polynomial differential equations is notoriously difficult. A standard approach aims at proving the occurrence of a Hopf bifurcation, where an equilibrium changes stability and generates a periodic orbit. Purely imaginary eigenvalues of the Jacobian are a necessary spectral condition for a Hopf bifurcation to occur. Therefore, the great majority of the literature in reaction networks employs an explicit Hurwitz criterion [27]. See among others [18, 13, 22, 21, 11, 34, 4]. The major drawback of the Hurwitz approach is its computational complexity, which limits its applicability to small networks. Moreover, such a computation may obfuscate, rather than illuminate, the underlying chemical mechanism that leads to oscillations.

With these motivations, we present two criteria that establish nonstationary periodic oscillations in mass action systems and do not require any Hurwitz computation. The first ingredient is the standard Jacobian parametrization by Clarke [10], which expresses the Jacobian matrix Jac at steady states in the form of

$$Jac = AD, \tag{1.1}$$

where D is a parametric positive diagonal matrix. Note that

$$\operatorname{rank} AD = \operatorname{rank} A, \tag{1.2}$$

and thus a change of stability by tuning parameters in D unequivocally leads to purely imaginary eigenvalues. The second ingredient are the linear algebra concepts of D-stability and P^- matrices, and in particular an old celebrated result by Fisher and Fuller [17, 16]. We rely on such results to provide manageable sufficient conditions on A for the existence of a positive diagonal matrix D^* such that AD^* has purely imaginary eigenvalues. Finally, we return to nonlinear dynamics: the third ingredient is a result by Fiedler [14] on *global Hopf bifurcation* that - together with the first two ingredients - guarantees the existence of nonstationary periodic orbits.

The paper is organized as follows. Section 2 introduces setting and notation. Section 3 is dedicated to linear algebra and presents in more detail the concepts of D-stability, P^--matrices, and the Fisher-Fuller result. Section 4 reviews the parametrization method Stoichiometric Network Analysis by Clarke. Section 5 contains the main Theorem 5.1 and - as Corollary 5.2 - the two criteria. Section 6 provides an interpretation of the chemical mechanism underlying the criteria: Criterion I concerns an unstable-positive feedback within a stable network; Criterion II concerns an unstable-negative feedback. We present examples for both criteria in Section 7. Finally, Section 8 provides an independent result for the special case of fully-open networks. Section 9 summarizes the paper and outlooks future directions.

2 Reaction networks

A reaction network $\mathbf{\Gamma} = (S, R)$ consists of a set S of species that interact via a set R of reactions. A reaction i is an ordered association between *reactant* and *product* species:

$$i: \quad s^i_1 X_1 + ... + s^i_{|S|} X_{|S|} \underset{i}{\longrightarrow} \tilde{s}^i_1 X_1 + ... + \tilde{s}^i_{|S|} X_{|S|}. \tag{2.1}$$

Here, $X_1, ..., X_{|S|}$ indicate $|S|$ distinct species and the nonnegative integer coefficients $s^i_m, \tilde{s}^i_m$ are the so-called *stoichiometric coefficients*. A reaction without reactants and

single product X_m is called *an inflow reaction* to X_m. Respectively, a reaction without products and a single reactant X_m is called *an outflow reaction* from X_m. A network is called *closed* if there are no inflow and outflow reactions. At the other extreme, a network whose reaction set R contains inflow reactions to all its species and outflow reactions from all of its species is called *fully open*. Finally, a reaction for which a species X_m is both a reactant and a product is called *explicitly autocatalytic*.

Consider the $|S|$-vector $x > 0$ of the positive species concentrations in a well-mixed reactor. The dynamics $x(t)$ follows the system of Ordinary Differential Equations:

$$\dot{x} = f(x) := N\mathbf{r}(x), \tag{2.2}$$

where N is the $|S| \times |R|$ *stoichiometric matrix*, defined by

$$N_{mi} := \tilde{s}^i_m - s^i_m, \tag{2.3}$$

and $\mathbf{r}(x)$ is the $|R|$-vector of *reaction rates* (kinetics). Equilibria vector $\bar{x}$ with

$$0 = f(\bar{x})$$

are called *steady-states* of $\mathbf{\Gamma}$. As our criteria are based on the bifurcation of steady-states, we consider throughout only networks $\mathbf{\Gamma}$ that admit at least one positive steady-state. This condition just requires the existence of at least one positive vector $\mathbf{v} \in \mathbb{R}^{|R|}_{>0}$, called here *steady-state flux vector* such that

$$N\mathbf{v} = 0, \tag{2.4}$$

i.e., $\mathbf{v}$ is a positive right kernel vector of the stoichiometric matrix. Networks, whose stoichiometric matrix satisfies (2.4) for a positive vector $\mathbf{v} > 0$, have been called *consistent* [3] or also *dynamically nontrivial* [4].

It is reasonable to assume that each reaction rate r_i is a positive monotone function of the concentrations $x_m > 0$ of those species X_m, which are reactants to i, i.e., for $s^i_m > 0$. This class of nonlinearities has been named *monotone chemical functions* [37] or *weakly monotone kinetics* [33] in the literature. A most prominent example is mass action kinetics [39], which considers any reaction rate r_i as a monomial function of the concentrations:

$$r_i(x) := a_i \prod_{m=1}^{|S|} x_m^{s^i_m}. \tag{2.5}$$

The coefficient $a_i > 0$ is a positive parameter, and the exponents s^i_m are the stoichiometric coefficients of species X_m as a reactant of the reaction i in (2.1). Note that the rate of an inflow reaction is then constant, i.e., $r_i(x) = a_i$. More general polynomial functions such as Generalized Mass Action kinetics [32] or rational functions such as Michaelis-Menten [30] and Hill [23] kinetics also fall within the class of monotone chemical functions.

3 Linear algebra: D-stability and P^- matrices

This section reviews the standard concepts of D-stability and P^- matrices. We refer to [19, 26] for a more extended overview. We start with the definition of *inertia* of a matrix.

Definition 3.1 (Inertia of a matrix)**.** The inertia of an $n \times n$ square matrix A is a nonnegative triple

$$\text{inertia}(A) := (\sigma^-_A, \sigma^+_A, \sigma^0_A),$$

where σ_A^-,σ_A^+ and σ_A^0 are the number of eigenvalues of A with negative-real part, positive-real part, and zero-real-part eigenvalues, respectively. The eigenvalues are counted with their multiplicities so that $\sigma_A^+ + \sigma_A^- + \sigma_A^0 = n$.

Definition 3.2 ((in)stability, D-(in)stability)**.** A $n \times n$ matrix A is *stable* if all of its eigenvalues have negative real part, i.e, its inertia is $(n, 0, 0)$. Conversely, A is *unstable* if at least one eigenvalue has a positive real part. Moreover, a matrix A is *D-stable* if AD is stable for any choice of a positive diagonal matrix D. Conversely, A is *D-unstable* if there exists a diagonal matrix D such that AD is unstable.

By choosing $D = \mathrm{Id}$, it is clear that D-stability implies stability, and that instability implies D-instability. In addition, the D-stability of A necessarily requires the D-stability of all its principal submatrices, as the next Lemma shows. We fix the notation: let κ be any choice of $k \leq n$ indices in $\{1, ..., n\}$. $A[\kappa]$ denotes the principal submatrix of A with column/row index κ.

