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Investigation of Invariants of a Chemical Reaction System with Algorithms of Computer Algebra

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Abstract

In this paper the qualitative study of a reversible chemical reaction model represented by a three-dimensional system of ordinary differential equations with nine parameters is performed. Algebraic invariant surfaces of the system are obtained by using methods of computational algebra. Then we look for singular points on the invariant surfaces and study their stability and bifurcations. Finally numerical simulations which confirm our theoretical results are presented. The study is carried out with help of computer algebra systems SINGULAR and MATHEMATICA.

1 Introduction

Many biological networks and chemical and physical phenomena can be modeled mathematically by dynamical systems described by ordinary differential equations. Lotka-Volterra systems being the most important dynamical systems have played important

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roles in modelling mathematical phenomena to describe such networks [2]. However studies of such models are often performed by numerical simulations. As rule such simulations only give information on a particular solution or a few solutions of the dynamical system, but they do not provide any information on the qualitative behavior of the system and the change of the behavior under perturbations. One important feature of biochemical models is that they are often described by differential equations with polynomial or rational functions on the right-hand side involving many parameters. Usually the first step in the investigation of a given system of differential equations is determining its singular points, which leads to the problem of solving a system of algebraic polynomial equations for above mentioned systems. Despite of the fact that many methods and powerful algorithm of symbolic computation based on the Groebner bases theory and the theory of characteristic sets have been developed in last few decades for solving systems of polynomials, they work well only for systems with very few parameters, which is not the case for biochemical systems, hence the problem of determining singular points of such a system remains open attracting many studies in recent years. Extremely important ones among singular points are so-called Hopf bifurcation points since one can determine oscillatory regimes of the model and study its bifurcations by knowing them (see e.g. [3, 9, 17] and references given there).

In this paper we propose an approach for determining the geometrical structure of the phase space and finding Hopf bifurcations in polynomial systems depending on many parameters – such systems are typical in biochemical network models – which combines some methods of qualitative analysis of autonomous systems of differential equations and effective methods and software tools of computational algebra. We use them to find invariant surfaces and parameter conditions under which Hopf bifurcations occur for the system in concern.

Biochemical networks can be described by the following differential equations derived using mass action kinetics,

$$\dot{x_i} = \sum_{j\in[1,r]} k_j S_{ij} \boldsymbol{x}^{\boldsymbol{\alpha_j}},\ i \in [1,n]. \tag{1.1}$$

where $k_j > 0, j \in [1,r]$ are kinetic constants, r is the number of reactions, S_{ij} are the elements of the so-called stoichiometric matrix, $\boldsymbol{\alpha}_j = (\alpha_1^j, \ldots, \alpha_n^j) \in \mathbb{Z}_+^n$ are multi-indices, $\boldsymbol{x}^{\boldsymbol{\alpha_j}} = x_1^{\alpha_1^j} \ldots x_n^{\alpha_n^j}$ and x_i, $i \in [1,n]$ are the species concentrations, n being the number of species.

The reaction network diagram of reversible Lotka-Volterra system is given in [13, 15] as follows

$$\tilde{X} + X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2X$$

$$X + Y \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} 2Y$$

$$Y \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \tilde{Y}$$

The corresponding differential equation system using mass-action law is written as

$$\begin{aligned} \dot{u} &= k_1 wu - k_2 uv - \varepsilon_1(k_{-1}u^2 - k_{-2}v^2), \\ \dot{v} &= k_2 uv - k_3 v - \varepsilon_1(k_{-2}v^2 - k_{-3}b), \\ \dot{w} &= -\varepsilon_2(k_1 wu - \varepsilon_1 k_{-1}u^2), \\ \dot{b} &= k_3 v - \varepsilon_1 k_{-3} b \end{aligned} \tag{1.2}$$

in which u, v, w and b are the concentrations of X, Y, $\tilde{X}$ and $\tilde{Y}$, respectively, ε_1 represents the ratio of time scales between k_1, k_2, k_3 and k_{-1}, k_{-2}, k_{-3} and ε_2 is the ratio of concentration scales between X, Y and $\tilde{X}$ and c_t is the total concentration of all molecules which is constant and is given by $c_t = u + v + w/\varepsilon_2 + b$. This constitutes the linear conservation law (as the sum of equations corresponding to $\dot{u}$, $\dot{v}$, $\dot{w}$, $\dot{b}$ is 0). Using the conservation law, chemical species $\tilde{Y}$ is eliminated by substituting b in the above equation system by $(c_t - u - v - w/\varepsilon_2)$ resulting in the following differential equation system

$$\begin{aligned} \dot{u} &= k_1 wu - k_2 uv - \epsilon_1(k_{-1}u^2 - k_{-2}v^2), \\ \dot{v} &= k_2 uv - k_3 v - \epsilon_1(k_{-2}v^2 - k_{-3}(c_t - u - v - \tfrac{w}{\epsilon_2})), \\ \dot{w} &= -\epsilon_2(k_1 wu - \epsilon_1 k_{-1}u^2). \end{aligned} \tag{1.3}$$

We demonstrate our approach on the reversible chemical reaction model given by system (1.3). It is assumed that all parameters of the system are non-negative.

