On the origin of Turing instability

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A reaction–diffusion system consisting of one, two or three chemical species and taking place in an arbitrary number of spatial dimensions cannot exhibit Turing instability if none of the reaction steps express cross-inhibition. A corollary of this result – obtained by elementary calculations – underlines the importance of nonlinearity in the formation of stationary structures, a kind of self-organization on a chemical basis. Relations to global stability of reaction–diffusion systems, and results on multispecies systems are also mentioned. The statements are not restricted to mass action type models. As a by-product, the solution of a basic inverse problem of formal kinetics is also presented which extends a previous result by Hárs and Tóth (1981) to models with arbitrary – including rational – functions as reaction rates so often occurring, e.g., in enzyme kinetics.

1. Introduction

According to the most naive – and most widespread – belief, thermodynamical systems tend to the same state no matter what their initial state was. To put it in terms of mathematics: they have a single globally asymptotically stable equilibrium state. This statement, however, is false even in the case of systems with a single degree of freedom. In the case of systems with more degrees of freedom the discrepancy from this simple, ideal behaviour might be great.

A phenomenon really strange if considered from the classical viewpoint above will be treated here: the interaction between reaction and diffusion predicted by Turing [76] more than 40 years ago. The phenomenon has also been shown to exist in an experimental setup several years ago. Here diffusion is the cause of (spatial) inhomogeneity contrary to the general expectation that it should, in general, equilibrate inhomogeneities.

The *Le Chatelier–Braun principle* [45, p. 145] and [13, p. 139] – stating that a system in a stable equilibrium tries to escape the constraint forced upon it – would imply that the effect of a perturbation on a reaction–diffusion system was flattened by the reaction too, in the same way as it is done in the case of other cross effects (thermomechanical effect as a result of coupling between the flow of mass and energy, Seebeck effect [13, p. 297] as a result of coupling between the flow of mass and electricity, Peltier effect [13, p. 299], etc.).

The phenomenon contradicts the *Curie principle* ("neither stated nor proved by herself" [77, p. 79]) too. This asserts that general forces can only cause flows of the same tensorial order, i.e., a scalar force causes a scalar flow, a vectorial force causes a vectorial flow, a tensorial force causes a tensorial flow. If the chemical affinity is considered to be a scalar force (the question, whose gradient it is, remains to be decided) then the corresponding scalar flow is reaction rate. The Curie principle excludes the possibility of cross effects between forces and flows of different tensorial order, e.g., chemical affinity cannot be combined with the concentration gradient.

Turning back to the phenomenon in question, it was A.M. Turing – a pioneer in computer science too – who made an approach to the clarification of emergence of asymmetric patterns in the embryo, totally symmetric at the beginning. He constructed a system which he considered a reaction–diffusion system (we are going to return to this point below) in which there exists a stable homogeneous stationary state losing its stability as a result of inhomogeneous perturbations. The importance of his paper has been recognized by theoreticians mainly of the Brussels school (see, e.g., [3,8,18,30,35,42,52,60,61]). However, no well-defined *experiments* had been made until very recent years. All the systems exhibiting spatial patterns either contained convection or surface effects, thus the origin of pattern formation has never been pure Turing instability. It was putting the CIMA reaction into the gel ring reactor – designed by Noszticzius et al. [58] – by DeKepper et al. [14,16] which is generally considered to have produced the long-sought-for result first: the emergence of stationary patterns as a result of diffusion driven instability. If the definition of a Turing structure is taken in a less restrictive sense as usual as, e.g., in [65, p. 10 477], then the early experiment by Flicker and Ross [29] may also be considered as an experimental realization.

Lengyel and Epstein [47] were able to illuminate the difference between the BZ-reaction used in [58] and the CIMA reaction used in [14,16]: the necessary difference between the diffusion constants of the different species *is* provided by the starch indicator present in the second system (cf. [64]).

In the present paper we try to elucidate the mathematical origin of Turing instability in the following way. By using *elementary* arguments, we show that the presence of cross-inhibition is a necessary condition of Turing instability, at least in the case of systems with one, two or three chemical species. This result implies that the presence of higher-than-first-order reactions is a necessary condition of Turing instability.

