Smallest chemical reaction system with Hopf bifurcation

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The smallest at most bimolecular chemical reaction system with Hopf bifurcation is presented. First the notion smallest reaction system is explained. Since the lowest number of intermediates has the highest priority in this characterization and since it has already been shown that three-component systems can have a Hopf bifurcation [1], the smallest reaction system must contain three intermediates. On the basis of a sufficient condition for a Hopf bifurcation in three-dimensional systems it is possible to find one reaction system which is according to the given characterization, the smallest one. In the first part of this paper it is shortly pictured and in the second part a more extensive proof that this system is really the searched smallest one is given.

1. Introduction

Starting-point of our considerations is the problem of the relation between the structural complexity and the dynamical behavior of a system. In a pioneering work, Gardner and Ashby [2] investigated the probability of stability as a function of the number of variables and the linear links between them; for related problems cf. [3–5]. Of course stability is only one point for a classification of the dynamical behavior, other ones could be oscillations or chaos. Sprott [6] investigated the probability of the occurrence of fixed points, limit cycles or chaos inside the stable region of the parameter space for about 4×10^7 maps and ordinary differential equations and found, e.g., that in low-dimensional, low-order polynomial maps the probability of chaos is decreasing with increasing dimension and order of the system. Despite of a high number of variables and nonlinearities complex chemical systems, e.g. biochemical reaction networks, often show rather simple dynamics. It has been pointed out that there are two mechanisms, which are responsible for the reduction of system variables in extremely wide system classes [7]. These are the very different time scales and mathematical principles which allow to describe the behavior of the system near a bifurcation point by a small number of order parameters. It has been argued that a strong separation of time constants observed in biochemical networks could be a result of evolutionary optimization [8].

However, it seems to be easier to concentrate on minimal systems for a certain kind of dynamical behavior, which perhaps makes the necessary conditions for its occurrence more evident than it is to find and analyse general mechanisms of model reduction. We confine ourselves to chemical reaction systems and in the present paper we look for the mathematically smallest system with a Hopf bifurcation. According to a result of Hanusse [9] a two-component chemical reaction system with only mono- and bimolecular reactions cannot show limit-cycle oscillations. That means, a minimal system for this kind of behavior either needs more than two agents or a reaction which is at least three-molecular.

A simple model in which primarily the number of components is low has been formulated by Selkov [10] in a theoretical investigation of glycolytic oscillations. It contains a constant influx of a compound X, a monomolecular efflux of a compound Y and a three-molecular positiv feedback described by a term XY^2. However, the occurrence of a three-molecular reaction is very improbable without suitable catalysts. This raises the question for the smallest system with only mono- and bimolecular reactions which can show oscillating concentrations. Hanusse [1] gave an example for a nice symmetric three-component system with Hopf bifurcation. But it consists of 8 bimolecular reactions and is not the smallest one.

In this paper first a definition of the smallest at most bimolecular system in the mathematical sense is given. On the basis of a necessary and sufficient condition it is possible to find the model for the minimal oscillating chemical reaction system with a Hopf bifurcation. Since in its differential equations only one quadratic term appears, this system seems to be well suited for analytical treatment. This paper only presents first results such as steady state solutions and the linear stability analysis, a bifurcation diagram and the estimation of the frequency near the Hopf bifurcation point.

2. The smallest system with Hopf bifurcation which only consists of mono- and bimolecular reactions

The smallest at most bimolecular reaction system with Hopf bifurcation in the mathematical sense can be characterized by the following 4 features with descending importance:

1. lowest number of reactants,

2. lowest number of quadratic terms,

3. minimal number of parameters, i.e. minimal number of reactions,

4. minimal number of bimolecular reactions.

It has already been shown that two-component systems with only mono- and bimolecular reactions cannot show limit-cycle oscillations [9,11], while a three-compo-

nent system with only bimolecular reactions can do so [1]. That's why the smallest system must contain three intermediates.

The starting-point for the following considerations is a sufficient condition for a Hopf bifurcation in three-dimensional systems:

Let

$$\lambda^3 - T\lambda^2 - K\lambda - D = 0 \tag{1}$$

be the characteristic polynom for a three-component system, where T, D indicate the trace and determinant, respectively. Then a Hopf bifurcation takes place at the transit through the surface

$$TK + D = 0 \tag{2}$$

if T, K, D < 0.