System (1.3) has three singular points:

$$A = (0, 0, c_t\epsilon_2),$$

$$B = (\frac{c_t\epsilon_2 k_1}{\epsilon_2 k_1 + \epsilon_1 k_{-1}}, 0, \frac{c_t\epsilon_1\epsilon_2 k_{-1}}{\epsilon_2 k_1 + \epsilon_1 k_{-1}}),$$

and $C = (c_u, c_v, c_w)$, where

$$\begin{aligned} c_u &= \frac{c_t\epsilon_1^2\epsilon_2 k_1 k_{-2} k_{-3}}{\epsilon_1^3 k_{-1}k_{-2}k_{-3} + \epsilon_2 k_1(\epsilon_1^2 k_{-2}k_{-3} + k_2(k_3 + \epsilon_1 k_{-3}))}, \\ c_v &= \frac{c_t\epsilon_1\epsilon_2 k_1 k_2 k_{-3}}{\epsilon_1^3 k_{-1}k_{-2}k_{-3} + \epsilon_2 k_1(\epsilon_1^2 k_{-2}k_{-3} + k_2(k_3 + \epsilon_1 k_{-3}))}, \\ c_w &= \frac{c_t\epsilon_1^3\epsilon_2 k_{-1} k_{-2} k_{-3}}{\epsilon_1^3 k_{-1}k_{-2}k_{-3} + \epsilon_2 k_1(\epsilon_1^2 k_{-2}k_{-3} + k_2(k_3 + \epsilon_1 k_{-3}))}. \end{aligned} \tag{1.4}$$

It is not difficult to determine the type of these singular points and find out that a Hopf bifurcation is not possible at these points for positive values of parameters by computing eigenvalues of the matrix of the linear approximation of system (1.3) at points A and B. However computing eigenvalues at the point C we obtain very cumbersome expressions (roots of a cubic polynomial) which prevent us from further analysis of the system. We need to impose some conditions on parameters to perform a further qualitative study of the system. Instead of choosing some parameters randomly, we look for conditions when the system has a simpler geometric structure – admits an invariant surface or first integral – and then study the obtained subsystems in more detail.

We recall that a first integral of a differential system

$$\begin{aligned} \dot{u} &= U(u,v,w),\\ \dot{v} &= V(u,v,w),\\ \dot{w} &= W(u,v,w). \end{aligned} \tag{1.5}$$

is a function $\Psi(u,v,w)$ such that

$$\mathcal{X}\Psi := \frac{\partial \Psi}{\partial u}U + \frac{\partial \Psi}{\partial v}V + \frac{\partial \Psi}{\partial w}W \equiv 0.$$

In this case the phase space of the system is foliated by infinitely many invariant surfaces $\Psi(u,v,w) = c$. The flow of the system is conserved on each surface $\Psi(u,v,w) = c$, so from biochemical point of view the first integral $\Psi(u,v,w) = c$ gives us a conservation law [7,8]. Knowing a first integral (conservation law) one can reduce the dimension of the system. An invariant algebraic surface of the system (1.5) is a smooth function $L(u,v,w)$ such that

$$\mathcal{X}L = KL \tag{1.6}$$

where K is a smooth function. From (1.6) we see that the flow of system (1.5) is invariant on the surface $L = 0$. From the biochemical point of view an invariant surface $L = 0$ can be used for model reduction: although one cannot reduce the dimension of the system, by the Center Manifold Theorem [1] in many cases the dynamics of the system is governed by the dynamics on the invariant surface $L = 0$, which often represents the so-called slow manifold.

The paper is organized as follows. In Section 2 we describe an approach to find algebraic invariant surfaces of polynomial systems of ODEs and use it to find all such surfaces of degree one for system (1.3). The approach is based on making use of algorithms

of computational commutative algebra related to the elimination theory. Then in Section 3 we perform a detailed study of the flow of the system in a neighborhood of one of such surfaces finding a subfamily of system (1.3) which admits Hopf bifurcation. Finally, we present our numerical simulations in Section 4.

2 Invariant algebraic planes of system (1.3)

We first recall few notions and one of main results of the elimination theory.

Consider a system of polynomials with coefficients in some field k,

$$f_1(x_1,\dots,x_n)=\cdots=f_k(x_1,\dots,x_n)=0, \tag{2.1}$$

and the corresponding ideal $I=\langle f_1,\dots,f_k\rangle\subset k[x_1,\dots,x_n]$.

Definition 1. *Let I be an ideal in $k[x_1,\dots,x_n]$ (with the implicit ordering of the variables $x_1>\cdots>x_n$) and fix $\ell\in\{0,1,\dots,n-1\}$. The* ℓ-th elimination ideal *of I is the ideal $I_\ell=I\cap k[x_{\ell+1},\dots,x_n]$.*

To eliminate $x_1,\dots,x_\ell$ $(0\le\ell<n)$ from system (2.1) one can use the following theorem (see e.g. [6,18] for the proof).