The structure of our paper is a follows. Firstly, we recapitulate the notions needed to the mathematical investigation of diffusive instabilities in reaction–diffusion systems. In this part we also present the solution of an inverse problem of formal reaction kinetics in the most general form. Secondly, we formulate our main results related to systems with one, two and three internal species. Finally, we provide a detailed discussion on the connections of the topics with global stability of reaction–diffusion systems and we also mention the possible applications of our mathematical results in the field of homogeneous reaction kinetics.

The result of the present paper follows from our more general earlier result [70] for the case of mass action type reactions. The main idea here was

- to obtain results for not necessarily mass action type kinetics,
- to provide an elementary method accessible for everyone, and finally,
- to discuss thermodynamical connections.

2. Turing instability in reaction–diffusion systems

2.1. Reaction–diffusion systems

Let us consider a vessel, i.e., a finite simply connected domain Ω in $\mathbf{R}^N$ (N is an arbitrary positive integer, the number of spatial dimensions). Let us suppose it contains M ($\in \mathbf{N}$) chemical species $\mathcal{A}(1), \ldots, \mathcal{A}(M)$ among which the following reaction steps take place:

$$\sum_{m=1}^{M} \alpha(m,r)\mathcal{A}(m) \to \sum_{m=1}^{M} \beta(m,r)\mathcal{A}(m) \quad (r = 1, \ldots, R). \tag{1}$$

The nonnegative integers $\alpha(m,r)$ and $\beta(m,r)$ are called *stoichiometric coefficients* making up two *multiindices* in the following way: $\alpha(\cdot\,,r) := (\alpha(1,r), \ldots, \alpha(M,r))$ and $\beta(\cdot\,,r) := (\beta(1,r), \ldots, \beta(M,r))$.

The usual mathematical model for this process, taking into account diffusion of the species, is the system of partial differential equations

$$\partial_t c_m(t,\mathbf{x}) = f_m(\mathbf{c}(t,\mathbf{x})) + D_m \Delta c_m(t,\mathbf{x}) \quad (m = 1, 2, \ldots, M), \tag{2}$$

where for $m = 1, 2, \ldots, M$, $r = 1, 2, \ldots, R$, $\bar{\mathbf{c}} := (\bar{c}_1, \bar{c}_2, \ldots, \bar{c}_M) \in (\mathbf{R}_0^+)^M$, $t \in \mathbf{R}$, $\mathbf{x} \in \Omega$:

- $c_m(t,\mathbf{x})$ is the concentration of species $\mathcal{A}(m)$ at time t at the location $\mathbf{x}$;
- $\mathbf{c}(t,\mathbf{x}) := (c_1(t,\mathbf{x}), \ldots, c_M(t,\mathbf{x}))$;
- $$f_m(\bar{\mathbf{c}}) := \sum_{r=1}^{R} \big(\beta(m,r) - \alpha(m,r)\big) w_r(\bar{\mathbf{c}}) \quad (\bar{\mathbf{c}} \in (\mathbf{R}_0^+)^M); \tag{3}$$
- $D_m \in \mathbf{R}^+$ is the diffusion constant of species $\mathcal{A}(m)$;
- $w_r(\bar{\mathbf{c}})$ is the rate of the rth reaction step at the concentration $\bar{\mathbf{c}}$; and it is supposed that $w_r \in \mathcal{C}^1((\mathbf{R}_0^+)^M, \mathbf{R}_0^+)$. We also require that
- $w_r(\bar{\mathbf{c}}) > 0$ if for all $m = 1, 2, \ldots, M$, $\alpha(m,r) > 0$ implies $\bar{c}_m > 0$, and that

- $w_r(\bar{\mathbf{c}}) = 0$ whenever there exists m such that $\bar{c}_m = 0$ and $\alpha(m,r) > 0$

(see, e.g., [23,27,75]).

The ordinary differential equation with the right-hand side (3) is said to be induced by the reaction (1).

