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Bistability and oscillations in chemical reaction networks

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Received: 4 April 2008
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Abstract Bifurcation theory is one of the most widely used approaches for analysis of dynamical behaviour of chemical and biochemical reaction networks. Some of the interesting qualitative behaviour that are analyzed are oscillations and bistability (a situation where a system has at least two coexisting stable equilibria). Both phenomena have been identified as central features of many biological and biochemical systems. This paper, using the theory of stoichiometric network analysis (SNA) and notions from algebraic geometry, presents sufficient conditions for a reaction network to display bifurcations associated with these phenomena. The advantage of these conditions is that they impose fewer algebraic conditions on model parameters than conditions associated with standard bifurcation theorems. To derive the new conditions, a coordinate transformation will be made that will guarantee the existence of branches of positive equilibria in the system. This is particularly useful in mathematical biology, where only positive variable values are considered to be meaningful. The first part of the paper will be an extended introduction to SNA and algebraic geometry-related methods which are used in the coordinate transformation and set up of the theorems. In the second part of the paper we will focus on the derivation of bifurcation conditions using SNA and algebraic geometry. Conditions will be derived for three bifurcations: the saddle-node bifurcation, a simple branching point, both linked to bistability, and a simple Hopf bifurcation. The latter is linked to oscillatory behaviour. The conditions derived are sufficient and they extend earlier results from

We have added a dedication of the paper to K. Gatermann.

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stoichiometric network analysis as can be found in (Aguda and Clarke in *J Chem Phys* 87:3461–3470, 1987; Clarke and Jiang in *J Chem Phys* 99:4464–4476, 1993; Gatermann et al. in *J Symb Comput* 40:1361–1382, 2005). In these papers some necessary conditions for two of these bifurcations were given. A set of examples will illustrate that algebraic conditions arising from given sufficient bifurcation conditions are not more difficult to interpret nor harder to calculate than those arising from necessary bifurcation conditions. Hence an increasing amount of information is gained at no extra computational cost. The theory can also be used in a second step for a systematic bifurcation analysis of larger reaction networks.

Keywords Polynomial differential equations · Bifurcation theory · Extreme currents

Mathematics Subject Classification (2000) 92C45 · 37G10 · 14A10

1 Introduction

Chemical reaction networks have been extensively studied for their interesting and complex dynamic behaviour [16–18, 28, 29, 34, 36]. However, often on account of their complex structures, analysing their dynamic behaviour via bifurcation analysis has proven to be difficult. Hence advanced methods such as stoichiometric network analysis (SNA) have been introduced. In this paper the ideas from stoichiometric network analysis will be used to formulate sufficient conditions for certain networks displaying some well-known dynamic behaviour. Such results are helpful in order to gain a better understanding of large reaction networks, or sub-networks that drive certain behaviours. The results derived in this paper should also simplify the inverse process of modeling, i.e. the search for reaction networks of a specific class defined by exhibiting a desired qualitative behaviour.

In this paper two different dynamic behaviours are of interest: bistability and oscillations. The former is a situation where a system has two stable equilibria. Both are central features of numerous chemical and biochemical processes. The work presented here is motivated by several seminal papers by Clarke [7–9] where stoichiometric network analysis was introduced to confirm whether some well-known chemical systems have the potential to display oscillations. The crux of Clarke’s idea was to observe the dynamics of the system in the reaction rate space, rather than in the species concentration space. This work was revolutionary, because it significantly simplified model analysis. Instead of searching for steady state solutions where all concentrations are unknown and parameters are not specified, their analysis was restricted to dealing only with reaction rates. Clarke and his collaborators extended this idea in [1, 10] where they derived several conditions on the reaction rates. By assuming the existence of a positive concentration steady state, its linearisation will have either a zero eigenvalue, or a pair of purely imaginary eigenvalues. These eigenvalue conditions will then form a necessary condition for the positive concentration steady state to be a saddle-node or Hopf bifurcation point. However, in this series of papers, Clarke and coauthors never confirmed the existence of the positive concentration steady state. This was done much later in a paper by Gatermann et al. in [21]. Gatermann et al. used toric geometry theory to prove that Clarke’s analysis of the cone of reaction rates was correct, and

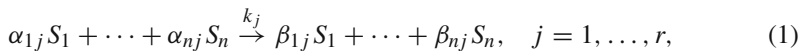
also derived conditions that guarantee the existence of positive concentration steady states, when the system is analysed in the reaction rate coordinates. The theory of toric geometry will be reviewed in Sect. 3. Gatermann et al. also mentioned the eigenvalue results published in [10], but they went no further in the notions of bifurcation analysis.

In this paper, it will be shown that the use of SNA and the associated algebraic geometry concepts lead to a general bifurcation analysis framework for polynomial systems. In this situation the algebraic information can be used to derive sufficient conditions for all major types of bifurcations. At the same time they guarantee that the equilibria discussed are positive, and hence physiologically meaningful. Our results are illustrated with several examples, some taken from the aforementioned papers for the sake of comparison.

Other important but not related approaches to investigate the qualitative behaviour of reaction systems are given in [12,33]. These papers also derive conditions under which a polynomial system might undergo certain bifurcations. But the methods are based on other algebraic concepts, a combination of graph theory and expansions of coefficients of the associated characteristic polynomial. An overview to different graph theoretical approaches to polynomial reaction systems can be found in [14].

1.1 Chemical reaction systems

A chemical reaction system with r reactions and m reacting species is described by a time-continuous dynamical system derived from reaction schemes. Each reaction can be written in the form



where the S_i , $1 \leq i \leq n$, are the chemical species and each k_j is the kinetic constant of the j th reaction. Kinetic coefficients take into account all effects on the reaction rate apart from reactant concentrations, for example, temperature, light conditions, or ionic strength in the reaction. The coefficients α_{ij} and β_{ij} represent the number of S_i molecules participating in j th reaction at reactant and product stages, respectively. The net amount of species S_i produced or consumed by the reaction is named the stoichiometric coefficient and defined by $n_{ij} := \beta_{ij} - \alpha_{ij}$. These coefficients are arranged in a *stoichiometric* matrix, denoted by N . The rate at which the j th reaction takes place is modeled under the assumption that reactions obey mass-action kinetics. This assumption means that the reaction rate must take the form of a monomial,

$$v_j(x, k_j) = k_j \prod_{i=1}^m x_i^{\kappa_{ij}},$$

where κ_{ij} is the molecularity of the species S_i in the j th reaction. In mass-action kinetics, the kinetic exponent κ_{ij} reduces to being simply α_{ij} . Kinetic exponents are arranged in a *kinetic* matrix, denoted by κ . The time evolution of the species concentrations is described by the following initial value problem:

$$\dot{x} = Nv(x, k), \quad (2)$$

$$x(0) > 0, \quad (3)$$

where $x(0)$ are initial species concentrations. Interesting qualitative behaviours such as bistability and oscillations have been observed in chemical reaction systems of mass-action type [12,30]. They can be interpreted to result from a bifurcation, i.e. a qualitative change in the behaviour of the system's solutions when one or more of the parameters are varied. Hence, a common approach in identifying such behaviour has been to derive conditions under which the system is able to undergo an associated bifurcation [21,33]. In this paper, sufficient conditions for bifurcations will be derived.

The paper is split into two parts. The first part contains an overview of stoichiometric network analysis (Sect. 2) and some eigenvalue results from [1,10]. It also contains some useful notions of algebraic geometry in Sect. 3. Second part of the paper is the new derivation of sufficient conditions for the saddle-node bifurcation (Sect. 4.1), simple branching point (Sect. 4) and a simple Hopf bifurcation (Sect. 5). In Sect. 4.3, a method for detecting bistability is discussed. Several examples in each section illustrate the theory.

Part A: algebraic geometry

2 Theory of stoichiometric network analysis

This part of the paper will show how essential algebraic concepts can be associated to reaction networks. In a further step this will be the basis for introducing higher algebraic structures, most importantly toric varieties. Stoichiometric Network Analysis (SNA), introduced in a seminal paper by Clarke [9], is one of the most prominent methods of analysing chemical and biochemical networks. Using the assumptions described in the introduction, the reaction network dynamics takes the form shown in (2). The local existence and uniqueness of the solutions to (2) are guaranteed [46]. Also all species concentrations will always stay in the positive orthant of the concentration space, namely $x(t) \geq 0$ ($x(t) > 0$) if $x(0) \geq 0$ ($x(0) > 0$) [45]. If $\text{rank}(N) = r \leq n$, then the reaction system has $(n - r)$ conservation relations [27]. A conservation relation is a relation between a set of species with their total concentration being preserved. The set of conservation relations takes the form

$$g_l^T x = c_l, \quad l = 1, \dots, n - r,$$

where each $g_l^T \in \ker(N)$ and $c_l \in \mathbb{R}_+$ is a constant describing the total conserved concentration. The set of conservation relations forms an invariant space [45]. Equilibria of the network (x_0) for chosen set of parameters k_0 are determined by the conditions

$$Nv(x_0, k_0) = 0, \tag{4}$$

$$x_0 > 0. \tag{5}$$

Any such equilibrium clearly depends on the kinetic parameters $k \in \mathbb{R}_+^p$, but also on the constants c_l , $l = 1, \dots, n - r$ from the conservation relations. Due to (4) and (5), all stationary reaction rates belong to an intersection of the kernel of N and the positive orthant of the reaction space,

$$v(x_0, k_0) \in \{z \in \mathbb{R}^r \mid Nz = 0, z \in \mathbb{R}_+^r\} = \text{Ker}(N) \cap \mathbb{R}_+^r, \quad (6)$$

which form a convex polyhedral cone K_v [35]. This cone K_v is spanned by a set of minimal generating vectors E_i 's,

$$K_v = \left\{ \sum_{i=1}^t j_i E_i : j_i > 0 \quad \forall i \right\}.$$

These generating vectors are unique up to scaling by a positive constant. They may be linearly dependent as the number of extreme currents may be greater than $\dim(\text{ker}(N))$. Here, as in [9], these vectors will be referred to as extreme currents. Extreme currents decompose the network into minimal steady-state generating subnetworks [9]. In the biochemical literature they are interpreted as switching on or off different parts of a metabolic pathway. The influence of a subnetwork on the full network dynamics (i.e., how much the given subnetwork plays a part in creating a certain steady state) depends on the constants j_i 's, which are called convex parameters. In fact the Jacobian of the network evaluated at any positive steady state, x_0 , can be written as a convex combination of contributions from the extreme currents:

$$D_x N v(x_0, k_0) \in \left\{ \sum_{i=1}^M j_i N \text{diag}(E_i) \kappa^T \text{diag}(h) : j_i > 0, h \in \mathbb{R}_+^m \right\}. \quad (7)$$

Here h is a vector defined as the inverses of any equilibrium concentrations x_0 , and $\text{diag}(v)$ is a diagonal matrix with the diagonal entries given by the vector v . The contribution of a single extreme current is given by the term

$$j_i N \text{diag}(E_i) \kappa^T \text{diag}(h),$$

which represents the Jacobian of the subnetwork generated by the extreme current E_i , evaluated at any of its positive steady states. The Jacobian description in the form of (7) comes from a simple observation that for positive steady states x_0 ,

$$D_x N v(x_0, k_0) = N \text{diag}(v(x_0, k_0)) \kappa^T \text{diag}(x_0^{-1}). \quad (8)$$

Together with the newly defined parameters, $h_s = x_s^{-1}$, $s = 1, \dots, n$, the convex parameters j replace the reaction constants k and the conserved mass constants c [9]. Detection of bifurcations [1, 10] consists of finding regions of the parameter space (j, h) where the Jacobian written in form of (8) could have a zero eigenvalue, or a pair of purely imaginary eigenvalues. One needs to consider the characteristic polynomial $\det(\lambda I - J)$, where I is the identity matrix and J is the Jacobian parametrized by (j, h) :

$$\det(\lambda I - J(j, h)) = \lambda^n + \alpha_{n-1}(j, h) \lambda^{n-1} + \dots + \alpha_1(j, h) \lambda + \alpha_0(j, h). \quad (9)$$

This polynomial has a zero solution (or the Jacobian has a zero eigenvalue, a necessary condition for a saddle-node bifurcation) when $\alpha_0(j, h) = 0$. Now Orlando's Formula in [20] implies that a condition on the $(n - 1)$ -st Hurwitz determinant $H_{n-1}(j, h) = 0$ is a necessary condition for the characteristic polynomial to have a pair of pure imaginary eigenvalues. In [1, 10] these conditions are employed to explore the parameter space (j, h) . The aim of the authors is to reduce the dimension of the system parameter space. For example, in [1] the authors perform their analysis on the convex polytope, which is the normalized version of the convex cone K_v . The normalization is a restriction on K_v such that $\sum_{j=1}^r v_j = 1$ for every $v = (v_1, \dots, v_r) \in K_v$. In a similar way no distinction will be made in this paper between points of the cone K_v and a ray passing through the point.

