Spatial Structures in a Model Substrate-Inhibition Reaction Diffusion System

Masayasu Mimura

Applied Mathematics, Konan University, Kobe, Japan

and J. D. Murray

Mathematical Institute, Oxford

Z. Naturforsch. **33 c**, 580–586 (1978) ; received May 18, 1978

Reaction-Diffusion, Spatial Pattern, Substrate Inhibition

An important new model universal oscillator proposed by Seelig which depends on substrate inhibition is considered. In a finite spatial domain with zero flux boundary conditions and in which the substrates can diffuse it is shown that diffusion-driven instability is possible and can result in finite amplitude spatial structures. Illustrative numerical results are presented which exhibit this behaviour.

Introduction and the Seelig Oscillator

The importance of oscillatory and wave phenomena in developing biological systems was first proposed by Turing [1] in a theoretical paper in 1952. With the increasing volume of experimental work on oscillatory phenomena their importance is now fairly generally accepted. The experimental systems studied are very complex and the current upsurge of interest in model reaction systems which exhibit oscillatory behaviour is both a recognition of the importance of the subject and an attempt to mirror the systems studied experimentally. It is hoped that a study of such models will provide some insight into various aspects of monphogenesis.

An early review article in 1967 by Higgins [2] discussed oscillating reactions in a biological and chemical context. More recent reviews have been given, for example, by Noyes and Field [3] and Goldbeter and Caplan [4]. The emphasis in the former is on the chemistry side and in the latter on the biology side. All of these reviews, however, are mainly concerned with homogeneous oscillations which necessitate the study of spatially uniform reacting systems in which diffusion plays no role. Spatial phenomena which arise in reation diffusion systems have been widely studied in the last few years. A substantial part of the book by Murray [5] is on this area. Much of the work on spatial phenomena has been in an ecological context: the models of population interactions with diffusion are formally in the same general class as reaction diffusion models. There is a recent review article from the ecological point of view by Levin [6].

A dramatic real oscillatory reaction is the Belousov-Zhabotinskii reaction [7] which is essentially the bromination of malonic acid in the presence of the catalyst cerium. Oscillations in the ratio of the concentrations of Ce III to Ce IV are dramatically exhibited if a suitable dye indicator is used. A 5-step model reaction, based on the detailed rather complicated kinetics, involving at most bi-molecular reactions was proposed by Field, Körös and Noyes [8]. A diffusional version of this model has been studied by Murray [9, 5] who showed the existence of propagating chemical fronts. A long review article on the reaction, its models and their analyses has been written by Tyson [10]. The oscillatory behaviour of the reaction depends on autocatalysis.

A widely studied model reaction which exhibits oscillations is that proposed by Prigogene and Lefever [11]. When diffusion is included Erneux and Herschkowitz-Kaufman [12] have demonstrated the presence of spatially rotating waves. The mathematical ramifications of this model are interesting and have indicated phenomena of potential experimental interest. The system however involves tri-molecular reactions and constant pool chemicals. This model and all of those for the Belousov reaction involve autocatalysis: in biological systems this is very rare.

Biological control is often effected by negative feedback mechanisms and in the form of substrate inhibition it is particularly common in many enzyme reactions. It is important, therefore, to find a model universal oscillator which relies on substrate inhibition and which is biochemically realistic. Such a model has been proposed by Seelig [13] and is

Requests for reprints should be sent to J. D. Murray, Mathematical Institute, University of Oxford, 24–29 st Giles, Oxford OX1 3 LB.

illustrated in Fig. 1. The possible chemical realization of the model has been discussed by Seelig [13]. Importantly the model involves at most bi-molecular reactions, avoids the requirement of constant pool chemicals by having the more practically realistic condition of constant fluxes, and exhibits negative feedback control. From an analytical point of view the model reduces to a reaction system involving only two species. It is this reaction mechanism, in which the species can diffuse and are restricted to a finite domain, that is discussed in this paper.