Theorem 1 (Elimination Theorem). *Let us fix the lexicographic term order on the ring $k[x_1,\dots,x_n]$ with $x_1>x_2>\cdots>x_n$ and let G be a Groebner basis for an ideal I of $k[x_1,\dots,x_n]$ with respect to this order. Then for every ℓ, $0\le\ell\le n-1$, the set*

$$G_\ell:=G\cap k[x_{\ell+1},\dots,x_n]$$

is a Groebner basis for the ℓ–th elimination ideal I_ℓ.

In this section we determine invariant algebraic planes of the form $L=a_0+a_1u+a_2v+a_3w$ of system (1.3) by making use of the Elimination Theorem.

Consider the system (1.5) and let L be a polynomial in the variables u,v,w. The polynomial L defines an invariant algebraic surface $L=0$ of system (1.5) if

$$\mathcal{X}L=KL$$

for some polynomial $K(u,v,w)$. The polynomial K is called the cofactor of L and has degree at most $n-1$, if the maximal degree of U,V,W is n.

In the next theorem we list parameter conditions for which system (1.3) has at least one invariant algebraic plane.

Theorem 2. *System* (1.3) *has an invariant algebraic plane if one of the following conditions holds:*

(i) $\epsilon_1 = k_2 = 0$;

(ii) $k_{-2} = \epsilon_2 k_1 k_3(\epsilon_2 k_1 + k_2 + \epsilon_1 k_{-1}) + \epsilon_1 k_{-3}(\epsilon_2 k_1 + k_2)(\epsilon_2 k_1 + \epsilon_1 k_{-1}) =$
$k_2(c_t \epsilon_2^2 k_1^2 - \epsilon_1^2 k_{-1} k_{-3}) + c_t \epsilon_2^3 k_1^3 + c_t \epsilon_1 \epsilon_2^2 k_1^2 k_{-1} = 0$;

(iii) $k_{-2} = k_2 = 0$;

(iv) $k_3 = 0$;

(v) $k_{-3} = k_2 = 0$;

(vi) $\epsilon_1 = k_1 = 0$;

(vii) $k_{-1} = k_1 = 0$.

Proof. We look for an algebraic invariant plane of the system (1.3) in the form

$$L(u, v, w) = 1 + a_1 u + a_2 v + a_3 w \tag{2.2}$$

with the corresponding cofactor

$$K(u, v, w) = s_0 + s_1 u + s_2 v + s_3 w. \tag{2.3}$$

We replace $1/\epsilon_2$ by ζ in (1.3) in order to avoid computations with fractions in SINGULAR [11] and substitute $L(u, v, w)$ from (2.2) and $K(u, v, w)$ from (2.3) into the equation (1.6) (with the vector field $\mathcal{X}$ corresponding to system (1.3)). Then we compare the coefficients of similar terms on both sides of (1.3) and we obtain the system of polynomials

$$f_1 = f_2 = \cdots = f_{10} = 0$$

where

$$f_1 = a_2 c_t \epsilon_1 k_{-3} - s_0$$

$$f_2 = -a_2 \epsilon_1 k_{-3} - a_1 s_0 - s_1$$

$$f_3 = -a_1 \epsilon_1 k_{-1} + a_3 \epsilon_1 \epsilon_2 k_{-1} - a_1 s_1$$

$$f_4 = -a_2 k_3 - a_2 \epsilon_1 k_{-3} - a_2 s_0 - s_2$$

$$f_5 = -a_1 k_2 + a_2 k_2 - a_2 s_1 - a_1 s_2$$

$$f_6 = a_1 \epsilon_1 k_{-2} - a_2 \epsilon_1 k_{-2} - a_2 s_2$$

$$f_7 = -a_2 \zeta \epsilon_1 k_{-3} - a_3 s_0 - s_3$$

$$f_8 = -a_3 s_3$$
$$f_9 = a_1 k_1 - a_3 \epsilon_2 k_1 - a_3 s_1 - a_1 s_3$$
$$f_{10} = -a_3 s_2 - a_2 s_3.$$

We denote the ideal generated by polynomials given above by $I := \langle f_1, f_2, \ldots, f_{10} \rangle$. We have to eliminate from the system the variables a_i and s_i to obtain conditions for existence of invariant planes. We observe that (1.6) always has the solution $L = 1$, $K = 0$. Thus, computing the 7-th elimination ideal of I we obtain the zero ideal, which means that the elimination is always possible. To overcome this difficulty we should impose the condition that $L \not\equiv 1$. To this end we add the polynomial $1 - wa_1$ to the ideal I . Since $\epsilon_2 = 1/\zeta$ we also add polynomial $1 - \epsilon_2 \zeta$ and we obtain the ideal $J = \langle 1 - wa_1, 1 - \epsilon_2 \zeta, I \rangle$. Ordering variables using a lexicographic ordering with $\{w, a_1, a_2, a_3, s_0, s_1, s_2, s_3, \zeta\} > \{k_1, k_2, k_3, k_{-1}, k_{-2}, k_{-3}, \epsilon_1, \epsilon_2, c_t\}$ with `eliminate` of SINGULAR we compute the 9-th elimination ideal J_9 of J (the obtained generating set for J_9 contains 55 polynomials so we do not present it here). The computation of minimal associate primes of J_9 with the routine `minAssGTZ`[1] of `primdec` library [12] of SINGULAR gives conditions $(i) - (iv)$ of Theorem 2 and one additional condition $k_{-1} = k_{-3} = k_1 = 0$.