3 The associated toric varieties

Behaviour of a chemical reaction system depends on the parameters k 's and c 's. For the characterization of a bifurcation, there must exist some information about the branches of the steady states parametrized by a chosen bifurcation parameter. For example, if a system undergoes a Hopf bifurcation there must be a smooth curve of steady states parametrized by a bifurcation parameter (we refer to Liu's theorem in Sect. 5). The achievement of this paper is to derive bifurcation conditions in terms of SNA. More precisely, a coordinate transformation will be performed such that bifurcation conditions can be placed on rays of the convex polyhedral cone, $z \in K_v$, and also the system parameters. It can be avoided to use any of the concentration variables (x). Transformation back to concentration space (and x variables) will be possible, because given choice of z and parameters k there exists at least one positive concentration steady state (x) such that

$$z = v(x, k) = x_0 v(x, k), \quad (10)$$

where the constant x_0 is introduced because of the ambiguous length of the ray z (using the notation already mentioned between rays and points). This can be done using theory from algebraic geometry. The introduction of algebraic geometry to SNA is an important extension to the bifurcation results formulated by Clarke et al. [1, 10]. While these authors derived very important conditions on the eigenvalues of the system via the reaction rates, they did not prove that for the given combination of currents and a chosen bifurcation parameter, there actually exists a positive concentration steady state. Gatermann et al. in [21] were the first to use the concepts from algebraic geometry. They showed that if the ray of the cone belongs to a particular set (which shall be described next) then there exists a positive solution x . Using algebraic geometry they gave a proof that the mapping $v : \mathbb{R}_+^n \rightarrow \mathbb{R}_+^r$ from the set $\{x \in \mathbb{R}_+^n : \exists k_{ij} > 0 \text{ with } Nv(x, k) = 0\}$ to the convex polyhedral cone $\ker(N) \cap \mathbb{R}_+^r$ is surjective. This validated Clarke's theory that the convex polyhedral cone is covered by the image of mapping v .

The theory presented in this section will be illustrated with an example, the modified Selkov model of glycolytic oscillations analyzed in [15]. Some SNA analysis and algebraic geometry analysis has already been applied to this model. Extreme currents

for this model were calculated in [39], and the deformed toric ideal of an extended model was computed in [38]. The model describes two species interacting through five reactions, where S_1 denotes the product Fructokinase-1,6-biphosphate (F1,6BP) and S_2 denotes adenosine triphosphate (ATP):

$$\begin{aligned}\dot{x}_1 &= k_1 x_1^2 x_2 + k_2 - k_3 x_1, \\ \dot{x}_2 &= -k_1 x_1^2 x_2 + k_4 - k_5 x_2.\end{aligned}$$

The stoichiometric matrix and vector of reaction rates are:

$$N = \begin{bmatrix} 1 & 1 & -1 & 0 & 0 \\ -1 & 0 & 0 & 1 & -1 \end{bmatrix} \quad \text{and} \quad v(x; k) = \begin{bmatrix} k_1 x_1^2 x_2 \\ k_2 \\ k_3 x_1 \\ k_4 \\ k_5 x_2 \end{bmatrix}. \quad (11)$$

This means the model consists of three extreme currents:

$$E_1 = (0, 1, 1, 0, 0), \quad E_2 = (0, 0, 0, 1, 1) \quad \text{and} \quad E_3 = (1, 0, 1, 1, 0). \quad (12)$$

The first two extreme currents describe subnetworks of inflow and outflow of F1,6BP and ATP, respectively. The third current combines the autocatalytic formation of F1,6BP via ATP with outflow of F1,6BP and inflow of ATP.

Consider the polynomial map $v : \mathbb{R}_+^n \rightarrow \mathbb{R}_+^r$. Let $x \in \mathbb{R}_+^n$ and $z \in \mathbb{R}_+^r$. The aim is to derive conditions on z that guarantee that z is in the image of the map v , namely $z \in \text{Im}(v)$. These conditions can be reinterpreted as conditions depending solely on z variables. In other words, the aim is to rewrite the system

$$z - v(x, k) = 0 \quad (13)$$

in terms of another set of equations with solution set $(z \in \text{Im}(v))$, but only with z variable terms. For this theory from algebraic geometry is needed. Therefore we introduce some definitions. One of the basic objects in algebra is a field. Intuitively, a field is a set where one can define addition, multiplication, division and subtraction with usual properties. A proper definition can be found in any introductory algebraic text book, such as Cox et al. [11]. Some examples of a field are the real numbers, \mathbb{R} , the complex numbers \mathbb{C} and rational numbers \mathbb{Q} . Integers \mathbb{Z} do not form a field, because division fails (namely 1 and $2 \in \mathbb{Z}$ but $1/2 \notin \mathbb{Z}$).

The set of equations in (13) can be rewritten as a set of polynomials $(z_i - v_i(x, k) \mid i = 1, \dots, r)$ whose zero solution set implicitly defines the image of v . This can be done once further definitions for polynomials and their zero solution sets are given.

Let $\mathbb{K}[y_1, \dots, y_m]$ denote a set of all polynomials of y_1, \dots, y_m with coefficients in a field \mathbb{K} . Similarly, a set of polynomials with real coefficients is denoted by $\mathbb{R}[y_1, \dots, y_m]$ and a set of polynomials with complex coefficients is denoted by

$\mathbb{C}[y_1, \dots, y_m]$ and so on. Polynomials, where coefficients are in terms of parameters k , belong to a set $\mathbb{K}(k)[x_1, \dots, x_n]$ where $\mathbb{K}(k)$ is an extension of a field \mathbb{K} . This paper will deal with the polynomials in the set $\mathbb{Q}(k)[x, z]$ with $x = (x_1, \dots, x_n)$ and $z = (z_1, \dots, z_r)$. A polynomial $f \in \mathbb{K}[y_1, \dots, y_m]$ which is split into monomials in the form of

$$f = h_N + h_{N-1} + \dots + h_0$$

is called homogeneous of degree l if each $h_i \in \mathbb{K}[y_1, \dots, y_m]$, $0 \leq i \leq N$ has total degree l . For a set of polynomials f_1, \dots, f_s in $\mathbb{K}[y_1, \dots, y_m]$, the set

$$\langle f_1, \dots, f_s \rangle = \left\{ \sum_{i=1}^s h_i f_i : h_1, \dots, h_s \in \mathbb{K}[y_1, \dots, y_m] \right\} \subseteq \mathbb{K}[y_1, \dots, y_m]$$

is an ideal *generated by* f_1, \dots, f_s . The zero set of solutions of the ideal is called an affine variety. For $\langle f_1, \dots, f_s \rangle$,

$$V(f_1, \dots, f_s) = \{(a_1, \dots, a_n) \in \mathbb{K}^n : f_i(a_1, \dots, a_n) = 0 \text{ for all } 1 \leq i \leq n\}$$

is the affine variety defined by f_1, \dots, f_s . For a set of polynomials satisfying (13) the ideal can be written as

$$I = \langle z_1 - v_1(x, k), z_2 - v_2(x, k), \dots, z_r - v_r(x, k) \rangle \subseteq \mathbb{Q}(k)[x, z]. \quad (14)$$

This ideal is also called an ideal passing from an image of a map v . This is because I is constructed in such a way that $Im(V)$ belongs to the zero set of I , or the variety $V(I)$. More formally, the ideal can be written as

$$I = \{f \in \mathbb{Q}(k)[x, z] : \exists x' \in \mathbb{R}_+^n \text{ with } f(x', z') = 0 \text{ for all } z' \in Im(v)\}. \quad (15)$$

Example 1 The image of $v(x, k)$ is in fact the vector of reaction rates. In the modified Selkov model, it comes in the form shown in Eq. (11). The ideal I , with $Im(v)$ as its variety is,

$$I = \langle z_1 - k_1 x_1^2 x_2, z_2 - k_2, z_3 - k_3 x_1, z_4 - k_4, z_5 - k_5 x_2 \rangle.$$

The Ideal-Variety Correspondence Theorem (stated in Chapter 6, Cox [11]) guarantees that for the image of the mapping v , with the ideal I constructed as in (15), it holds that $(z', x') \in V(I)$ for some $x' \in \mathbb{R}_+^n$ if and only if $z' \in Im(v)$. It is possible to create other ideals passing from the image of $Im(v)$. As has been mentioned before, the aim is to rewrite polynomials in (13) as a set of polynomials with the same zero solution set, but with z terms only. Two ideals will be of use here: the deformed toric ideal and the homogeneous deformed toric ideal. Both of these ideals can be created from the ideal I in the form of (14), after a change of basis and with some elimination theory. First the ideal in (14) needs to be stated in terms of other basis elements (polynomials)

which show explicitly the relations between the z variables. Note that a careful extension of the basis of the ideal does not change the variety of the ideal. The basis which will be needed is a Gröbner basis (of the ideal). Gröbner bases are useful because they usually give most insight and information on an given ideal. They can be efficiently calculated with powerful computer algebra systems such as Magma [4], Macaulay2 [23], Singular [24, 42], CoCoA [6], and even Mathematica or Maple. A more complete list of software is given in on website maintained by the RICAM institute (<http://www.ricam.oeaw.ac.at/Groebner-Bases-Implementations/view/SystemList.php>).

A Gröbner basis is a basis which depends on a specific ordering of the monomials that belong to the ideal. A formal definition of Gröbner basis and monomial orderings can be found in any standard algebraic geometry book such as [11]. A Gröbner basis exists for any monomial ordering and is not unique. Some standard methods for computing them are Buchberger's algorithm and Faugères F4 algorithm. The methods for computing Gröbner basis are continuously improving. One example is calculating Gröbner basis via modular methods [2]. This has been implemented in Singular, a symbolic algebra software library [26].

Some standard monomial orderings are lexicographic (lex) and graded reverse lexicographic ordering (grlex). In a lexicographic ordering one writes $\gamma >_{lex} \delta$ for $\gamma = (\gamma_1, \dots, \gamma_n)$ and $\delta = (\delta_1, \dots, \delta_n) \in \mathbb{Z}_{\geq 0}^{n+r}$, if in the vector difference $\gamma - \delta \in \mathbb{Z}^{n+r}$ the leftmost entry is positive. For two monomials f and g with orders γ and δ , we write $f >_{lex} g$ if $\gamma >_{lex} \delta$. For the graded reverse lexicographic ordering one writes $\gamma >_{grlex} \delta$ if $|\gamma| = \sum_{i=1}^{n+r} \gamma_i > |\delta| = \sum_{i=1}^{n+r} \delta_i$ or $|\gamma| = |\delta|$, and the rightmost nonzero entry of $\gamma - \delta \in \mathbb{Z}^{n+r}$ is negative.

Note that is possible to convert one Gröbner basis with respect to one monomial ordering into a Gröbner basis with respect to a different ordering via algorithms such as the FGLM algorithm or the Gröbner walk algorithm. These are often employed to compute lexicographic Gröbner bases from grevlex Gröbner bases, because a lexicographic ordering can be harder to compute than a graded reverse lex ordering. They have been implemented in Singular libraries [24].