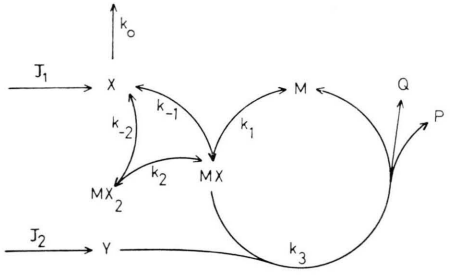

Fig. 1. Seelig's [13] model oscillator mechanism.

The overall reaction is $X + Y \rightarrow P + Q$ effected by a catalyst M, an enzyme for example. The substrates X and Y are supplied by constant fluxes J_1 and J_2 respectively and there is a first order reaction efflux of X. The substrate X is inhibited by extracting some of the active catalyst M by forming the inert complex MX_2. The reversible reactions are taken to be fast and the irreversible ones slow. On this basis the rate equations governing the catalyst M and its complexes MX and MX_2 are all essentially at equilibrium with respect to the time scale of the rate equations for X and Y. The kinetic equations for the reaction mechanism in Fig. 1 are then given by

$$\begin{aligned} \frac{d[X]}{dt'} &= J_1 - k_0[X] - R([X], [Y]), \\ \frac{d[Y]}{dt'} &= J_2 - R([X], [Y]), \end{aligned} \tag{1}$$

where [ ] denotes active concentrations, t' time and

$$R([X], [Y]) = \frac{k_{-1} M_0 \cdot \frac{k_1[X]}{k_{-1}} \cdot \frac{k_3[Y]}{k_{-1}}}{1 + \frac{k_1[X]}{k_{-1}} + \frac{k_3[Y]}{k_{-1}} + \frac{k_2 k_{-1}}{k_{-2} k_1}\left(\frac{k_1[X]}{k_{-1}}\right)^2} \tag{2}$$

where M_0 is the total amount of catalyst M present. The two species system (1) with (2) are the kinetic equations for Seelig's [13] model oscillator.

It is convenient to introduce non-dimensional quantities (the choice of which is suggested by (1) and (2))

$$\left.\begin{aligned} x &= \frac{k_1[X]}{k_{-1}}, & y &= \frac{k_3[Y]}{k_{-1}}, \\ t &= k_0 t', & K &= \frac{k_2 k_{-1}}{k_{-2} k_1}, \\ j_1 &= \frac{k_1 J_1}{k_0 k_{-1}}, & j_2 &= \frac{k_3 J_2}{k_0 k_{-1}}, \\ \beta &= \frac{M_0 k_1}{k_0}, & \gamma &= \frac{M_0 k_3}{k_0} \end{aligned}\right\} \tag{3}$$

and the non-dimensional system (1) with (2) becomes

$$\frac{dx}{dt} = j_1 - x - \beta r(x, y) = f(x, y), \tag{4}$$

$$\frac{dy}{dt} = j_2 - \gamma r(x, y) = g(x, y)$$

$$r(x, y) = xy/(1 + x + y + Kx^2), \tag{5}$$

where $f(x, y)$ and $g(x, y)$ are defined by (4).

If we now consider the space to be unidirectional with coordinate S say, and the species X and Y to diffuse with diffusion coefficients D_x and D_y respectively then denoting the space dimension by L, nondimensional diffusion coefficients and space variable s are defined by

$$d_x = \frac{D_x}{L^2 k_0}, \qquad d_y = \frac{D_y}{L^2 k_0}, \qquad s = \frac{S}{L}. \tag{6}$$

The reaction diffusion system for Fig. 1 in non-dimensional form, from (4) and (5) with (6), is then given by

$$\left.\begin{aligned} \frac{\partial x}{\partial t} &= j_1 - x - \beta r(x, y) + d_x \frac{\partial^2 x}{\partial s^2} \\ &= f(x, y) + d_x \frac{\partial^2 x}{\partial s^2} \\ \frac{\partial y}{\partial t} &= j_2 - \gamma r(x, y) + d_y \frac{\partial^2 y}{\partial s^2} \\ &= g(x, y) + d_y \frac{\partial^2 x}{\partial s^2} \\ r(x, y) &= xy/(1 + x + y + Kx^2). \end{aligned}\right\} \tag{7}$$

