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Turing instabilities in general systems

Abstract. We present necessary and sufficient conditions on the stability matrix of a general $n(\geq 2)$-dimensional reaction-diffusion system which guarantee that its uniform steady state can undergo a Turing bifurcation. The necessary (kinetic) condition, requiring that the system be composed of an unstable (or activator) and a stable (or inhibitor) subsystem, and the sufficient condition of sufficiently rapid inhibitor diffusion relative to the activator subsystem are established in three theorems which form the core of our results. Given the possibility that the unstable (activator) subsystem involves several species (dimensions), we present a classification of the analytically deduced Turing bifurcations into p $(1 \leq p \leq (n-1))$ different classes. For $n = 3$ dimensions we illustrate numerically that two types of steady Turing pattern arise in one spatial dimension in a generic reaction-diffusion system. The results confirm the validity of an earlier conjecture [12] and they also characterise the class of so-called *strongly stable* matrices for which only necessary conditions have been known before [23, 24]. One of the main consequences of the present work is that biological morphogens, which have so far been expected to be single chemical species [1–9], may instead be composed of two or more interacting species forming an unstable subsystem.

1. Introduction

A large amount of research has been devoted to the study of symmetry breaking instabilities leading to steady-state solutions in models for chemical and biological pattern formation employing reaction-diffusion systems. One of the most intensively studied of such models is that of Turing [1], which consists of a pair of reaction-diffusion equations. In this model, instability is driven by diffusion [1–6, 9]. Some 40 years after Turing's paper, his theories were confirmed by chemical experiments [7–8], resulting in renewed experimental and theoretical interest across many disciplines into clarifying, extending and applying this idea of pattern formation. In the past decade alone, more than 250 papers were published citing the

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Turing scenario of pattern formation[1]. Despite this huge amount of research the actual mechanism is still elusive and there is no clear-cut experimental evidence in any biological system of the morphogenic substance as envisaged by Turing.

The majority of theoretical studies in reaction-diffusion theory focus on the analysis of systems composed of only two species with kinetics chosen to interact in the way necessary for a Turing instability, that is, one chemical (the activator) activates the production of the other (the inhibitor) which, in turn, inhibits the production of the activator. This can lead to a stable dynamic equilibrium in the absence of diffusion, which can, however, be destabilised in the presence of unequal diffusion. While this approach captures the essence of the Turing instability, it is often not realistic since chemical and biochemical reactions usually involve more than two dynamically independent species. In a recent paper [12] the authors considered systems with three interacting species. They showed that a necessary condition for a Turing instability to take place in these systems is that they must contain an unstable (or activator) subsystem, which may be composed of one or two species. For general n-dimensional systems the full conditions for Turing instability however remained unresolved.

Our main goal is to establish general conditions for the Turing instability in a system of n ($n \geq 2$) reacting and diffusing chemical species. Consequently, we extend the concept of "morphogen" to mean not necessarily a single substance but instead a network of reacting species [28] whose interaction leads locally to an increase in the concentration of one (or more) of its species. This may occur through indirect autocatalysis, end-product inhibition or a combination thereof [28]. In Theorem 1 (Section 2) we derive the necessary and sufficient conditions on the kinetics of an n-dimensional system under which diffusion-driven instability will arise.

There are a number of papers that are related to the theme of diffusive instability in multi-component systems. An early paper [17] classifies completely the bifurcation structure from uniform steady states, but its results for the n-species case ($n \geq 3$) pertain only to weakly coupled systems, which are a particular instance of the general case established here. More recently [18] a set of necessary conditions is given for diffusion-driven instability in a three species system, motivated by examples arising in ecology. Only in some restrictive cases were the authors able to give sufficient conditions for the bifurcation. Their methods were not designed to be generalised to higher-dimensional systems.

More closely related to our approach is [23] where necessary conditions for the kinetics matrix to be "strongly stable" in the terminology of [24] are presented (actually, the results of [24] are reproduced). Both of these authors did not realise that the conditions they derived were also sufficient for this type of stability. We establish this result in Section 2 (Theorem 2). Aided by a heuristic argument [23, p.195] it is, however, shown how the instability arises if one of the necessary conditions for strong stability is broken. As these arguments were sketched without formal proof, we reconsider them in a more formal and complete way (Section 2, Theorem 3). To our knowledge, this is the first time that the Turing instability problem for a general n-dimensional system has been fully characterised and resolved.

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[1] Data from the Web of Science database.

In short, the practical consequence of the present work is that Turing instability in n-species reaction networks may arise through activators, or unstable subsystems, involving up to $p = n - 1$ species. The number of *a priori* possibilities of finding an activator in such a reaction increases rapidly with n – an issue that is of central importance in Kauffman's arguments [26] regarding the spontaneous emergence of autocatalytic sets (and life) in large reaction networks.

The paper is structured as follows. In Section 2 we derive the three key theorems mentioned above. In Section 3 we present some examples to illustrate the applications of these theorems. We show in Section 4 how one may apply these methods to reaction-diffusion-advection systems (the differential-flow induced instability problem). The implications of the analysis are discussed in Section 5.

2. The main results

A coupled system of n ($n \geq 1$, n integer) species (concentrations of chemicals) which interact in a nonlinear manner and diffuse may be modelled by the n equations

$$\frac{\partial u_j}{\partial t} = D_j \Delta u_j + f_j(u), \quad x \in R, \ t \in [0, T), \ T > 0 \tag{2.1}$$

with the initial condition

$$u_j(x, 0) = u_{j0}(x), \quad j = 1 \ldots n \tag{2.2}$$

Here R is a subset of $(-\infty, \infty)$ and $u = (u_1, u_2, \ldots, u_n)$ is the vector of concentrations for the interacting species at position x and time t, and f_j, $j = 1, \ldots, n$, represent the local reaction terms. The initial concentrations are non-negative and the problem (2.1–2) is closed by imposing appropriate boundary conditions (for example zero-flux across the boundaries). In the following we suppose that (2.1–2) with boundary conditions admits a solution, $u = u_s$, which is spatially and temporally uniform.