The Gröbner basis used must be formed by a monomial ordering which is also an elimination ordering. Let G be a Gröbner basis of I with such an elimination ordering. The intersection $I \cap \mathbb{Q}[z]$ is an ideal in $\mathbb{Q}[z]$ and it is called an n th elimination ideal (because all n of the x variables have been eliminated). $I \cap \mathbb{Q}[z]$ is a ideal of $\mathbb{Q}[z]$, but it is also an ideal passing from image of v . $I \cap \mathbb{Q}[z]$, called the deformed toric ideal, is of the form

$$I_{\text{tor}}^{\text{def}} = \{f \in \mathbb{Q}[z] : f(v(x, k)) = 0\} \subseteq \mathbb{Q}(k)[z]. \quad (16)$$

By elimination theory, $G \cap \mathbb{Q}[z]$ (G basis elements with only z variables) are a Gröbner basis of $I \cap \mathbb{Q}[z]$. So basis polynomials of G with only z variables also have $Im(v)$ as their zero solution set. But elimination theory can only be used if Gröbner basis is formed with elimination monomial ordering. It must be mentioned that the deformed toric ideal is an ideal formed from $Im(v)$. By the Ideal-Variety Correspondence Theorem, the variety of the deformed toric ideal is such that $z \in V(I_{\text{tor}}^{\text{def}})$ if and only if $z \in Im(v)$. A monomial order $>$ on $\mathbb{K}[x_1, \dots, x_n]$ is said to be of l -elimination type provided that any monomial involving one of x_1, \dots, x_l is

greater than all monomials in $\mathbb{K}[x_{l+1}, \dots, x_n]$. A Gröbner basis with an n th elimination monomial ordering is required in order for all x variables to be eliminated.

The lexicographic order is an n -elimination monomial ordering. The elimination ordering used in calculations is the pure lexicographic ordering with

$$x_1 >_{\text{lex}} \dots >_{\text{lex}} x_n >_{\text{lex}} z_1 >_{\text{lex}} \dots >_{\text{lex}} z_r.$$

A Gröbner basis with this ordering represents most information about the ideal, but usually can be hard to compute [43]. In the upcoming examples, this ordering is used nevertheless and all calculations were performed with the Gröbner package in MAPLE. As mentioned there exist other orders [3] which are more efficient and easier to compute, for example the product order that induces grevlex on both $\mathbb{Q}[x_1, \dots, x_n]$ and on $\mathbb{Q}[z_1, \dots, z_r]$. Writing monomials in $n + r$ variables as $x^\alpha z^\beta$, where $\alpha \in \mathbb{Z}_{\geq 0}^n$ and $\beta \in \mathbb{Z}_{\geq 0}^r$, this product order is defined by

$$x^\alpha z^\beta >_{\text{mixed}} x^\gamma z^\delta \iff x^\alpha >_{\text{grevlex}} x^\gamma \text{ or } x^\alpha =_{\text{grevlex}} x^\gamma \text{ and } z^\beta >_{\text{grevlex}} z^\delta.$$

From this ordering we can revert back to lexicographic ordering by using the algorithms as mentioned above. For larger reaction networks the aforementioned algebraic packages would increase significantly the speed of the calculations. The above concepts are now illustrated by using the Selkov model example:

Example 2 The ideal of I for the Selkov model has the basis $F = \{z_1 - k_1 x_1^2 x_2, z_2 - k_2, z_3 - k_3 x_1, z_4 - k_4, z_5 - k_5 x_2\}$. Buchberger's algorithm is used to derive a Gröbner basis of I . Some preliminary definitions are needed: for $f_i \in F$ denote by $LM(f_i)$ the monomial of f_i with the largest exponent, and likewise $LT(f_i)$ as the largest term of f_i , both with respect to a monomial ordering. Assume the lex ordering where $x_1 >_{\text{lex}} x_2 >_{\text{lex}} z_1 >_{\text{lex}} z_2 >_{\text{lex}} z_3 >_{\text{lex}} z_4 >_{\text{lex}} z_5$. For any pair $f_i, f_j \in F$ let s be the least common multiple of $LM(f_i)$ and $LM(f_j)$, namely $s = LCM(LM(f_i), LM(f_j))$. Define an S -polynomial of f_i and f_j as the combination,

$$S(f_i, f_j) = \frac{s}{LT(f_i)} \cdot f_i - \frac{s}{LT(f_j)} \cdot f_j.$$

One can write $\overline{S(f_i, f_j)}^F$ to denote the remainder on division of $S(f_i, f_j)$ by the elements of F . Buchberger's algorithm is based on extending F to a Gröbner basis by successively adding non-zero remainders $\overline{S(f_i, f_j)}^F$ to F . Only $S(f_1, f_3)$ and $S(f_1, f_5)$ are non-zero S -polynomials. In fact for $S(f_1, f_5)$ we have

$$\begin{aligned} S(f_1, f_5) &= \frac{1}{k_1} f_1 - \frac{x_1^2}{k_5} f_5, \\ &= \frac{1}{k_1} (z_1 - k_1 x_1^2 x_2) - \frac{x_1^2}{k_5} (z_5 - k_5 x_2), \\ &= \frac{1}{k_1} z_1 - \frac{x_1^2}{k_5} z_5. \end{aligned}$$

Using the division algorithm it can be shown that

$$S(f_1, f_5) = \left(\frac{1}{k_3 k_5} x_1 z_5 + \frac{1}{z_3^2 k_5} z_3 z_5 \right) f_3 - \left(\frac{1}{k_1} z_1 - \frac{1}{k_3^2 k_5} z_3^2 z_5 \right), \quad (17)$$

where $f_3 = z_3 - k_3 x_1$, and so $\overline{S(f_1, f_5)}^F = \frac{1}{k_1} z_1 - \frac{1}{k_3^2 k_5} z_3^2 z_5$. Clearly $\overline{S(f_1, f_5)}^F = k_3^2 k_5 z_1 - k_1 z_3^2 z_5$, once the polynomial is multiplied by the factor $k_1 k_3^2 k_5$. Repeating above calculations it can be shown that $\overline{S(f_1, f_3)}^F = \overline{S(f_1, f_5)}^F$. Thus $\overline{S(f_1, f_5)}^F$ is the only new element to be added to the basis F to form the Gröbner basis. Since the element f_1 is linearly dependent on other elements of F and $\overline{S(f_1, f_5)}^F$, we know from Eq. (17) that the Gröbner basis of I is the set $G = \{k_5 k_3^2 z_1 - k_1 z_3^2 z_5, z_2 - k_2, z_3 - k_3 x_1, z_4 - k_4, z_5 - k_5 x_2\}$. Since the respective Gröbner basis of the deformed toric ideal is $G \cap \mathbb{Q}(k)[z]$, we have

$$I_{\text{tor}}^{\text{def}} = \langle k_5 k_3^2 z_1 - k_1 z_3^2 z_5, z_2 - k_2, z_4 - k_4 \rangle.$$

Now, $z \in V(I_{\text{tor}}^{\text{def}})$ if and only if $z \in \text{Im}(v)$.

Note that the deformed toric ideal is not the only ideal passing from $\text{Im}(v)$. In our study we are interested in the analysis of the convex polyhedral cone $\text{Ker}(N) \cap \mathbb{R}_+^r$. As mentioned earlier, a ray of the cone can be of any arbitrary length. In this analysis, the size of any kinetic parameter or concentration values are not necessarily known. Hence, a ray of the cone is not necessarily finite. Previous concepts can be generalized by enlarging \mathbb{C}^r with the addition of points at ∞ to create an n -dimensional projective space $\mathbb{P}^{r-1}(\mathbb{C})$. Working with projective spaces usually simplifies computations.

Before we give a description of the ideal of $\text{Im}(v)$ in projective space some definitions are needed. Define an equivalence relation \sim on the lines of the field \mathbb{C} by letting two lines be equivalent if they are parallel in \mathbb{C} . An n -dimensional projective space $\mathbb{P}^{r-1}(\mathbb{C})$ over a field \mathbb{C} is a set of equivalence classes \sim on $\mathbb{C}^r - \{0\}$, namely,

$$\mathbb{P}^{r-1}(\mathbb{C}) = (\mathbb{C}^r - \{0\}) / \sim.$$

Each nonzero r -tuple $z_1, \dots, z_r \in \mathbb{C}^r$ defines a point $p \in \mathbb{P}^{r-1}(\mathbb{C})$. $z_1, \dots, z_r \in \mathbb{C}^r$. They are referred to as the homogeneous coordinates of p . Geometrically, one can think of \mathbb{P}^{r-1} as a set of lines through the origin in \mathbb{C}^r . In fact,

$$\mathbb{P}^{r-1}(\mathbb{C}) \cong \{\text{lines through the origin in } \mathbb{C}^r\}.$$

So every ray of the convex cone, independent of its length, is a single point in projective space. This is precisely the reason why the notation used did not distinguish between points and rays. A homogeneous deformed toric ideal is defined as

$$\hat{I}_{\text{tor}}^{\text{def}} = \{f \in \mathbb{Q}[z] : f(v(x, k)) = 0, f \text{ is homogeneous}\} \subseteq \mathbb{Q}(k)[z]. \quad (18)$$

The variety of the homogeneous deformed toric ideal is the so called Zariski closure of the image of the mapping v in projective space. This is the smallest variety (with respect to set inclusion) that contains the image of v in the projective space. The variety of $\hat{I}_{\text{tor}}^{\text{def}}$ is $V(\hat{I}_{\text{tor}}^{\text{def}}) \subseteq \mathbb{P}^{r-1}$. The homogeneous deformed toric ideal is formed from $Im(v)$. By the Ideal-Variety Correspondence $[z] \in V(I_{\text{tor}}^{\text{def}})$ if and only if, $z \in Im(v)$.

Note that different choices of parameters k_{ij} give a parametrization of the family of projective varieties. By defining the variety of the deformed toric ideal and the variety of the homogeneous deformed toric ideal, the conditions for z solutions in (13) have been rewritten in terms of equations with z and kinetic parameters k only, as given by $V(I_{\text{tor}}^{\text{def}})$ or $V(\hat{I}_{\text{tor}}^{\text{def}})$. This corresponds to a coordinate transformation with potentially less basis elements. However, it still needs to be confirmed that for a specific choice of z and k there exists a positive steady state x such that $z = x_0 v(x, k)$. But this is true, since $z \in V(I_{\text{tor}}^{\text{def}})$ if and only if $z \in Im(v)$.

Since the cone is parametrized by convex parameters j , the conditions on the z variables ($z \in V(I_{\text{tor}}^{\text{def}})$) can be reformulated in terms of conditions on convex parameters j . Take an ideal $J \subseteq \mathbb{Q}(k)[j]$ by substituting $z = \sum_{i=1}^M j_i E_i$ into basis elements of $I_{\text{tor}}^{\text{def}}$. Then for a chosen parameter set k , if $j \in V(J) \cap \mathbb{R}_+^M$, a positive solution x exists for $\sum_{i=1}^M j_i E_i = v(x, k)$. We return to the example for illustration:

Example 3 As shown earlier, the Selkov model has three currents E_1 , E_2 and E_3 , see (12). So, $z_1 = j_3$, $z_2 = j_1$, $z_3 = j_1 + j_3$, $z_4 = z_2 + z_3$, $z_5 = j_2$. Substituting j coordinates into the deformed toric ideal yields

$$J = \langle k_5 k_3^2 j_3 - k_1 (j_1 + j_3)^2 j_2, j_1 - k_2, j_2 + j_3 - k_4 \rangle.$$

The equations for $j \in V(J)$ are

$$\begin{aligned} k_5 k_3^2 j_3 - k_1 (j_1 + j_3)^2 j_2 &= 0 & j_1 - k_2 &= 0, \\ j_2 + j_3 - k_4 &= 0. \end{aligned}$$

For $j \in V(J)$, the system has at least one positive steady state for chosen k parameters. By using the Hermite Normal Form some of these steady states can be calculated:

$$x_1 = \frac{j_1 + j_3}{k_3}, \quad (19)$$

$$x_2 = \frac{j_2}{k_5}. \quad (20)$$

The above results can now be applied to formulate a general framework for a ‘non-negative’ bifurcation theory of time-continuous dynamical systems with polynomial right hand sides, such as the ones given by mass-action reaction networks. This will be the topic of the second part of the paper.