In the spatially uniform situation, that is system (4) and (5), Seelig [13] has shown that for a broad range of the parameters finite amplitude limit cycle oscillations exist. That is the steady state

(x_0, y_0) given by

$$\left.\begin{aligned} f(x_0, y_0) = 0 = g(x_0, y_0) \Rightarrow\ & x_0 = j_1 - \frac{\beta}{\gamma} j_2, \\ & y_0 = \frac{j_2(1 + x_0 + K x_0^2)}{\gamma j_1 - (\beta + 1) j_2}, \end{aligned}\right\} \tag{8}$$

is unstable and the instability manifests itself in a limit cycle and so $x(t)$ and $y(t)$ are periodic in time. Note that from (8) the steady state (x_0, y_0) lies in the positive quadrant only if $\gamma j_1 - (\beta+1) j_2 > 0$ a condition which we assume obtains.

Using a two-cell Turing model in which the concentrations are uniform in each cell and the diffusion terms in (7) replaced by differences in the concentrations in the two cells Seelig [14] demonstrated a flipflop behaviour which is, in effect, a temporal spatial heterogeneity.

Of particular interest in developmental biology is the possible existence of spatial structures which arise from the interaction of diffusion with chemical reaction: this possibility was first suggested by Turing [1]. Our interest here is in the appearance of spatial structures which arise from a diffusive driven instability of a spatial uniform state. Models which exhibit this have mainly arisen in ecological contexts: see for example Segel and Jackson [15], Levin and Segel [16] and Levin [6]. A general mathematical discussion has been given by Fife [17]: see also the references given there.

In this paper we consider the system (7) and demonstrate diffusional instability of the steady state (x_0, y_0) for a range of parameters for a bounded spatial domain with zero flux boundary conditions. Numerical results for typical stable *finite* amplitude spatial structures which exist for large time, are given and a conjecture made which relates details of the *linearised* instability behaviour to the ultimate nonlinear *finite* amplitude spatially heterogeneous state. Finally we describe what can be called *pseudo-stable domains* for general models of the form

$$\begin{aligned} \frac{\partial x}{\partial t} &= f(x, y) + d_x \nabla^2 x, \\ \frac{\partial y}{\partial t} &= g(x, y) + d_y \nabla^2 y. \end{aligned} \tag{9}$$

where ∇^2 is the Laplacian in three-dimensional space. The concept equally applies to systems with any number of species.

With respect to general systems it is heuristically to be expected that if the diffusional effects are sufficiently large then spatial inhomogeneities cannot exist. This has been proved for a wider class which includes reaction convection diffusion systems by Conway, Hoff and Smoller [18]. Global stability of such systems has also been discussed by Conway and Smoller [19].

Diffusional Instability

We consider the reaction diffusion system (7) for $x(s, t)$ and $y(s, t)$ in a finite spatial domain $0 \leqq s \leqq 1$ with zero flux boundary conditions

$$\frac{\partial x}{\partial s} = 0 = \frac{\partial y}{\partial s} \text{ for } s = 0, 1 \text{ for all } t \geqq 0. \tag{10}$$

The single steady state (x_0, y_0) is the intersection in the x, y phase plane of $f(x, y) = 0 = g(x, y)$, with these functions defined by (7). These isoclines are illustrated in Fig. 2 for typical values of

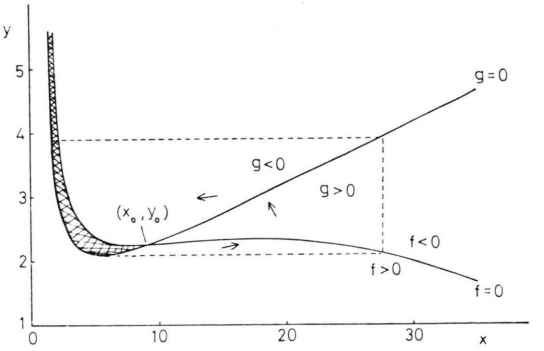

Fig. 2. Typical isoclines $f(x, y) = 0$, $g(x, y) = 0$ (see equation (7)). Values used: $j_1 = 50$, $j_2 = 0.984$, $\beta = 41$, $\gamma = 0.984$, $K = 0.1$: Steady state $(x_0, y_0) = (9, 2.2625)$.

the parameters. The region enclosed by the dashed line is a confined set, that is if the initial conditions for $x(s, 0)$ and $y(s, 0)$ lie within this domain then for all time $t > 0$ the solutions $x(s, t)$ and $y(s, t)$ of (7) will also lie in this closed region.