We wish to investigate the conditions under which the system (2.1–2) undergoes Turing instability. The solution $u = u_s$ is said to be Turing unstable if it is locally stable as a solution of the kinetic system:

$$\frac{\partial u_j}{\partial t} = f_j(u), \quad u_j(0) = u_{j0} \quad \text{(for } j = 1 \ldots n \text{ with } t > 0) \tag{2.3}$$

but it is unstable for the full reaction-diffusion system (2.1–2) (i.e. with respect to nonhomogeneous perturbations). Let us denote by $A = (a_{ij})$, $1 \leq i, j \leq n$, the Jacobi matrix associated with (2.3) at $u = u_s$, i.e. $a_{ij} = \frac{\partial f_i}{\partial u_j}(u_s)$, $1 \leq i, j \leq n$. From the first condition on u_s it follows that all the eigenvalues of A have negative real parts. We now consider the Jacobi matrix associated with (2.1–2) at $u = u_s$, i.e. $C = (c_{ij})$, $1 \leq i, j \leq n$. We have that

$$c_{ij} = a_{ij} - D_i k^2 \delta_{i,j} \tag{2.4}$$

where $\delta_{i,j}$ is the Kronecker delta symbol and k is the wavenumber characterising the small perturbation imposed upon $u = u_s$ (in the Fourier series expansion), k is a real number. Our main concern here is to study the conditions on the diffusion coefficients D_i, $1 \leq i \leq n$, and/or on the kinetics matrix A for which there is at least one eigenvalue for (2.4) with positive real part. Before proceeding further we recall the classic Turing result [1, 5]. It states that for a system composed of two species the necessary and sufficient conditions for diffusive instability are that the system consists of a pair of activator and inhibitor species and that the diffusion coefficient of the inhibitor is sufficiently greater than that of the activator.

We begin our analysis by considering the case $n = 1$. Although this is an extreme situation, which is more of theoretical than of practical interest, we start with this case for the sake of completeness. We show that no Turing bifurcation is possible in this case.

A single scalar reaction-diffusion equation takes the form:

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} + f(u) \tag{2.5}$$

(here $u = u_1$ and we have scaled D, the diffusion coefficient, to 1) and let us denote by S the set $\{u_s > 0 | f(u_s) = 0\}$ of all uniform stable steady states of (2.5). Therefore for any member, u_s, of this set we have

$$K_s = f'(u_s) < 0 \tag{2.6}$$

Now studying the stability of the elements in the set S to non-uniform perturbations with a typical wavenumber k we find, in the usual way, that the eigenvalues are given by

$$\omega = -k^2 + K_s \tag{2.7}$$

From (2.7) it is therefore clear that $\text{Re}(\omega) < 0$ for all real k. Therefore no Turing bifurcation is possible and the only interesting case remaining is when $n \geq 2$.

Our next step is to give a necessary condition on the kinetics matrix A for a Turing bifurcation to be possible. This extends the result mentioned above for $n = 2$ and the one given in [12] for $n = 3$ to the general case. To this end we introduce a couple of definitions which generalize those given in [12] to arbitrary $n \geq 2$. These definitions refer to the linear system associated with the matrix A.

Let $1 \leq i_1, i_2, \ldots, i_p \leq n$ $(1 \leq p \leq n)$ be distinct indices from the set $1, 2, \ldots, n$. We denote by $A_{i_1 i_2 \ldots i_p}$ the square submatrix obtained from A by taking exactly the rows and the columns of indices $i_1, i_2, \ldots, i_p$. By $\Delta_{i_1 i_2 \ldots i_p}$ we denote its determinant (a minor of order p for A). We call the full system associated with A the linear system

$$u_t = Au, \quad u(x, 0) = u_0(x). \tag{2.8}$$

Any p-dimensional subsystem of (2.8) with matrix $A_{i_1 i_2 \ldots i_p}$ (of order p) is called *stable* if the necessary and sufficient stability conditions set by the Routh-Hurwitz criterion [13] are fulfilled. We recall these conditions as we make reference to them repeatedly in what follows. To this end let us denote by $\omega_{i_1}, \omega_{i_2}, \ldots, \omega_{i_p}$

the eigenvalues associated with the matrix $A_{i_1 i_2 \ldots i_p}$. We construct the symmetric fundamental sums of these values, i.e.

$$a_{i_1} = -\sum_{i_1 \le i \le i_p} \omega_i; \quad a_{i_2} = \sum_{i_1 \le i, k \le i_p} \omega_i \omega_k; \ldots; \quad a_{i_p} = (-1)^p \omega_{i_1} \omega_{i_2} \ldots \omega_{i_p}$$

(2.9)

A necessary and sufficient condition for $A_{i_1 i_2 \ldots i_p}$ to be a stable matrix is that

$$D_{i_k} = \begin{vmatrix} a_{i_1} & a_{i_3} & \cdots & \cdots & 0 \\ 1 & a_{i_2} & a_{i_4} & \cdots & 0 \\ 0 & a_{i_1} & a_{i_3} & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & a_{i_k} \end{vmatrix} > 0, \quad \text{for all } k = 1, \ldots, p \quad (2.10)$$

together with the condition that all the a_{i_k} in (2.9) are positive. Note that this definition implies that all the eigenvalues of the matrix $A_{i_1 i_2 \ldots i_p}$ have negative real parts. We call $A_{i_1 i_2 \ldots i_p}$ s-stable if, for any minor $\Delta_{j_1 j_2 \ldots j_q}$ of order $q (1 \le q \le p)$, we have

$$\text{sgn}(\Delta_{j_1 j_2 \ldots j_q}) = (-1)^q \quad (2.11)$$

Therefore the whole system (2.8) associated with A is s-stable if each of its subsystems is stable.

With these definitions in place we now proceed to our first result:

Theorem 1. *If the kinetic system* (2.8) *of the problem* (2.1–2) *is s-stable then no Turing bifurcation is possible from the uniform steady state solution u_s for any $n \ge 1$.*

Proof. For $n = 1$ the result was shown above, it is well known for $n = 2$ [1, 4, 24] and was proved for $n = 3$ in [12, 24]. The idea for a general proof is by induction on n. Our induction hypothesis is this: we take a system of n interacting species such that every $(n - 1)$ dimensional subsystem is s-stable. We want to show that the whole system is s-stable. To this end we need to show that the matrix C defined by (2.4) is s-stable.

First note that it is sufficient to establish this when only one of the diffusion coefficients D_i is non-zero (we choose it to be D_1, say) as the proof for the general case follows from this (see the remarks following the proof). Therefore we need to show that if A is s-stable then the matrix $C = A - dB$ is s-stable too. Here $d = D_1 k^2 > 0$ and B is the $n \times n$ matrix with all the elements equal to zero except in the left upper corner (element b_{11}) which is equal to 1.