Part B: bifurcation analysis

In bifurcation theory the dimension of a given parameter space is obviously important. Working with the deformed toric variety allows some of the kinetic parameters to be restated in terms of convex parameters j and a subset of remaining kinetic parameters, denoted by \tilde{k} . We explain this construction. By using the deformed toric ideal J a parameter set k can be split into two disjoint sets k^* and \tilde{k} . This can be done such that each element of k^* is a C^1 function of \tilde{k} and j , namely, $k^* = k^*(j, \tilde{k})$. The advantage of this parameter change is the following important property: if $j \in V(J)$, then for any choice of (j, \tilde{k}) there exists at least one positive steady state x .

In standard bifurcation analysis additional conditions would have to be posed to guarantee such a positive steady state. Consider the well-known Brusselator system, reviewed in Example 5.2. It has four kinetic parameters, labeled k_1 to k_4 . Performing SNA analysis yields two convex parameters, j_1 and j_2 . It is easy to show that $\tilde{k} = \{k_1, k_3\}$. In order for the Brusselator to have a simple Hopf bifurcation at a positive steady state x (that will be derived later), parameters (j, \tilde{k}) must satisfy the condition:

$$j_2 = \left(1 - \frac{k_1 j_2^3}{k_3^3 j_1}\right) j_1.$$

Standard bifurcation theory leads to two conditions:

$$\begin{aligned} k_4^2 k_1 + k_3^3 - k_2 k_3^2 &= 0, \\ \frac{k_1 k_4}{k_2 k_3} - \frac{k_3}{k_4} &\neq 0 \end{aligned}$$

and it is not guaranteed that the corresponding steady state x is positive. Obviously in biology and chemistry applications only positive steady states are meaningful and of interest. The Brusselator therefore highlights the real advantage of the bifurcation conditions derived via SNA and toric geometry. Moreover, because $j \in V(J)$ are zero-set solutions of polynomials in $\mathbb{Q}(k)(j)$, the toric variety conditions guarantee the existence of a respective branch of equilibria on which the bifurcation occurs. One way of calculating this branch of equilibria is to use the Hermite Normal Form to solve the system $Nv(x, k) = \sum_{i=1}^M j_i E_i$, where $j \in V(J) \cap \mathbb{R}_+^M$. From now on, when referring to the variable h (the inverse of a steady state), the following convention shall be assumed:

$$h_s := h_s(j, \tilde{k}) = 1/x_s(j, \tilde{k}) \quad (1 \leq s \leq n), \quad (21)$$

with $x(j, \tilde{k})$ as the solution of

$$Nv(x, (k^*, \tilde{k})) = \sum_{i=1}^M j_i E_i, \quad j \in V(J) \cap \mathbb{R}_+^M. \quad (22)$$

Here $k^* = k^*(j, \tilde{k})$. The existence of a branch of equilibria is especially important for the Hopf bifurcation theorem. While the theorem from Liu [32] (given in Sect. 5) and all bifurcation theorems stated in [25] assume the existence of a smooth curve of

equilibria close to the Hopf bifurcation point, the SNA conditions derived in Theorem 6 will automatically guarantee the existence of a respective branch of positive equilibria. Finally, it should be noted that the change to convex parameters does not necessarily increase the dimension of the parameter space, as can be seen from the examples illustrating the bifurcation theorems.

4 Branching and bifurcations from simple eigenvalues

In this section conditions for existence of saddle-node bifurcations points and simple branching points are derived. Both bifurcations are associated with the occurrence of multistability.

4.1 Saddle-node bifurcation

Consider the mass-action ODE system (2) of the chemical reaction scheme (1) with M extreme currents. Assume that the chemical reaction network has no conservation relations, namely $\ker(N^T) = \{0\}$. If there are conservation relations, they can be incorporated into ODEs to generate a new set with no conservation relations, we refer to Example 4.1.2. In one parameter continuation all system parameters are kept fixed and only one is allowed to vary. As explained earlier, the parameter set is reparametrized as $\{j(\mu), \tilde{k}(\mu)\}$, where now μ is the free parameter. Typically one chooses one of the j 's or \tilde{k} 's as such a μ . We state the saddle-node bifurcation theorem:

Theorem 1 *Consider the mass-action chemical reaction system (2) with $\ker(N^T) = \{0\}$. Assume the system has M extreme currents and parametrization $\{j(\mu), \tilde{k}(\mu)\}$, where $j \in V(J) \cap \mathbb{R}_+^M$. Let H_i denote the $i \times i$ Hurwitz determinants of the characteristic polynomial (9) and define \bar{w} and \bar{y} to be the left and right eigenvectors of $Jac(j, h)$, with $h(\mu)$ from (21). Let the following conditions hold for some value of $\mu = \mu_0$:*

- (SNB1) $\alpha_0(j(\mu_0), h(\mu_0)) = 0$ and $H_{n-1}(j(\mu_0), h(\mu_0)) \neq 0$.
- (SNB2) $\bar{w}^T N_i \neq 0$ $i = 1, \dots, r$, where N_i is i th column of N , and
- (SNB3) $\bar{w}^T N \text{diag}(\sum_{i=1}^M j_i(\mu_0) E_i) S \text{diag}(h(\mu_0)) \bar{y} \neq 0$, where each column of the matrix S is defined by $S_i := \text{diag}(\kappa^i) \kappa^T \text{diag}(h(\mu_0)) \bar{y}$, with κ^i denoting the i th row of the kinetic matrix.

Then there exists a smooth positive curve of equilibria in $\mathbb{R}^n \times \mathbb{R}$ passing through $(1/h(\mu_0), \mu_0)$ at which the system undergoes a saddle-node bifurcation. Moreover, there exists a corresponding kinetic parameter vector $k \in \mathbb{R}_+^r$ such that system (2) undergoes the saddle-node bifurcation.

The proof will rely on establishing an equivalence with the following conditions described in [25]:

Theorem 2 *Let*

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

be a system of differential equations with equilibrium p at $\mu = \mu_0$. Assume that at this equilibrium the following hypotheses are satisfied:

- (SN1) $D_x f_{\mu_0}(p)$ has a simple eigenvalue 0 with right eigenvector y and left eigenvector w . Also $D_x f_{\mu_0}(p)$ has k eigenvalues with negative real parts and $(n - k - 1)$ eigenvalues with positive real parts (counting multiplicity),
- (SN2) $w^T (\frac{\partial}{\partial \mu} f_{\mu}(p, \mu_0)) \neq 0$, and
- (SN3) $w^T (D_x^2 f_{\mu_0}(p)(y, y)) \neq 0$.

Then there is a smooth curve of equilibria in $\mathbb{R}^n \times \mathbb{R}$ passing through (p, μ_0) tangent to the hyperplane $\mathbb{R}^n \times \mu_0$. Depending on the signs of expressions in (SN2) and (SN3) there are no equilibria near (p, μ_0) when $\mu < \mu_0$ (or $\mu > \mu_0$) and two equilibria near (p, μ_0) when $\mu > \mu_0$ (or $\mu < \mu_0$). These two equilibria near (p, μ_0) are hyperbolic and have manifolds of dimensions k and $k + 1$, respectively.

Proof It will be shown that conditions (SNB1)–(SNB3) imply conditions (SN1)–(SN3). Since $j(\mu_0) \in V(J) \cap \mathbb{R}_+^M$, by our choice of $(j(\mu_0), \bar{k}(\mu_0))$ there exists at least one positive solution, i.e., $x = p$. It can be calculated by recovering k^* parameters. If we define $h(\mu_0)$ to be the inverse of the positive solution, then $Jac(j(\mu_0), h(\mu_0))$ is the Jacobian of the system evaluated at a positive steady state. A necessary and sufficient condition for $Jac(j, h)$ to have a zero eigenvalue is that $\alpha_0(j, h) = 0$. A necessary condition for a characteristic polynomial to have at least a pair of pure imaginary eigenvalues or multiple zero eigenvalues is $H_{n-1}(j, h) = 0$, a result from Orlando's formula [20]. Hence, (SNB1) implies (SN1).

Now, since each parameter k_i only features in one corresponding reaction rate, $v_i(x, k)$, the partial derivative of the vector field with respect to k_i is

$$\frac{\partial}{\partial k_i} N v(x, k) = N \frac{\partial}{\partial k_i} v(x, k) = \frac{v_i(x, k)}{k_i} N_i = \left(\prod_{l=1}^n x_l^{\alpha_{li}} \right) N_i,$$

where N_i is the i th column of N . We reparametrize the ODE modeling (2) as $k = k(\mu)$, by choosing any k_i is as the bifurcation parameter μ and keeping the remaining k 's as constants. At the corresponding positive steady state $p = (p_1, \dots, p_n)$, condition (SN2) can be rewritten as,

$$\begin{aligned} w^T \frac{\partial}{\partial k_i} N v(p, k(\mu_0)) &= w^T \left(\prod_{l=1}^n p_l^{\alpha_{li}} N_i \right) \\ &= \left(\prod_{l=1}^n p_l^{\alpha_{li}} \right) w^T N_i, \quad \text{for any } i = 1, \dots, r. \end{aligned}$$

Since $(\prod_{l=1}^n p_l^{\alpha_{li}}) > 0$, it follows that (SNB2) implies (SN2). Now, with all above conditions satisfied, we will show that they together imply (SN3). First, the tensor product $D_x^2 N v(x, k)(r, r)$ for $r \in \mathbb{R}^n$, must be rewritten in form similar to (8). Let

$$D_x^2 N v(x, k)(r, r) = T(x, k, r)r \quad (23)$$

where the i th column of matrix $T(x, k, r)$ is

$$T_i = \frac{\partial}{\partial x_i} D_x N v(x, k) r.$$

Because of the form of Jacobian $D_x N v(x, k)$ taken from (8), by the chain rule we get

$$\begin{aligned} & \frac{\partial}{\partial x_i} D_x N v(x, k) \\ &= N \frac{\partial}{\partial x_i} (\text{diag}(v(x, k))) \kappa^T \text{diag}(x^{-1}) + N \text{diag}(v(x, k)) \kappa^T \frac{\partial}{\partial x_i} (\text{diag}(x^{-1})). \end{aligned}$$

Taking κ^i as i th row of κ ,

$$\begin{aligned} \frac{\partial}{\partial x_i} (\text{diag}(v(x, k))) &= \text{diag}(v(x, k)) \text{diag}(\kappa^i) x_i^{-1}, \\ \frac{\partial}{\partial x_i} (\text{diag}(x^{-1})) &= -\text{diag}((x^{-1})) \Phi_i x_i^{-1}, \end{aligned}$$

with Φ_i defined as a matrix of zeros with only the $i \times i$ th entry equal to 1. Considering each i th column of T is multiplied by factor of $(x^{-1})_i$, and that each column can also be written as a vector difference, it holds that

$$T = N \text{diag}(v(x, k)) S \text{diag}(x^{-1}) - N \text{diag}(v(x, k)) \kappa^T U \text{diag}(x^{-1}),$$

where S and U are matrices with the i th columns equal to

$$\begin{aligned} S_i &= \text{diag}(\kappa^i) \kappa^T \text{diag}(x^{-1}) r, \\ U_i &= \Phi_i \text{diag}(x^{-1}) r = \text{diag}(x^{-1}) \Phi_i r. \end{aligned}$$

But $U = \text{diag}(x^{-1}) \text{diag}(r)$, and hence

$$T = N \text{diag}(v(x, k)) S \text{diag}(x^{-1}) - D_x N v(x, k) \text{diag}(r) \text{diag}(x^{-1}). \quad (24)$$

Using Eqs. (23) and (24), condition (SN3) can be rewritten as

$$\begin{aligned} w^T D_x^2 N v(p, k(\mu_0))(y, y) &= w^T T(p, k(\mu_0), y) y \\ &= w^T N \text{diag}(v(p, k(\mu_0))) S \text{diag}(p^{-1}) y, \end{aligned}$$

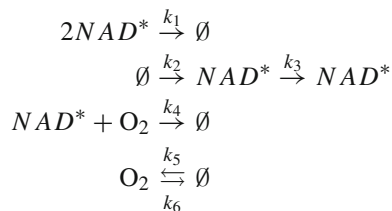
since $w^T \in \text{Ker}(D_x N v(p, k(\mu_0)))$. From here it is easy to see that (SNB3) is sufficient for (SN3) to be true.