Now consider linear perturbations of the system (7) about the steady state (x_0, y_0) given by (8). Introduce the vector and matrix quanties

$$\boldsymbol{w} = \begin{pmatrix} x - x_0 \\ y - y_0 \end{pmatrix}, \quad M = \begin{pmatrix} \dfrac{\partial f}{\partial x} & \dfrac{\partial f}{\partial y} \\ \dfrac{\partial g}{\partial x} & \dfrac{\partial g}{\partial y} \end{pmatrix}_{\substack{x = x_0 \\ y = y_0}} \tag{11}$$

then the linearized form of the system (7) about (x_0, y_0) is

$$\boldsymbol{w}_t - D\boldsymbol{w}_{ss} - M\boldsymbol{w} = 0, \quad D = \begin{pmatrix} d_x & 0 \\ 0 & d_y \end{pmatrix}. \tag{12}$$

Now write the solution of (12) in Fourier spectrum form

$$\boldsymbol{w}(s,t) = e^{\lambda t}\boldsymbol{w}(s), \quad \boldsymbol{w}(s) = \sum_{n=0}^{\infty} \boldsymbol{a}_n \cos \sigma x, \quad \sigma = n\pi, \tag{13}$$

which automatically satisfies the zero flux boundary conditions (10). We are interested in the sign of the real part of the eigenvalues λ which are given, on substitution of (13) into (12), as the solutions of

$$\left| \begin{matrix} d_x\sigma^2 - \dfrac{\partial f}{\partial x} + \lambda & -\dfrac{\partial f}{\partial y} \\ -\dfrac{\partial g}{\partial x} & d_y\sigma^2 - \dfrac{\partial g}{\partial y} + \lambda \end{matrix} \right|_{\substack{x=x_0 \\ y=y_0}} = 0, \quad \sigma^2 = n^2\pi^2, \tag{14}$$

that is, solutions of the quadratic

$$\lambda^2 + \lambda\left[(d_x + d_y)\sigma^2 - \left(\frac{\partial f}{\partial x} + \frac{\partial g}{\partial y}\right)_{x_0, y_0}\right] + \left[\left(d_x\sigma^2 - \frac{\partial f}{\partial x}\right)\left(d_y\sigma^2 - \frac{\partial g}{\partial y}\right) - \frac{\partial f}{\partial y}\frac{\partial g}{\partial x}\right]_{x_0, y_0} = 0. \tag{15}$$

We are concerned here with the situation where the steady state (x_0, y_0) is *stable* when the system is spatially homogeneous. In this case, from (15) with $d_x = 0 = d_y$,

$$\lambda^2 + \lambda\left[-\left(\frac{\partial f}{\partial x} + \frac{\partial g}{\partial y}\right)_{x_0, y_0}\right] + \left(\frac{\partial f}{\partial x}\frac{\partial g}{\partial y} - \frac{\partial f}{\partial y}\frac{\partial g}{\partial x}\right)_{x_0, y_0} = 0, \tag{16}$$

has roots λ where $Rl\,\lambda < 0$. This means from (16) that the parameter range for j_1, j_2, β, γ and K in (7) are such that

$$-\left(\frac{\partial f}{\partial x} + \frac{\partial g}{\partial y}\right)_{x_0, y_0} > 0, \qquad \cdot\left(\frac{\partial f}{\partial x}\frac{\partial g}{\partial y} - \frac{\partial f}{\partial y}\frac{\partial g}{\partial x}\right)_{x_0, y_0} > 0. \tag{17}$$

A typical set of parameters in this range are those used in Fig. 2. If the parameter range is such that (17) is violated then the spatially homogeneous system (7) is linearly unstable and homogeneous limit cycle behaviour is obtained [13].