We start by computing the characteristic polynomial of the matrix $C = (c_{ij})$, $1 \le i, j \le n$ introduced in (2.4). This can be done inductively, for any $n \ge 2$, and the result is of the form

$$p_n(\omega) = \omega^n + c_1 \omega^{n-1} + \cdots + c_{n-1} \omega + c_n \quad (2.12)$$

The coefficients in (2.12) are given by:

$$c_1 = d - \sum_{i=1}^{n} \Delta_i = d + a_1 \tag{2.13.1}$$

$$c_2 = -d \sum_{i=2}^{n} \Delta_i + \sum_{1 \le i < j \le n} \Delta_{ij} = -d \sum_{2}^{n} \Delta_i + a_2 \tag{2.13.2}$$

$$\vdots$$

$$c_n = d(-1)^{n-1} \Delta_{2...n} + (-1)^n \Delta_{12...n} \tag{2.13.n}$$

Note that due to the hypothesis on A (see (2.11)), c_i is positive for each $i = 1, \ldots, n$. Indeed, this is true for each of the terms within the definition of c_i, for each $i = 1, \ldots, n$, because

$$\Delta_i < 0, \quad \Delta_{ij} > 0, \ldots, \text{sgn}(\Delta_{12...n}) = (-1)^n \tag{2.14}$$

and $d > 0$. Thus we have in (2.12) a polynomial of degree n with all coefficients real and positive. Thus we deduce that all its real roots must be negative. This does not preclude it from having complex roots – a possibility that we now analyse in greater detail.

Let us remark that the coefficients in (2.13) are differentiable functions of $d > 0$ with the property that

$$c_i(0) = a_i \quad \text{and} \quad c_i(d) > a_i \tag{2.15}$$

for all $i = 1, \ldots, n$. Also by taking the derivative (denoted by $'$) of each in turn with respect to d we have

$$c_1' = 1; \quad c_2' = -\sum_{i=2}^{n} \Delta_i; \ldots; \quad c_n' = (-1)^{n+1} \Delta_{23...(n-1)} \tag{2.16}$$

From (2.14) we see that all these derivatives are positive.

To decide whether or not the matrix C has eigenvalues with positive real parts (and possibly complex eigenvalues) we adopt the following strategy. Consider C as being the matrix of constant coefficients of a linear $n \times n$ system of first order differential equations

$$\frac{dx}{dt} = Cx, \quad \text{for} \quad x \in R^n, \ t > 0 \quad \text{and} \quad x(0) = x_0 \tag{2.17}$$

The sign of the real parts of the eigenvalues of C dictates the asymptotic behaviour of the solutions. To quantify this behaviour we employ the method of steepest descents. Namely we consider the equation $p(\omega(x)) = 0$ with x taken to be complex. The asymptotic dynamics as $t \to \infty$ may be determined by looking at the *saddle points*, i.e. those points in the complex plane where

$$\frac{d\omega}{dx} = 0 \tag{2.18}$$

From the characteristic equation we find

$$\omega'[n\omega^{n-1} + (n-1)c_1\omega^{n-2} + \cdots + c_{n-1}] + c_1'\omega^{n-1} + c_2'\omega^{n-2} + \cdots + c_n' = 0 \tag{2.19}$$

Thus the saddle points satisfy a polynomial equation of degree $(n-1)$. In other words there are exactly $n-1$ complex values ω_j such that $\omega' = 0 \Rightarrow \omega = \omega_j$, $j = 1, \ldots, n-1$, namely those satisfying the $(n-1)$ degree polynomial with coefficients c_j', $j = 1, 2, \ldots, n$.

We now further note from (2.13, 2.16) that the equation

$$c_1'\omega^{n-1} + c_2'\omega^{n-2} + \cdots + c_n' = 0 \tag{2.20}$$

corresponds exactly to a relation of the form (2.12) i.e. it represents the characteristic polynomial of the system with $n-1$ species which is the subsystem of A with matrix $A_{2\ldots n}$. Consequently it follows from the induction hypothesis that

$$\operatorname{Re}\omega_j < 0 \tag{2.21}$$

for all $j = 1, \ldots, n-1$. We therefore deduce that the function $\operatorname{Re}\omega(d)$ is maximal for $\omega = \omega_j$ and therefore, for all $d > 0$ we have

$$\operatorname{Re}\omega \le \operatorname{Re}\omega_j < 0 \tag{2.22}$$

where $\omega = \omega(d)$ is any solution of (2.12). This ends the proof by induction.

Remark 1. The general case where all diffusion coefficients are non-zero may be readily obtained by applying inductively the above proof to each coefficient in turn. Indeed this can be achieved by realizing that once A is s-stable then the matrix C is s-stable too. This may be generalised by considering each entry from the main diagonal iteratively.

Remark 2. The following observation for the case $n = 2$ gives more insight into the relations between the spectrum of the matrices C and A.

For $d > 0$ we have $C(d) = A - dB$; let $\sigma_1(C)$ be the eigenvalue of C with maximal real part. Similarly let $\sigma_1(A)$ be the eigenvalue of A with maximum real part. Several situations can arise.

If both A and C have complex eigenvalues then it is clear that

$$2\operatorname{Re}(\sigma_1(A)) = -a_1 = \Delta_1 + \Delta_2 \ge \Delta_1 + \Delta_2 - d = 2\operatorname{Re}(\sigma_1(C))$$

If A has real eigenvalues and C complex eigenvalues then

$$2\sigma_1(A) \ge -a_1 \ge -c_1 = 2\operatorname{Re}(\sigma_1(C))$$

However, in general it is not true that $\operatorname{Re}(\sigma_1(C)) \le \operatorname{Re}(\sigma_1(A))$ for all $d > 0$. Indeed if both A and C have real eigenvalues then $2\sigma_1(A) = -a_1 + \sqrt{a_1^2 - 4\Delta_{12}}$ and $2\sigma_1(C) = -c_1 + \sqrt{c_1^2 - 4(\Delta_{12} - d\Delta_2)}$. We have that $c_1 > a_1$ and a simple calculation shows that $\sigma_1(A) - \sigma_1(C)$ depends on the sign of the product $e = a_{12}a_{21}$ (the

sign of the elements on the cross diagonal). Namely $\sigma_1(A) - \sigma_1(C) > 0 \Leftrightarrow e > 0$. This can be interpreted in a sense by saying that in the conditions of Theorem 1 the conclusion is "maximal". By this we mean that although the spectrum of C is a perturbation of that of A their sets can, in general, have disjoint parts.