Let us consider the example of the CIMA-reaction [14,16,47]. Here

$$M := 3, \qquad \mathcal{A}(1) := \mathrm{I}_2, \qquad \mathcal{A}(2) := \mathrm{I}^-, \qquad \mathcal{A}(3) := \mathrm{ClO}_2^-.$$

As the reaction steps are

$$\mathcal{A}(1) \to \mathcal{A}(2), \qquad \mathcal{A}(2) \to \mathcal{A}(3), \qquad 4\mathcal{A}(2) + \mathcal{A}(3) \to \mathcal{O},$$

one has

$$\alpha := \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 4 \\ 0 & 0 & 1 \end{pmatrix}, \qquad \beta := \begin{pmatrix} 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \end{pmatrix}.$$

The reaction rates are usually taken to be

$$w_1(\bar{c}_1, \bar{c}_2, \bar{c}_3) := k_1\bar{c}_1, \qquad w_2(\bar{c}_1, \bar{c}_2, \bar{c}_3) := k_2\bar{c}_2, \qquad w_3(\bar{c}_1, \bar{c}_2, \bar{c}_3) := k_3\frac{\bar{c}_2\bar{c}_3}{u + \bar{c}_2^2}$$

with $k_1, k_2, k_3, u \in \mathbf{R}^+$. These reaction rates obviously fulfil the three requirements on w above. Rational functions as reaction rates also occur in enzyme kinetics.

The most often used form of w_r is of the *mass action type* when there exist positive real numbers k_r $(r = 1, \dots, R)$ such that

$$w_r(\bar{\mathbf{c}}) = k_r \prod_{p=1}^{M} \bar{c}_p^{\alpha(p,r)} \quad \left(=: k_r \bar{\mathbf{c}}^{\alpha(\cdot,r)} \right).$$

Mass action type reaction rates obviously fulfil the three mentioned requirements.

In order to uniquely define the system, initial and boundary conditions are to be specified. We take the initial conditions

$$c_m(0,\mathbf{x}) = c_m^0(\mathbf{x}) \quad (\mathbf{x} \in \Omega;\ m = 1, \dots, M), \tag{4}$$

and we can either take *fixed boundary conditions*

$$c_m(t,\mathbf{x}) = c_m^* \quad (\mathbf{x} \in \Omega;\ m = 1, \dots, M), \tag{5}$$

where c_m^* is the mth coordinate of the homogeneous steady state, or the *zero flux boundary conditions*:

$$\partial_{\nu(\mathbf{x})} c_m(t,\mathbf{x}) = 0 \quad (\mathbf{x} \in \partial\Omega;\ m = 1, \dots, M), \tag{6}$$

where $\nu(\mathbf{x})$ denotes the outer normal to $\partial\Omega$ at the point $\mathbf{x} \in \Omega$.

A large number of questions relating existence, uniqueness, blowing up, long time behaviour, etc., arises here. We only focus upon a special mechanism of emergence of periodic structures as stationary states.

2.2. *Turing instability*

Consider the *kinetic differential equation*

$$\dot{\mathbf{c}}(t) = \mathbf{f}\big(\mathbf{c}(t)\big), \tag{7}$$

where the coordinate functions of the function $\mathbf{f} := (f_1, f_2, \ldots, f_M)$ are defined as in (3). Suppose that there exists a nonnegative steady-state solution $\mathbf{c}^* \in \mathbf{R}^M$ to (7). In other words, $\mathbf{c}^*$ fulfils $\mathbf{f}(\mathbf{c}^*) = \mathbf{0}$.

The steady state solution $\mathbf{c}^*$ to (7) is said to be *Turing unstable* if it is an asymptotically stable equilibrium to the kinetic differential equation (7) but it is unstable with respect to solutions of (2), (4) and either (5) or (6) [15].

Obviously, this formal definition corresponds to the generally accepted notion and differs from that given by [65]. Our results pertain to the usually accepted, more stringent definition. Let us remark in passing that a rigorous treatment of the Ross case would pose essential difficulties.