Lemma 3.3. *If any of the principal submatrices of A is D-unstable, then A is D-unstable.*

Proof. By assumption, there exists a choice of κ such that $A[\kappa]$ is D-unstable. Without loss of generality, we can assume $\kappa = \{1, ..., k\}$. Choose now $D[\kappa] = \mathrm{diag}(d_1, ..., d_k)$ such that $A[\kappa]D[\kappa]$ is unstable, and rescale all other entries of D, d_i with $i > k$, as $d_i = \varepsilon$. Consider now the family of matrices $AD(\varepsilon)$. Clearly, for $\varepsilon = 0$, the spectrum of $AD(0)$ corresponds to the spectrum of $A[\kappa]D[\kappa]$ plus $n - k$ eigenvalues zero. In particular $AD(0)$ is unstable by construction. The continuity of the eigenvalues with respect to the entries guarantees that such instability persists for ε small enough, which yields the instability of AD, for a choice of positive D, and thus the D-instability of A. □

Unfortunately, proving that a square matrix A is D-stable is computationally nontrivial. It may precisely reduce to exclude purely-imaginary eigenvalues of AD for any choice of D, via the Hurwitz computation. To avoid being a dog chasing its tail, we have to rely on sufficient conditions on A that guarantee the existence of positive diagonal matrices D_1 and D_2 such that

$$\mathrm{inertia}(AD_1) \neq \mathrm{inertia}(AD_2), \tag{3.1}$$

which sufficiently guarantees that A is not D-stable. The key here is the concept of P^- matrices.

Definition 3.4 (P^- and P_0^- matrices)**.** A $n \times n$ matrix A is called a P^- matrix if all of its k-principal minors have sign $(-1)^k$. A $n \times n$ matrix A is called a P_0^- matrix if all of its *nonzero* k-principal minors $A[\kappa]$ have sign $(-1)^k$.

The set of P_0^- matrices is just the closure of the open set of P^- matrices. We recall two standard results that relate D-stability and P_0^- matrices. The first proposition follows directly from Lemma 3.3.

Proposition 3.5. *Let A be a $n \times n$ matrix that is not a P_0^- matrix. Then there exists a positive diagonal D such that AD is unstable.*

Proof. If A is not a P_0^- matrix, then A possesses a principal submatrix $A[\kappa]$ such that

$$\det A[\kappa] = (-1)^{k-1}.$$

In particular $A[\kappa]$ possesses an odd number of real positive eigenvalues, and it is thus unstable. Recalling that instability implies D-instability, Lemma 3.3 yields the statement. □

The second is a celebrated result by Michael E. Fisher and A. T. Fuller in 1958 [17], elaborated also by Franklin M. Fisher in [16]. For the full generality of this theorem, a further definition is required.

Definition 3.6 (Fisher and Fuller P_{FF}^- matrices)**.** A P_0^- matrix A is called a P_{FF}^- matrix, or *Fisher&Fuller matrix* if there is at least a sequence of nested nonsingular principal matrices

$$(A[\kappa_1], A[\kappa_2], ..., A[\kappa_{n-1}], A),$$

of every order $|\kappa_i| = i = (1, ..., n)$, such that $A[\kappa_{i-1}]$ is a principal submatrix of $A[\kappa_i]$.

Clearly, the following set inclusion holds:

$$P^- \text{ matrices} \quad \subset \quad P_{FF}^- \text{ matrices} \quad \subset \quad P_0^- \text{ matrices}.$$

A warning: Fisher [16] uses the word *Hichsian* to refer to P_{FF}^- matrices. I have found that such a name can be also found in the literature [19] to refer to P^- matrices.

Theorem 3.7 (Theorem 1' in [16])**.** *Let A be a P_{FF}^- matrix. Then there exists a positive diagonal D such that AD has all eigenvalues that are real, negative, and simple.*

We can derive easy conditions for (3.1) based on Proposition 3.5 and Theorem 3.7. We do this explicitly in the next two corollaries.

Corollary 3.8 (of Proposition 3.5)**.** *Consider a $n \times n$ matrix A that is not a P_0^- matrix. Further, assume that A has no eigenvalue with a positive-real part. Then there exist two diagonal matrices D_1 and D_2 such that (3.1) holds.*

Corollary 3.9 (of Theorem 3.7)**.** *Consider an unstable P^- matrix A. Then there exist two diagonal matrices D_1 and D_2 such that (3.1) holds.*

Proof of both corollaries. Just consider $D_1 = \mathrm{Id}$ and let D_2 be the matrix satisfying the statement of Proposition 3.5, or respectively Theorem 3.7. In the case of Corollary 3.8, $AD_1 = A\,\mathrm{Id} = A$ has no eigenvalues with positive real part while AD_2 has an eigenvalues with positive real part via Proposition 3.5. Complementarily, in the case of Corollary 3.9 $AD_1 = A\,\mathrm{Id} = A$ has eigenvalues with positive real part while AD_2 has only eigenvalues with negative real part via Theorem 3.7. □

Purely imaginary eigenvalues of AD The condition (3.1) implies the existence of a positive matrix D^* such that AD^* has purely imaginary eigenvalues. We formally argue as follows. Let $\mathbf{d}_1$ and $\mathbf{d}_2$ indicate the vectors in $\mathbb{R}^n_{>0}$ such that $D_1 = \mathrm{diag}(\mathbf{d}_1)$ and $D_2 = \mathrm{diag}(\mathbf{d}_2)$. Consider any regular curve

$$\gamma(t) : [0, 1] \mapsto \mathbb{R}^n,$$

such that $\gamma(0) = \mathbf{d}_1$ and $\gamma(1) = \mathbf{d}_2$, and the associated *eigenvalue curve*

$$\Lambda(t) : [0, 1] \mapsto \mathbb{R}^n \quad \text{defined by} \quad \Lambda(t) = (\lambda_1(t), ..., \lambda_n(t)) = \text{eigenvalues}(A\,\mathrm{diag}(\gamma(t)).$$

The condition (3.1) implies a change in the sign of the real part of at least one of the eigenvalues along the path γ: intermediate value theorem guarantees then the existence of at least one t^* such that $\Lambda(t^*)$ identifies at least one eigenvalue with zero-real part. Note that

$$\mathrm{rank}\, A\,\mathrm{diag}(\gamma(t)) = \mathrm{rank}\, A$$

prevents real zero eigenvalues, and thus t^* identifies at least one pair of purely imaginary eigenvalues. We conclude this section with an open linear algebra question:

$$\begin{gathered}\mathbf{Q}^*: \text{Does it always exist a choice of path } \gamma \text{ such that} \\ \text{(i) } A\,\mathrm{diag}(\gamma(t^*)) \text{ has a } \textit{simple} \text{ pair of purely imaginary eigenvalues } \lambda_{i,j}, \\ \text{(ii) } \Re(\lambda_{i,j}(t))' \neq 0?\end{gathered}$$

In the next section, we show how a Jacobian matrix evaluated at steady-states of mass action systems can be expressed precisely as a product AD. A positive answer to $\mathbf{Q}^*$ would guarantee the applicability of the standard local Hopf theorem [20] (or Theorem 8.1 in Section 8) to prove the existence of periodic orbits. As we do not know the answer to $\mathbf{Q}^*$ yet, we will argue instead via *global Hopf bifurcation*. Before doing so, the next section recalls the standard method *Stoichiometric Network Analysis* to parametrize the Jacobian at steady-states of mass action systems.

4 Jacobian parametrization

Bruce L. Clarke developed *Stoichiometric Network Analysis* in a series of papers: see [10] and references therein. In the very same paper [10], Clarke also commented on one possibility to circumvent the computation of Hurwitz determinants by studying the D-stability of the Jacobian matrix in convex coordinates. This comment highly resonates with the content of our main Theorem 5.1 below. Clarke further cited a paper of his with some announced related network results, submitted to '*Linear Algebra and Applications*'. To my best effort, however, I have been unable to retrieve such a paper and even to confirm its publication anywhere: it is not listed as a paper in the database of *Linear Algebra and its Applications* nor in Clarke's publication list. It is nevertheless possible that what we state here connects to what Clarke had in mind.