Now consider (15) and investigate the possibility that with $d_x \neq 0$, $d_y \neq 0$ and f and g satisfying (17) solutions λ exist such that $Rl\,\lambda > 0$, that is the steady state is unstable as a direct consequence of the diffusion. Because of the first of (17) the coefficient of λ in (15) is always positive and so for λ to have a positive real part we must have

$$\left[\left(d_y\sigma^2 - \frac{\partial f}{\partial x}\right)\left(d_x\sigma^2 - \frac{\partial g}{\partial y}\right) - \frac{\partial f}{\partial y}\frac{\partial g}{\partial x}\right]_{x_0, y_0} < 0,$$

that is there must be a positive solution for σ^2 which gives an integer n satisfying

$$d_x d_y \sigma^4 - \sigma^2\left[d_x\frac{\partial g}{\partial y} + d_y\frac{\partial f}{\partial x}\right]_{x_0, y_0} + \left[\frac{\partial f}{\partial x}\frac{\partial g}{\partial y} - \frac{\partial f}{\partial y}\frac{\partial g}{\partial x}\right]_{x_0, y_0} < 0. \tag{18}$$

Because of the second of (17) the only term which can cause such positive solutions is if the coefficient of σ^2 is negative, that is

$$-\left(d_x\frac{\partial g}{\partial y} + d_y\frac{\partial f}{\partial x}\right)_{x_0, y_0} < 0. \tag{19}$$

Because of the first of (17) the last relation immediately shows that diffusional instability can only be caused if the diffusion coefficients are unequal that is $d_x \neq d_y$.

Returning now to the specific form for f and g given by (7)

$$\frac{\partial g}{\partial y} = -\gamma\frac{\partial r}{\partial y} = -\left.\frac{\gamma x(1 + x + Kx^2)}{(1 + x + y + Kx^2)^2}\right|_{x_0, y_0} < 0, \tag{20}$$

and so to satisfy (17) and (19) we must have at the very least

$$\frac{\partial f}{\partial x} = -1 - \beta\frac{\partial r}{\partial x} = -1 - \left.\frac{\beta y(1 + y - Kx^2)}{(1 + x + y + Kx^2)^2}\right|_{x_0, y_0} > 0, \quad d_x < d_y. \tag{21}$$

With (17), (19) and (20) satisfied, there must exist a least positive solution for $\sigma^2 (= n^2\pi^2)$ of (18), and hence a least n which gives an eigenvalue with $Rl\,\lambda > 0$. The steady state is then linearly unstable and is a diffusion-driven instability. As long as $d_x > 0$ (and so from (20) $d_y > 0$) there is only a finite range for the unstable modes since the term $d_x d_y \sigma^4$ in (18) eventually dominates and violates the condition. Let the integer N be the least value of n in the Fourier spectrum which makes the last square bracket in (15) negative.

If we introduce $\delta = d_y/d_x (> 1)$ the finite range of integers $n \geqq N$ which give rise to unstable modes

is obtained from (18) using (20) and (21) in terms of $r(x, y)$ (see (7)) as those satisfying

$$\left.\begin{aligned} &\frac{1}{2\,d_y\,\pi^2}\,[A-(A^2-4\,B)^{1/2}]<n^2<\frac{1}{2\,d_y\,\pi^2}\,[A+(A^2-4\,B)^{1/2}],\\ &A=\left[\frac{\partial g}{\partial y}+\delta\,\frac{\partial f}{\partial x}\right]_{x_0,\,y_0}=-\left[\gamma\,\frac{\partial r}{\partial y}+\delta\left(1+\beta\,\frac{\partial r}{\partial x}\right)\right]_{x_0,\,y_0},\\ &B=\delta\left[\frac{\partial f}{\partial x}\,\frac{\partial g}{\partial y}-\frac{\partial f}{\partial y}\,\frac{\partial g}{\partial x}\right]_{x_0,\,y}=\delta\left[\gamma\,\frac{\partial r}{\partial y}\right]_{x_0,\,y_0}, \end{aligned}\right\} \tag{22}$$

where (x_0, y_0) is given by (8).