Remark 3. In [24, Theorem 1, page 255] it is shown that if A is such that the matrix C in (2.4) has its entire spectrum in the left-hand plane for all values of $D_i \geq 0$ (a property called *strong stability*) then A is s-stable according to our definition. Thus our result in Theorem 1 and the result in [24] are complementary. Combining these two, the following result (characterisation of the strong stability) can be stated:

Theorem 2. *A is strongly stable if and only if A is s-stable.*

We now consider the coefficient c_n in (2.13.n) in greater detail. We take C as defined in (2.4) (i.e. all the diffusion coefficients are non-zero). Our aim is to show that the condition from Theorem 1 is optimal in the sense that if A is not s-stable then we can tune the diffusion coefficients so that the uniform steady state solution, u_s, undergoes a Turing bifurcation for the full problem (2.1–2).

Theorem 3. *If the kinetic system (2.8) of the problem (2.1–2) contains an unstable subsystem in the above sense, then Turing bifurcation is possible from the uniform steady state solution u_s.*

Proof. Direct calculation shows (as in (2.12–13)) that

$$c_n = k^{2n} D_1 D_2 \dots D_n - k^{2n-2} \sum_{\substack{\{i_1,\dots,i_p\}= \\ \{1,\dots,n\}-\{i\}}} \Delta_i D_{i_1} D_{i_2} \dots D_{i_p} +$$

$$+ k^{2n-4} \sum_{\substack{\{i_1,\dots,i_p\}= \\ \{1,\dots,n\}-\{i,j\} \\ i<j}} \Delta_{ij} D_{i_1} \dots D_{i_p} - \dots + (-1)^n \Delta_{12\dots n} \quad (2.23)$$

From the hypothesis we deduce that there are distinct indices $1 \leq i_1, i_2, \dots, i_p \leq n$ ($1 \leq p \leq n$) taken from the set $1, 2, \dots, n$ such that the corresponding subsystem is unstable. We also note that $p < n$ because the kinetics matrix A is stable by hypothesis. We show that in this case we can choose the diffusion coefficients in such a way that the matrix C in (2.4) has a zero eigenvalue. Obviously this happens if c_n becomes zero for suitably chosen diffusion coefficients $D_i, i = 1, \dots, n$. To this end we choose a positive, small number ε and let

$$D_{i_1} = D_{i_2} = \dots = D_{i_p} = \varepsilon \quad (2.24)$$

Let $q = n - p$ and denote by $j_1, j_2, \dots, j_q$ the remaining indices from the set $1, 2, \dots, n$. From (2.23) we can see that if all but one of the diffusion coefficients (D_{j_1} say) are equal to ε then we have

$$c_n = (-1)^{n-1} \Delta_J D_{j_1} + (-1)^n \Delta_{12\dots n} + O(\varepsilon), \quad (2.25)$$

where $J = \{1, 2, \ldots, n\}\setminus\{j_1\}$. Note that we can always assume that Δ_J is non-zero. Otherwise, we would have that all the minors of order $n - 1$ are zero and this would imply that the kinetics matrix is singular. This contradicts the hypothesis that the matrix A has eigenvalues with only negative real parts. Then it is clear that, independent of the sign of Δ_J, we can always find a critical value $\delta_c(\varepsilon)$ (>0) such that choosing D_{j_1} sufficiently close to $\delta_c(\varepsilon)$ will make c_n take both negative and positive values depending on whether D_{j_1} is less than, or equal to $\delta_c(\varepsilon)$, or greater than $\delta_c(\varepsilon)$. Thus c_n is zero exactly when $D_{j_1} = \delta_c(\varepsilon)$ and therefore C has a zero eigenvalue. Furthermore the argument shows that at $\delta_c(\varepsilon)$ there is a pitchfork bifurcation (with a zero eigenvalue) which corresponds to a Turing bifurcation for the full system, and the theorem is proved.

Remark 4. Othmer [23] hinted that a result similar to Theorem 3 can be established to show the existence of time-periodic patterns in a reaction-diffusion system with $n > 2$ equations in view of the necessary and sufficient conditions for a s-stable matrix given by Theorem 2. However, this issue is not explored here.

Remark 5. We have obtained a necessary (Theorem 1) and a sufficient condition (Theorem 3) for a steady Turing bifurcation to occur in a general n-dimensional reaction-diffusion system. Suppose that all the eigenvalues of the kinetics matrix A have negative real parts. The following nomenclature serves to distinguish the different possible cases.

Definition. *We define as a Turing bifurcation of the first type* (I) *the case where* $\Delta_i = a_{ii} > 0$ *for some i, $1 \leq i \leq n$.*

We define as a *Turing bifurcation of the second type* (II) the case where there are $1 \leq i, j \leq n$ such that $\Delta_{ij} < 0$ and the bifurcation is not of first type.

In general, we inductively introduce the definition of a *Turing bifurcation of type p $(<n)$* as being that bifurcation associated with a kinetics matrix for which there are indices $1 \leq i_1, i_2, \ldots, i_p < n$ such that $\text{sgn}(\Delta_{i_1 i_2 \ldots i_p}) = (-1)^{p+1}$, and as not being associated with a Turing bifurcation of any previous type.

In other words, the dimension of the unstable subsystem determines the type of the general Turing bifurcation. Note that for $n = 2$ the only Turing bifurcation that is possible is of the first type; it is usually simply referred to as a Turing bifurcation.

3. Examples and illustrations

We now consider some examples which illustrate the applications of the above theory.

3.1. Example 1

This illustration shows how one can achieve, for any given dimension p, p even integer, a Turing bifurcation of order p. It is an adaptation of an example from Meinhardt [27, p. 36] who proposed a system that achieves instability by the *inhibition of an inhibitor*. Consider the following reaction-diffusion system with Michaelis-Menten type kinetics:

$$\frac{\partial a_1}{\partial t} = \frac{1}{a_p^2} - a_1, \quad \frac{\partial a_2}{\partial t} = \frac{a_3}{a_1} - a_2, \ldots, \quad \frac{\partial a_p}{\partial t} = \frac{a_{p+1}}{a_{p-1}} - a_p \qquad \text{(A)}$$

$$\frac{\partial a_{p+1}}{\partial t} = a_1 - a_{p+1} + D_{p+1}\frac{\partial^2 a_{p+1}}{\partial x^2} \qquad \text{(B)}$$

where we have $p + 1$ reacting components with $p \geq 2$ (our previous results show that for generalised Turing instability any such example should have at least three interacting species). Here $D_{p+1} > 0$ is the constant diffusion coefficient of the $(p + 1)$ reacting species $a_i(x, t)$. This system has a uniform steady state $a_1 = a_2 = \cdots = a_p = a_{p+1} = 1$. Suppose now that p is even and the initial conditions are small perturbations close to this steady state. From the equations (A) we see that any small local increase in the concentration of a_1 will lead to a decrease in the concentration of a_2 which in turn will increase a_3, and so on culminating with an decrease in a_p which (from the first equation in (A)) will further increase a_1 again. Thus the subsystem $(a_1, a_2, \ldots, a_p)$ plays effectively the role of an activator. If, for example, $p = 2$, we have that $\Delta_{12} = -1$ which, according to Theorem 1, shows that the kinetics matrix associated with the system (A)–(B) is not s-stable and therefore we have a Turing bifurcation of type II. Clearly the above example can be adapted to any higher, integer dimension and accordingly, similar higher Turing order instabilities can be easily obtained.