We introduce only the necessary standard technicalities, we again refer to [10] for a thorough overview of the subject. Consider the *steady-state flux cone* $\mathcal{F}$, i.e. the set of steady-state flux vectors:

$$\mathcal{F} \quad := \quad \{\mathbf{v} \in \mathbb{R}^{|R|}_{>0} \quad | \quad N\mathbf{v} = 0\}.$$

In his work, Clarke uses convex coordinates to parametrize $\mathcal{F}$. In particular, via convexity, one can consider the extreme rays of $\mathcal{F}$, $\{E_1, ..., E_p\}$, and express each steady-state flux $\mathbf{v} \in \mathcal{F}$ as a linear combination of such extreme rays:

$$\mathbf{v} = E\mathbf{j},$$

where $\mathbf{j} \in \mathbb{R}^p_{\geq 0}$, and the $|R| \times p$ *extreme-ray matrix* E has columns $\{E_1, ..., E_p\}$. The chosen parametrization of the flux cone is anyway not relevant in the following arguments.

The relevant observation is perhaps only that the derivative of a univariate polynomial $p(x) = ax^n$ can be expressed as

$$p'(x) = n\ ax^{n-1} = n\ ax^{n-1}\ \frac{x}{x} = np(x)\frac{1}{x}. \tag{4.1}$$

This implies that the Jacobian matrix Jac of mass action systems (2.2) at a steady-state $\bar{x}$ reads:

$$Jac = f_x(x)|_{x=\bar{x}} = N\frac{\mathbf{r}(x)}{\partial x}\bigg|_{x=\bar{x}} = N\frac{\mathbf{r}(x)}{\partial x}\bigg|_{x=\bar{x}} \mathrm{diag}\left(\frac{\bar{x}}{\bar{x}}\right) = B(\bar{\mathbf{v}})\,\mathrm{diag}\left(\frac{1}{\bar{x}}\right), \tag{4.2}$$

where $B(\bar{\mathbf{v}})$ only depends on the choice of $\bar{\mathbf{v}}$ and not on the value of $\bar{x}$ anymore. Following Clarke, a straightforward computation generalizes (4.1) and shows that

$$B(\bar{\mathbf{v}}) = N \operatorname{diag}(\bar{\mathbf{v}}) Y^T, \tag{4.3}$$

where the $|S| \times |R|$ *kinetic matrix* Y is defined as

$$Y_{mi} := s_i^m.$$

Y encodes the exponents of the monomials in (2.2) endowed with mass action kinetics.

Note that the values $1/\bar{x}_i$ can be thought of as positive parameters themselves, $h_i := 1/\bar{x}_i$. Thus, the theory of Stoichiometric Network Analysis identifies two sets of parameters: $(\mathbf{h}, \mathbf{j})$. One parameter set, $\mathbf{j}$, determines the steady-state flux vector $\bar{\mathbf{v}}$; the other parameter set, $\mathbf{h}$, determines the steady-state concentrations. The Jacobian matrix can then be expressed as

$$Jac(\mathbf{h}, \mathbf{j}) = N \operatorname{diag} E\mathbf{j} \operatorname{diag}(\mathbf{h})$$

or, having chosen $\bar{\mathbf{v}}$ a priori, simply

$$Jac(\mathbf{h}, \bar{\mathbf{v}}) = B(\bar{\mathbf{v}}) \operatorname{diag}(\mathbf{h}).$$

We are now ready to proceed to our main result.

5 Nonlinear dynamics: one theorem and two criteria

This section glues the results from Sections 3 and 4 to establish periodic orbits for mass action systems without any Hurwitz computation. The central nonlinear argument relies on the theory of global Hopf bifurcation. This body of work appears to be essentially unknown in reaction network literature, which is mostly concerned with local methods based on Hurwitz computation. A relevant exception is the work [15] by Fiedler, which however focuses on the restricted stoichiometric structure of feedback cycles and does not cover mass action kinetics.

A short guide for neophytes: Alexander & Yorke [1] addressed the possibility of global bifurcation of periodic orbits. In particular, they established periodic orbits whenever an *odd* number of pairs of complex conjugate eigenvalues crosses the imaginary axis, at an equilibrium with an invertible Jacobian. A joint effort by Chow, Mallet-Paret, and Yorke [9] extended the very same result to include any net change of stability. The description of the global continua of periodic orbits, so-called *snakes*, have been addressed in [29] for a generic situation. Alligood and Yorke [2] lifted the result in the non-generic case. Via a further analyticity assumption, Fiedler's work [14] on general parabolic systems included Hopf points that are not necessarily isolated: these are the generalities we consider in the following Theorem 5.1. We state our main result.

Theorem 5.1. *Let* $\mathbf{\Gamma}$ *be a network with stoichiometric matrix* N *and kinetic matrix* Y*. Consider a steady-state flux vector* $\bar{\mathbf{v}} > 0$ *such that for*

$$A := B(\bar{\mathbf{v}}) = N \operatorname{diag}(\bar{\mathbf{v}}) Y^T,$$

$\operatorname{rank} A = \operatorname{rank} N$*. Assume moreover that there exist two positive diagonal matrices* D_1 *and* D_2 *such that* (3.1) *holds, i.e.,*

$$\operatorname{inertia} AD_1 \neq \operatorname{inertia} AD_2.$$

Then there exists a choice of reaction rates such that the associated mass action system (2.2) *admits nonstationary periodic solutions.*

Proof. Recall the parameters $h_i = 1/\bar{x}_1$. We have

$$\operatorname{rank}(Jac(\mathbf{h}, \bar{\mathbf{v}})) = \operatorname{rank}(B(\bar{\mathbf{v}}) \operatorname{diag}(\mathbf{h})) = \operatorname{rank}(B(\bar{\mathbf{v}})) = \operatorname{rank} N,$$

that is, the number of zero-eigenvalues is constant for any choice of $\mathbf{h}$ and corresponds only to the trivial zero-eigenvalues coming from linear conserved quantities.

Consider now the two choices of $\mathbf{h}_i$, $i = 1, 2$ such that

$$\operatorname{diag}(\mathbf{h}_1) = D_1 \qquad \text{and} \qquad \operatorname{diag}(\mathbf{h}_2) = D_2.$$

In analogy to what we discussed in Section 3, we may consider any *analytic* curve $\gamma(\beta)$ in $\mathbb{R}^{|S|}_{>0}$, $\beta \in [0, 1]$ with $\gamma(0) = \mathbf{h}_1$, $\gamma(1) = \mathbf{h}_2$. That is, γ connects $\mathbf{h}_1$ to $\mathbf{h}_2$ and thus parametrizes a family of steady-states of (2.2) with a constant number of zero-eigenvalues and a change of inertia from $\beta = 0$ to $\beta = 1$. Due to the analyticity of mass action systems and the curve $\gamma(\mathbf{h})$, we can apply [14, Theorem 4.7] and global Hopf bifurcation yields nonstationary periodic orbits. □

Based on the abstract Theorem 5.1, we simply use Corollaries 3.8 and 3.9 to state computationally manageable sufficient criteria for periodic orbits in mass action systems. Criterion I builds on Corollary 3.8, and Criterion II on Corollary 3.9.