This can be proven as follows:
Let

$$q = \frac{-T^3}{27} - \frac{TK}{6} - \frac{D}{2}, \tag{3}$$

$$p = \frac{-3K - T^2}{9}. \tag{4}$$

At the surface (2) it is

$$q^2 + p^3 > 0. \tag{5}$$

According to the *Cardanic formula* the characteristic polynom in this case has one real and two (conjugate) complex roots. The real root reads

$$\lambda_{real} = \sqrt[3]{-q + \sqrt{q^2 + p^3}} + \sqrt[3]{-q - \sqrt{q^2 + p^3}} + \frac{T}{3}. \tag{6}$$

Because first $\lambda_{real} < 0$ if $TK = -D$ and $T, K < 0$ and second the stability changes according to the *Hurwitz criterion*, the conjugate complex root becomes purely imaginary, i.e. a Hopf bifurcation takes place at this surface. Condition (2) is also necessary for a Hopf bifurcation because it follows immediately from expanding the characteristic polynomial

$$(\lambda + i\omega)(\lambda - i\omega)(\lambda - \lambda_{real}) = 0, \tag{7}$$

where ω denotes the imaginary part of the conjugate complex eigenvalue.

The present study shows that there is exactly one system which follows from the given characterization of the smallest reaction system with Hopf bifurcation. Its mechanism is depicted in scheme 1.
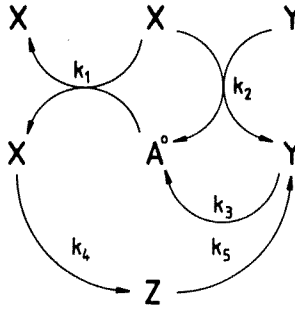
Scheme 1. Reaction scheme of the smallest chemical reaction system with Hopf bifurcation. A^0 denotes outer reactants and for thermodynamical reasons it must represent at least two different substances.

The dynamics of the system is governed by the differential equations:

$$\dot{X} = (k_1 A - k_4)X - k_2 XY,$$
$$\dot{Y} = -k_3 Y + k_5 Z,$$
$$\dot{Z} = k_4 X - k_5 Z, \tag{8}$$

where A denotes the fixed concentration of the outer reactant of the autocatalytic reaction. It has two steady states:

$$1. \quad \bar{X}_1 = \bar{Y}_1 = \bar{Z}_1 = 0, \tag{9}$$

$$2. \quad \bar{X}_2 = \left(\frac{k_1 A - k_4}{k_2 k_4}\right)k_3, \quad \bar{Y}_2 = \frac{k_1 A - k_4}{k_2}, \quad \bar{Z}_2 = \left(\frac{k_1 A - k_4}{k_2 k_5}\right)k_3. \tag{10}$$

At the first and second steady state the coefficients of the characteristic polynom (1) are

$$T_1 = k_1 A - k_3 - k_4 - k_5, \tag{11}$$

$$K_1 = (k_1 A - k_4)(k_3 + k_5) - k_3 k_5, \tag{12}$$

$$D_1 = (k_1 A - k_4)k_3 k_5, \tag{13}$$

$$T_2 = -k_3 - k_5, \tag{14}$$

$$K_2 = -k_3 k_5, \tag{15}$$

$$D_2 = (k_4 - k_1 A)k_3 k_5. \tag{16}$$

Since

$$T_1 K_1 + D_1 > 0 \quad \text{if } k_1 A < k_4, \tag{17}$$

$$T_2 K_2 + D_2 = k_3 k_5 (k_3 + k_4 + k_5 - k_1 A),\qquad (18)$$

it follows from the Hurwitz criterion with (11)–(16) that the first steady state is stable within the range $0 \leqslant k_1 A < k_4$ and the second one within the range $k_4 < k_1 A < k_3 + k_4 + k_5$.

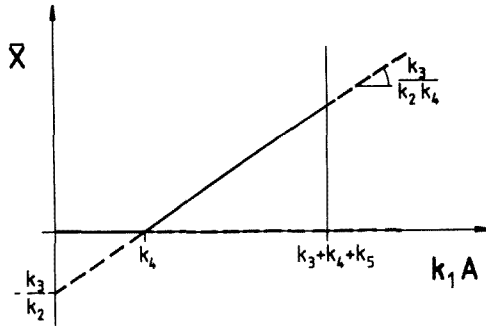The bifurcation diagram is given in fig. 1.