3.2. Example 2

Turing's original model [1] considered a coupled system of two species with linear reaction kinetics. This leads to physically unrealistic unbounded growth. However, this can be overcome by taking into account that at the heart of every competition patterning process is the subtle interplay between the initial, exponential linear growth that is subsequently balanced by the nonlinear saturation to finite amplitude through reaction and diffusion [1–4]. It naturally follows that the simplest system to illustrate the results of Section 2 is a linear one but with some kind of control of the synthesis rate of each species. As our results in Section 2 are general, i.e. they are valid for every n-dimensional reaction-diffusion system, we can use a similar idea here. This leads us to consider a system of three species in which we impose piecewise linear kinetics.

Let $u(x, t)$, $v(x, t)$ and $w(x, t)$ satisfy the reaction-diffusion system:

$$\frac{\partial u}{\partial t} = d_1\frac{\partial^2 u}{\partial x^2} + b_{11}u + b_{12}v + b_{13}w + q_1 - s_1u \qquad \text{(3.1)}$$

$$\frac{\partial v}{\partial t} = d_2\frac{\partial^2 v}{\partial x^2} + b_{21}u + b_{22}v + b_{23}w + q_2 - s_2v \qquad \text{(3.2)}$$

$$\frac{\partial w}{\partial t} = d_3\frac{\partial^2 w}{\partial x^2} + b_{31}u + b_{32}v + b_{33}w + q_3 - s_3w \qquad \text{(3.3)}$$

where $0 < x < l$ for some fixed l. The boundary conditions are taken as being zero flux:

$$\frac{\partial u}{\partial x}\Big|_{x=0} = \frac{\partial u}{\partial x}\Big|_{x=l} = 0 \tag{3.4}$$

with analogous relations for the v and w species. The initial conditions are taken as in (2.2) in the form of some small perturbations from the uniform solution S:

$$u(x, 0) = u_s + u_0(x), \quad |u_0(x)| \ll |u_s| \tag{3.5}$$

with similar relations for the remaining species. Here $d_1, d_2, d_3 > 0$ are the diffusion coefficients and $s_1, s_2, s_3 > 0$ are the decay rates of the species. Although for each $j = 1, 2, 3$, the quantities $b_{jj} - s_j$ can generally be of either sign, we have deliberately considered the above form of equations to account explicitly for the linear growth. To control the growth on the synthesis rate of each species we impose:

$$0 \leq b_{11}u + b_{12}v + b_{13}w \leq u_l \tag{3.6}$$

where u_l is a fixed positive number, with analogous expressions for the other two species. Thus, this model may be thought of as an extension to three species of the two species model proposed recently by Kondo and Asai [14] to account for pigmentation patterning in certain fish species. It may also be considered as a simplified version of any generic nonlinear dynamical interaction for systems such as the Gierer-Meinhardt, Gray-Scott or Thomas systems [4, 16, 27].

It is an immediate consequence of relations (3.6), via applying a comparison principle for scalar equations for each equation in turn, that system (3.1–6) has global existence and uniqueness properties of the solutions (for all finite positive times). Thus we can consider the solutions to this system and we now present the results of numerical simulations for this model. In all that follows we chose a computational domain of length $l = 40$ (by using $m = 4000$ spatial grid points 0.01 unit lengths apart). The system is solved with an implicit finite-difference method using the Crank-Nicolson algorithm [19]. The patterning process is greatly influenced by choices of the bounds u_l, v_l, w_l and the length of the computational domain. This is however of little concern here, as we are mainly interested in the qualitative behaviour arising generically from such a system. Indeed it is not possible to completely map out the whole parameter domain in view of the 22 parameters involved. However, we performed simulations for a large set of parameter values. Here we review only some generic cases, which illustrate the results of the theorems presented in Section 2.

We first explored the possibilities for *Turing structures of the first type (I)*. Three different cases were considered, corresponding to the different phase relationships in the spatial oscillations between the stable and unstable subsystems. These are presented in Figures 1 and 2. In Figure 1.1 we show the three profiles of the solutions at time $t = 2189$. It is apparent from this plot that the amplitude of oscillation of the "unstable" species (u) is much higher than the other two. This is a feature characteristic in all the numerical solutions we explored (see also Figure 2.1 and Figure 2.2) and it is as one would expect intuitively. Figure 1.2 presents
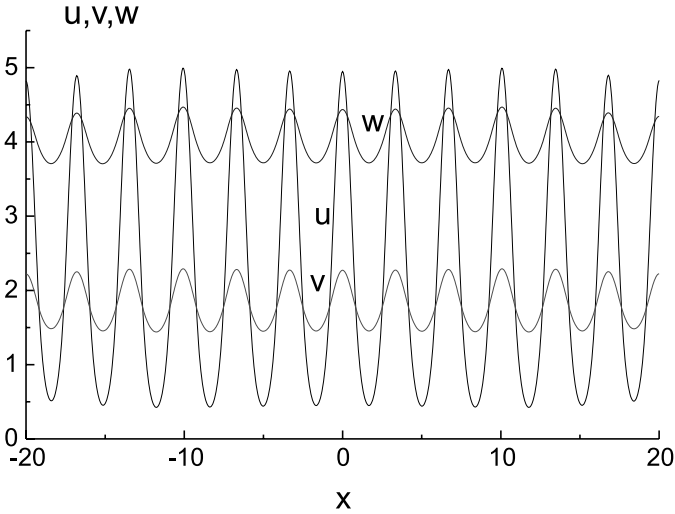
Fig. 1.1. Concentration profiles for the three species taken at $t = 2189$ when a steady structure (type (I) Turing pattern) is fully established in the domain for problem (3.1–5). The three species oscillate "in phase". Parameter values are: $d_1 = 0.005$, $d_2 = 0.1$, $d_3 = 0.1$, $b_{11} = 0.08$, $b_{12} = -0.08$, $b_{13} = -0.01$, $b_{21} = 0.1$, $b_{22} = 0.0$, $b_{23} = 0.0$, $b_{31} = 0.1$, $b_{32} = 0.0$, $b_{33} = 0.01$, $q_1 = 0.05$, $q_2 = -0.15$, $q_3 = -0.25$, $s_1 = 0.03$, $s_2 = 0.06$, $s_3 = 0.02$, $u_l = 0.5$, $v_l = 0.5$, $w_l = 0.5$.

a space-time plot of the u-component of the solution. It displays the dynamical process of evolution from the initial perturbation of the steady state up to the formation of the spatially-periodic stationary patterns. In this case all components oscillate "in phase".