Corollary 5.2. *Assume there exists a steady-state flux vector $\bar{\mathbf{v}}$ such that one of the two following conditions holds.*

1. ***Criterion I:*** *$B(\bar{\mathbf{v}})$ is stable and not a P_0^- matrix;*
2. ***Criterion II:*** *$B(\bar{\mathbf{v}})$ is an unstable P_{FF}^- matrix.*

then there exists a choice of reaction rates such that the associated mass action system (2.2) admits nonstationary periodic solutions.

Remark 5.3 (Conserved quantities). The formulation of Theorem 5.1 applies also to systems with conserved quantities. For simplicity of presentation, however, the two sufficient criteria verbatim apply only to systems without conserved quantities. In fact, the presence of conserved quantities prevents $B(\bar{\mathbf{v}})$ from having full-rank, and thus in our definitions $B(\bar{\mathbf{v}})$ cannot be stable nor a P_{FF}^- matrix. It is clear that this is no issue, as the criteria can be applied identically for the *reduced Jacobian* in each stoichiometric compatibility class, after a standard reduction procedure [7, 12].

Remark 5.4. P_0^- matrices as Jacobians have been addressed in reaction networks in [6, 37]. In the first contribution [6], it is shown that a P_0^- Jacobian implies the *injective property* and thus excludes multistationarity, i.e., the coexistence of multiple steady-states in the same stoichiometric compatibility class. Criterion II above, in particular, describes a mechanism for periodic oscillations in monostationary networks. See [35] for a discussion with examples of the relationship between periodic oscillations and multistationarity in chemical reaction networks.

6 Interpretation: Positive and negative feedbacks

In biochemical systems, periodic oscillations have long been associated with the presence of *positive and negative feedbacks*, see [36] for a review with historical chemical references. More abstractly, Thomas conjectured in 1981 that the presence of a *'negative loop'* in the system is *necessary* for stable periodic behavior. In contrast, Ivanova [25] generalized

positive-feedback cycles into *'critical fragments'* of the network and conjectured a complementary condition for oscillations: the existence of a critical fragment that does not involve all species in the network. See Mincheva and Roussel [31] for a review of Ivanova's work in English. In the same paper, the authors however note that *oscillations can occur because of factors with different combinations of positive and negative cycles*. Gatermann et al. [18] also acknowledge that oscillations can arise both from positive and negative feedback. In their own words, they *'distinguish the type of instability according to the sign of the underlying feedback loop. If the loop is positive the system is called autocatalytic. [...] An unstable chemical reaction with only a negative loop with at least three elements is called a nonautocatalytic oscillator.'*

In this section, we interpret our results from such historical perspective. We argue that the first of our criteria can be interpreted as the presence of unstable positive feedback within a stable subnetwork, while the second as the presence of unstable negative feedback. To keep this presentation simple, we proceed informally. We refer the interested reader to [37, 38], where the following ideas have been discussed in full generality.

Again, let us start with pure linear algebra. We call *unstable core* an invertible $n \times n$ matrix with a negative diagonal, which is unstable and such that none of its principal submatrices is unstable. The sign of the determinant distinguishes *unstable-positive feedback*, with sign $(-1)^{n-1}$, and *unstable-negative feedback* with sign $(-1)^n$. As a direct consequence, unstable-positive feedbacks have one single real positive eigenvalue, while unstable-negative feedbacks have no real positive eigenvalues [38, Lemma 6.3]. Such definition generalizes positive and negative feedback cycles as, e.g.,

$$F^+ := \begin{pmatrix} -1 & 0 & 1 \\ 1 & -1 & 0 \\ 0 & 1 & -1 \end{pmatrix} \quad \text{and} \quad F^- := \begin{pmatrix} -1 & 0 & -1 \\ 1 & -1 & 0 \\ 0 & 1 & -1 \end{pmatrix},$$

where 'positive' vs 'negative' typically refers to the product of the off-diagonal entries.

The instability of a positive feedback cycle can be always achieved by choosing the product of the off-diagonal entries larger than the product of the diagonal entries e.g.

$$F_u^+ := \begin{pmatrix} -1 & 0 & 2 \\ 1 & -1 & 0 \\ 0 & 1 & -1 \end{pmatrix}, \quad \text{with eigenvalues } (-1.63 \pm 1.09i, 0.26).$$

The instability of a positive feedback cycle, in particular, does not depend on its length, i.e. on the size of the matrix. Consider now a stable 4×4 matrix with a negative diagonal, such that F_u^+ is one of its principal matrices, e.g.

$$A_s := \begin{pmatrix} -1 & 0 & 2 & 0 \\ 1 & -1 & 0 & 2 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & -1 & -1 \end{pmatrix}, \quad \text{with eigenvalues } (-1, -1, -1, -1). \tag{6.1}$$

A_s is indeed stable and can be seen as an overlap of the positive feedback cycle F_u^+ and the negative feedback cycle in $A[(2, 3, 4)]$. By construction, it is not a P_0^- matrix because one of its principal submatrices is an unstable-positive feedback. A stable matrix that is not a P_0^- matrix is precisely what our Criterion I requires $B(\bar{\mathbf{v}})$ to be. We underline the assonance with Ivanova's condition: if A is not a P_0^- matrix but is stable, then the unstable principal submatrix $A[\kappa]$ is necessarily a strict submatrix of A, i.e., $k < n$.

In striking contrast, instability for negative feedback cycles does depend on the length of the cycle. For instance, a negative feedback cycle with diagonal entries $F^-_{ii} = -1$ and off-diagonal entries $F^-_{i(i-1)} = 1$ for $i = 2, ..., n$ and $F^-_{1n} = -2$ becomes unstable only for $n \geq 8$:

$$F^-_u := \begin{pmatrix} -1 & 0 & 0 & 0 & 0 & 0 & 0 & -2 \\ 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 \end{pmatrix}, \tag{6.2}$$

with eigenvalues approximately $(-2.01 \pm 0.42i, -1.42 \pm 1.01i, -0.58 \pm 1.01i, 0, 0075 \pm 0.41i)$. We refer to such a heuristic observation as

Negative-feedback instability requires length!

Note also that F^-_u is indeed an unstable P^- matrix as Criterion II requires $B(\bar{\mathbf{v}})$ to be. We refer to [28, 15] for an extended analysis of the spectrum of feedback cycles.

We now return to reaction networks and interpret such matrices as stoichiometric matrices of a (sub)network. The negative-diagonal condition simply reflects the fact that the species X_i corresponding to the i^{th} row is a reactant to the reaction $J(i)$ corresponding to the i^{th} column. For a general algebraic treatment based on injective 'Child-Selection maps' J, we refer again to [37, 38]. Negative-diagonal stoichiometric matrices have been called *Child-Selection (CS-) matrices*. In its full generality, omitted here, such an approach does not depend on the chosen labeling of the network and naturally generalizes to CS-matrices that do not necessarily have a negative diagonal, depending on the presence of explicitly autocatalytic reactions. Moreover, *stoichiometric autocatalysis*, as defined by Blokhuis et al. [8], has been proven equivalent to the presence of an unstable-positive feedback that is a Metzler matrix, i.e., has nonnegative off-diagonal entries [38, Thm. 7.3]. With a degree of consistency to Gatermann et al. [18], autocatalytic instabilities are then only due to the presence of a special type of unstable-positive feedback, while unstable-negative feedbacks always identify non-autocatalytic instabilities.