Let us introduce

$$\sigma(A) := \{\lambda \in \mathbf{C};\ \lambda \text{ is an eigenvalue of } A\}$$

for the *spectrum* of an arbitrary matrix $A \in \mathbf{A}^{M\times M}$, and let

$$r(A) := \max\big\{\Re(\lambda);\ \lambda \in \sigma(A)\big\}$$

be the *spectral abscissa* of A.

If the real parts of all the eigenvalues of the Jacobian $\mathbf{f}'(\mathbf{c}^*)$ are negative, i.e.,

$$r\big(\mathbf{f}'(\mathbf{c}^*)\big) < \mathbf{0}, \tag{8}$$

then the equilibrium point $\mathbf{c}^*$ is called a *sink*. This is a sufficient condition (but it is only necessary in the case of a linear $\mathbf{f}$, see, e.g., [56]), of the asymptotic stability of the steady state $\mathbf{c}^*$ of the kinetic differential equation describing the spatially homogeneous case. Inequality (8) obviously implies that the solution to the full nonlinear reaction–diffusion system (2), (4) and either (5) or (6) returns to the spatially homogeneous state $\mathbf{c}^*$ after a small spatially homogeneous perturbation.

Let Ω be a sufficiently regular bounded domain in $\mathbf{R}^N$. It is known that all eigenvalues $\kappa_0, \kappa_1, \ldots$ of the Laplace operator on Ω under the given boundary conditions are negative. Martin's result [51] implies that if for all $k = 0, 1, \ldots,$

$$r\big(\mathbf{f}'(\mathbf{c}^*) + \kappa_k D\big) < 0 \tag{9}$$

with $D := \mathrm{diag}(D_1, \ldots, D_M)$ then $\mathbf{c}^*$ is a globally uniformly asymptotically stable solution of the nonlinear reaction–diffusion equation in the maximum norm.

If condition (8) is fulfilled and there exists κ_k for which (9) does *not* hold this *may* imply that stable inhomogeneous stationary patterns emerge in the original nonlinear system (2). This phenomenon has been observed numerically, but a global analytical investigation of the nonlinear system is quite difficult even in simple special cases.

2.3. *Cross-inhibition and the absence of negative cross-effects*

Before investigating some simpler special cases in detail, two further important notions have to be introduced.

At first, we give a characterization of kinetic differential equations which is a far reaching generalization of earlier results of [34].

Firstly, we delineate the class of differential equations within which the characterization will be given.

Let M, R be positive integers: $M, R \in \mathbf{N}$; $\mathbf{a}_r = (a_r^1, \dots, a_r^M) \in (\mathbf{N}_0)^M$ $(r \in \{1, 2, \dots, R\})$ be multiindices, $g(m, r)$ $(m \in \{1, 2, \dots, M\},\ r \in \{1, 2, \dots, R\})$ be arbitrary real numbers, and $v_r(\mathbf{a}_r, \cdot)$ $(r \in \{1, 2, \dots, R\})$ be functions with the properties prescribed for the functions w_r above.

The function $\mathbf{F} := (F_1, F_2, \dots, F_M)$ (which is usually used as the right-hand side of an ordinary differential equation) with the coordinate functions

$$F_m(\bar{\mathbf{c}}) = \sum_{r=1}^{R} g(m, r) v_r(\mathbf{a}_r, \bar{\mathbf{c}}) \quad (m \in \{1, 2, \dots, M\}) \tag{10}$$

is said to contain *negative cross-effect at the point* $\bar{\mathbf{c}}$, if there exist numbers $m \in \{1, 2, \dots, M\}$ and $r \in \{1, 2, \dots, R\}$ such that

$$g(m, r) v_r(\mathbf{a}_r, \bar{\mathbf{c}}) < 0 \tag{11}$$

and

$$a_r^m = 0. \tag{12}$$

Theorem 1. The function (3) does not contain negative cross-effect at any point $\bar{\mathbf{c}}$.