Fig. 1. Bifurcation diagram for the smallest chemical reaction system with Hopf bifurcation. ——— stable, $---$ unstable steady states.
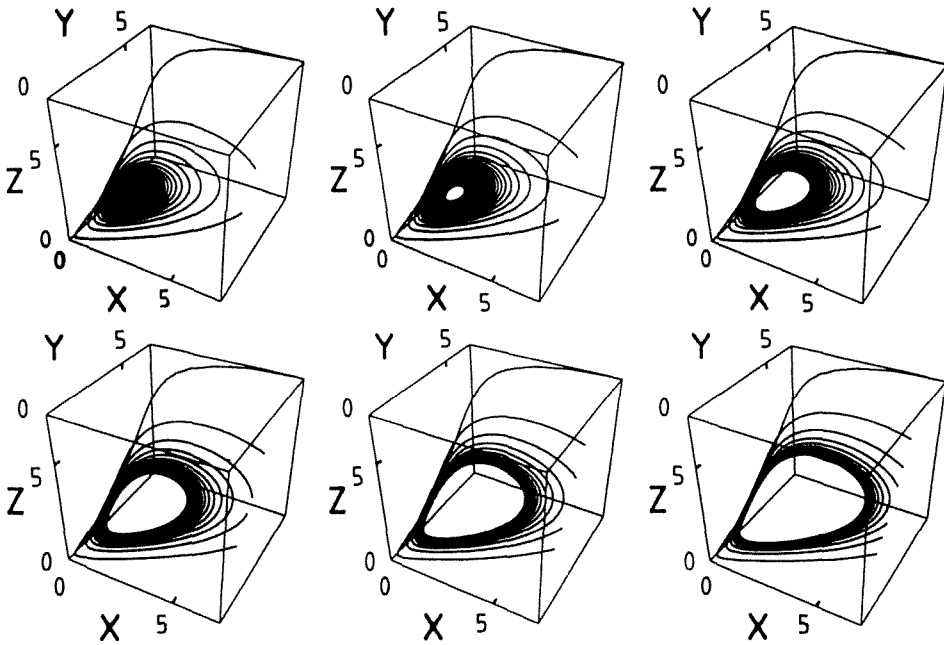

Fig. 2. Numerical integration at both sides of the Hopf bifurcation point. Parameter values: $k_2 = k_3 = k_4 = k_5 = 1$. According to (20) and (10) the Hopf bifurcation is at $k_1 A = 3$ and the concentrations at the second steady state are: $\bar{X}_2 = \bar{Y}_2 = \bar{Z}_2 = k_1 A - 1$. Values for $k_1 A$: (a) 2.95, (b) 3.0, (c) 3.05, (d) 3.1, (e) 3.15, (f) 3.2.

The system has two bifurcation points:

1. *Transcritical bifurcation* at $\quad k_1 A = k_4$, $\qquad\qquad\qquad$ (19)
2. *Hopf bifurcation* $\qquad$ at $\quad k_1 A = k_3 + k_4 + k_5$.

The frequency of the limit cycle near the Hopf bifurcation follows from the Eigenvalues of the Jacobian at the bifurcation point. It is

$$\lambda_1 = -k_3 - k_5, \qquad\qquad\qquad (21)$$

$$\lambda_{2/3} = \pm i\sqrt{k_3 k_5}. \qquad\qquad\qquad (22)$$

Therefore the angular frequency ω is

$$\omega = \sqrt{k_3 k_5} \qquad\qquad\qquad (23)$$

and the time of period $T = 2\pi/\omega$.

Figure 2 gives results of numerical integrations of this system at both sides of the Hopf bifurcation point.

3. Proof of the hypothesis

In three-component systems for a given component X only 4 types of quadratic nonlinearities are possible:

$$\dot{X} = \ldots - X^2,$$
$$\dot{X} = \ldots + Y^2,$$
$$\dot{X} = \ldots \pm XY,$$
$$\dot{X} = \ldots + YZ. \qquad\qquad\qquad (24)$$

In (24) X denotes the concentration of one of the three reactants, Y denotes one of the two other and YZ the product of the two other components. The signs of the terms Y^2 and YZ follow from the condition that in chemical reaction systems all terms at the right side of a differential equation of a special reactant which do not contain the concentration of this reactant must be larger than or equal zero. Otherwise the trajectory of the system could leave the subspace of positive concentrations. The term X^2 enters (24) with negative sign because three- and higher molecular reactions are excluded. For only one of these four terms (XY) both signs are possible, since $X + Y$ reacting e.g. to $Y +$ *outer reactant* gives the negative sign and reacting to $X + X$ gives the positive sign.