We look at the stoichiometry of a network with these lenses: we aim to derive conclusions about the dynamical stability of a steady state. We put mass action systems aside for a moment, and we consider at first a more general Michaelis–Menten nonlinearity:

$$r_i = a_i \prod_{m=1}^{|S|} \left(\frac{x_m}{1 + b^m_i x_m} \right)^{s^i_m}, \quad a_i > 0, b^m_i \geq 0. \tag{6.3}$$

Mass action is recovered as the limit case when $b^m_i = 0$ for any m and i. The advantage of including also the b^m_i parameters is that the mere presence of an unstable core implies the existence of a choice of parameters a_i, b^m_i such that the system admits an unstable steady-state [38, Corollary 5.1]. Moreover, the presence of stoichiometry like A_s, (6.1), (which we refer to as *unstable-positive feedback within a stable subnetwork*) and F^-_u, (6.2), (*unstable-negative feedback*) is already a sufficient condition for the presence of a steady-state with purely imaginary eigenvalues of the Jacobian [37, Corollary 5.17], pointing at periodic oscillations. The mathematical argument is analogous to Criteria I and II, respectively. The advantage of considering Michaelis–Menten over mass action is precisely

that the sufficient conditions can be expressed at the level of naked stoichiometry, without taking into consideration the steady-state constraints imposed by the flux vector $\bar{\mathbf{v}}$.

Such arguments identically apply to a general class of monotone chemical functions named *parameter-rich* [38]. Parameter-rich kinetics include e.g. Michaelis–Menten, Hill, and Generalized mass action kinetics. Unfortunately, mass action kinetics is not parameter-rich: the restriction to mass action, $b_i^m \equiv 0$ for any m and i, is then more challenging. However, it has been proved [6, 37] that the absence of unstable-positive feedbacks implies that the Jacobian is a P_0^- matrix. Thus, Criterion I necessarily requires an unstable-positive feedback. Furthermore, [38] also conjectured that the absence of D-unstable CS-matrices characterizes networks that only admit a unique and locally stable steady-state for any parameter choice. We may then still interpret Criteria I and II in terms of positive/negative feedback, but the presence of stoichiometries like A_s and F_u^- is no longer a sufficient condition for the assumptions of Criteria I and II to hold.

At present, the above observations offer thus only guidance on how to find periodic oscillations in mass action systems. In the next section, based on the above intuitions, we present three examples that admit periodic orbits.

7 Examples

The first example builds on an unstable-positive feedback within a stable subnetwork, i.e. stoichiometry of the type of A_s (6.1), and applies Criterion I. The second and third examples are centered on unstable-negative feedbacks, i.e. stoichiometry of the type of F_u^- (6.2), and apply Criterion II.

7.1 Example I: unstable-positive feedback within a stable subnetwork

Consider the following network with 5 species and 5 reactions:

$$\begin{cases} A+B & \underset{1}{\to} & C \\ B+C & \underset{2}{\to} & E \\ C & \underset{3}{\to} & A+D \\ D & \underset{4}{\to} & 2B \\ E & \underset{5}{\to} & C \end{cases} \tag{7.1}$$

The stoichiometric matrix and the kinetic matrix read:

$$N = \begin{pmatrix} -1 & 0 & 1 & 0 & 0 \\ -1 & -1 & 0 & 2 & 0 \\ 1 & -1 & -1 & 0 & 1 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 1 & 0 & 0 & -1 \end{pmatrix} \quad Y = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 \\ 0 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix} \tag{7.2}$$

Note the presence of an unstable-positive feedback

$$\begin{pmatrix} -1 & 0 & 1 \\ -1 & -1 & 0 \\ 1 & -1 & -1 \end{pmatrix}, \quad \text{with eigenvalues approx } (0.32, -1.66 \pm 0.56i), \tag{7.3}$$

as a principal submatrix of a stable negative-diagonal matrix:

$$\begin{pmatrix} -1 & 0 & 1 & 0 \\ -1 & -1 & 0 & 2 \\ 1 & -1 & -1 & 0 \\ 0 & 0 & 1 & -1 \end{pmatrix}, \quad \text{with eigenvalues approx } (-0.34 \pm 0.56i, -1, -2.32).$$

The unique steady-state flux vector is

$$\bar{\mathbf{v}} = (c, c, c, c, c), \text{ for } c \in \mathbb{R}_{>0}.$$

Clearly, the same vector identifies also a right-kernel vector and thus there is a conserved quantity Ω, the total concentration:

$$\Omega := x_A + x_B + x_C + x_D + x_E.$$

The network is indeed closed, i.e., it does not possess inflows or outflows. The associated mass action system is:

$$\begin{cases} \dot{x}_A = -k_1 x_A x_B + k_3 x_C \\ \dot{x}_B = -k_1 x_A x_B - k_2 x_B x_C + 2k_4 x_D \\ \dot{x}_C = k_1 x_A x_B - k_2 x_B x_C - k_3 x_C + k_5 x_E \\ \dot{x}_D = k_3 x_C - k_4 x_D \\ \dot{x}_E = k_2 x_B x_C - k_5 x_E \end{cases} \tag{7.4}$$

Without loss of generality, we fix $c = 1$ and thus $\bar{\mathbf{v}} = (1, 1, 1, 1, 1)$ and $\operatorname{diag}(\bar{\mathbf{v}}) = \mathrm{Id}$. We can then easily compute $B(\bar{\mathbf{v}})$:

$$\begin{aligned} B(\bar{\mathbf{v}}) = N \,\mathrm{Id}\, Y^T &= \begin{pmatrix} -1 & 0 & 1 & 0 & 0 \\ -1 & -1 & 0 & 2 & 0 \\ 1 & -1 & -1 & 0 & 1 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 1 & 0 & 0 & -1 \end{pmatrix} \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 \\ 0 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix} \\ &= \begin{pmatrix} -1 & -1 & 1 & 0 & 0 \\ -1 & -2 & -1 & 2 & 0 \\ 1 & 0 & -2 & 0 & 1 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 1 & 1 & 0 & -1 \end{pmatrix} \end{aligned} \tag{7.5}$$

The eigenvalues of $B(\bar{\mathbf{v}})$ are

$$(\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5) \approx (-3, -2.6, -1, -0.38, 0); \tag{7.6}$$

note the trivial eigenvalue zero due to the presence of one conserved quantity. On the other hand, corresponding to the unstable positive-feedback (7.3), there is still a 3-principal minor with determinant of sign $(-1)^{3-1} = 1$,

$$\det \begin{pmatrix} -1 & -1 & 1 \\ -1 & -2 & -1 \\ 1 & 0 & -2 \end{pmatrix} = 1, \tag{7.7}$$

and thus $B(\bar{\mathbf{v}})$ is not a P_0^- matrix. Our Criterion I implies nonstationary periodic orbits. Note that the equilibrium $\bar{x} = (1, 1, 1, 1, 1)$ is stable in its stoichiometric compatibility class, because of (7.6). Intuitively, to make the instability of (7.7) dominant, and thus achieve a Hopf bifurcation, we need to choose $h_4 = 1/\bar{x}_D$ and $h_5 = 1/\bar{x}_E$ small enough, i.e., $\bar{x}_D$ and $\bar{x}_E$ big enough. For example, the equilibrium $\bar{x} = (1, 1, 1, 10, 10)$ is unstable and encircled by a stable limit cycle. We confirm this via numerical simulations, see Figure 1.