As a numerical example suppose we choose the parameter values used in Fig. 2, that is

$$\left.\begin{aligned} &j_1=50,\ \beta=41,\ j_2=0.984=\gamma,\ K=0.1\\ &x_0=9,\ y_0=2.2625, \end{aligned}\right\} \tag{23}$$

and using (20) and (21) condition (19) requires δ to satisfy

$$0.38659-0.08226\,\delta<0\Rightarrow\delta\gtrsim 4.7,\quad \delta=d_y/d_x. \tag{24}$$

To be numerically specific let us take as an illustration $\delta=300$ and (22) then gives the unstable Fourier modes as those n satisfying, approximately

$$0.662<n^2\,d_y<1.80. \tag{25}$$

In dimensional terms $d_y=D_y/L^2\,k_0$ and so the last inequalities give

$$0.814<\frac{n}{L}\left(\frac{D_y}{k_0}\right)^{1/2}<1.34.$$

Suppose $L^2=L_1{}^2=D_y/k_0$ (that is $d_y=1$) which gives the domain length L_1, the last inequalities show that the only linearly unstable mode is $n=1$. If we have a domain $4\,L_1$ then $3.256<n<5.36$ and the unstable modes are $n=4$ and $n=5$. It is clear that there is an intimate relationship between all of the parameters of the problem and the number of unstable modes. The dependence of n on L is linear, we come back to this important point later. From (25) as d_y increases beyond the bifurcation value 1.80 the system becomes stable since no integer can satisfy the inequality.

We have thus shown that a stability bifurcation surface (or surfaces) exists in the parameter space which is a direct result of diffusion-driven instability, a typical Turing type situation.

Numerical Results and Pseudo-Steady Domains

In the last section we obtained the necessary conditions for diffusion-driven linear instability, namely (19) and (22). As specific numerical examples we computed the long time behaviour of several solutions from the full nonlinear system (7) with zero flux boundary conditions (10) and given initial conditions and where linearised unstable modes were present: two typical results are given in Figs. 3 a, b. The final state was independent of the

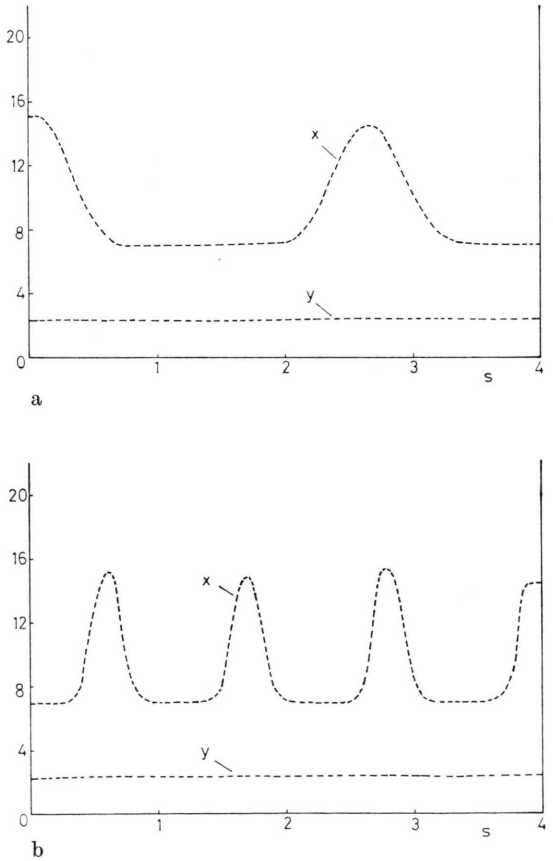

Fig. 3. Long time finite amplitude spatial structures for diffusion-driven instability of the system (7) with parameter values as in Fig. 2 $(x_0, y_0)=(9, 2.2625)$, $d_y/d_x=300$, domain length $L=4$ and a) $d_y=1.5$ which has linearly unstable modes $n=3$, 4 and b) $d_y=0.3$ which has linearly unstable modes $n=7$, 8, 9.