We are looking for a three-component system which contains only one quadratic nonlinearity at the right side of $(\dot{X}, \dot{Y}, \dot{Z})^T = f(X, Y, Z)$. First, we can state that the terms Y^2 and YZ at the right side of (24) cannot be the only quadratic nonlinear-

ity in the whole three-dimensional system. Second, from all bimolecular reactions yielding the terms X^2 and XY, there are only two different ones possible so that only one quadratic term appears at the right side of the differential equation system:

(a) $X + X \rightarrow X +$ outer reactant,

   $X + X \rightarrow$ outer reactants,

(b) $X + Y \rightarrow Y +$ outer reactant. $\hspace{3cm}$ (25)

It will be shown now that in case (25a) the term $TK + D$ is always larger than zero, so that a Hopf bifurcation can be excluded:

The most general case for such a system is:

$$\dot{X} = a_1 A \pm a_2 X + a_3 Y + a_4 Z - a_5 X^2,$$
$$\dot{Y} = b_1 B + b_2 X - b_3 Y + b_4 Z,$$
$$\dot{Z} = c_1 C + c_2 X + c_3 Y - c_4 Z \hspace{3cm} (26)$$

with

$$a_i, b_i, c_i \geqslant 0 \quad \text{for } i = 1, 2,$$

$$a_3, a_4, b_4, c_3 \geqslant 0,$$

$$a_5, b_3, c_4 > 0.$$

Here A, B, C denote the concentrations of constant outer reactants and a_i, b_i, c_i denote rate constants. For the existence of a finite steady state it is necessary that the terms $-b_3 Y$ and $-c_4 Z$ have a negative sign.

The Jacobian of system (26) may be written as

$$J = \begin{pmatrix} \overset{\leqslant}{a_{11}} & \overset{\geqslant}{a_{12}} & \overset{\geqslant}{a_{13}} \\[2mm] \overset{\geqslant}{a_{21}} & \overset{<}{a_{22}} & \overset{\geqslant}{a_{23}} \\[2mm] \overset{\geqslant}{a_{31}} & \overset{\geqslant}{a_{32}} & \overset{<}{a_{33}} \end{pmatrix}. \hspace{2cm} (27)$$

The signs of the elements at a steady state are indicated by the signs above them. For the evaluation of the sign of $a_{11} = \pm a_2 - 2a_5 \bar{X}$ it has been taken into account that in any mono- and bimolecular reaction system all the elements of the trace of the Jacobian at the steady state must be smaller or equal zero [1]. It follows that

$$\overset{\leqslant}{T} = \overset{<}{a_{11}} + \overset{\cdot}{a_{22}} + \overset{<}{a_{33}}, \tag{28}$$

$$\overset{\geqslant}{K} = \overset{\geqslant}{a_{12}a_{21}} + \overset{\geqslant}{a_{13}a_{31}} + \overset{\leqslant}{a_{23}a_{32}} - \overset{\leqslant}{a_{11}a_{22}} - \overset{<}{a_{11}a_{33}} - a_{22}a_{33}, \tag{29}$$

$$\overset{\leqslant}{D} = \overset{\geqslant}{a_{11}a_{22}a_{33}} + \overset{\geqslant}{a_{12}a_{23}a_{31}} + a_{13}a_{21}a_{32}$$

$$\overset{\geqslant}{-\ a_{12}a_{21}a_{33}} - \overset{\geqslant}{a_{11}a_{23}a_{32}} - \overset{\geqslant}{a_{13}a_{22}a_{31}}. \tag{30}$$

The signs over all the terms denote in each case the sign of the whole term, i.e. of the term including its *plus* or *minus* sign. A necessary condition for Hopf bifurcation is $T, K, D < 0$. It can be seen that for $D < 0$ it is necessary that

$$a_{11} < 0, \tag{31}$$

$$a_{11}a_{22} > a_{12}a_{21}, \tag{32}$$

$$a_{11}a_{33} > a_{13}a_{31}. \tag{33}$$

With (28)–(30) one obtains:

$$\begin{aligned}
TK + D = {} & a_{11}(a_{12}a_{21} \underline{+ a_{23}a_{32}} - a_{11}a_{22} - a_{11}a_{33} \underline{- a_{22}a_{33}}) \\
& + a_{22}(a_{12}a_{21} \underline{+ a_{13}a_{31}} + a_{23}a_{32} - a_{11}a_{22} - a_{11}a_{33} - a_{22}a_{33}) \\
& + a_{33}(\underline{a_{12}a_{21}} + a_{13}a_{31} + a_{23}a_{32} - a_{11}a_{22} - a_{11}a_{33} - a_{22}a_{33}) \\
& \underline{+ a_{11}a_{22}a_{33}} + a_{12}a_{23}a_{31} + a_{13}a_{21}a_{32} \\
& \underline{- a_{12}a_{21}a_{33}} - a_{11}a_{23}a_{32} - a_{13}a_{22}a_{31} \\
& > 0
\end{aligned} \tag{34}$$

The result $TK + D > 0$ holds since:
(a) the sum of the underlined terms is zero;
(b) the first summand of (34) is larger than zero because of (31–33);
(c) $a_{22}(K - a_{13}a_{31}) > 0$ and $a_{33}(K - a_{12}a_{21}) > 0$ must be true for $K < 0$;
(d) $a_{12}a_{23}a_{31} \geqslant 0$ and $a_{13}a_{21}a_{32} \geqslant 0$.
Therefore, in the case (25a) a Hopf bifurcation is not possible.

System (26) is also the most general system in the case (25b) except for the quadratic term which is now $-a_5XY$ (cf.(A.1)). In particular its Jacobian is the same as

(27), with the only difference that $a_{12} = a_3 - a_5 \bar{X}$ can also become negative. Obviously, it has necessarily to be negative, because otherwise the proof that a Hopf bifurcation is never possible would exactly be the same as for the case (25a).

In order to find the smallest oscillating system, it is also necessary to search for the minimal number of parameters, i.e. the minimal number of reactions. (cf. point 3 in the characterization of the smallest system.) The easiest way to find it is to successively add the necessary terms to the quadratic nonlinearity $-a_5 XY$. The terms $-b_3 Y$ and $-c_4 Z$ must appear for the reason mentioned above. In appendix A it can be seen that in addition to the requirement $a_{12} < 0$ the elements a_{23} and a_{31} of the Jacobian must be larger than zero for $TK + D = 0$. Therefore, the differential equations for the minimal system with Hopf bifurcation must include the following terms:

$$\dot{X} = \ldots - a_5 XY,$$
$$\dot{Y} = -b_3 Y + b_4 Z,$$
$$\dot{Z} = c_2 X - c_4 Z,$$
$$a_i, b_i, c_i > 0. \tag{35}$$

Obviously, in $\dot{X}$ at least one positive summand must be added in order to make a positive steady state possible. It is shown in the appendix B that for a Hopf bifurcation in case (35) a positive term $a_2 X$ must exist in $\dot{X}$. This can only be realized with a bimolecular autocatalytic reaction $X + A \rightarrow X + X$. In the sense of point 3 and 4 of the characterization of the smallest system, the easiest representation therefore is system (8) shown in scheme 1. The minimal number of reactions can be reached when $b_4 = c_4$ (reaction $Z \rightarrow Y$) and the lowest number of bimolecular reactions if the term $c_2 X$ represents a monomolecular reaction $X \rightarrow Z$, so that $a_2 X$ consists of two summands, one resulting from the degradation of X and the other from the autocatalytic reaction.

4. Discussion

In the present paper the mathematically smallest chemical reaction system with Hopf bifurcation is deduced. From the mathematical point of view the given system shows some similarities to the well known system proposed by Rössler [12], since it also is a three-dimensional one with only one quadratic nonlinearity. However, the Rössler system cannot be interpreted as a chemical reaction system, because the trajectories are not confined to the positive orthant.

We have shown that there is only one system which satisfies all conditions for a minimal system according to the characterization given at the beginning of section 2. Point 4 demands the lowest number of bimolecular reactions. If this point were replaced by the requirement of *minimal number of summands at the right side of*

the differential equations, which would more consequently aim at mathematical simplicity, the resulting system would closely be related to that given in eqs. (8) with the only difference that the monomolecular reaction $X \rightarrow Z$ would be replaced by $X + A \rightarrow X + Z$, so that the whole system would have three bimolecular reactions. Nevertheless, if one compares the resulting reaction scheme with that given in Scheme 1 it is reasonable to characterize the system represented by eqs. (8) as the most simple one.