We obtain additionally condition (v) of Theorem 2 by computing the decomposition of the variety of the 9-th elimination ideal of $\tilde{J} = \langle 1 - wa_2, 1 - \epsilon_2 \zeta, I \rangle$. Conditions (vi), (vii) are obtained by computing the 9-th elimination ideal of $\hat{J} = \langle 1 - wa_3, 1 - \epsilon_2 \zeta, I \rangle$. Since the condition $k_{-1} = k_{-3} = k_1 = 0$ mentioned above is a subcase of condition (vii), we see that if one of conditions $(i) - (vii)$ of the theorem is satisfied then system (1.3) can have an invariant plane of the form (2.2).

Similarly as above we looked for conditions for existence of invariant plane of the form

$$\tilde{L}(u, v, w) = a_1 u + a_2 v + a_3 w$$

but all conditions which we obtained are subcases of conditions $(i) - (vii)$ of the theorem.[2]

We now show that if one of conditions $(i) - (vii)$ is satisfied, then system (1.3) admits an invariant plane of the form (2.2). We prove this by finding an invariant plane for each case.

[1]The routine `eliminate` is based on Theorem 2 and `minAssGTZ` on the algorithm of [10]

[2]It is possible to look for invariant plane in the form $L(u, v, w) = a_0 + a_1 u + a_2 v + a_3 w$, however the computation of the elimination ideal is a very laborious procedure, so to simplify calculations we split them into two cases

In cases (i) and (iii) the system has the first integral $\Psi_1 = 1 + \epsilon_2 u + w$ which defines a family of invariant planes. Additionally, in case (iii) we obtain the invariant plane $L_1 = 1 - \frac{u}{c_t} - \frac{k_3+\epsilon_1 k_3}{c_t \epsilon_1 k_3} v - \frac{w}{c_t \epsilon_2}$.

In case (ii) we obtain the invariant plane $L_2 = 1 + \frac{\epsilon_1 k_{-1}}{c_t \epsilon_2 k_1} u + \frac{\epsilon_2 k_1}{\epsilon_1 k_{-3}} v - \frac{1}{c_t \epsilon_2} w$.

If system (1.3) satisfies the conditions of case (iv) there is the invariant plane

$$L_3 = 1 - \frac{u}{c_t} - \frac{v}{c_t} - \frac{w}{c_t \epsilon_2}.$$

In case (v) system (1.3) has the invariant plane $L_4 = 1 + \frac{\epsilon_1 k_{-2}}{k_3} v$.

Systems of the form (1.3) satisfying condition (vi) or (vii) admit the first integral $\Psi_2 = 1 + a_3 w$ defining a family of invariant planes. □

Remark. We also tried to find invariant surfaces of system (1.3) defined by polynomials of degree two. However since the computation of the elimination ideal is very time and memory consuming procedure we were not able to complete calculations using our computational facilities.

In fact in cases (i), (iii), (vi) and (vii) we have conservation laws which allow to reduce the corresponding systems to two-dimensional ones. Since dynamics of the reduced systems is not very interesting below we consider only cases (ii), (iv) and (v).

3 Flow on the invariant plane

In this section we study case (iv) of Theorem 2 in more details and we also mention some results for cases (ii) and (v). One of our aims is to demonstrate how the routine `Reduce` of the computer algebra system MATHEMATICA can be used to determine types of singular points and Hopf bifurcations in systems of ODEs depending on parameters.

3.1 Singular points

System (1.3) satisfying condition (iv) of Theorem 2 is written as

$$\begin{aligned} \dot{u} &= k_1 w u - k_2 u v - \epsilon_1 (k_{-1} u^2 - k_{-2} v^2), \\ \dot{v} &= k_2 u v - \epsilon_1 (k_{-2} v^2 - k_{-3} (c_t - u - v - \tfrac{w}{\epsilon_2})), \\ \dot{w} &= -\epsilon_2 (k_1 w u - \epsilon_1 k_{-1} u^2). \end{aligned} \tag{3.1}$$