It must be emphasized that the chemical reaction network must be written in the form that already incorporates the conservation relations, which means $\text{Ker}(N^T)$

must be an empty set. Assume the opposite, i.e. that the system contains r conservation relations. Because of the form of the Jacobian, $D_x Nv(x_0, k_0)$ in (8), $Ker(N^T) \subseteq Ker(D_x^T Nv(x_0, k_0))$. Each conservation relation implies that there is a column of $D_x Nv(x_0, k_0)$ which is a linear combination of the other columns. Hence one zero eigenvalue of $D_x^T Nv(x_0, k_0)$ corresponds to each conservation relation. In order for a saddle-node bifurcation to appear in a system with r conservation relations, the number of zero eigenvalues of $D_x^T Nv(x_0, k_0)$ must be $r + 1$. However, the dimension of the eigenspace of the zero eigenvalues is always less or equal to the algebraic multiplicity of the eigenvalue, in this case $r + 1$. Therefore it is possible that $Ker(N^T) = Ker(D_x^T Nv(x_0, k_0))$, in which case the left eigenvectors \bar{w} of $D_x Nv(x_0, k_0)$ will never satisfy condition (SNB3). Next the applicability of the saddle node bifurcation theorem will be shown with two examples.

4.1.1 Subnetwork of the peroxidase–oxidase reaction system

The following model is a core bistable subnetwork of a peroxidase–oxidase reaction model from [5], as described in [38]. An analysis of the necessary bistability conditions (necessary saddle-node conditions) for the *full* PO reaction system is given in [1]. Here the model includes also reactions between the NAD^* free radicals and O_2 :



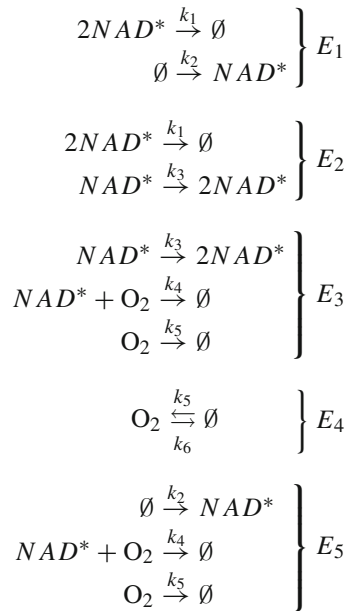
The first and second reaction model the inflow and outflow of NAD^* , while the third models the autocatalytic formation of NAD^* . The fourth reaction is the oxidation of NAD^* when in contact with O_2 , and the fifth and sixth reaction model the inflow and outflow of O_2 . Given mass-action kinetics the differential equations describing this process are

$$\begin{aligned} \dot{x}_1 &= -2k_1x_1^2 + k_2 + k_3x_1 - k_4x_1x_2, \\ \dot{x}_2 &= k_5 - k_6x_2 - k_4x_1x_2. \end{aligned}$$

Here x_1 and x_2 denote the concentrations of NAD^* and O_2 , respectively. The system has six kinetic parameters and the network consists of five extreme currents:

$$\begin{aligned} E_1 &= (1, 2, 0, 0, 0, 0), \\ E_2 &= (1, 0, 2, 0, 0, 0), \\ E_3 &= (0, 0, 1, 1, 1, 0), \\ E_4 &= (0, 0, 0, 0, 1, 1), \\ E_5 &= (0, 1, 0, 1, 1, 0). \end{aligned}$$

The extreme currents (in same order) represent the following reaction subnetworks, each admitting steady state solutions:



From the variety of the deformed toric ideal the following relations for the kinetic parameters and convex parameters can be derived:

$$\begin{aligned}
 k_3^2 (j_1 + j_2) - k_1 (2j_2 + j_3)^2 &= 0, \\
 2j_1 + j_5 - k_2 &= 0, \\
 -k_6 k_3 (j_3 + j_5) + k_4 (2j_2 + j_3) j_4 &= 0, \\
 j_3 + j_4 + j_5 - k_5 &= 0.
 \end{aligned} \tag{25}$$

With these relations four of the kinetic parameters k_1, k_2, k_4 and k_5 can be rewritten as convex parameters, with k_3 and k_6 remaining parameters in the transformed system. For the convex parameters j s satisfying above relations positive species variables exist. Their inverses are calculated via Hermite Normal form:

$$\begin{aligned}
 h_1 &= \frac{k_3}{2j_2 + j_3}, \\
 h_2 &= \frac{k_6}{j_4}.
 \end{aligned} \tag{26}$$

The Jacobian matrix in convex parameters reads

$$Jac(j, h) = \begin{bmatrix} (-4j_1 - 2j_2 - j_5) h_1 & -(j_3 + j_5) h_2 \\ -(j_3 + j_5) h_1 & -(j_3 + j_4 + j_5) h_2 \end{bmatrix},$$

and the characteristic polynomial takes the form

$$\lambda^2 + \alpha_1 \lambda + \alpha_0.$$

Here the coefficients are

$$\begin{aligned}\alpha_0 &= j_4 h_2 h_1 (4j_1 + 2j_2 + j_5) + h_1 h_2 (j_3 + j_5) (4j_1 + 2j_2) - h_1 h_2 j_3 \\ &\quad \times (j_3 + j_5) (j_3 + j_4 + j_5), \\ \alpha_1 &= (4j_1 + 2j_2 + j_5) h_1 + (j_3 + j_4 + j_5) h_2.\end{aligned}$$

Since α_1 is always positive, (SNB1) is satisfied when $\alpha_0 = 0$:

$$j_4(4j_1 + 2j_2 + j_5) + (j_3 + j_5)(4j_1 + 2j_2) - j_3(j_3 + j_5)(j_3 + j_4 + j_5) = 0. \quad (27)$$

The right and left eigenvectors of $Jac(j, h)$ subject to (27) are

$$\overline{w(j)} = c_1 \left[-\frac{1}{\frac{(j_3+j_5)}{j_3+j_4+j_5}} \right] \quad \text{and} \quad \overline{y(j, h)} = c_2 \left[-\frac{1}{\frac{(j_3+j_5)h_1}{(j_3+j_4+j_5)h_2}} \right],$$

with some arbitrary lengths $c_1, c_2 \in \mathbb{R}$. Then (SNB2) reduces to

$$j_5 + j_3 \neq 0 \quad \text{and} \quad j_4 \neq 0, \quad (28)$$

but these conditions are automatically satisfied if all convex parameters are positive. Next for (SNB3) to hold the following condition needs to be satisfied:

$$\begin{aligned}0 \neq & -(4j_3 j_2 j_4 + j_3 j_5^2 - 3j_5^2 j_4 + 2j_2 j_5^2 + j_3^3 + 2j_3^2 j_5 + 2j_2 j_3^2 - j_5 j_4^2 \\ & + 2j_2 j_4^2 + 4j_3 j_2 j_5 + 4j_4 j_2 j_5 - 4j_3 j_5 j_4 - j_4 j_3^2) h_2^2 (j_3 + j_4 + j_5) h_1^2,\end{aligned} \quad (29)$$

where h_1 and h_2 are of the forms given in Eq. (26). When convex parameters j and kinetic parameters k_3 and k_6 satisfy conditions (27) and (29), then the system undergoes a saddle-node bifurcation. Numerous values can be chosen in order to satisfy these conditions. All other kinetic parameters and species concentration values can be retrieved by substituting the results into Eqs. (25) and (26). Figure 1 shows a plot of the SNB curves in two-parameter space calculated via the SNA method and via XPPaut, i.e. numerically. Here the values taken are: $k_3 = 2$, $k_6 = 0.14$, and for the convex parameters: $j_1 = 0.05$, $j_2 = 0.0337$, $j_3 = 1.4268$, $j_4 = 3.1732$, $j_5 = 0.4$. All kinetic parameter values could be retrieved by back-substitution. Bifurcation parameters are k_1 and k_4 , respectively (because XPPaut does not work with convex parameters).

4.1.2 A cell-cycle model

The given cell cycle is a complex network that can be described in terms of three modules as introduced by Tyson et al. [44]. Two of these modules have been identified as bistable networks, where the levels of cyclin serve as an indicator for the cell to

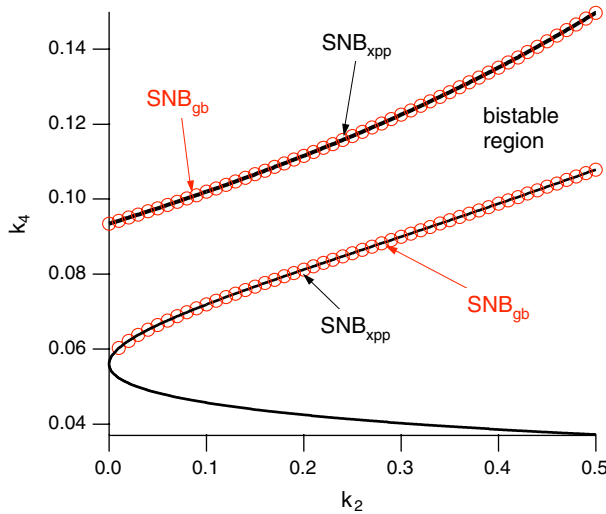
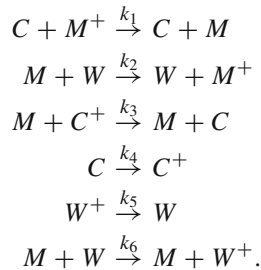


Fig. 1 Two-parameter bifurcation diagram of the peroxidase-oxidase reaction model for $k_1 = 0.3k_3 = 2$, $k_5 = 5$, $k_6 = 0.14$. Moreover k_4 and k_2 are bifurcation parameters. SNB_{xpp} and SNB_{gb} denote saddle-node bifurcations detected by XPPaut and the SNA method, respectively. SNA conditions cannot detect a curve for $k_4 < 0.056$ detected by XPPaut, since for these parameter values the SNB is not a positive steady state. A numerical survey with XPPaut shows that the model is bistable for pairs of (k_4, k_2) between the two upper SNB_{xpp} curves

switch from one phase to another. The second module regulates the cell's transition from G_2 phase to M-phase, which is mitosis. Here a model of the second module proposed by [41] is considered:



Here M and M^+ denote active and inactive concentrations of MPF (mitosis promoting factors). C and W with same superscripts denote inactive(+) and active concentrations of cyclin cdc-25, and Myt-1, a member of the *wee1* family of protein kinases. The model has three conservation relations. It is assumed that the total concentrations of MPF, cdc-25 and Myt-1 (denoted by m_t , c_t and w_t) are constant. In [41] the authors derive the model in terms of the active form

$$\begin{aligned}
 \dot{m} &= k_1 c(m_t - m) - k_2 m w, \\
 \dot{c} &= k_3 m(c_t - c) - k_4 c, \\
 \dot{w} &= k_5(w_t - w) - k_6 m w.
 \end{aligned}$$

Since m_t , c_t and w_t are parameters, the system is rewritten as

$$\begin{aligned}\dot{m} &= k_7c - k_1mc - k_2mw, \\ \dot{c} &= k_8m - k_3mc - k_4c, \\ \dot{w} &= k_9 - k_5w - k_6mw,\end{aligned}$$

to continue with familiar labeling. We have $k_7 = k_1m_t$, $k_8 = k_3c_t$ and $k_9 = k_5w_t$. There are nine kinetic parameters in this system. It can be written again in terms of convex parameters associated to six extreme currents:

$$\begin{aligned}E_1 &= (1, 0, 0, 0, 0, 0, 1, 0, 0), \\ E_2 &= (0, 1, 0, 0, 0, 0, 1, 0, 0), \\ E_3 &= (0, 0, 1, 0, 0, 0, 0, 1, 0), \\ E_4 &= (0, 0, 0, 1, 0, 0, 0, 1, 0), \\ E_5 &= (0, 0, 0, 0, 1, 0, 0, 0, 1), \\ E_6 &= (0, 0, 0, 0, 0, 1, 0, 0, 1).\end{aligned}$$