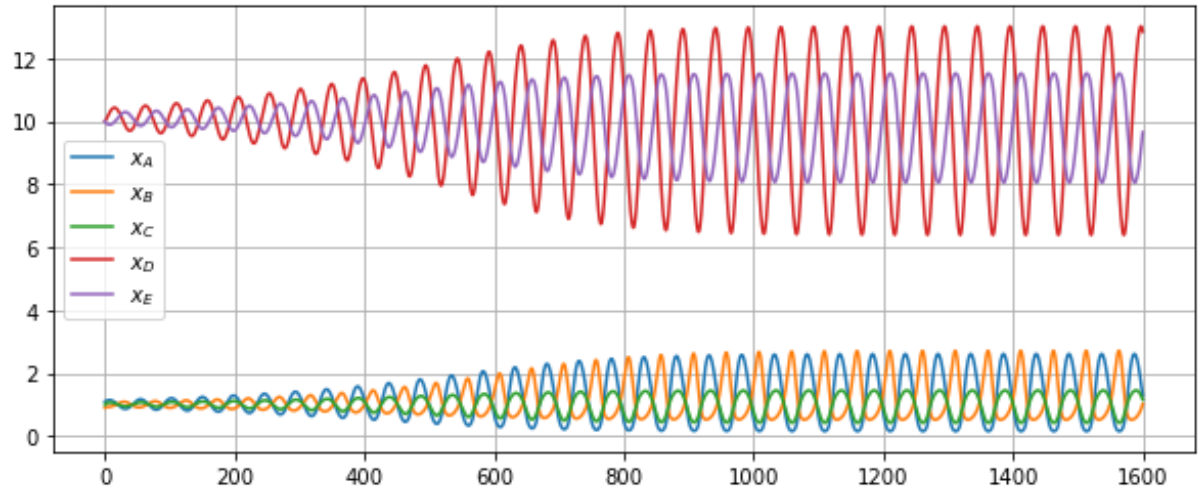

Figure 1: Numerical simulations for system (7.4). The steady-state flux vector has been chosen as $\bar{\mathbf{v}} = (1, 1, 1, 1, 1)$. The values of the (unique) unstable steady-states are $\bar{x} = (1, 1, 1, 10, 10)$, which imply a chice of rates $(k_1, k_2, k_3, k_4, k_5) = (1, 1, 1, 0.1, 0.1)$. Initial conditions have been chosen $x(0) = (1.1, 0.9, 1, 10, 10)$. The plot shows convergence to a stable limit cycle.

7.2 Example II and Example III: unstable-negative feedback

Example II For the second case study, we elaborate on a family of examples presented by Claude Hyver in [24]. The examples comprise $n + 2$ species and $n + 2$ reactions:

$$\begin{cases} \underset{F}{\rightarrow} \quad A_1 \quad \underset{1}{\rightarrow} \quad A_2 \quad \underset{2}{\rightarrow} \quad \dots \quad \underset{n-1}{\rightarrow} \quad A_n \quad \underset{n}{\rightarrow} \quad B + C \\ \qquad\qquad A_1 + B \quad \underset{n+1}{\rightarrow} \quad \dots \\ \qquad\qquad A_1 + C \quad \underset{n+2}{\rightarrow} \quad \dots \end{cases} \tag{7.8}$$

The actual example discussed in [24] included a few more species, probably to enhance its chemical realism. We focus on the above simplification since it already contains all the mathematical features of our interest. The associated mass action system is:

$$\begin{cases} \dot{x}_{A_1} = F - k_1 x_{A_1} - k_{n+1} x_{A_1} x_B - k_{n+2} x_{A_1} x_C \\ \dot{x}_{A_2} = k_1 x_{A_1} - k_2 x_{A_2} \\ \vdots \\ \dot{x}_{A_n} = k_{n-1} x_{A_{n-1}} - k_n x_{A_n} \\ \dot{x}_B = k_n x_{A_n} - k_{n+1} x_{A_1} x_B \\ \dot{x}_C = k_n x_{A_n} - k_{n+2} x_{A_1} x_C \end{cases} \tag{7.9}$$

The stoichiometric matrix and the kinetic matrix are of the form:

$$N = \begin{pmatrix} 1 & -1 & 0 & ... & 0 & -1 & -1 \\ 0 & 1 & -1 & ... & 0 & 0 & 0 \\ 0 & 0 & 1 & ... & 0 & 0 & 0 \\ & & & \vdots & & & \\ 0 & 0 & 0 & ... & -1 & 0 & 0 \\ 0 & 0 & 0 & ... & 1 & -1 & 0 \\ 0 & 0 & 0 & ... & 1 & 0 & -1 \end{pmatrix} \quad \text{and} \quad Y = \begin{pmatrix} 0 & 1 & 0 & ... & 0 & 1 & 1 \\ 0 & 0 & 1 & ... & 0 & 0 & 0 \\ 0 & 0 & 0 & ... & 0 & 0 & 0 \\ & & & \vdots & & & \\ 0 & 0 & 0 & ... & 1 & 0 & 0 \\ 0 & 0 & 0 & ... & 0 & 1 & 0 \\ 0 & 0 & 0 & ... & 0 & 0 & 1 \end{pmatrix} \tag{7.10}$$

Without the first inflow column, the stoichiometric matrix is a P^- matrix for any n, and an unstable-negative feedback for $n \geq 7$ large enough. Note that it is just a variant of the negative feedback cycles F_u^-, (6.2), where the principal submatrix

$$\begin{pmatrix} -1 & -2 \\ 1 & -1 \end{pmatrix},$$

in (6.2) has been replaced by the principal submatrix:

$$\begin{pmatrix} -1 & -1 & -1 \\ 1 & -1 & 0 \\ 1 & 0 & -1 \end{pmatrix}.$$

The unique steady-state flux vector is

$$\bar{\mathbf{v}} = (3c, c, c, ..., c, c, c).$$

Choosing $c = 1$ without loss of generality, we can compute $B(\bar{\mathbf{v}})$:

$$\begin{aligned} B(\bar{\mathbf{v}}) &= N \operatorname{diag}(3, 1, 1, ..., 1, 1, 1) Y^T \\ &= \begin{pmatrix} -3 & 0 & ... & 0 & -1 & -1 \\ 1 & -1 & ... & 0 & 0 & 0 \\ 0 & 1 & ... & 0 & 0 & 0 \\ & & \vdots & & & \\ 0 & 0 & ... & -1 & 0 & 0 \\ -1 & 0 & ... & 1 & -1 & 0 \\ -1 & 0 & ... & 1 & 0 & -1 \end{pmatrix}. \end{aligned} \tag{7.11}$$

$B(\bar{\mathbf{v}})$ is a P^- matrix for any n. To confirm this, we argue by induction on $n \geq 2$, as it is enough to note that an increase in n only adds a column and a row

$$\begin{pmatrix} & & 0 & & & & \\ & & \vdots & & & & \\ 0 & ... & 0 & -1 & 0 & ... & 0 \\ & & & 1 & & & \\ & & & \vdots & & & \\ & & & 0 & & & \end{pmatrix},$$

with negative entry on the diagonal, and one single nonzero element in the lower triangular part. Thus, it boils down only to check whether

$$\begin{pmatrix} -3 & 0 & -1 & -1 \\ 1 & -1 & 0 & 0 \\ -1 & 1 & -1 & 0 \\ -1 & 1 & 0 & -1 \end{pmatrix} \tag{7.12}$$

