Reaction-Diffusion Patterns on Growing Domains

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Abstract

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The reaction-diffusion (Turing) mechanism is one of the simplest and most elegant theories for biological pattern formation. The recent experimental realisation of Turing patterns in chemical systems has fostered renewed interest in reaction-diffusion theory, however, its relevance to many biological problems has been questioned because of the perceived failure of the mechanism to generate patterns reliably. A recent paper suggesting the involvement of reaction-diffusion in fish skin patterns has implicated domain growth as an important mechanism controlling pattern selection. In this thesis we present a systematic study of the effects of domain growth on reaction-diffusion patterns, and discuss the implications for reliable pattern generation.

Starting from the postulate that tissue growth rates are locally determined, we derive general evolution equations for reaction-diffusion on growing domains as a problem in kinematics. We argue that the biologically plausible scenario is to consider domain growth on a longer timescale than pattern formation. Then it is found that the solution goes through a sequence of recognisable (quasi-steady) patterns. Using symmetry arguments relating different pattern modes we show that for uniform domain growth the solution evolves by frequency-doubling, the regular splitting or insertion of peaks in the pattern. For pattern formation in two spatial dimensions domain growth is found to select rectangular lattices, rather than the hexagonal planform that is preferred on the fixed domain. For nonuniform growth the local tissue expansion rate varies across the domain and splitting or insertion may be restricted to regions of the domain where the growth is sufficiently fast.

The behaviour of solutions can be studied asymptotically and peak splitting and insertion are shown to occur according to the form of the reaction nullclines. We highlight a novel behaviour, frequency-tripling, where both mechanisms operate simultaneously, which is realised when quadratic terms are absent from the reaction kinetics. Any particular pattern in a sequence remains established until the domain is sufficiently large that a transition to a higher pattern mode occurs. This presents a degree of scale invariance. The pattern which persists finally is not strongly dependent on the final domain size, and hence domain growth can provide a mechanism for reliable pattern selection.

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Contents

A. Reaction Schemes: Chemical and Population Kinetics

In this appendix we briefly introduce the various reaction schemes used in this thesis. Employing the notation introduced in Chapter 2, the nondimensionalised concentrations are labelled $u, v, \ldots$ and written in order of decreasing diffusivity, so that for two-species models u represents the inhibitor and v the activator.

A.1 The Schnakenberg System

Schnakenberg [119] introduced a kinetic scheme derived from a hypothetical autocatalytic set of chemicals involving a trimolecular step:

$$X \rightleftharpoons A, \quad B \to Y, \quad 2X + Y \to 3X. \tag{A.1}$$

The quantities A and B are external reactants, assumed to be of constant concentration. Application of the law of mass action and definition of appropriate nondimensional quantities (see Murray's book [88]), with $u(t)$ and $v(t)$ representing the variation over time of the concentrations Y and X respectively, gives

$$\frac{\mathrm{d}u}{\mathrm{d}t} = b - uv^2 = f(u,v) \tag{A.2}$$

$$\frac{\mathrm{d}v}{\mathrm{d}t} = a + uv^2 - v = g(u,v) \tag{A.3}$$

where a and b are nondimensional parameters, and usually a is small ($\sim b/10$).

The Schnakenberg kinetic scheme is of *cross* activator-inhibitor type (see Section 2.2.3) and has a unique kinetic steady state, (u_s, v_s), for which

$$f(u_s, v_s) = g(u_s, v_s) = 0, \tag{A.4}$$

given here by

$$u_s = \frac{b}{(a+b)^2}, \quad v_s = a + b. \tag{A.5}$$

We can expand the kinetic functions in powers of u and v about this steady state, writing $\bar{u} = u - u_s$ and $\bar{v} = v - v_s$, and then, dropping the over-bars,

$$f(u,v) = -v_s^2 u - 2u_s v_s v - 2v_s uv - uv^2 \tag{A.6}$$

$$g(u,v) = v_s^2 u + (2u_s v_s - 1)\, v + 2v_s uv + u_s v^2 + uv^2 \tag{A.7}$$

showing the presence of quadratic as well as cubic terms for both f and g (see section 5.2).