A smallest system in the physical sense would be defined by the characterization given in section 2 if point 2 which demands the lowest number of quadratic terms, were cancelled. The present analysis does not exclude the possibility of an oscillating system with, for example, four reactions and more than one nonlinearity. All these systems discussed so far are idealized insofar as they contain irreversible reactions which in a strong thermodynamic sense do not exist. This raises the question for the smallest chemical system with the lowest number of reversible reactions only. However, if there were a system with less than 5 reactions, reversible or irreversible, which could show a Hopf bifurcation, it follows from the present analysis that in the sense of the given characterization of the smallest system it would mathematically be more difficult.

It is shown in the appendix that for system (35) the existence of an autocatalytic reaction is a necessary condition for a Hopf bifurcation. This is in agreement with the general statement that for the occurrence of oscillations a chemical reaction system must contain some kind of autocatalytic or negative feedback reaction. The bifurcation diagram in fig. 1 shows that a sufficiently large velocity constant $k_1 A$ of the autocatalytic bimolecular reaction is necessary for oscillations, whereas high rate constants of the three monomolecular reactions tend to stabilize the system.

The proof of the stability of the periodic orbit of system (8) is a still pending problem. Since only one of the coupled differential equations has a nonlinearity, this should be possible by applying the Hopf-Friedrich theory in the explicit algebraic form (see e.g. MacDonald [13], Poore [14]).

The given system could also be of biological interest. It can be interpreted, e.g., as an oscillation model in population kinetics. X could denote the parental generation which produces the descendants Y over an intermediate Z, whereas Y exterminates its parents X.

However, the concept of analysing and discussing minimal systems in different senses and for different purposes seems to be promising in order to tackle the problem of the relation between the structural complexity and the dynamical behavior of systems.

Acknowledgement

Appendix A

In this appendix it will be proven in two independent parts that in case (25b) $a_{31} > 0$ as well as $a_{23} > 0$ are necessary conditions for $TK + D = 0$.

The most general system is represented by the equations

$$\dot{X} = a_1 A \pm a_2 X + a_3 Y + a_4 Z - a_5 XY,$$
$$\dot{Y} = b_1 B + b_2 X - b_3 Y + b_4 Z,$$
$$\dot{Z} = c_1 C + c_2 X + c_3 Y - c_4 Z \qquad (A.1)$$

with

$$a_i, b_i, c_i \geqslant 0 \quad \text{for } i = 1, 2,$$

$$a_3, a_4, b_4, c_3 \geqslant 0,$$

$$a_5, b_3, c_4 > 0.$$

1. *A three-component reaction system with the nonlinearity following from the reaction of case (25b) cannot have a Hopf bifurcation if $a_{31} = 0$:*

The term $TK + D$ of system (A.1) reads if $a_{31} = c_2 = 0$:

$$
\begin{aligned}
TK + D = {} & a_{11}(\underline{a_{12}a_{21} + a_{23}a_{32}} - a_{11}a_{22} - a_{11}a_{33} \underline{- a_{22}a_{33}}) \\
& + a_{22}(a_{12}a_{21} + a_{23}a_{32} - a_{11}a_{22} - a_{11}a_{33} - a_{22}a_{33}) \\
& + a_{33}(\underline{a_{12}a_{21}} + a_{23}a_{32} - a_{11}a_{22} - a_{11}a_{33} - a_{22}a_{33}) \\
& \underline{+ a_{11}a_{22}a_{33}} + a_{13}a_{21}a_{32} \underline{- a_{12}a_{21}a_{33}} - a_{11}a_{23}a_{32}.
\end{aligned}
\qquad (A.2)
$$

The sum of the underlined terms is zero. According to a result of section 3 $a_{12} = a_3 - a_5 \bar{X} < 0$ is a necessary condition for a Hopf bifurcation in this case so that the only negative summands which can appear in (A.2) are $a_{22}a_{23}a_{32}$ and $a_{33}a_{23}a_{32}$. For $TK + D = 0$ it is, therefore, necessary that

$$a_{23}a_{32} \geqslant a_{22}a_{33}. \qquad (A.3)$$

It is shown now that (A.3) is in contradiction to other necessary conditions for a Hopf bifurcation. The following two cases are distinguished: a) $a_{21} = b_2 = 0$ and b) $a_{21} = b_2 > 0$.