Proof. Suppose that $(\beta(m, r) - \alpha(m, r)) w_r(\bar{\mathbf{c}}) < 0$ for some $m \in \{1, 2, \dots, M\}$, $r \in \{1, 2, \dots, R\}$ and $\bar{\mathbf{c}} \in (\mathbf{R}_0^+)^M$. Since $w_r(\bar{\mathbf{c}}) > 0$ and $\beta(m, r) < \alpha(m, r)$ then (because of the nonnegativity of $\beta(m, r)$) $\alpha(m, r)$ should also be strictly positive. $\square$

Theorem 2. Suppose that (10) does not contain negative cross-effect. Then, there exists a reaction having (10) as its induced kinetic differential equation.

Proof. We construct an appropriate reaction. Let $\alpha(\cdot, r) := \mathbf{a}_r$. For the terms, for which $g(m, r) v_r(\mathbf{a}_r, \bar{\mathbf{c}}) > 0$, let

$$\beta(m, r) := \alpha(m, r) + 1 \quad \text{and} \quad w_r(\bar{\mathbf{c}}) := g(m, r) v_r(\mathbf{a}_r, \bar{\mathbf{c}}).$$

For the terms, for which $g(m, r) v_r(\mathbf{a}_r, \bar{\mathbf{c}}) < 0$, let $\beta(m, r) := \alpha(m, r) - 1$ which is a nonnegative number because of the absence of nonnegative cross-effects. Let $w_r(\bar{\mathbf{c}}) := -g(m, r) v_r(\mathbf{a}_r, \bar{\mathbf{c}})$. It is easy to show that the reaction defined in this way induces the given ordinary differential equation. $\square$

Let us recall our earlier result on the characterization of *mass action type* kinetic differential equations within the class of polynomial differential equations. Suppose the kinetic differential equation (7) is of the mass action type. Then, it is a polynomial differential equation, but not all polynomial differential equations may be considered to be models of chemical reactions [34], only those without negative cross-effect.

Let us consider Turing's [76] example:

$$\dot{x} = 5x - 6y + 1, \qquad \dot{y} = 6x - 7y + 1.$$

The term $-6y$ on the right hand side of the first equation expresses the fact that x decreases in a process in which it does not take part, or expresses negative cross-effect. Kinetic differential equations are characterized by the absence of such terms, thus Turing's example is *nonkinetic* and *linear*, contrary to Epstein's statement [21, p. 155]: "Turing showed that a sufficiently nonlinear set of reaction kinetics coupled to diffusion could give rise to pattern formation..."

We remind the reader that our statements up to know do not help in the case when the right hand side is ill-formulated. There *is* negative cross-effect in the equation $\dot{x} = 2y - y \ldots$, and no reaction can induce this equation. However, there is *no* negative cross-effect in the equation $\dot{x} = y$.

Thus, we have found in the mass action case that

- negative cross-effects cannot be transformed out from an equation like Turing's example,
- negative cross-effect can be obtained if one allows a monomial to occur more than once so as in the last example.

The situation will be much clearer after the next statement.

Theorem 3. Suppose that the functions $v_r(\mathbf{a}_r, \cdot)$, $r \in \{1, 2, \ldots, R\}$, are linearly independent and function (10) contains negative cross-effect at a point $\bar{\mathbf{c}}$. Then any decomposition of it in the form (3) using the functions $v_r(\mathbf{a}_r, \cdot)$, $r \in \{1, 2, \ldots, R\}$, possibly more then once – also do contain negative cross-effect.

Proof. Suppose there exists $\bar{\mathbf{c}}$ and a term $g(m, r)v_r(\mathbf{a}_r, \bar{\mathbf{c}})$ in the function

$$F_m(\bar{\mathbf{c}}) = \sum_{r=1}^{R} g(m, r)v_r(\mathbf{a}_r, \bar{\mathbf{c}}) \tag{13}$$

such that $g(m, r) < 0$ and $a_r^m = 0$, and consider the sum

$$F_m(\bar{\mathbf{c}}) = \sum_{r=1}^{R} \left(\sum_{\rho=r} g'(m, \rho)v_\rho(\mathbf{a}_\rho, \bar{\mathbf{c}}) \right) = \sum_{r=1}^{R} \left(\sum_{\rho=r} g'(m, \rho) \right) v_r(\mathbf{a}_r, \bar{\mathbf{c}}); \tag{14}$$

because of independency we have $g(m, r) = \sum_{\rho=r} g'(m, \rho)$. As $g(m, r) \leqslant 0$, at least one of the terms in the sum on the right-hand side must also be negative. $\square$

We have proved that under the conditions of the theorem even negative coefficients cannot be “transformed out” – let alone negative cross-effect.