A.2 The Gray-Scott Model

The Gray-Scott [45] model,[1] a variant of the autocatalytic model of glycolysis proposed by Sel'kov [122], considers the autocatalytic production of chemical B which decays to form product P in the irreversible reactions

$$A + 2B \to 3B, \quad B \to P. \tag{A.8}$$

Here B is self-activating (autocatalytic) while A is a substrate for which higher concentrations increase the rate of its own removal. In a closed reactor, for which initial concentrations of A and B are specified and no material is allowed to enter or leave the reactor, eventually all of the reactants would be converted to product. However, nonequilibrium conditions may be maintained by a constant feed of the reactant A and removal of the product P. After nondimensionalisation, under these nonequilibrium conditions, the (cross-) kinetics are given by

$$f(u,v) = F(1-u) - uv^2 \tag{A.9}$$

$$g(u,v) = -(F+k)v + uv^2 \tag{A.10}$$

where u is the nondimensional concentration of the substrate (A) and v of the activator (B). Here F is the (nondimensional) flow rate of substrate A into the reactor and k is effectively the rate constant for decay of B to form the product P. By varying these two parameters the kinetics may have a single (trivial) steady state

$$u_r = 1, \quad v_r = 0 \tag{A.11}$$

known as the the *red* state, or may exhibit bistability when the discriminant $\Delta = 1 - 4(F+k)^2/F > 0$, giving two additional steady states arising in a saddle-node bifurcation

$$u_b = \frac{1}{2}\left(1 - \sqrt{\Delta}\right), \qquad v_b = \frac{F}{2(F+k)}\left(1 + \sqrt{\Delta}\right) \tag{A.12}$$

$$u_i = \frac{1}{2}\left(1 + \sqrt{\Delta}\right), \qquad v_i = \frac{F}{2(F+k)}\left(1 - \sqrt{\Delta}\right) \tag{A.13}$$

where the *intermediate* state (u_i, v_i) is unstable and the *blue* state (u_b, v_b) is stable.

This model has been widely studied, both as the simplest chemically plausible model which gives oscillations in the continuously stirred reactor and also in the context of chemical pattern formation in reaction-diffusion equations. In the vicinity of the bistable regime the Gray-Scott model has been studied in the context of self-replicating phenomena, as is discussed in Chapter 2.

[1]Known by its originators as the cubic autocatalysis model

A.3 Gierer-Meinhardt Kinetics

Gierer and Meinhardt proposed several kinetic models based on biologically plausible arguments in their paper on biological pattern formation [41], including activator-inhibitor (pure) and activator-substrate (cross) kinetic schemes. The scheme which has come to be known in the literature as the Gierer-Meinhardt model[2] considers autocatalytic activation of A and self-inhibition of H

$$\frac{\partial A}{\partial t} = \rho_0 \rho + c\rho \frac{A^p}{H^q} - \mu A + D_A \frac{\partial^2 A}{\partial x^2} \tag{A.14}$$

$$\frac{\partial H}{\partial t} = c' \rho' \frac{A^r}{H^s} - \nu H + D_H \frac{\partial^2 H}{\partial x^2} \tag{A.15}$$

where $0 < (p-1)/q < r/(s+1)$, which is postulated to explain the regenerative properties of hydra observed in various transplantation experiments. Here the authors consider inhomogeneous distributed source terms $\rho(x)$ and $\rho'(x)$, usually taken to be simple gradients across the solution domain. However, for constant parameters these kinetics may admit the diffusion-driven instability. The standard values assumed for the powers in the quotients are $p = r = 2$, $q = 1$ and $s = 0$, and the nondimensionalised kinetics may be written as

$$f(u, v) = \nu_1 v^2 - \mu_1 u \tag{A.16}$$

$$g(u, v) = \nu_2 \frac{v^2}{u} - \mu_2 v + \delta \tag{A.17}$$

where u is the inhibitor (or substrate) and v the activator.

A.4 A Three-Species Model Arising in Population Dynamics

White and Gilligan [131] propose a model for the population dynamics of a host-parasite-hyperparasite system, to account for persistent spatio-temporal patterns in population densities in a homogeneous environment. The population dynamics is described by local interaction terms and diffusion is assumed to model the spatial spread and dispersion of each species. (Diffusion is commonly used as a model for the spatial spread of root systems and for the dispersal of spores.) In the field, patchiness has been observed for timescales much longer than those one would associate with stochastic heterogeneities (where eventually a uniform infestation of parasite would be expected). Phenomena monitored experimentally include drifting disease 'hot-spots' and periodic occurrence of disease at a particular spatial location.

[2]Denoted in their paper as *Activator-Inhibitor Model with Different Sources*

In dimensional form the local dynamics are governed for host (H), parasite (P) and hyperparasite (Q) by the system

$$\frac{\mathrm{d}H}{\mathrm{d}t} = rH\left(1 - \frac{H}{k}\right) - aPH \tag{A.18}$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = bPH - \frac{cP}{1+eP}Q \tag{A.19}$$

$$\frac{\mathrm{d}Q}{\mathrm{d}t} = lP - dQ \tag{A.20}$$

where the host plant H grows logistically and is removed by the parasite P at a rate a per unit parasite and has conversion factor b per unit host. Predation of the hyperparasite Q on the parasite is a saturating function of parasite population, with conversion at a rate l per unit parasite, and the hyperparasite has a natural decay rate d.