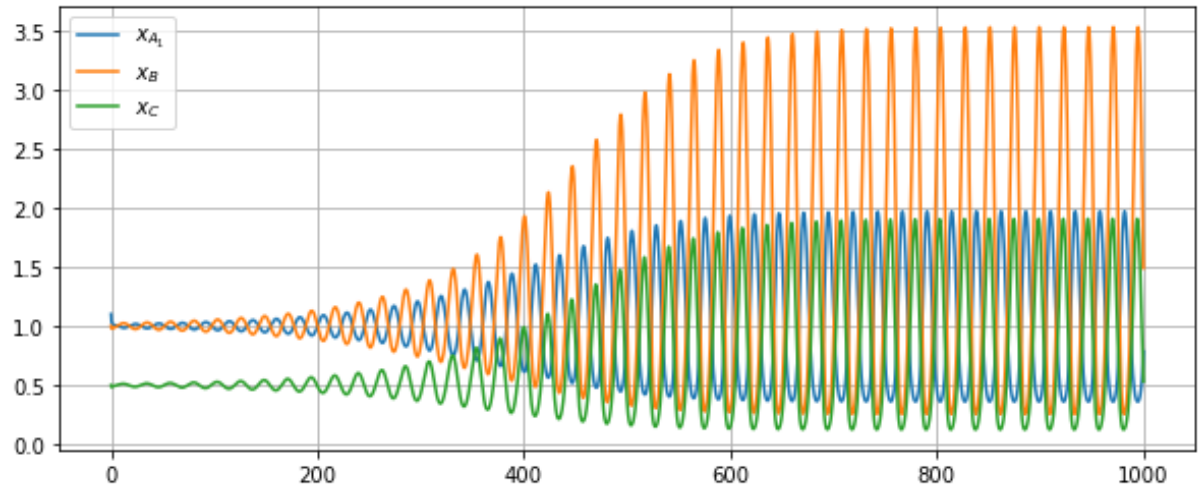

Figure 2: Numerical simulations for system (7.9),with $n = 10$. The steady-state flux vector has been chosen as $\bar{\mathbf{v}} = (3, 1, 1, ..., 1, 1)$. The values of the (unique) unstable steady-states are $\bar{x} = (1, 1, ..., 1, 0.5)$, which imply a choice of rates $(F, k_1, ..., k_{12}) = (3, 1, 1, ..., 1, 2)$. We have opted to choose $\bar{x}_B \neq \bar{x}_C$ because the two trajectories would fully overlap otherwise. Initial conditions have been chosen $x(0) = (1.1, 1, 1, ..., 1, 0.5)$. The plot shows convergence to a stable limit cycle. For graphical simplicity, we only include trajectories for A_1, B, C.

is a P^- matrix, which can be done by explicit computation. The case $n = 1$ must be checked independently, as $B(\bar{\mathbf{v}})$ takes the different form:

$$B(\bar{\mathbf{v}}) = \begin{pmatrix} -3 & -1 & -1 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{pmatrix},$$

which is a P^- matrix, since it is upper triangular with negative diagonal.

On the other hand, for n large enough, the stability of $B(\bar{\mathbf{v}})$ is lost, and our Criterion II implies the existence of periodic orbits. We do not analytically prove here that $B(\bar{\mathbf{v}})$ is definitely unstable for n large enough. We just check explicitly that for $n < 10$ $B(\bar{\mathbf{v}})$ is stable, while for $n = 10, 11, 12, 13$ a pair of complex conjugate eigenvalues with positive real part appears:

$$\begin{cases} n = 1, ..., 9: & \text{all eigenvalues with negative real part;} \\ n = 10: & \text{one pair of eigenvalues with positive real part:} \quad 0.0049 \pm 0.2631i; \\ n = 11: & \text{one pair of eigenvalues with positive real part:} \quad 0.0091 \pm 0.2424i; \\ n = 12: & \text{one pair of eigenvalues with positive real part:} \quad 0.0119 \pm 0.2248i; \\ n = 13: & \text{one pair of eigenvalues with positive real part:} \quad 0.0139 \pm 0.2096i. \end{cases}$$

We note a monotonicity in the values of the unstable eigenvalues. This family of networks confirms that the length of the structure helps periodic oscillations to appear. In Figure 2, numerical simulations for $n = 10$, and initial conditions nearby the (unstable) equilibrium $\bar{x} = (1, 1, 1, ..., 1, 0.5)$, shows convergence to a stable limit cycle.

Example III For the third case study, we generalize Example C from [38] into a family of networks with $n + 1$ species, $A_1, ..., A_n, B$, $n > 1$, and $2n + 1$ reactions:

$$\begin{cases} \underset{F_k}{\rightarrow} A_k, & 2A_k + A_{k+1} \underset{k}{\rightarrow} 2A_k + B \quad k \in \mathbb{Z}^n \\ B \underset{n+1}{\rightarrow} \end{cases} \tag{7.13}$$

In [38], numerical simulations for $n = 5$ showed the presence of a stable limit cycle. Note that species $A_1, ..., A_n$ together with reactions $1, ..., n$ give rise to a stoichiometry:

$$\begin{pmatrix} 0 & 0 & ... & 0 & -1 \\ -1 & 0 & ... & 0 & 0 \\ 0 & -1 & ... & 0 & 0 \\ & & \vdots & & \\ 0 & 0 & ... & -1 & 0 \end{pmatrix}, \tag{7.14}$$

which is indeed a P_0^- matrix for any n and unstable for $n \neq 2, 4$: eigenvalues can be expressed in terms of roots of unit. The matrix does not have a negative-diagonal since all reactions are explicitly autocatalytic, but in the full generality addressed in [38] such matrix is also an unstable-positive feedback for $n \neq 2, 4$. Again, the length of the cycle helps instability to arise. The associated mass action system reads:

$$\begin{cases} \dot{x}_{A_k} = F_k - a_{k-1} x_{A_{k-1}}^2 x_{A_k} \quad \text{for } k \in \mathbb{Z}^n, \\ \dot{x}_B = \sum_{k=1}^n a_{k-1} x_{A_{k-1}}^2 x_{A_k} - a_{n+1} x_B. \end{cases} \tag{7.15}$$

Fixing all inflow constants $F_k \equiv 1$ yields a steady-state flux vector

$$\bar{\mathbf{v}} = (1, 1, 1, ..., 1, 1, n).$$

We compute

$$B(\bar{\mathbf{v}}) = N \operatorname{diag}(\bar{\mathbf{v}}) Y^T = \begin{pmatrix} -1 & 0 & ... & 0 & -2 & 0 \\ -2 & -1 & ... & 0 & 0 & 0 \\ 0 & -2 & ... & 0 & 0 & 0 \\ & & \vdots & & & 0 \\ 0 & 0 & ... & -2 & -1 & 0 \\ 0 & 0 & ... & 0 & 0 & -n \end{pmatrix}, \tag{7.16}$$

which is a P^- matrix. $B(\bar{\mathbf{v}})$ also inherits the instability of (7.14) for $n \geq 5$. Criterion II implies nonstationary periodic orbits for $n \geq 5$. Note that the form (7.15) suggests the applicability of a Poincaré-Bendixson criterion for monotone cyclic feedback cycles [28]: we do not pursue here this direction.

8 Fully-open systems

Albeit rather irrealistic, fully-open networks have been considered in relevant reaction network literature by Shinar & Feinberg [33] and Banaji & Craciun [5], among others. Our result characterizes the capacity of fully-open networks for Hopf bifurcation in terms of their capacity to admit a steady state with a complex-conjugate pair of eigenvalues with a positive-real part. For simplicity, we focus on *local Hopf bifurcation*. We recall the standard theorem [20].

Theorem 8.1 (local Hopf bifurcation)**.** *Suppose that a parametric system*

$$\dot{x} = f(x, \beta), \quad x \in \mathbb{R}^n, \ \beta \in \mathbb{R},$$

has a steady-state $(\bar{x}^*, \beta^*)$ *at which the following two conditions hold:*

1. *the Jacobian* $f_x(x)|_{(\bar{x}^*,\beta^*)}$ *has a simple pair of purely imaginary eigenvalues* $\lambda_{1,2}$ *and* $n-2$ *eigenvalues with nonzero real part;*

2. $\Re(\lambda_{1,2}(\beta^*))' \neq 0$.