Even the characterization of mass action type kinetic differential equations has proved quite useful to study kinetic gradient systems [72], to design oscillatory reactions [73], or to investigate chaos in chemical reactions [74].

A related but different notion is the presence of *cross-inhibition* (cf. [4]). The chemical species $\mathcal{A}(m)$ is said to cross-inhibit $\mathcal{A}(p)$ at the concentration $\bar{\mathbf{c}}$, if $\partial_m f_p(\bar{\mathbf{c}}) < 0$ $(m, p = 1, 2, \ldots, M;\ m \neq p)$. Obviously, for polynomial differential equations in general the presence of negative cross-effect implies the presence of cross-inhibition, at least if the corresponding term does depend at all on the corresponding variable x_m. Kinetic differential equations, however, are only able to show cross-inhibition.

3. A necessary condition of Turing instability

Theorem 4. The presence of cross-inhibition is a necessary condition of Turing instability in the case of 3 chemical species.

The statement above is obviously implied by the following statement. (The simpler cases with $M = 1, 2$ will separately be treated below.)

Theorem 5. Let

$$A := \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix}$$

be an essentially nonnegative matrix (i.e., $a_{mp} \geqslant 0$ if $m \neq p$; $m, p = 1, 2, 3$) and suppose $r(A) < 0$. Then, for all

$$d_1, d_2, d_3 \in \mathbf{R}_0^+,$$

$r(\widetilde{A}) < 0$ holds, as well, if

$$\widetilde{A} := \begin{pmatrix} a_{11} - d_1 & a_{12} & a_{13} \\ a_{21} & a_{22} - d_2 & a_{23} \\ a_{31} & a_{32} & a_{33} - d_3 \end{pmatrix}.$$

Crucial as it is, the following statement will be proved first.

Lemma 6. Let

$$A := \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix}$$

be an essentially nonnegative matrix. Then, $r(A) < 0$ if and only if

$$a_{ii} < 0, \quad i = 1, 2, 3, \tag{15}$$

$$A_{ii} > 0, \quad i = 1, 2, 3, \tag{16}$$

$$\det(A) < 0, \quad i = 1, 2, 3, \tag{17}$$

hold, where A_{ii} $(i = 1, 2, 3)$ is the cofactor corresponding to the element a_{ii}.

Proof of lemma 6. The characteristic polynomial of A is

$$\lambda \to \lambda^3 - (a_{11} + a_{22} + a_{33})\lambda^2 + (A_{11} + A_{22} + A_{33})\lambda - \det(A).$$

According to the Routh–Hurwitz criterion, all the roots of this polynomial have a negative real part (the polynomial is said to be *stable* in this case) if and only if

$$(a_{11} + a_{22} + a_{33}) < 0, \tag{18}$$

$$(A_{11} + A_{22} + A_{33}) > 0, \tag{19}$$

$$\det(A) < 0, \tag{20}$$

$$(a_{11} + a_{22} + a_{33})(A_{11} + A_{22} + A_{33}) < \det(A). \tag{21}$$

(A) Suppose $r(A) < 0$. Then, (18)–(21) hold, and we have to show that (15)–(17) hold, as well. (17) is the same as (20).

Now we show that (18)–(21) can only hold if

$$a_{11} < 0, \qquad a_{22} < 0, \qquad a_{33} < 0.$$

All the diagonal elements of A cannot be zero because of (18).

If two of the diagonal elements of A were 0, then – because of the essential nonnegativity of A – the sum $A_{11} + A_{22} + A_{33}$ would be nonpositive, as the definition of the terms show, in contradiction to (19).

If one of the diagonal elements of A would be 0, then (18) and (19) would imply the negativity of the other two diagonal elements, which excludes (20). Therefore, all the diagonal elements of A are different from 0.