System (3.1) has three singular points namely:

$$T_1(0, 0, \epsilon_2 c_t),$$

$$T_2(\frac{c_t \epsilon_2 k_1}{\epsilon_2 k_1 + \epsilon_1 k_{-1}}, 0, \frac{c_t \epsilon_1 \epsilon_2 k_{-1}}{\epsilon_2 k_1 + \epsilon_1 k_{-1}}),$$

and $T_3(u_0, v_0, w_0)$, where

$$\begin{aligned} u_0 =& \frac{c_t\epsilon_1\epsilon_2 k_1 k_{-2}}{\epsilon_1^2 k_{-1}k_{-2} + \epsilon_2 k_1(k_2 + \epsilon_1 k_{-2})} \\ v_0 =& \frac{c_t\epsilon_2 k_1 k_2}{\epsilon_1^2 k_{-1}k_{-2} + \epsilon_2 k_1(k_2 + \epsilon_1 k_{-2})} \\ w_0 =& \frac{c_t\epsilon_1^2\epsilon_2 k_{-1} k_{-2}}{\epsilon_1^2 k_{-1}k_{-2} + \epsilon_2 k_1(k_2 + \epsilon_1 k_{-2})}. \end{aligned}$$

First we perform the substitution

$$u \to x - \frac{c_t\epsilon_2 - \epsilon_2 y - z}{\epsilon_2}, v \to y, w \to z$$

in system (3.1) (using again the notation u, v, w for x, y, z) to obtain the system

$$\begin{aligned} &\dot{u} = -\epsilon_1 k_{-3} u, \\ &\dot{v} = -(\epsilon_2 k_2 v^2 + \epsilon_1\epsilon_2 k_{-2} v^2 - c_t\epsilon_2 k_2 v - \epsilon_2 k_2 uv + k_2 wv + \epsilon_1\epsilon_2 k_{-3} u)/\epsilon_2, \\ &\dot{w} = (c_t\epsilon_2 + \epsilon_2 u - \epsilon_2 v - w)(c_t\epsilon_1\epsilon_2 k_{-1} + \epsilon_1\epsilon_2 k_{-1} u - \epsilon_1\epsilon_2 k_{-1} v - \epsilon_1 k_{-1} w - \epsilon_2 k_1 w)/\epsilon_2 \end{aligned} \tag{3.2}$$

with singular points

$$T_1'(0, 0, c_t\epsilon_2),$$

$$T_2'(0, 0, \frac{c_t\epsilon_1\epsilon_2 k_{-1}}{\epsilon_2 k_1 + \epsilon_1 k_{-1}}),$$

and

$$T_3'(0, v_0, w_0),$$

where v_0 and w_0 are defined above. We compute the Jacobian of system (3.2) and find that system (3.2) has two real nonzero eigenvalue and one zero eigenvalue at the point T_1' and three real eigenvalues at the point T_2'. At point T_3' we obtain three eigenvalues where two of them might be complex. Therefore, to detect Hopf bifurcations in system (3.2) we have to consider only point T_3'. First, we move this point to the origin performing the linear change

$$u \to x, v \to y + v_0, w \to z + w_0$$

and obtain the system

$$\dot{x} = P(x, y, z), \quad \dot{y} = Q(x, y, z), \quad \dot{z} = R(x, y, z), \tag{3.3}$$

where

$$
\begin{aligned}
P(x,y,z) =& -\epsilon_1 k_{-3} x,\\
Q(x,y,z) =& -\big[\epsilon_2 k_{-1}k_{-2}^2 y^2\epsilon_1^3 + \epsilon_2 k_{-1}k_{-2}k_{-3}x\epsilon_1^3 + \epsilon_2^2 k_1 k_{-2}^2 y^2\epsilon_1^2 + \epsilon_2 k_2 k_{-1}k_{-2}y^2\epsilon_1^2\\
&+ \epsilon_2^2 k_1 k_{-2}k_{-3}x\epsilon_1^2 - \epsilon_2 k_2 k_{-1}k_{-2}xy\epsilon_1^2 + k_2 k_{-1}k_{-2}yz\epsilon_1^2 + 2\epsilon_2^2 k_1 k_2 k_{-2}y^2\epsilon_1\\
&+ \epsilon_2^2 k_1 k_2 k_{-3}x\epsilon_1 + c_t\epsilon_2^2 k_1 k_2 k_{-2}y\epsilon_1 - \epsilon_2^2 k_1 k_2 k_{-2}xy\epsilon_1 + \epsilon_2 k_1 k_2 k_{-2}yz\epsilon_1\\
&+ \epsilon_2^2 k_1 k_2^2 y^2 - c_t\epsilon_2^2 k_1 k_2^2 x + c_t\epsilon_2^2 k_1 k_2^2 y - \epsilon_2^2 k_1 k_2^2 xy + c_t\epsilon_2 k_1 k_2^2 z\\
&+ \epsilon_2 k_1 k_2^2 yz\big]\Big/\big[\epsilon_2(k_{-1}k_{-2}\epsilon_1^2 + \epsilon_2 k_1 k_{-2}\epsilon_1 + \epsilon_2 k_1 k_2)\big],\\
R(x,y,z) =& \big[\big(\epsilon_1\epsilon_2 k_{-1}x - \epsilon_1\epsilon_2 k_{-1}y - \epsilon_2 k_1 z - \epsilon_1 k_{-1}z\big)(\epsilon_2 k_{-1}k_{-2}x\epsilon_1^2 - \epsilon_2 k_{-1}k_{-2}y\epsilon_1^2\\
&- k_{-1}k_{-2}z\epsilon_1^2 + c_t\epsilon_2^2 k_1 k_{-2}\epsilon_1 + \epsilon_2^2 k_1 k_{-2}x\epsilon_1 - \epsilon_2^2 k_1 k_{-2}y\epsilon_1 - \epsilon_2 k_1 k_{-2}z\epsilon_1\\
&+ \epsilon_2^2 k_1 k_2 x - \epsilon_2^2 k_1 k_2 y - \epsilon_2 k_1 k_2 z)\big]\Big/\big[\epsilon_2(k_{-1}k_{-2}\epsilon_1^2 + \epsilon_2 k_1 k_{-2}\epsilon_1 + \epsilon_2 k_1 k_2)\big].
\end{aligned}
\tag{3.4}
$$