Then there is a local curve of steady-states $\bar{x}(\beta)$ *that changes stability at* $\bar{x}^* = \bar{x}(\beta^*)$. *For some* β *values in a neighborhood of* β^*, *the system admits periodic orbits.*

The localization of the periodic orbits in the neighborhood of β depends on the so-called *Lyapunov coefficients*, which we do not discuss here. If $\dot{x} = f(x,\beta)$ satisfies the two conditions of Theorem 8.1, we say that the system undergoes a local Hopf bifurcation at $\beta = \beta^*$. We characterize local Hopf bifurcations for fully-open networks.

Theorem 8.2 (Hopf bifurcation for fully-open networks)**.** *Consider a fully-open reaction network* $\mathbf{\Gamma}$ *with associated mass action system 2.2. The following are equivalent:*

1. *There is a choice of reaction rates such that the system undergoes a local Hopf bifurcation.*

2. *There is a choice of reaction rates such that the system possesses a positive steady-state* $\bar{x}$ *such that its Jacobian matrix* $f_x(x)|_{x=\bar{x}}$ *has a simple pair of complex conjugate eigenvalues* $\lambda_{1,2}$ *with positive real part* $\Re(\lambda_1) = \Re(\lambda_2) > 0$ *and no further eigenvalues* λ_i, $i \neq 1,2$, *with* $\Re(\lambda_i) = \Re(\lambda_1)$.

Proof. The direction $(1 \Rightarrow 2)$ is trivial, as it is just one of the conclusions of Theorem 8.1. For the other direction $(2 \Rightarrow 1)$, consider the positive steady state $\bar{x}$ of $\mathbf{\Gamma}$ satisfying the assumptions. Introduce the positive bifurcation parameter $\beta \in \mathbb{R}_{>0}$ and define

$$\begin{cases} \Delta(\beta) := \beta\,\mathrm{Id}_{|S|}; \\ \mathbf{F}(\beta) := \Delta(\beta)\bar{x}. \end{cases}$$

Above, $\mathrm{Id}_{|S|}$ indicates the $|S| \times |S|$ identity matrix. We can then consider the following perturbation of $f(x)$

$$\dot{x} = h(x,\beta) = f(x) + \mathbf{F}(\beta) - \Delta(\beta)x.$$

Clearly, $h(x,0) = f(x)$. Moreover, $h(x,\beta)$ is fully-open as f: we interpret the vector $\mathbf{F}(\beta)$ as a perturbation of the inflow rates of f and the diagonal entries of $\Delta(\beta)$ as a perturbation of the outflow rates of f. Moreover, by construction,

$$h(\bar{x},\beta) = f(\bar{x}) + \mathbf{F}(\beta) - \Delta(\beta)\bar{x} = f(\bar{x}) = 0,$$

i.e., $\bar{x}$ is a steady state of $h(\beta)$ for any choice of β. For such perturbed choice of reaction rates, however, the Jacobian $h_x(x,\beta)$ of h at $\bar{x}$ reads

$$h_x(x,\beta)|_{x=\bar{x}} = f_x(x)|_{x=\bar{x}} - \beta\,\mathrm{Id}_{|S|},$$

i.e., its spectrum corresponds to the spectrum of $f_x(x)|_{x=\bar{x}}$ translated to the left by β. Consider now the bifurcation value $\beta^* := \Re(\lambda_1) > 0$. By construction and assumption, $h_x(x,\beta)|_{x=\bar{x}}(\bar{x},\beta^*)$ possesses a simple pair of purely imaginary eigenvalues μ_1,μ_2 and no other eigenvalues with zero real part. Moreover, $\mu_1(\beta),\mu_2(\beta)$ cross the imaginary axis transversely, i.e., $\Re(\mu'_{1,2}(\beta^*))' \neq 0$. Indeed: simply note that $\mu_{1,2}(\beta) = \lambda_{1,2} - \beta$, and thus $|\mu'_{1,2}(\beta)| \equiv 1 \neq 0$. Thus, we can apply Theorem 8.1, and the fully-open system admits a local Hopf bifurcation. □

Remark 8.3. For consistency with the rest of the paper, Theorem 8.2 is stated for mass action systems. An identical proof holds for any fully-open system where inflow rates are constants and outflow rates are linear: a standard assumption in the dynamical modeling of biochemical systems. Theorem 8.2 also holds if the outflow rates follow Generalized Mass Action, Michaelis–Menten, or Hill kinetics. The proof requires a minimal adaptation in the choice of rates to compute the Hopf bifurcation point. To do this, we refer again to the concept of parameter-rich kinetics [38].

9 Conclusion

We have stated two complementary criteria that guarantee the insurgence of nonstationary periodic orbits in mass action systems via a Hopf bifurcation. The criteria rely on the concept of P^- matrices and are thus based on the sign of principal minors of the Jacobian. They consequently offer an evident computational advantage in comparison to the usual Hurwitz computation. More in detail, via Stoichiometric Network Analysis, we have expressed the Jacobian matrix Jac evaluated at a steady state $\bar{x}$ as

$$Jac = B(\bar{\mathbf{v}})\,\mathrm{diag}(1/\bar{x}_i),$$

where $\bar{\mathbf{v}}$ is a steady-state flux vector. The first criterion requires that $B(\bar{\mathbf{v}})$ is stable but not a P_0^- matrix, while the second requires that $B(\bar{\mathbf{v}})$ is an unstable P^- matrix. Moreover, we have interpreted the underlying chemical mechanisms as an unstable-positive feedback within a stable network (Criterion I) and an unstable-negative feedback (Criterion II).

We have presented three examples where the criteria have been put into practice. Example I is a closed network with 5-species and a 3-species unstable-positive feedback: Criterion I proves the occurrence of a Hopf bifurcation as soon as the concentrations of the 3 species involved in the unstable-positive feedback become large in comparison to the others: this way the unstable-positive feedback becomes dominant and drives the dynamics towards an unstable region with the appearance of a stable limit cycle. Examples II and III are built around unstable-negative feedbacks of size n and apply Criterion II. We have noted that the instability of negative feedback appears only for a sufficiently large size. Consequently, both examples are families of networks of any size n: this confirms the validity of our criteria especially to address large networks. Periodic orbits appear for n large enough: $n \geq 10$ in Example II, $n \geq 5$ in Example III.

Finally, as an independent observation, we have proved that the capacity for Hopf bifurcation of fully-open systems is equivalent to the capacity for an unstable steady-state with a simple pair of eigenvalues with positive-real part.

Outlook By simple inspection of the stoichiometric matrix N, unstable-positive feedbacks within a stable subnetwork and unstable-negative feedbacks are sufficient for purely-imaginary eigenvalues of the Jacobian at steady-states of reaction systems endowed with parameter-rich kinetics as e.g. Michaelis–Menten. The two criteria, which we stated for mass action, would offer in principle a similar interpretation but they are nevertheless sufficient statements only on $B(\bar{\mathbf{v}})$, for a proper choice of steady-state flux vector $\bar{\mathbf{v}}$. A clear connection between the bare stoichiometry N and the assumptions of the criteria is still to be investigated. The final goal is to find simple stoichiometric patterns that sufficiently guarantee the applicability of the criteria. Clarifications in this direction will help a deeper chemical understanding of the chemical mechanism that governs oscillations in mass action systems. In conclusion, we underline that the stability of the periodic orbits

is not determined by the stated criteria, and it deserves further analysis.

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