Case (a). The determinant D of the Jacobian at a steady state of system (A.1) is

$$D = (\pm a_2 - a_5 \bar{Y})(b_3 c_4 - b_4 c_3). \qquad (A.4)$$

For $D < 0$ it is necessary that $a_{11} = \pm a_2 - a_5 \bar{Y} < 0$ and $b_3 c_4 = a_{22}a_{33} > a_{23}a_{32} = b_4 c_3$ which is in contradiction to (A.3).

Case (b). From (A.1) follows for positive steady state concentrations

$$b_3 > \frac{b_4 \bar{Z}}{\bar{Y}}, \qquad (A.5)$$

$$c_4 \geqslant \frac{c_3 \bar{Y}}{\bar{Z}}, \qquad\qquad\qquad (A.6)$$

and therefore $b_3 c_4 = a_{22} a_{33} > a_{23} a_{32} = b_4 c_3$ which contradicts (A.3).

2. *A three-component reaction system with the nonlinearity following from the reaction of case (25b) cannot have a Hopf bifurcation if $a_{23} = 0$:*

The term $TK + D$ of system (A.1) reads if $a_{23} = b_4 = 0$:

$$\begin{aligned}
TK + D = {} & a_{11}(a_{12}a_{21} + a_{13}a_{31} - a_{11}a_{22} - a_{11}a_{33} \underline{- a_{22}a_{33}}) \\
& + a_{22}(a_{12}a_{21} \underline{+ a_{13}a_{31}} - a_{11}a_{22} - a_{11}a_{33} - a_{22}a_{33}) \\
& + a_{33}(\underline{a_{12}a_{21}} + a_{13}a_{31} - a_{11}a_{22} - a_{11}a_{33} - a_{22}a_{33}) \\
& + \underline{a_{11}a_{22}a_{33}} + a_{13}a_{21}a_{32} \underline{- a_{12}a_{21}a_{33}} - a_{13}a_{22}a_{31}.
\end{aligned} \qquad (A.7)$$

The sum of the underlined terms is zero. With $a_{12} < 0$ in (A.7) only the terms $a_{11}a_{13}a_{31}$ and $a_{33}a_{13}a_{31}$ may be negative. For $TK + D = 0$ it is, therefore, necessary that

$$a_{13}a_{31} > a_{11}a_{33}. \qquad\qquad\qquad (A.8)$$

Case (a) $a_{21} = b_2 = 0$: The determinant D of the Jacobian at steady state is

$$D = -b_3(c_4(a_5 \bar{Y} \pm a_2) - a_4 c_2). \qquad\qquad (A.9)$$

For $D < 0$ it is necessary that $a_{11} = \pm a_2 - a_5 \bar{Y} < 0$ and $c_4(a_5 \bar{Y} \pm a_2) = a_{33}a_{11} > a_{13}a_{31} = a_4 c_2$ which contradicts condition (A.8).

Case (b) $a_{21} = b_2 > 0$: In the steady state it is

$$\bar{X}^2 + \bar{X}\left(\frac{b_1 B}{b_2} - \frac{a_3}{a_5} - \frac{a_2 b_3}{a_5 b_2} - \frac{a_4 c_3}{a_5 c_4} - \frac{a_4 b_3 c_2}{a_5 b_2 c_4}\right) - \frac{a_1 A b_3}{a_5 b_2} - \frac{a_3 b_1 B}{a_5 b_2} - \frac{a_4 b_1 B c_3}{a_5 b_2 c_4}$$

$$- \frac{a_4 b_3 c_1 C}{a_5 b_2 c_4} = 0, \qquad\qquad\qquad (A.10)$$

therefore

$$\bar{X}_1 < 0 \quad \text{for all allowed parameter values}, \qquad\qquad (A.11)$$

$$\bar{X}_2 = \frac{a_3}{a_5} + \frac{a_2 b_3}{a_5 b_2} + \frac{a_4 c_3}{a_5 c_4} + \frac{a_4 b_3 c_2}{a_5 b_2 c_4} - \frac{b_1 B}{b_2} + v, \quad v > 0. \qquad (A.12)$$

With

$$\bar{Y} = \frac{b_2 \bar{X} + b_1 B}{b_3} \qquad\qquad\qquad (A.13)$$

it follows that

$$\bar{Y}_2 = \frac{a_2}{a_5} + \frac{a_3 b_2}{a_5 b_3} + \frac{a_4 c_2}{a_5 c_4} + \frac{a_4 b_2 c_3}{a_5 b_3 c_4} + \tilde{v}, \quad \tilde{v} > 0. \qquad (A.14)$$

Since

$$a_{13}a_{31} = a_4c_2 , \qquad (A.15)$$

$$a_{11}a_{33} = a_5c_4 \bar{Y}_2 - a_2c_4 , \qquad (A.16)$$

one obtains with (A.14) $a_{13}a_{31} \leqslant a_{11}a_{33}$ which completes the proof.