Standard analysis (see, for example, [4]) shows that for the case of a two-component reaction-diffusion system in 1-D, near a primary Turing bifurcation point, the spatial profiles of the components are either exactly in phase or exactly out of phase. For (3.1–6) there are essentially two cases to consider depending on whether one or both of the remaining species oscillate in opposite phase. Two illustrations of these situations a re shown in Figures 2.1 and 2.2. A general feature of all "out of phase" cases was that the parameter domain in which they occur is considerably smaller than the corresponding domain for the "in phase" oscillations. In practice this means that such structures are less likely to occur. Note also the u, v patterns formed in Figure 2.1 and the high amplitude of the u-oscillations in Figure 2.2. Figure 2.3 gives a surface plot of the concentration u, which shows the spatio-temporal evolution from the initial conditions to a steady structure for parameter values similar to those in Figures 1.1.

We next studied the formation of *Turing patterns of the second type (II)*. A typical situation is displayed in Figures 3.1 and 3.2. Here the three concentrations oscillate in phase. Note that although they all have amplitudes of similar magnitude, the pair of "unstable" components has somewhat higher amplitude of oscillation than the remaining inhibitor species. The v-species has the highest amplitude since
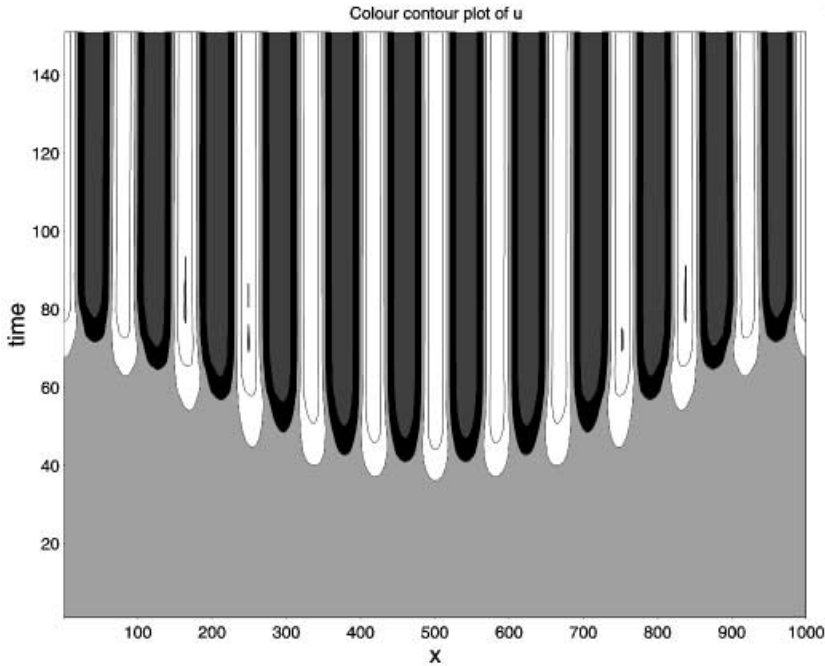
Fig. 1.2. Grey scale contour space-time plot of the u solution in Figure 1.1 showing the evolution from some small initial perturbation to a steady type (I) Turing structure for problem (3.1–5). Parameter values are the same as in Figure 1.1.

it has the smallest diffusion coefficient. In Figure 3.2 we show a contour plot of the u-species for the same parameter values as in Figure 3.1. As was the case for Turing structures of the first kind, there is also the possibility of out of phase solutions of the second kind, but this situation is not presented here.

We conclude by emphasising our finding that the high amplitude of the activator species (i.e. those composing the unstable subsystem) oscillations appears to be generic for all type p (here $p = $ I, II) Turing patterns. In general, there are parameter domains where type I and type II Turing structures overlap and where hysteresis is expected to occur.