The variety of the deformed toric ideal for convex parameters gives rise to the following six relations:

$$\begin{aligned}k_8k_7j_1 - k_1(j_1 + j_2)(j_3 + j_4) &= 0, \\ -k_2j_6 + k_6j_2 &= 0, \\ k_8k_7j_3 - (j_3 + j_4)(j_1 + j_2)k_3 &= 0, \\ -k_4(j_1 + j_2) + k_7j_4 &= 0, \\ -k_5k_8j_6 + k_6(j_3 + j_4)j_5 &= 0, \\ j_5 + j_6 - k_9 &= 0.\end{aligned}\tag{30}$$

This implies six of the kinetic parameters (say, $k_3, k_5, k_6, k_7, k_8, k_9$) can be rewritten as combinations of convex parameters and the other three kinetic parameters (k_1, k_2, k_4). For convex parameters satisfying the relations in (30) positive values of m , w and c can be retrieved. Via Hermite Normal Form, their inverses are:

$$\begin{aligned}1/m = h_1 &= \frac{k_1j_4}{k_4j_1}, \\ 1/c = h_2 &= \frac{k_4}{j_4}, \\ 1/w = h_3 &= \frac{j_1k_2k_4}{j_2j_4k_1}.\end{aligned}$$

The Jacobian matrix in convex parameters reads

$$Jac(j, h) = \begin{bmatrix} (-j_1 - j_2) h_1 & j_2 h_2 & -j_2 h_3 \\ j_4 h_1 & (-j_3 - j_4) h_2 & 0 \\ -j_6 h_1 & 0 & (-j_5 - j_6) h_3 \end{bmatrix}.$$

Here the characteristic polynomial of the Jacobian matrix is a cubic polynomial of the form

$$\lambda^3 + \alpha_2 \lambda^2 + \alpha_1 \lambda + \alpha_0.$$

All coefficients of the characteristic polynomial are positive except α_0 . Hence, for (SNB1) to hold we only need to check that $\alpha_0 = 0$. Therefore we have

$$j_1 j_4 j_6 + j_1 j_3 j_5 + j_1 j_3 j_6 + j_1 j_4 j_5 + j_2 j_3 j_5 - j_2 j_4 j_6 = 0. \quad (31)$$

The right and left eigenvectors of $Jac(j, h)$ subject to (31) are

$$\overline{w}(j) = c_1 \begin{bmatrix} -\frac{j_5+j_6}{j_2} \\ -\frac{j_5+j_6}{j_3+j_4} \\ 1 \end{bmatrix} \quad \text{and} \quad \overline{y}(j, h) = c_2 \begin{bmatrix} -\frac{(j_5+j_6)h_3}{j_6 h_1} \\ -\frac{h_3 j_4 (j_5+j_6)}{h_2 j_6 (j_3+j_4)} \\ 1 \end{bmatrix},$$

with $c_1, c_2 \in \mathbb{R}$. Then (SNB2) reduces to the condition

$$j_5 + j_6 \neq 0. \quad (32)$$

Obviously, this condition holds for all positive convex parameters. Finally (SNB3) takes the form

$$\begin{aligned} \overline{w}^T N \text{diag}(v(j)) S \text{diag}(h) \overline{y} &= \frac{h_3^2 (j_5 + j_6)}{j_2 j_6^2 (j_3 + j_4)^2} \left(-3 j_5 j_2 j_6 j_4^2 + 3 j_1 j_5^2 j_4^2 + 3 j_1 j_6^2 j_4^2 \right. \\ &\quad - j_2 j_6^2 j_4^2 + 6 j_1 j_5 j_6 j_4^2 + 3 j_5^2 j_2 j_3 j_4 + 4 j_1 j_5^2 j_3 j_4 \\ &\quad + 8 j_1 j_5 j_6 j_3 j_4 + 4 j_1 j_6^2 j_3 j_4 + j_3 j_2 j_6^2 j_4 + j_1 j_5^2 j_3^2 \\ &\quad \left. - j_5 j_2 j_6 j_3^2 + j_5^2 j_2 j_3^2 + j_1 j_6^2 j_3^2 + 2 j_1 j_5 j_6 j_3^2 \right) \\ &\neq 0. \end{aligned} \quad (33)$$

If there are convex parameters j satisfying conditions (31) and (33), then the system undergoes a saddle-node bifurcation. If k_1, k_2 and k_4 are fixed the precise values of other kinetic parameters and also the variable values (m, w, c) can be calculated such that a saddle-node bifurcation will occur. A comparison of these results with those of XPPaut is given in Fig. 2. In this two-parameter (k_1, k_7) bifurcation plot, the full curve of XPPaut cannot be traced. This is because for $k_7 > 2.5$ the saddle-node bifurcation

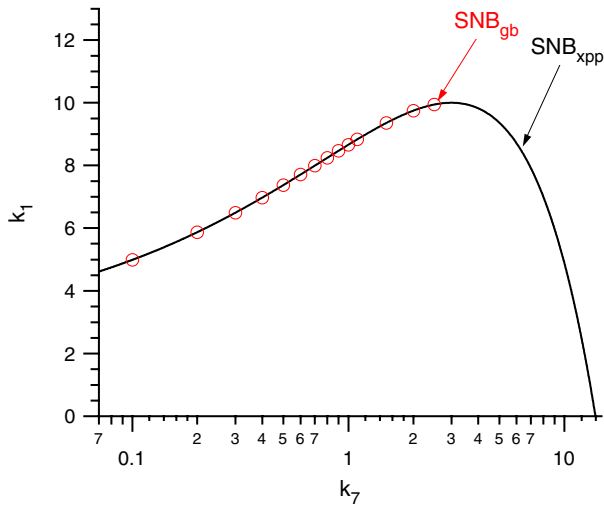


Fig. 2 Two-parameter bifurcation diagram of the cell cycle model for $k_2 = 1$, $k_3 = 1$, $k_4 = 10$, $k_5 = 2.5$, $k_6 = 1$, $k_8 = 1$ and $k_9 = 2.5$. k_1 and k_7 are bifurcation parameters. SNB_{xpp} and SNB_{gb} denote saddle-node bifurcations detected by XPPaut and our method, respectively. SNA conditions cannot detect SNBs for $k_7 > 2.5$ since for these parameter values the SNB is not a positive steady state

is not a positive steady state (and not biologically meaningful), and hence the SNA conditions cannot detect it.

4.2 Simple branching point

For completeness we also consider simple branching points. One can restate the condition for a curve of equilibria given by

$$Nv(x, k) = 0 \quad (34)$$

as a curve in \mathbb{R}^{n+1} defined by n equations:

$$F(y) = 0, \quad F : \mathbb{R}^{n+1} \rightarrow \mathbb{R}^n. \quad (35)$$

Here the computation of the equilibria is parametrised by one parameter, say k_l . A zero solution $y^* \in \mathbb{R}^{n+1}$ of F is called a *branching point* if there are at least two different smooth curves satisfying (35), and passing through y^* . Some of the well known branching points are: The pitchfork bifurcation (a situation where a stable steady state loses stability to two new simultaneously created steady states as the bifurcation parameter is varied), and the transcritical bifurcation (where two steady states of different stability types coalesce and exchange their stability types). The pitchfork bifurcation is associated with bistability. The conditions for a simple branching point to occur can be stated with SNA theory. But for above more specific branching points some additional conditions are needed, and this will not be covered in this paper. Denote a transpose of an extended kinetic matrix as

$$\tilde{\kappa}^T = [\kappa^T | e_l],$$

where e_l is a normalized basis vector in \mathbb{R}^n , with the l th entry being the only non-zero entry. Each i th row of $\tilde{\kappa}$ is denoted $\tilde{\kappa}^i$. Let $\tilde{h} = (h, k_l^{-1})$. The Jacobian matrix of (35) in convex pair (j, h) coordinates becomes

$$J(j, h) = N \operatorname{diag} \left(\sum_{i=1}^M j_i E_i \right) \tilde{\kappa}^T \operatorname{diag}(\tilde{h}).$$

For any vectors $x, w \in \mathbb{R}^{n+1}$ and $u \in \mathbb{R}^n$, consider a matrix $S(x)$ to be an $(n+1) \times (n+1)$ matrix with each i th column defined by

$$S(x)_i := \operatorname{diag}(\tilde{\kappa}^i) \tilde{\kappa}^T \operatorname{diag}(\tilde{h}) x.$$

Consider a function $b : \mathbb{R}^n \times \mathbb{R}^m \times \mathbb{R}^m \rightarrow \mathbb{R}$ where

$$b(u, x, w) = u^T N \operatorname{diag} \left(\sum_{i=1}^M j_i E_i \right) S(x) \operatorname{diag}(\tilde{h}) w.$$

With these notations we can state the following theorem:

Theorem 3 Consider the mass-action chemical reaction system (2) with M extreme currents and corresponding convex parameters j_1, \dots, j_M . Assume the system has a parametrization $\{j(\mu), \tilde{k}(\mu)\}$, where $j \in V(J) \cap \mathbb{R}_+^M$. If at some $\mu = \mu_0$,

- (BP1) $\operatorname{rank}(J(j(\mu_0), h(\mu_0))) = n - 1$, and with q_1, q_2 being two linearly independent left eigenvectors, and r a right eigenvector of $J(j(\mu_0), h(\mu_0))$, it holds that
- (BP2) $b(r, q_1, q_1)b(r, q_2, q_2) - b(r, q_1, q_2)^2 < 0$, then there exist branches of positive equilibria locally which intersect at a simple branching point.

Proof The conditions can be derived from any standard conditions for a simple branching point, see [31]. The local existence of branches follows from the use of the toric variety $V(J)$. \square

4.3 Bistability

Bistability describes a situation where a network contains two stable equilibria. Recently a plethora of theoretical and numerical evidence has emerged that suggest the importance of bistability in a number of chemical and biochemical systems, see [13]. Bistability is often characterized as a result of a bifurcation, and then most frequently is created by the occurrence of two saddle-node bifurcations, as a bifurcation parameter is varied. Hence for bistability to occur two saddle node bifurcations need to be identified as one of the parameters is varied. By fixing some values for all but one parameter in the peroxidase–oxidase subnetwork, it can be confirmed that there

are two values of the bifurcation parameter where a saddle-node bifurcations occurred (Fig. 1). In the cell-cycle model, when biologically feasible parameters from [41] were used, it only gave rise for one saddle-node bifurcation. This is to be expected, since in modeling the cell-cycle, the authors of [41] made the simplifying assumption that one of the saddle-node bifurcations takes place when cdc-25 and Myt are at zero concentrations. As mentioned earlier, stoichiometric network analysis cannot be applied to non-positive steady states, hence both saddle-node bifurcations could not be identified.

4.4 Another method for identifying bistability

The following interpretation of the bistability criteria is a small extension of the method applied and published in [38] and [40]. The aim is to find a parametrization $k(\mu)$ for which bistability occurs as μ is varied. Usually $\mu = k_i$ for some $i = 1, \dots, p$. With the network described via extreme currents, (j, h) have to satisfy condition (SNB1) in order to guarantee existence of positive concentration steady states. Along the curve of $(j(k), h(k), k)$, three values of k need to be determined where $\alpha_0(j(k), h(k))$ changes sign three times in order of increasing (or decreasing) k values, and $H_{n-1}(j(k), h(k)) \neq 0$. Then a parametrization $k(\mu)$ is chosen and one should calculate μ values such that $\alpha_n(j(k(\mu)), h(k(\mu))) = 0$, and finally one needs to check conditions (SNB2) and (SNB3) for these points.