Suppose one of the diagonal elements, say a_{11}, is negative, and the other two are positive. Then, (18) implies

$$a_{22} + a_{33} < -a_{11},$$

and, because the geometric mean of positive numbers is not greater than their arithmetic mean, we have

$$\begin{aligned} a_{22}a_{33} &\leqslant (a_{22} + a_{33})^2/4 = (a_{22} + a_{33})(a_{22} + a_{33})/4 \\ &< (a_{22} + a_{33})(a_{22} + a_{33}) < -a_{11}(a_{22} + a_{33}), \end{aligned}$$

therefore

$$A_{11} + A_{22} + A_{33} < 0$$

contradictory to (19).

Suppose two of the diagonal elements, say a_{11} and a_{22}, are negative, and the third one is positive. Then, because of (19), we have

$$a_{11}a_{22} - a_{12}a_{21} > -a_{11}a_{33} - a_{22}a_{33} + a_{13}a_{31} + a_{23}a_{32} > 0,$$

thus

$$\begin{aligned}\det(A) = {}& a_{33}(a_{11}a_{22} - a_{12}a_{21}) - a_{11}a_{32}a_{23} - a_{22}a_{13}a_{31}\\ &+ a_{12}a_{23}a_{31} + a_{13}a_{21}a_{32} > 0,\end{aligned}$$

contradicting to (20).

Thus, we have proved that (18)–(21) together imply (15).

Finally, let us prove that they also imply (16). If, on the contrary, we had, e.g.,

$$A_{11} = a_{22}a_{33} - a_{23}a_{32} \leqslant 0,$$

then we would also have

$$\begin{aligned}\det(A) = {}& a_{11}(a_{22}a_{33} - a_{23}a_{32}) - a_{22}a_{13}a_{31} - a_{33}a_{12}a_{21}\\ &+ a_{12}a_{23}a_{31} + a_{13}a_{21}a_{32} \geqslant 0\end{aligned}$$

which is impossible because of (20).

(B) Suppose (15)–(17) hold. Then, in order to prove $r(A) < 0$, it is enough to show the fulfilment of (18)–(21). It is trivially true that (18)–(20) is fulfilled, what remains to prove is (21). Let us simply calculate the two sides of the inequality

$$(a_{11} + a_{22} + a_{33})(A_{11} + A_{22} + A_{33}) < \det(A)$$

to obtain

$$\begin{aligned}& a_{11}a_{22}a_{33} + a_{22}^2a_{33} + a_{33}^2a_{22} - a_{11}a_{23}a_{32} - a_{22}a_{23}a_{32} - a_{33}a_{23}a_{32}\\ &\quad + a_{11}^2a_{22} + a_{22}^2a_{11} + a_{11}a_{22}a_{33} - a_{11}a_{12}a_{21} - a_{22}a_{12}a_{21} - a_{33}a_{12}a_{21}\\ &\quad + a_{11}^2a_{33} + a_{11}a_{22}a_{33} + a_{11}a_{33}^2 - a_{11}a_{13}a_{31} - a_{22}a_{13}a_{31} - a_{33}a_{13}a_{31}\\ &\qquad < a_{11}a_{22}a_{33} - a_{11}a_{32}a_{23} - a_{22}a_{13}a_{31} - a_{33}a_{12}a_{21} + a_{12}a_{23}a_{31} + a_{13}a_{21}a_{32}.\end{aligned}$$

As the above inequality is the same as

$$\begin{aligned}& a_{22}A_{11} + a_{33}A_{11} + a_{11}A_{33} + a_{22}A_{33} + 2a_{11}a_{22}a_{33} + a_{11}A_{22} + a_{33}A_{22}\\ &\quad < a_{12}a_{23}a_{31} + a_{13}a_{21}a_{32},\end{aligned}$$

properties (15) and (16) imply that we only have negative terms on the left-hand side, and essential nonnegativity implies that we only have positive terms on the right-hand side of the inequality, and the steps can obviously be reversed. □

Proof of theorem 4. In order to prove theorem 4 it is enough to investigate if (15)–(17) is true for the matrix $\widetilde{A}$.