initial conditions. The parameter values used are those given in (23) with $L=4$, $\delta=300$ and two values of d_y namely

$$\left.\begin{matrix} d_y=0.3 \\ d_y=1.5 \end{matrix}\right\} \Rightarrow \text{ unstable modes } \begin{cases} n=7,\ 8,\ 9 \\ n=3,\ 4 \end{cases}. \quad (26)$$

One of the interesting, but not unexpected facts which emerged from the numerical study and is demonstrated in Figs. 3 a, b is that the mode of the finite amplitude spatial structure is equal to the smallest unstable mode in the linearised analysis. On a linearised basis the smallest n mode had the largest growth, that is the largest $R\,l\,\lambda>0$. This is probably a general principle for diffusion-driven instabilities in bounded domains with zero flux boundary conditions, that is the finite amplitude mode is the one coming from the largest $R\,l\,\lambda>0$. In Fig. 3 b for example, the least mode on a linear analysis is $n=7$ which is the basic finite amplitude structure mode.

It is clear that the ultimate spatial structure is tied up with the specific boundary conditions taken. For example if the boundary conditions were taken to be $x=0=y$ on $s=0$ and $s=1$ then since $x=0=y$ is unstable, it is clear that if the diffusion coefficients are not sufficiently large for the diffusional flux out of the domain to overcome the reaction instability then spatial structure with result. It is much less obvious when zero flux boundary condition are taken. In this case the relative difference in the internal diffusional fluxes, the destabilising factor, overcome the stability forces of the reaction terms. An introductory discussion of these different aspects of spatial structure has been given by Murray [5].

In Figs. 3 a, b the variation or spatial structure in the species y is so small as to be essentially negligible: in these cases the maximum change was less than 1%. The reason for this could be due to the fact that the stabilising effect on y is (with $\delta=300$) 300 times stronger than on x. It could also reflect the fact that the multivalued region $y\sim x$ in Fig. 2 has a very small y-range. What is perhaps related to this is the fact that near the asymptotes of the isoclines $f(x,\ y)=0=g(x,\ y)$ there is a domain where both f and g are close to zero. This is the shaded region in Fig. 2. The asymptotes for $f(x,\ y)=0$ and $g(x,\ y)=0$ are, from (4) and (5), $x=j_1/(\beta+1)$ and $x=j_2/\gamma$ respectively. Thus a measure of the separation of the two isoclines for values of $x<x_0$ is given by $j_1/(\beta+1)-j_2/\gamma$ (equal to 0.19 for the values in Fig 1).

The trajectory path for an initial value of x and y can be indicated by the sign of f and g in the equation system (7). It is given by (4) in the spatially uniform state. When a spatially inhomogeneous solution enters the shaded region where f and g are near zero the normal smoothing diffusion process takes place and tends to stabilise the spatial structuring. If the isoclines are very close together here the system (7) is to a first approximation essentially simply two uncoupled pure diffusion equations, the solutions of which, with zero flux boundary conditions, tend to spatial uniformity with time. In this situation although there is diffusion-driven instability the spatial structure which obtains is of very small amplitude. We describe this region where diffusion stabilising forces are dominant for part of the domain as a *pseudosteady state domain*. From a numerical solution point of view it might appear in fact that there is no spatial structure but this would be strictly not the case. The existence of such pseudo-steady state domains is immediately obvious from the isocline curves $f(x,\ y)=0=g(x,\ y)$. Since the asymptotes for these curves when $y\to\infty$ are respectively $j_1/(\beta+1)$ and j_2/γ we found that if these differ by less than 10^{-2} such a pseudo-steady state domain exists and spatial structures were of $0(10^{-6})$.