5 The Hopf bifurcation

In this section we will use SNA theory to derive sufficient conditions for a reaction network to enable having a simple Hopf bifurcation. Similar results for identifying a Hopf bifurcation in chemical reaction networks via SNA have been published by Sensse et al. [21,37,39] on which we base our results. We will rely on the Routh Hurwitz theorem which states

Theorem 4 (Routh–Hurwitz) *The number of eigenvalues of $D_x N v(x; k)$ with positive real part equals the sum of the number of sign changes in the two sequences*

$$\{1, H_1, H_3, \dots\} \quad \text{and} \quad \{1, H_2, H_4, \dots\}$$

where each H_i is the $i \times i$ th Hurwitz determinant derived from (9) in the form described in [20].

Gatermann et al. [21] and Sensse and Eiswirth [39] were the first to employ use of the deformed toric ideal in SNA and suggest a method to search for the Hopf bifurcation. Their suggestion is to follow a path of steady states $(x(k), k)$ and search for a point where the number of sign changes in the sequences of Hurwitz determinants jumps by two. Then, via Routh–Hurwitz theorem, there is a point on the curve $(x(k), k)$ where two eigenvalues cross the imaginary axis. However, it is possible that these two eigenvalues at the bifurcation point are not purely imaginary. They could have multiple zeros. The authors suggest monitoring the values of a_0 , or the determinant of the

Jacobian. If the determinant does not change sign, then the pair of eigenvalues cannot be a pair of zeros. In [21, 39], it is also suggested to monitor the derivative of the sign changing Hurwitz determinants vanishing, to make sure the pair of eigenvalues crosses the imaginary axis. However, these conditions rely on the explicit reformulation of conditions in terms of the concentration steady states. This paper presents a mathematical formulation for a simple Hopf bifurcation and several examples. The theorem derived relies on an application of conditions from the following ‘local’ Hopf bifurcation theorem stated in terms of Hurwitz determinants:

Theorem 5 [32] *Assume that for a system*

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

there exists a smooth curve of equilibria $(x(k), k)$ with $x(k_0) = k_0$. This system has a simple Hopf bifurcation if the following conditions on the coefficients of the characteristic polynomial of the Jacobian $D_x f(x_0, k_0)$ hold:

- (CH1) $a_0(k_0) > 0, H_1(k_0) > 0, \dots, H_{n-2}(k_0) > 0, H_{n-1}(k_0) = 0$; and
 (CH2) $\frac{d}{dk} H_{n-1}(k_0) \neq 0$.

where each H_i is the i th Hurwitz determinant.

This theorem assumes the existence of a smooth curve of equilibria close to a Hopf bifurcation point. Based on the condition stated we will derive conditions for a simple Hopf bifurcation in terms of convex parameters (extending previous work in SNA), but will also exploit algebraic geometry: in addition conditions can be given that guarantee the existence of a respective branch of positive equilibria on which such a simple Hopf bifurcation occurs. The existence of such a local branch of equilibria follows from the usage of the toric variety $V(J)$. One way of calculating the branch of equilibria is to use the Hermite Normal Form to solve the system $Nv(x, k) = \sum_{i=1}^M j_i E_i$, where $j \in V(J) \cap \mathbb{R}_+^M$.

In case that we interpret the extreme currents as subnetworks in equilibrium, the theorem also gives sufficient conditions such that by variation of the strength of the subnetworks, measured in terms of j , the total network is able to oscillate. The potential of such findings is that biologists might have an indication of which parts of the network may be more important to generate oscillatory behaviour. For example, if there exists a reaction rate parametrized only by a current which does not even occur in the sufficient conditions stated below, then one would expect that the corresponding reaction is not crucial to generate any oscillations.

Theorem 6 *Consider the mass-action chemical reaction system (2) with M extreme currents and parametrization $\{j(\mu), \tilde{k}(\mu)\}$, where $j \in V(J) \cap \mathbb{R}_+^M$. Let H_i denote the $i \times i$ Hurwitz determinants of the characteristic polynomial (9) with $h(\mu)$ from (21). Let for some value of $\mu = \mu_0$ the following conditions hold:*

- (HB1) $\alpha_0(j(\mu_0), h(\mu_0)) > 0, H_1(j(\mu_0), h(\mu_0)) > 0, \dots, H_{n-2}(j(\mu_0), h(\mu_0)) > 0, H_{n-1}(j(\mu_0), h(\mu_0)) = 0$.
 (HB2) $\sum_{s=1}^M \frac{\partial H_{n-1}}{\partial j_s} \frac{\partial j_s}{\partial \mu} \neq 0$.

Then there exist kinetic parameter vectors $k \in \mathbb{R}_+^p$ and a local smooth curve of positive equilibria parametrised by k such that the reaction network undergoes a simple Hopf bifurcation.

Proof For every $j \in V(J) \cap \mathbb{R}_+^M$, there exists a curve of concentration steady states parametrized by k , namely $(x(k), k)$ such that $Nv(x(k), k) = 0$, see [21]. Moreover, there exists at least one k_0 such that the corresponding steady state $x(k_0) = x_0 \in \mathbb{R}_+^n$ [21]. The choice of h is in fact $1/x_0$. $Jac(j, h)$ is the Jacobian evaluated at this steady state x_0 . (HB1) implies condition (CH1) and by the chain rule, (HB2) implies (CH2). \square

- Remarks 1* (i) Theorem 6 makes no distinction of the type of simple Hopf bifurcation: whether it is supercritical, subcritical or degenerate. This would require additional conditions on the higher order terms of the system. Such effort requires a lengthy computation of the dynamics restricted to the centre manifold and involves coordinate changes that have no clear interpretation in terms of extreme currents. This is a limitation of the method.
- (ii) A good future direction would be to extend the sufficient conditions for a simple Hopf bifurcation to a general Hopf bifurcation. Here the problem lies in finding sufficient conditions for the existence of two eigenvalues with non-zero imaginary part that will cross the imaginary axis along the curve of equilibria $(x(k), k)$, while all other eigenvalues can have positive or negative real parts.

The following is a list of prominent examples that have been studied in the literature. It will be shown that the conditions of the Hopf bifurcation theorem in low-dimensional examples (with up to 4 variables) can be computed relatively easily. For higher-dimensional models, more sophisticated symbolic computations will have to be implemented, as discussed in Sect. 3.

5.1 Calcium dynamics

This example is a completion of an extensive analysis of the model of intracellular calcium oscillations published in [21]. The model describes enzymatic transfer of calcium ions Ca^{+2} across the cell membrane and is a modification of model of Ca^{+2} -induced oscillations in muscle cells proposed by Dupont and Goldbeter [22].

Four species take part in the reactions. Variables x_1 and x_2 denote the concentrations of Ca^{+2} ions in the cytosol and the endoplasmic reticulum, respectively. Variable x_3 is the concentration of the enzyme catalyzing the absorption of Ca^{+2} back into the endoplasmic reticulum, and x_4 is the concentration of the complex formed when enzyme binds to cytosolic calcium. Influx and efflux of cytosolic calcium across the cell membrane are modeled by reaction constants k_{12} and k_{21} respectively. Calcium-induced-calcium-release (CICR) is modeled as an autocatalytic production of cytosolic calcium with rate constant k_{43} . Absorption of calcium back into the endoplasmic reticulum is an enzymatic reaction, involving binding and dissociation of the enzyme with cytosolic calcium, at rate constants k_{56} and k_{65} respectively, and conversion of the calcium–enzyme complex back to endoplasmic calcium at rate k_{76} . The differential equations describing this process are

$$\begin{aligned}
\dot{x}_1 &= -k_{12}x_1 + k_{21} + k_{43}x_1x_2 + k_{56}x_4 - k_{65}x_1x_3, \\
\dot{x}_2 &= -k_{43}x_1x_2 + k_{76}x_4, \\
\dot{x}_3 &= k_{56}x_4 - k_{65}x_1x_3 + k_{76}x_4, \\
\dot{x}_4 &= -k_{56}x_4 + k_{65}x_1x_3 - k_{76}x_4.
\end{aligned}$$

The total concentration of enzyme (free enzyme x_3 and bound enzyme in the complex x_4) is conserved:

$$x_3 + x_4 = c. \quad (36)$$

The model has seven parameters: six kinetic parameters and one conservation parameter. This model contains three extreme currents (three steady-state generating sub-networks):

$$E_1 = (1, 1, 0, 0, 0, 0), \quad E_2 = (0, 0, 0, 1, 1, 0), \quad \text{and} \quad E_3 = (0, 0, 1, 0, 1, 1).$$

In given order, they correspond to influx and efflux of cytosolic calcium, association and dissociation of the enzyme–substrate binding complex, and autocatalytic release of endoplasmic calcium into the cytosol offset by enzymatic absorption of cytosolic calcium into the endoplasmic reticulum. The deformed toric ideal of convex parameters is

$$J = \langle k_{76}j_2 - k_{56}j_3, j_1 - k_{21} \rangle.$$

Reparametrizing several kinetic constants as combinations of convex parameters leads to

$$k_{21} = j_1, \quad (37)$$

$$k_{56} = \frac{k_{76}j_2}{j_3}. \quad (38)$$

Via Hermite Normal Form, with restrictions from (37) and (38) positive species concentrations can be calculated. Their inverses come in the form

$$(h_1(k), h_2(k), h_3(k), h_4(k)) = \left(\frac{k_{12}}{j_1}, \frac{j_1k_{43}}{k_{12}j_3}, \frac{j_1k_{65}}{(\frac{j_2}{j_3} + 1)k_{12}j_3}, \frac{k_{76}}{j_3} \right). \quad (39)$$

Substituting them back into (36) gives a restriction on c parameter,

$$c = \frac{k_{12}k_{56} + k_{12}k_{76}k_{21}k_{65}}{j_1k_{76}k_{65}j_3}. \quad (40)$$

The model in convex parameters has seven parameters: three convex parameters and four kinetic parameters, k_{12} , k_{43} , k_{65} , k_{76} . All other parameters and variable values can be retrieved using previous equations. The convex Jacobian is

$$Jac(j, h) = \begin{bmatrix} (-j_1 - j_2)h_1 & j_3h_2 & (-j_2 - j_3)h_3 & j_2h_4 \\ -j_3h_1 & -j_3h_2 & 0 & j_3h_4 \\ (-j_2 - j_3)h_1 & 0 & (-j_2 - j_3)h_3 & (j_2 + j_3)h_4 \\ (j_2 + j_3)h_1 & 0 & (j_2 + j_3)h_3 & (-j_2 - j_3)h_4 \end{bmatrix},$$

where h are of the form (39). One eigenvalue of this Jacobian is always zero (because of the conservation relation) and hence the part of characteristic polynomial that is of interest becomes

$$\lambda^3 + \alpha_3\lambda^2 + \alpha_2\lambda + \alpha_1.$$

All coefficients except α_2 are positive:

$$\begin{aligned} \alpha_1 &= h_1j_1j_3h_2h_3j_2 + h_1j_1j_3^2h_2h_3 + h_1j_1j_3h_2j_2h_4 + h_1j_1j_3^2h_2h_4, \\ \alpha_2 &= j_3^2h_2h_4 + j_3^2h_2h_3 + j_3^2h_1h_2 - h_1h_3j_3^2 + h_1j_1h_3j_3 + h_1j_1j_3h_2 - h_1j_2h_3j_3, \\ &\quad + h_1j_2j_3h_2 + j_3h_2j_2h_4 + j_3h_2h_3j_2 + h_1j_1j_2h_4 + h_1j_1j_3h_4 + h_1j_1h_3j_2 \\ \alpha_3 &= j_2h_4 + j_3h_4 + h_3j_2 + h_3j_3 + j_3h_2 + h_1j_1 + h_1j_2. \end{aligned}$$

Hence, (HB1) reduces to condition

$$H_2 = \alpha_2\alpha_3 - \alpha_1 = 0, \quad (41)$$

with α_i being the coefficients given above. If we choose k_{43} (reaction constant of CICR) as our bifurcation parameter, condition (HB2) involves checking

$$\frac{\partial H_2}{\partial k_{43}} = -j_3 \frac{j_3k_{12}}{k_{21}k_{43}^2} \neq 0. \quad (42)$$

Because all parameters are assumed to be positive, Eq. (42) is automatically satisfied. The calcium model has at least one simple Hopf bifurcation if convex parameters and kinetic parameters $k_{12}, k_{43}, k_{65}, k_{76}$ can be chosen so that they satisfy Equation (41). One possible choice is to have $j_1 = 1, j_2 = 1.4786, j_3 = 2.9567, k_{43} = 1, k_{76} = 1, k_{12} = 2.4, k_{65} = 5.211$. The values for species concentrations and other parameters can be retrieved via Eqs. (37)–(40). Figure 3 shows results of Theorem 6 plotted against those reproduced by the numerical bifurcation package XPPaut. The plot is a two-parameter bifurcation plot with bifurcation parameters k_{12} and k_{65} . It shows good agreement for these two parameters. All other values of parameters and variables were checked and showed good agreement.