4. Extensions of the main result

Although the analysis in Section 2 was carried out for a reaction-diffusion system, it can provide insight to more general systems. In this regard it is instructive to give an application of Theorem 1 in connection to the *differential-flow instability* property of a system (*DIFI* [10, 11, 30]). Specifically let us consider a general n-dimensional reaction-diffusion-convection system with the corresponding kinetics matrix being s-stable. We show here that if the system is unstable to differential-flow then the instability must be of *convective* type. In other words the system is stable in the fixed frame of reference but there is a moving frame in which any
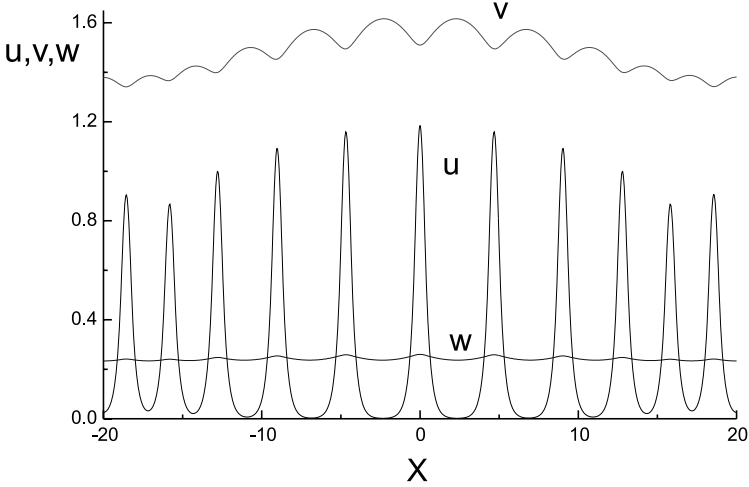
Fig. 2.1. Concentration profiles for the three species taken at $t = 2436$ when a steady structure (type (I) Turing pattern) has been well established in the domain for problem (3.1–5). For better graphical display the plot here shows $v - 4.75$. The v species oscillates "out of phase" from u and w. Parameter values are similar to those for Figure 1.1.
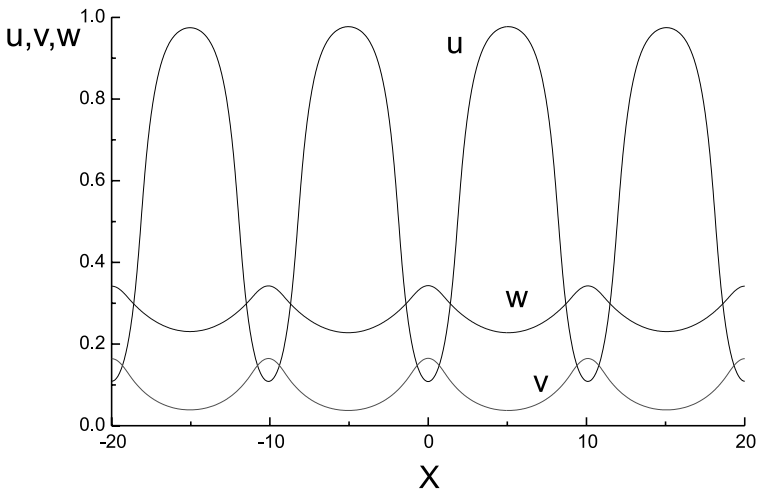
Fig. 2.2. Co ncentration profiles for the three species taken at $t = 4667$ for problem (3.1–5) when a steady structure (type (I) Turing pattern) has been well established in the domain. The values of the u species are scaled down by a factor of 10 for better graphical display. The v and w species oscillate "out of phase" to u. Parameter values are similar to those for Figure 1.1.
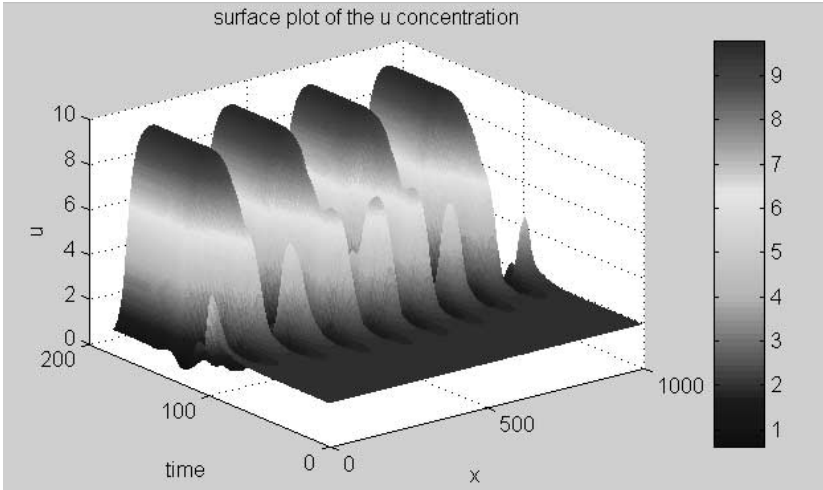
Fig. 2.3. Grey scale surface plot of the spatio-temporal evolution of the u concentration. The plot shows the dynamical evolution from some small initial perturbation from the steady state up to a steady (periodic) type (I) Turing pattern. Parameter values are similar to those for Figure 1.1.
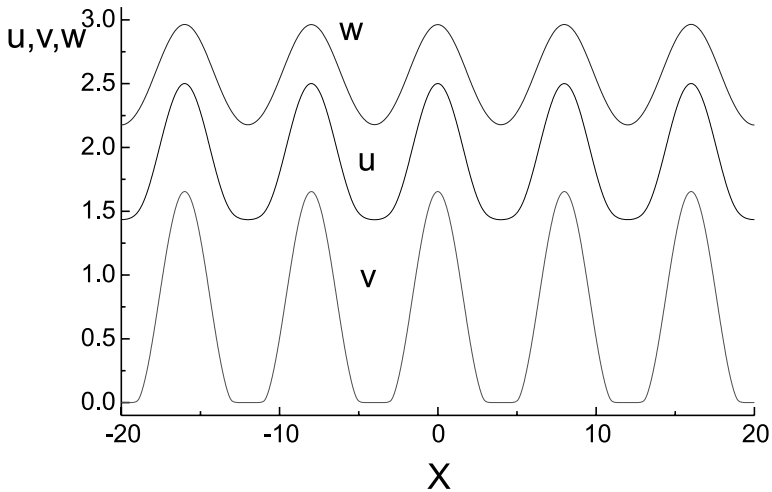

Fig. 3.1. Concentration profiles for the three species taken at $t = 20434$ for problem (3.1–5) when a steady structure (type (II) Turing pattern) has been well established in the domain. The three species oscillate "in phase". Parameter values: $d_1 = 0.007$, $d_2 = 0.001$, $d_3 = 0.2$, $b_{11} = 0.01$, $b_{12} = 0.02$, $b_{13} = -0.01$, $b_{21} = 0.1$, $b_{22} = 0.0$, $b_{23} = 0.0$, $b_{31} = 0.1$, $b_{32} = 0.0$, $b_{33} = 0.01$, $q_1 = 0.05$, $q_2 = -0.15$, $q_3 = -0.15$, $s_1 = 0.03$, $s_2 = 0.06$, $s_3 = 0.025$, $u_l = 0.2$, $v_l = 0.5$, $w_l = 0.2$.
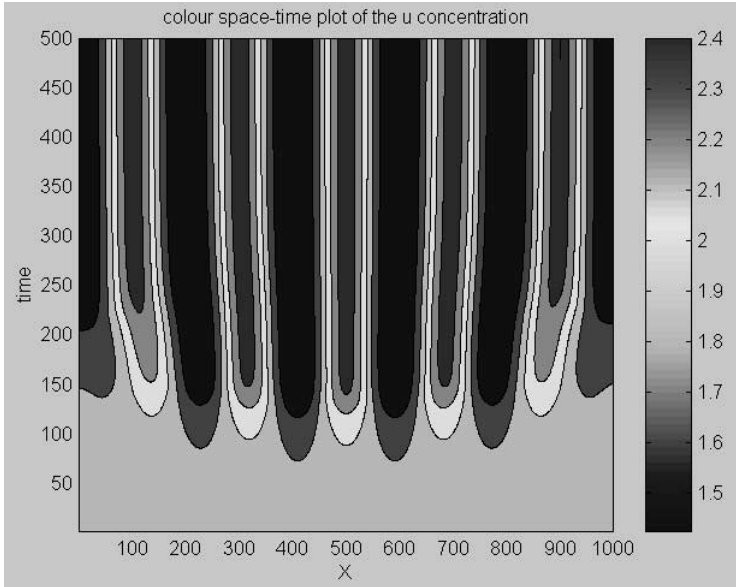
Fig. 3.2. Grey scale contour plot of the u solution in Figure 3.1. showing the evolution from some small initial perturbation to a steady type (II) Turing structure. Parameter values are the same as in Figure 3.1.

localised perturbation grows as it is convected out of the physical domain. This was proved for a particular case of the Gray-Scott kinetics model with two components in [19].