The plane $x = 0$ is an invariant plane of the system (3.3) and after the rescaling of time by

$$c = \epsilon_2(\epsilon_1^2 k_{-1}k_{-2} + \epsilon_2 k_1(k_2 + \epsilon_1 k_{-2}))$$

the flow on it is reduced to

$$
\begin{aligned}
\dot{y} =& -\big(c_t\epsilon_2 k_1 k_2 + \big(k_{-1}k_{-2}\epsilon_1^2 + \epsilon_2 k_1(k_2 + \epsilon_1 k_{-2})\big)\, y\big)\,(\epsilon_2(k_2 + \epsilon_1 k_{-2})y + k_2 z)\\
\dot{z} =& (\epsilon_2 k_1 z + \epsilon_1 k_{-1}(\epsilon_2 y + z))\,\big(k_{-1}k_{-2}\epsilon_1^2 + \epsilon_2 k_1(k_2 + \epsilon_1 k_{-2})\big)\,(\epsilon_2 y + z) - c_t\epsilon_1\epsilon_2^2 k_1 k_{-2}.
\end{aligned}
\tag{3.5}
$$

Since trajectories of the vector field (3.3) contract (if $\epsilon_1 k_{-3} > 0$) or extend (if $\epsilon_1 k_{-3} < 0$) along the x-axis, the dynamics of system (3.3) is mainly described by the dynamics of the reduced system (3.5). So we study the behavior of trajectories of system (3.5).

Computing the Jacobian J of the matrix of the linear approximation of (3.5) at the origin and then the eigenvalues of J we find that they are

$$\lambda_{1,2} = -\frac{a \pm \sqrt{b}}{2},$$

where

$$a = c_t\epsilon_2 k_1 k_2^2 + c_t\epsilon_1\epsilon_2^2 k_1^2 k_{-2} + c_t\epsilon_1\epsilon_2 k_1 k_2 k_{-2} + c_t\epsilon_1^2\epsilon_2 k_1 k_{-1}k_{-2},$$

$$b = \epsilon_2^2 k_1^2((k_2^2 + \epsilon_1 k_2 k_{-2} + \epsilon_1(\epsilon_2 k_1 + \epsilon_1 k_{-1})k_{-2})^2 - 4\epsilon_1 k_2 k_{-2}(\epsilon_1^2 k_{-1}k_{-2} + \epsilon_2 k_1(k_2 + \epsilon_1 k_{-2}))).$$

System (3.5) can have a singular point of center or focus type if $b < 0$. Hopf bifurcation occurs for $a = 0$, $b < 0$. From the equality $a = 0$ we obtain

$$k_1 = -\frac{k_2^2 + \epsilon_1 k_2 k_{-2} + \epsilon_1^2 k_{-1}k_{-2}}{\epsilon_1\epsilon_2 k_{-2}}. \tag{3.6}$$

Then, the chemically relevant values of parameters where Hopf bifurcation is possible satisfy the following system of semi-algebraic equations:

$$b < 0 \wedge c \neq 0 \wedge c_u > 0 \wedge c_v > 0 \wedge c_w > 0 \wedge k_2 \geq 0 \wedge k_1 \geq 0 \wedge k_{-2} \geq 0 \tag{3.7}$$

(where c_u, c_v, c_w are defined by (1.4)).

To solve system (3.7) we use the `Reduce` routine of MATHEMATICA [19] to solve system. For algebraic functions `Reduce` constructs equivalent simple polynomial systems and then uses cylindrical algebraic decomposition (CAD) introduced by Collins in [5] for real domains and Groebner basis methods for complex domains. Another powerful tool for solving semi-algebraic systems is `RegularChains` library of MAPLE [4].

The computation with `Reduce` yields `False`. This means that system (3.7) has no solution. Therefore Hopf bifurcations in system (3.1) are not possible for values of parameters admissible for the model.

Using the same approach we also studied cases (ii) and (v) of Theorem 2 and found out that Hopf bifurcations are also not possible in these cases.

3.2 Hopf bifurcations in system (3.1)

A common way to determine Hopf bifurcations presented in most textbooks is via computations of normal forms (see e.g. [14]). However the computation of normal form is a very laborious procedure. In this subsection we propose another approach based on making use of Lyapunov functions and the routine `Reduce` of MATHEMATICA, which appears much simpler and more efficient.