Appendix B

The most general form of the minimal system (35) is

$$\dot{X} = a_1A + a_2X + a_3Y + a_4Z - a_5XY ,$$
$$\dot{Y} = -b_3Y + b_4Z ,$$
$$\dot{Z} = c_2X - c_4Z ,$$
$$a_1A, a_3, a_4 \geqslant 0 ,$$
$$a_5, b_3, b_4, c_2, c_4 > 0 . \qquad (B.1)$$

In the following the proof is given that $a_2 > 0$ is a necessary condition for a Hopf bifurcation in this system:

In the steady state it is

$$\bar{Y}_{1/2} = \Big(a_2b_3c_4 + a_3b_4c_2 + a_4b_3c_2$$
$$\pm \sqrt{(a_2b_3c_4 + a_3b_4c_2 + a_4b_3c_2)^2 + 4a_1a_5b_3b_4c_2c_4A} \Big)/(2a_5b_3c_4) , \quad (B.2)$$

i.e.

$$\bar{Y}_1 \leqslant 0 \quad \text{for all allowed parameter values}, \qquad (B.3)$$

$$\bar{Y}_2 = \frac{a_2}{a_5} + \frac{a_4c_2}{a_5c_4} + \frac{a_3b_4c_2}{a_5b_3c_4} + w \quad (w \geqslant 0)$$
$$> 0 . \qquad (B.4)$$

The possibility for a Hopf bifurcation at the positive steady state must be proven. With

$$\bar{X}_2 = \frac{b_3c_4}{b_4c_2} \bar{Y}_2 , \qquad (B.5)$$

the Jacobian of the system at this point is

$$J = \begin{pmatrix} a_2 - a_5\bar{Y}_2 & a_3 - \frac{a_5b_3c_4}{b_4c_2}\bar{Y}_2 & a_4 \\ 0 & -b_3 & b_4 \\ c_2 & 0 & -c_4 \end{pmatrix} , \qquad (B.6)$$

therefore,

$$T = a_2 - a_5 \bar{Y}_2 - b_3 - c_4 , \tag{B.7}$$

$$K = a_4 c_2 + a_2 b_3 + a_2 c_4 - a_5 \bar{Y}_2 b_3 - a_5 \bar{Y}_2 c_4 - b_3 c_4 , \tag{B.8}$$

$$D = a_2 b_3 c_4 + a_3 b_4 c_2 + a_4 b_3 c_2 - 2 a_5 \bar{Y}_2 b_3 c_4 \tag{B.9}$$

and

$$\begin{aligned} TK + D = {}& a_2 K \\ & + a_5 \bar{Y}_2 (\overline{- a_4 c_2} - a_2 b_3 \overline{- a_2 c_4} + a_5 \bar{Y}_2 b_3 + \overline{a_5 \bar{Y}_2 c_4 + b_3 c_4}) \\ & + b_3 (\underline{- a_4 c_2} - a_2 b_3 \overline{- a_2 c_4} + a_5 \bar{Y}_2 b_3 \overline{+ a_5 \bar{Y}_2 c_4} + b_3 c_4) \\ & + c_4 (\overline{- a_4 c_2} - a_2 b_3 \overline{- a_2 c_4} + \underline{a_5 \bar{Y}_2 b_3} \overline{+ a_5 \bar{Y}_2 c_4} + b_3 c_4) \\ & + \underline{a_2 b_3 c_4 + a_3 b_4 c_2 + a_4 b_3 c_2 - 2 a_5 \bar{Y}_2 b_3 c_4} . \end{aligned} \tag{B.10}$$

The sum of the underlined terms is zero. From (B.4) it follows

$$a_5 \bar{Y}_2 c_4 = a_2 c_4 + a_4 c_2 + \frac{a_3 b_4 c_2}{b_3} + \tilde{w} \quad (\tilde{w} \geqslant 0) . \tag{B.11}$$

Therefore, the sum of the overlined terms is larger than or equal zero for all allowed parameter values and together with the necessary condition $K < 0$ it follows that $TK + D$ can only be zero if $a_2 > 0$.

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