To see this let us take A as above (representing the linearisation of the kinetics matrix around a spatially uniform steady-state). It is clearly sufficient to establish the result when only one of the species is flowing and the others are all immobilised (following an argument similar to the one used in proof of Theorem 1 and Remark 1 and see also [12]). Suppose then that the first species flows at a constant rate $\phi > 0$ and diffuses as well. Without restriction we can scale its diffusion coefficient to 1. Now we shall show that the system is stable to small, spatially localised perturbations in any given stationary frame of reference. Let $\alpha = k^2 + ik\phi$ and consider the matrix of the resulting linearised system which we denote by $D(k, \phi)$. The proof proceeds by induction, as in Theorem 1 above, and because the verification step is clear we shall only give the general induction step here. From a simple calculation we obtain the characteristic polynomial:

$$q_n(\omega) = \omega^n + d_1\omega^{n-1} + \cdots + d_{n-1}\omega + d_n \qquad (4.1)$$

where

$$d_1 = \alpha - \sum_{i=1}^{n} \Delta_i = \alpha + a_1 \qquad (4.1.1)$$

$$d_2 = -\alpha \sum_{i=2}^{n} \Delta_i + \sum_{1 \le i < j \le n} \Delta_{ij} = -\alpha \sum_{2} \Delta_i + a_2 \qquad (4.1.2)$$

$$\vdots$$

$$d_n = \alpha(-1)^{n-1}\Delta_{2\ldots n} + (-1)^n \Delta_{12\ldots n} \qquad (4.1.n)$$

These coefficients are obtained in a similar manner to the coefficients of p_n in (2.13). Now we apply again the method of steepest descents to determine the behaviour of the linear solutions (as $t \to \infty$). By computing the saddle points of (4.1) we arrive at the relation

$$\left(z^{n-1} - \left(\sum_{i=1}^{n-1} \Delta_i \right) z^{n-2} + \cdots + \Delta_{12\ldots n-1} \right)(2k + i\phi) = 0 \qquad (4.2)$$

where the eigenvalues at the saddle points are denoted by z. Now if the first factor is zero then clearly we have $\mathrm{Re}(z) < 0$ because these eigenvalues are associated with the kinetics matrix which is s-stable. If the second factor is zero then the saddle is located at

$$k_s = -\frac{i}{2}\phi \qquad (4.3)$$

By putting this value of k back into (4.1) we arrive at a polynomial equation in z of degree n exactly as (2.12–2.13) but with D being replaced by $\frac{\phi^2}{4} > 0$. It follows from Theorem 1 that all the roots of this polynomial equation have negative real part. This establishes that our reaction-diffusion-convection system is absolutely stable and the result is proved.

From this proof it appears that the result may not hold in general if the stability matrix of the kinetics system is not s-stable. Indeed in [25] it is established (again for the example of the Gray-Scott kinetics) that the instability may be absolute for specific values of the kinetics which render the kinetics matrix non s-stable (for example in the Hopf oscillatory domain).

5. Conclusions

We have reconsidered Turing's theory of pattern formation [1] with the aim of extending it to the interaction of more than two species. We have established necessary and sufficient conditions (in terms of the kinetics matrix and the diffusion rates of the interacting species) which guarantee the occurrence of a Turing bifurcation from a spatially uniform steady state in a system of n reaction-diffusion equations. Our results show that the dimension p of the unstable subset may be in the range $1 \le p \le (n-1)$. This implies that there are *a priori* $(n-1)!$ distinct ways, depending on the reaction mechanism, in which an unstable or autocatalytic subset may arise. Each member of this hierarchy of $(n-1)!$ steady Turing bifurcations has further subclasses defined by the phase-relationships of the species.

We showed how the above results may be applied by considering a number of pattern generating mechanisms, ranging from the "inhibitor-of-an-inhibitor" patterning scheme proposed by Meinhardt [27], to a generalisation of a model recently proposed for pigmentation patterns on certain fish species [14, 15], to an extension of the recently investigated differential-flow-induced instability and flow distributed oscillations which have been applied to chemical systems and may also have important application in biological patterning mechanisms that involve clocks, such as somitogenesis [29].

We have shown that Turing instability in n-species reaction networks may arise through activators, or unstable subsystems, involving up to $p = n - 1$ species. The number of *a priori* possibilities of finding an activator in such a reaction increases rapidly with n – an issue that is of central importance in Kauffman's arguments [26].

We believe that the work presented in this paper is another step towards understanding pattern formation in systems of reaction-diffusion equations involving more than two species. Given that most realistic chemical and biochemical reactions do involve more than two species, such an analysis is crucial if one is going to verify models by comparing model predictions to experimental data. One of the conclusions of the above work is that the patterning morphogen envisioned by Turing may, in effect, be a system of chemicals interacting in a specific way.

It is known [18] that time-varying spatio-temporal structures may arise in reaction-diffusion systems with more than two interacting species. A condition for this type of structure is presented in [18] for a general three-species system. It remains a task for future research to generalise this formally to the general n-dimensional case, probably involving ideas similar to those employed here. Another open question arising from this work is its impact on patterns in two and three spatial dimensions, e.g. the issues of coexistence/competition of patterns belonging to different types, of morphological differences and of dividing spots [20] and lamellar structures [21].

Finally we mention the analogous problem of a reaction-convection-(diffusion) system for which these results do not hold in the same way. In [12] it has been shown that, at least for $n = 3$, the differential-flow-induced instability (DIFI) can arise in a generic system even in the absence of an unstable subsystem (activator). Although this result was established only for $n = 3$ dimensions we believe that it is more general (i.e. valid for any $n \geq 3$). One reason for this difference might be in the different character of the two instabilities (i.e. Turing and DIFI) the former being always of absolute type whereas the latter can be either of absolute or of convective type. In this respect we have given already an application showing that for the s-stable kinetics the ensuing flow-driven instability must be convective. However, the general problem is under consideration at the present time. Nevertheless, it is simple to show that for the case $n = 2$ we do require the presence of an activator species in the system in order for DIFI to take place [30].

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