In passing, a comparison can be made with the analysis of necessary conditions from [21]. Since all coefficients of the characteristic polynomial, except α_2 are positive, the necessary conditions for a Hopf bifurcation to occur reduce to finding two values of k parameters where H_2 is of different sign. This is just a different formulation of

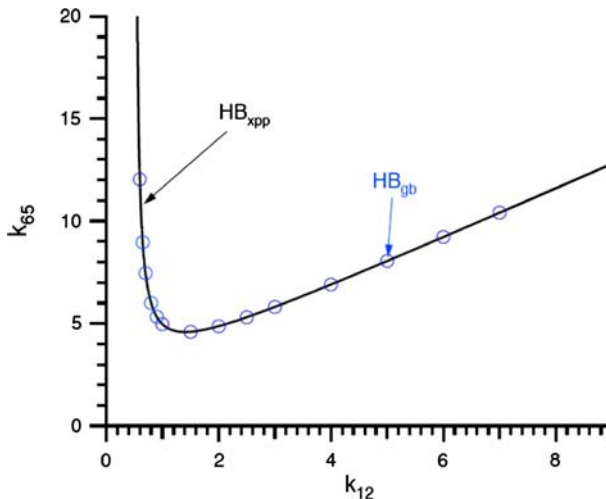


Fig. 3 Two-parameter bifurcation diagram of the calcium model for $k_{21} = 1.0$, $k_{43} = 1.0$, $k_{56} = 0.5$, $k_{76} = 1.0$ and $c = 5$. k_{12} and k_{65} are bifurcation parameters. HB_{xpp} and HB_{gb} denote Hopf bifurcations detected by XPPaut and conditions of Theorem 6, respectively

the second sufficient condition, (HB1). The only additional computation for sufficient conditions, not needed in [21], is one extra algebraic conditions coming from (HB2). This condition is automatically satisfied for any positive parameter values, hence the calculation of sufficient Hopf conditions is not more computationally expensive.

5.2 Brusselator

Now conditions from Theorem 6 will be applied to the Brusselator, a well-known example of an autocatalytic oscillating chemical reaction system. Its mechanism relies on interaction of two species whose dynamics are described by following ODEs:

$$\dot{x}_1 = k_1 x_1^2 x_2 - k_2 x_1 - k_3 x_1 + k_4,$$

$$\dot{x}_2 = -k_1 x_1^2 x_2 + k_2 x_1,$$

where x_1 and x_2 are the species concentrations, and k 's denote the kinetic constants. The search for a simple Hopf bifurcation (and ultimately oscillations) without any additional knowledge about the system depends on four kinetic parameters. In standard bifurcation theory, conditions from the Hopf bifurcation theorem could be used. Numerical analysis via XPPaut could be laborious exercise if parameters are chosen inappropriately. The Brusselator can be written as product of a stoichiometric matrix and velocity vector:

$$\dot{x} = N v(x, k),$$

where $x = (x_1, x_2)$ and

$$N = \begin{bmatrix} 1 & -1 & -1 & 1 \\ -1 & 1 & 0 & 0 \end{bmatrix} \quad \text{and} \quad v(x; k) = \begin{bmatrix} k_1 x_1^2 x_2 \\ k_2 x_1 \\ k_3 x_1 \\ k_4 \end{bmatrix}.$$

Two extreme currents are identified in the model,

$$E_1 = (1, 1, 0, 0) \quad \text{and} \quad E_2 = (0, 0, 1, 1).$$

These decompose the system into two subnetworks: the first is an autocatalytic production of x_1 with consumption of x_2 , as well as conversion of x_1 into x_2 . The second extreme current models the subnetwork of inflow and outflow of x_1 . The deformed toric ideal of the system in convex parameters is

$$J = \langle k_3 j_1 - k_2 j_2, j_2 - k_4 \rangle.$$

To find the variety of J ($V(J)$) one must solve

$$\begin{aligned} k_3 j_1 - k_2 j_2 &= 0, \\ j_2 - k_4 &= 0. \end{aligned} \tag{43}$$

If relations in (43) hold for chosen j and k , for these j the system has positive concentration steady states. Via Hermit Normal Form, their inverses can be calculated, $h_1 = \frac{k_3}{j_2}$ and $h_2 = \frac{k_1 j_2^2}{k_3^2 j_1}$. Moreover, some of the kinetic parameters k s can be rewritten in terms of other kinetic parameters or convex parameters using equations in (43). Namely, one can substitute $k_4 = j_2$ and $k_2 = k_3 \frac{j_1}{j_2}$. We have four parameters: two convex parameters j_1 and j_2 and two kinetic parameters k_1 and k_3 . The convex Jacobian of the Brusselator is

$$Jac(j) = \begin{bmatrix} (j_1 - j_2)h_1 & j_1 h_2 \\ -j_1 h_1 & -j_1 h_2 \end{bmatrix},$$

where h are defined as above, $h_1 = \frac{k_3}{j_2}$ and $h_2 = \frac{k_1 j_2^2}{k_3^2 j_1}$. The characteristic polynomial is

$$\lambda^2 + (j_1 h_2 - j_1 h_1 + h_1 j_2) \lambda + h_1 j_2 j_1 h_2.$$

Finally the Hurwitz determinants follow as

$$\begin{aligned} a_0 &= h_1 j_2 j_1 h_2, \\ H_1 &= j_1 h_2 - j_1 h_1 + h_1 j_2. \end{aligned}$$

Condition (HB2) is satisfied if $j_2 = (1 - \frac{k_1 j_2^3}{k_3^3 j_1}) j_1$. Also $\frac{\partial H_1}{\partial k_3} = -\frac{k_1 j_2^2}{k_3^2} - \frac{j_1}{j_2} - 1 < 0$, so (HB3) holds independently of parameter values chosen. The conditions derived from Theorem 6 state that one only needs to choose positive parameters k_2, k_3, j_1 and j_2 that satisfy (HB1) in order to guarantee that Brusselator has a simple Hopf bifurcation. Obviously, it is possible to find at least one set of parameters so that this condition is true. Hence the Brusselator has at least one simple Hopf bifurcation. Note that working backwards, one can retrieve all kinetic parameters and concentration values (k_1, k_4, x_1, x_2) where the Brusselator will undergo a simple Hopf bifurcation. The standard simple Hopf bifurcation theorem would give the same conditions for kinetic parameters, but it would also need to be checked that concentration steady states (corresponding to these parameters) are positive. Using the conditions from Theorem 6 this is not necessary.

5.3 Model of glycolytic oscillations

Conditions from Theorem 6 can be applied to the model of glycolytic oscillations from [15]. Most calculations were already preformed in Sect. 3. The convex Jacobian with substituted values for h_1 and h_2 is

$$Jac(j) = \begin{bmatrix} (j_3 - j_1) \frac{k_3}{j_1 + j_3} & j_3 \frac{k_5}{j_2} \\ -2j_3 \frac{k_3}{j_1 + j_3} & -(j_2 + j_3) \frac{k_5}{j_2} \end{bmatrix},$$

where Hurwitz determinants follow as

$$a_0 = j_3 \frac{k_5 k_3}{j_2(j_1 + j_3)} (j_3^2 - j_3 j_2 + j_1 j_3 + j_1 j_2),$$

$$H_1 = k_5 + j_3 \frac{k_5}{j_2} + \frac{k_3(j_1 - j_3)}{j_1 + j_3}.$$

Condition (HB1) is satisfied if $a_0 > 0$ and $H_1 = 0$. It only needs to be checked that there exist j 's such that $H_1 = 0$, because if this is true, then $a_0 > 0$. (HB2) is always satisfied, because $\frac{\partial H_1}{\partial k_5} = 1 + \frac{j_3}{j_2}$ is positive for any positive parameter values. Hence, for the model to have simple Hopf bifurcation, one only needs to find values of convex parameters and k_1, k_3 and k_5 such that $H_1 = 0$ and $(j_3^2 - j_3 j_2 + j_1 j_3 + j_1 j_2) > 0$ are satisfied. Numerous choices are available. One possible choice is to take, $j_1 = 1, j_2 = 2.85, j_3 = 1.15$ and $k_3 = 10, k_5 = 0.5$. Figure 4 compares the Hopf bifurcation calculated via conditions from Theorem 6 and a Hopf bifurcation calculated by XPPaut. There is good agreement between the two curves of bifurcations. In order to make this comparison values for all kinetic parameters k and concentrations x have to be calculated, because XPPaut handles the original equations.

6 Discussion

This paper describes *sufficient* conditions for three important types of bifurcations, a saddle-node bifurcation, the simple branching point and a simple Hopf bifurcation.

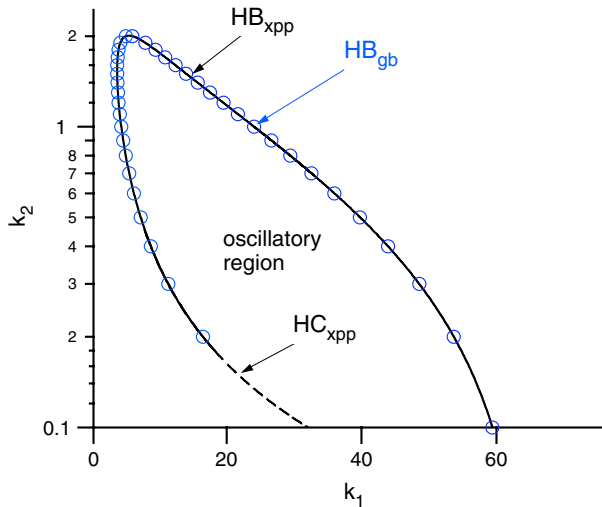


Fig. 4 Two-parameter bifurcation diagram of the glycolytic model for $k_3 = 10$, $k_4 = 4$, $k_5 = 0.5$. k_1 and k_2 are bifurcation parameters. HB_{xpp} and HB_{gb} denote Hopf bifurcations detected by XPPaut and conditions from Theorem 6, respectively. XPPaut also detects a line of homoclinic bifurcations (HC)

Restricting to reaction systems with polynomial right hand sides theorems can be derived that state the possibility of such bifurcations in terms of contributions of subnetworks represented by extreme currents. In case of the saddle-node bifurcation the approach has been used to describe a method for detecting bistability in reaction network. The conditions allow the calculation of the exact parameter values where bifurcations occur. Also these conditions are not always more complicated to analyse than the necessary conditions found in [21]. In general the work shows how abstract mathematics, in this case Algebraic Geometry (applied to reaction systems in the pioneering work of Gatermann), is immensely useful in real applications.

Several extensions of this work are possible. As mentioned in an earlier commentary, extension of the sufficient conditions from a simple Hopf bifurcation to a general Hopf bifurcation is a possible direction. In more general terms also other branching and bifurcation conditions could be transcribed along the lines of this paper.

Finally it should be said the conditions derived can easily be applied to small chemical and biochemical networks. Their implementation into existing software for extreme currents such as Fluxanalyzer [19] or Copasi, would be useful for analysis of larger systems and hence another interesting direction. The discussion in Sect. 3 shows that many necessary computational tools are already available.

Acknowledgments MirelaDomijan acknowledges the support from Commonwealth Scholarship. This paper is part of the research activities also supported by UniNet contract 12990 funded by the European Commission in the context of the VI Framework Programme. The authors wish to thank the Editor for the care and effort in the shaping the presentation of this paper.

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