As it is mentioned above Hopf bifurcation cannot occur in system (3.1) for values of parameters interesting for the chemical analysis of the model. However since this system is relatively simple but not trivial, we demonstrate our approach for finding Hopf bifurcations using the system but allowing some quantities to be negative. The computations are performed for k_1 defined by (3.6).

It is well known (see e.g. [18]) that for any system of the form

$$\begin{aligned} \dot{u} &= -v + P(u,v) = \widetilde{P}(u,v) \\ \dot{v} &= u + Q(u,v) = \widetilde{Q}(u,v) \end{aligned} \tag{3.8}$$

it is always possible to find a function $\Phi(u,v)$ of the form

$$\Phi(u,v) = u^2 + v^2 + \sum_{j+k=3} \phi_{jk} u^j v^k, \tag{3.9}$$

such that

$$\frac{\partial \Phi}{\partial u}\widetilde{P} + \frac{\partial \Phi}{\partial v}\widetilde{Q} = g_1(u^2+v^2)^2 + g_2(u^2+v^2)^3 + \dots. \tag{3.10}$$

We see that Φ is a Lyapunov function for (3.8), so by the Lyapunov theorem on asymptotic stability [16] the origin is a stable focus if the first nonzero coefficient g_i on the right hand side of (3.10) is negative, and it is an unstable focus if the coefficient is positive. If we now transform the system

$$\begin{aligned} \dot{u} &= a_1 u + a_2 v + P(u,v) = \widetilde{P}(u,v) \\ \dot{v} &= a_3 u - a_1 v + Q(u,v) = \widetilde{Q}(u,v), \end{aligned} \tag{3.11}$$

which is a system where the trace of the matrix of the linear approximation is zero (note that this is the case for system (3.5)), to the form (3.8) we obtain expressions involving radicals. To avoid working with radicals we look for system (3.11) for a positive defined Lyapunov function Ψ of the form

$$\Psi(u,v) = \alpha u^2 + \beta uv + \gamma v^2 + \sum_{j+k=3} \Psi_{jk} u^j v^k, \tag{3.12}$$

satisfying (3.10). Computations show that the equality (3.10) can take place if we set

$$\alpha = -\frac{a_3\beta}{2a_1}, \quad \gamma = \frac{a_2\beta}{2a_1}. \tag{3.13}$$

As it is known the quadratic form $\alpha u^2 + \beta uv + \gamma v^2$ is positive defined if $\alpha > 0$ and $4\alpha\gamma - \beta^2 > 0$. In view of (3.13) $4\alpha\gamma - \beta^2 = \frac{-\beta^2\left(a_1^2 + a_2 a_3\right)}{a_1^2}$. Then when the origin of (3.11) is a center or a focus the quadratic form is positive defined.

For system (3.5) setting α, β, γ according to the rule given above and performing computation we find that

$$\alpha = \frac{-\beta\epsilon_1^2\epsilon_2 k_{-1}k_{-2}}{2k_2(k_2+\epsilon_1 k_{-2})}, \; 4\alpha\gamma - \beta^2 = -\frac{\beta^2(k_2^2 + 2\epsilon_1 k_2 k_{-2} + \epsilon_1^2 k_{-2}(k_{-1}+k_{-2}))}{(k_2+\epsilon_1 k_{-2})^2},$$

$$g_1 = \frac{A}{B},$$

where

$$\begin{aligned} A =& -\beta\epsilon_2 k_2^4 \left(k_{-2}(k_{-1}+k_{-2})\epsilon_1^2 + 2k_2 k_{-2}\epsilon_1 + k_2^2\right)^3; \\ B =& c_t \epsilon_1^2 k_{-2}^2 (k_2+\epsilon_1 k_{-2}) \left(k_2^2 + \epsilon_1(k_2+\epsilon_1 k_{-1})k_{-2}\right) \\ & \left(3\epsilon_1^4 k_{-1}^2 k_{-2}^2 \epsilon_2^4 + 8\epsilon_1 k_2^3 k_{-2}\epsilon_2^2 + 2\epsilon_1^2 k_2^2 k_{-2}(2k_{-2}-k_{-1})\epsilon_2^2 + \left(4\epsilon_2^2+3\right)k_2^4\right). \end{aligned}$$

Calculations with `Reduce` in `Mathematica` show that a Hopf bifurcation is not possible if all parameters of system (3.1) are positive. So we allow k_{-2} be negative. Then computing with `Reduce` we see that the system

$$g_1 < 0 \wedge \alpha > 0 \wedge 4\alpha\gamma - \beta^2 > 0 \wedge b < 0 \wedge c \neq 0 \wedge \epsilon_1 \geq 0$$
$$\wedge\, \epsilon_2 \geq 0 \wedge k_{-1} \geq 0 \wedge k_1 \geq 0 \wedge c_t \geq 0 \wedge k_2 \geq 0$$

has no solution. It means that a supercritical Hopf bifurcation is not possible in the system for values of parameters given above.