What we have shown in this paper is that the universal oscillator in Fig. 1 proposed by Seelig [13] and in which there is only a single steady state can display spatially uniform limit cycle oscillations, and diffusion-driven instabilities in the spatial context which, in a finite domain with zero flux boundary conditions, results in spatial structuring. In a spatial context in which the parameters give limit cycle behaviour the existence of travelling wave train solutions is possible [20]. This model can also be shown to exhibit threshold behaviour which in a spatial context results in solitary wave propagation: this will be reported elsewhere. Thus as a model relevant to biology it exhibits many of the features which have been observed experimentally such as in regeneration in the hydroid *Tubularia* [21]. The model relies on the common biological feature, negative feedback control, it avoids some of the drawbacks of other models like tri-

molecular reactions and so on, mentioned above, but yet reduces to a two-species system. As such it warrants further study. For example in two or three dimensions the type of spatial structures which can exist would be of particular interest.

As pointed out above if there is a given instability range of n for a given L then in for example a growing domain characterised by L the n range will vary with the least mode *increasing*. That is the number of finite amplitude waves increases with growth, that is increasing L. This could perhaps be the way reaction diffusion theory describes in a morphogenetic sense, the sequential development of compartment boundaries. An interesting recent paper by Kauffman *et al.* [22] discusses this potential aspect in connection with *Drosophila*.

[1] A. M. Turing, Phil. Trans. Roy. Soc. Lond. **B 237,** 37 (1952).
[2] J. Higgins, Ind. Eng. Chem. **59,** 18 (1967).
[3] R. M. Noyes and R. J. Field, Rev. Phys. Chem. **25,** 95 (1974).
[4] A. Goldbeter and S. R. Caplan, Ann. Rev. Biophys. Bioeng. **5,** 449 (1976).
[5] J. D. Murray, Nonlinear Differential Equation Models in Biology, Oxford University Press, 1977.
[6] S. A. Levin, Math. Assoc. of America Study in Math. Biol. **Vol. II,** Populations and Communities (S. A. Levin, ed.), (1977).
[7] B. P. Belousov, Sborn. Referat. Radiat. Med., Medgiz, Moscow, p. 145 (1959).
[8] R. J. Field, E. Körös, and R. M. Noyes, J. Amer. Chem. Soc. **94,** 8649 (1972).
[9] J. D. Murray, J. Theor. Biol. **56,** 329 (1976).
[10] J. T. Tyson, The Belousov-Zhabotinskii Reaction, Lect. Notes in Biomath., Springer-Verlag (1976).
[11] I. Prigogine and R. Lefever, J. Chem. Phys. **48,** 1665 (1968).
[12] Th. Erneux and M. Herschkowitz-Kaufman, J. Chem. Phys. **66,** 248 (1977).
[13] F. F. Seelig, Z. Naturforsch. **31 a,** 731 (1976).
[14] F. F. Seelig, Ber. Bun.-Ges. Phys. Chem. **80,** 1126 (1976).
[15] L. A. Segel and J. L. Jackson, J. Theor. Biol. **37,** 545 (1972).
[16] S. A. Levin and L. A. Segel, Nature **259,** 659 (1976).
[17] P. C. Fife, Nonlinear Diffusion (W. E. Fitzgibbon and H. F. Walker, eds.), Pitman, London 1977.
[18] E. D. Conway, D. Hoff, and J. A. Smoller, SIAM J Appl. Math. **34** (in print) (1978).
[19] E. D. Conway and J. A. Smoller, SIAM J. Appl. Math. **33,** 673 (1977).
[20] N. Kopell and L. N. Howard, Studies Appl. Math. **L 11,** 291 (1973).
[21] B. C. Goodwin, Theoria to Theory **10,** 33 (1976).
[22] S. A. Kauffman, R. M. Shymko, and K. Trabert, Science **199,** 259 (1978).
[23] J. P. Kernevez, M. C. Duban, G. Toly, and D. Thomas, Stud. in Natural Sci. (A. Perlmutter and L. Scott, eds.), **13,** 327 (1977).

Note added in proof: A model which describes the behaviour of immobilized enzyme systems in aritficial membranes proposed by Kernevez *et al.* [23] (see also references) gives rise to a system which is qualitatively similar to that studied here.