(15) is obviously true.

Let us prove (16), e.g., for $i := 1$. As

$$(a_{22} - d_2)(a_{33} - d_3) - a_{23}a_{32} = (a_{22}a_{33} - a_{23}a_{32}) - d_2a_{33} - d_3a_{22} + d_2d_3$$

and here the first term is positive, the other terms are nonnegative, (16) is also true.

Finally,

$$\begin{aligned}\det\bigl(\widetilde{A}\bigr) = {} & \det(A) - (d_1A_{11} + d_2A_{22} + d_3A_{33}) \\ & + (d_1d_2a_{33} + d_2d_3a_{11} + d_1d_3a_{22}) - d_1d_2d_3\end{aligned}$$

and inspection of all the terms shows that $\det(\widetilde{A})$ is negative.

Now we turn to the recapitulation of known results for the special cases $M = 1, 2$.

If $M = 1$ then $r(f'(c^*)) = f'(c^*)$, therefore (8) implies (9) for any kind of reaction.

If $M = 2$ and the reactions are of the first order with mass action type reaction rates then (8) is equivalent to stating

$$a_{11} + a_{22} < 0 \tag{22}$$

and

$$\det(A) := a_{11}a_{22} - a_{12}a_{21} > 0. \tag{23}$$

Inequality (23) can only hold if $a_{11}a_{22} > 0$ because of the essential nonnegativity of A. Taking into consideration (22) one obtains $a_{11} < 0$ and $a_{22} < 0$. Therefore, for all $d_1, d_2 \in \mathbf{R}^+$,

$$a_{11} + a_{22} - (d_1 + d_2) < 0 \tag{24}$$

and

$$\det(A) - (d_1a_{22} + d_2a_{11}) + d_1d_2 > 0. \tag{25}$$

Inequalities (24) and (25) together imply (9) if one takes

$$d_1 := -\kappa_k D_1, \qquad d_2 := -\kappa_k D_2.$$

Thus, theorem 3 remains true for two chemical species as well.

A simple consequence of theorem 3 is that Turing instability cannot appear in a reaction with first order reaction steps if the kinetics is of the mass action type.

Nevertheless, higher-than-first-order reactions with mass action rates (including cross-inhibition) [35,57], or reactions with non mass action type rates [30,52] are capable of producing the necessary set of inequalities.

Now let us make a final remark on the case $M = 3$.

Yatsimirskii et al. [78,79] and Li and Wu [50] have found three species systems with higher order formal reaction steps (including cross-inhibition) which are capable of producing Turing instability.

4. Discussion

It is obvious that the proofs of the present paper are very hard to transfer to the case of M-species systems with $M > 3$. Therefore, we looked for, and succeeded in finding another method for those cases [70]. This means that *all of our results remain valid for the case* $M > 3$ too – at least for kinetics of the mass action type.

It is an interesting question if Turing instability can emerge in a first order, *time-dependent* reaction–diffusion system (e.g., in the presence of changing temperature).

We only remark in passing some of our further results on the applications of the present statements to *homogeneous* kinetics to be published later. These results again are valid for the M-species general case. Suppose we are given a mass action kinetic homogeneous reaction with no cross-inhibition and with the property that the steady state is a sink. Then, the steady state will remain asymptotically stable even after adjoining *autoinhibitory* steps (steps, for which $\partial_m f_m(\bar{\mathbf{c}}) < 0$ holds). The same holds true for putting the system into a CSTR, and letting to flow in and out the material from the reactor according to the usual assumptions.

A next step in the theoretical investigation of Turing structures might be the search for general sufficient conditions of not only Turing instability but of the emergence of Turing structures which seems to be a hard task. However, Lengyel and Epstein [47] made a promising start in this direction in the series "Systematic design of chemical oscillations". Farkas and Cavani (and the authors cited in their works) provided exact sufficient conditions for special model systems in another context [15,24].

Finally, it is quite natural to recur to biology again, and try to provide detailed chemical mechanism to biological phenomena as it has been initiated by Hjelmfelt et al. [37,38].

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