Similarly, looking with `Reduce` for solution of the semi-algebraic system the solution to

$$g_1 > 0 \wedge \alpha > 0 \wedge 4\alpha\gamma - \beta^2 > 0 \wedge b < 0 \wedge c \neq 0 \wedge \epsilon_1 \geq 0$$
$$\wedge\, \epsilon_2 \geq 0 \wedge k_{-1} \geq 0 \wedge k_1 \geq 0 \wedge c_t \geq 0 \wedge k_2 \geq 0$$

we obtain

$$\beta > 0 \wedge k_2 > 0 \wedge k_{-1} > 0 \wedge c_t > 0 \wedge \epsilon_2 > 0 \wedge \gamma_1 < 0 \wedge$$
$$((k_{-1} + k_{-2} = 0 \wedge k_{-2}(2\epsilon_1 k_{-2} + k_2) > 0) \vee \gamma_2 \vee \gamma_3)\,.$$

where

$$\gamma_1 = k_{-1}\left(2\epsilon_1 k_{-1} + k_2\left(-\sqrt{1 - \frac{4k_{-1}}{k_{-2}}}\right) + k_2\right),$$

$$\gamma_2 = \left(k_{-1} + k_{-2} > 0 \wedge k_{-2} < 0 \wedge \sqrt{-\frac{{k_2}^2 k_{-1}}{k_{-2}(k_{-1} + k_{-2})^2}} < \epsilon_1 + \frac{k_2}{k_{-1} + k_{-2}}\right),$$

and

$$\gamma_3 = \left(\epsilon_1 + \sqrt{-\frac{{k_2}^2 k_{-1}}{k_{-2}(k_{-1} + k_{-2})^2}} + \frac{k_2}{k_{-1} + k_{-2}} > 0 \wedge k_{-1} + k_{-2} < 0\right).$$

When the coefficients of (3.1) satisfy the conditions given above the system has a unstable focus at the singular points and admits a subcritical Hopf bifurcation.

4 Numerical example

In previous section we have shown that a Hopf bifurcation can occur in system (1.3) if parameters of the system satisfy condition (3.2), for instance, for

$$(k_2, k_{-1}, k_{-2}, \epsilon_1, \epsilon_2, c_t) = (1, 2, -3, \frac{1}{5}, 1, \frac{1}{4}). \tag{4.1}$$

Then by (3.6) $k_1 = \frac{4}{15}$. For these values of parameters the corresponding system (3.2) reduced on the plane $u = 0$ is

$$\dot{v} = -\frac{2v^2}{5} - vw + \frac{v}{4}, \quad \dot{w} = \frac{2v^2}{5} + \frac{16vw}{15} - \frac{v}{5} + \frac{2w^2}{3} - \frac{4w}{15} + \frac{1}{40}$$

Since $g_1 > 0$ the singular point $C = (-\frac{1}{2}, \frac{9}{2})$ of the system is unstable focus. If we now change k_1 choosing it slightly larger than $\frac{4}{15}$ then the focus becomes stable and a supercritical Hopf bifurcation occurs in the system, see Fig. 1.

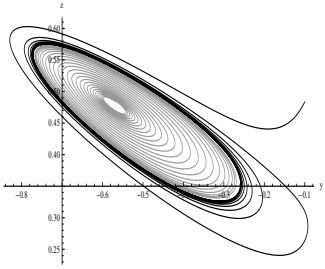

Figure 1: Unstable limit cycle of system (3.2) reduced on the invariant plane $u = 0$ for values of parameters defined by (4.1) and $k_1 = \frac{4}{15} + \frac{1}{50}$; the inner spiral is the trajectory passing through the point $y = -0.566809, z = 0.483723$, the outer one passes through $y = -0.1, z = 0.483723$

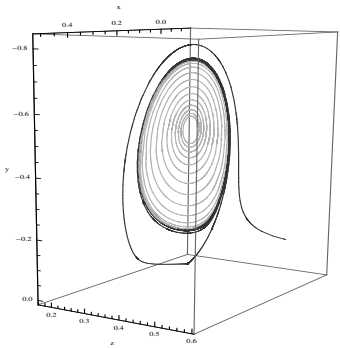

Figure 2: Unstable limit cycle of system (3.1) with the parameters satisfied (4.1), $k_1 = \frac{4}{15} + \frac{1}{50}$, $k_{-3} = -1$ and $k_3 = 0.002$

Fig. 2 shows that a limit cycle exist in the three dimensional system closed to the considered above even when the invariant plane is destroyed.

To conclude, in the paper we have presented an approach to find invariant surfaces in polynomial systems of ODEs and an approach for finding Hopf bifurcations. Both approaches rely essentially on algorithms of computational algebra. In particular, the routine `Reduce` of MATHEMATICA, and `eliminate` and `minAssGTZ` of SINGULAR have

been very helpful for the study. Using the presented approach it is possible to look for invariant surfaces and first integrals of higher orders but it requires powerful computational facilities, since elimination algorithm are extremely time and memory consuming.

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