Nondimensionalising in the manner described in Chapter 2, we reorder the system with decreasing diffusivity. In their paper White and Gilligan assume $D_Q > D_H > D_P$, i.e. the hyperparasite is fastest dispersing and the parasite is the slowest. Following the authors we scale the population densities with their steady state values when $k = \infty$, namely $(Q_s^\infty, H_s^\infty, P_s^\infty)$, such that $u = Q/Q_s^\infty$, $v = H/H_s^\infty$ and $w = P/P_s^\infty$ and then for $d_v = D_H/D_Q$ and $d_w = D_P/D_Q$ we have

$$u_t = \frac{1}{\gamma}u_{xx} - \delta\,(u - w) \tag{A.21}$$

$$v_t = \frac{d_v}{\gamma}v_{xx} + v\left(1 - \frac{v}{\kappa}\right) - vw \tag{A.22}$$

$$w_t = \frac{d_w}{\gamma}w_{xx} + \mu\left(v\frac{w}{1+\beta} - u\frac{w}{1+\beta w}\right) \tag{A.23}$$

where the rescaled variables $\delta = d/r$, $\kappa = k/H_s$, $\mu = cQ_s/r$ and $\beta = bP_s$. Time is nondimensionalised with the rate parameter r. Here, as elsewhere, γ is the dimensionless scaling parameter which uniformly transforms the one-dimensional solution domain to the unit interval. Labelling the kinetic functions f, g and h we find that for this model $f = f(u,w)$, $g = g(v,w)$ and $h = h(u,v,w)$. Naturally, in general for the interaction of three species each kinetic function may depend on u, v and w.

B. Some Results from Fluid Mechanics

The results we reproduce below may be found in many elementary texts on fluid mechanics (see, for example, Acheson [1] or Chorin and Marsden [16]) and are employed in Chapter 3 to derive a reaction-diffusion-advection equation.

Firstly we recall the definition of the material derivative. If for some scalar quantity of interest, $G = G(\mathbf{x}, t) = G(x_1, x_2, x_3, t)$, then $\partial G/\partial t$ is the rate of change of G at constant $\mathbf{x} = (x_1, x_2, x_3)$ and the material derivative, $\mathrm{D}G/\mathrm{D}t$, is the rate of change of G following a fluid element

$$\frac{\mathrm{d}}{\mathrm{d}t} G(x_1(t), x_2(t), x_3(t), t) = \frac{\partial G}{\partial t} + \mathbf{a} \cdot \nabla G = \frac{\mathrm{D}G}{\mathrm{D}t}, \tag{B.1}$$

with $x_1(t)$, $x_2(t)$, $x_3(t)$ changing with time due to a flow velocity field $\mathbf{a}(\mathbf{x}, t)$.

B.1 Reynolds Transport Theorem

This theorem concerns the rate of change of volume integrals over the finite but time varying fluid element $V(t)$.

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_{V(t)} G(\mathbf{x}, t)\, \mathrm{d}\mathbf{x} = \int_{V(t)} \left[\frac{\mathrm{D}G}{\mathrm{D}t} + G \nabla \cdot \mathbf{a} \right] \mathrm{d}\mathbf{x} \tag{B.2}$$

where $G(\mathbf{x}, t)$ is any scalar or vector function, and $V(t)$ is a region of space occupied by a finite deforming fluid element. The range of integration implies 'following the fluid' as the fluid element $V(t)$ is moving with the flow. The theorem may be proved by considering a change of variables to the Lagrangian description of the flow, in which spatial position $\mathbf{x}$, with respect to some Cartesian coordinates, is parameterised by position at time $t = 0$, $\mathbf{X} = (X_1, X_2, X_3)$, giving $\mathbf{x} = \mathbf{x}(\mathbf{X}, t)$. Then the range of integration is no longer a function of time, and the differential operator can be brought inside the integral as a rate of change following the flow, giving

$$\begin{aligned} \frac{\mathrm{d}}{\mathrm{d}t} \int_{V(t)} G(\mathbf{x}, t)\, \mathrm{d}x_1\, \mathrm{d}x_2\, \mathrm{d}x_3 &= \frac{\mathrm{d}}{\mathrm{d}t} \int_{V(0)} G(\mathbf{X}, t) J(\mathbf{X}, t)\, \mathrm{d}X_1\, \mathrm{d}X_2\, \mathrm{d}X_3 \\ &= \int_{V(0)} \left[\frac{\mathrm{D}G}{\mathrm{D}t} J + G \frac{\mathrm{D}J}{\mathrm{D}t} \right] \mathrm{d}X_1\, \mathrm{d}X_2\, \mathrm{d}X_3 \end{aligned} \tag{B.3}$$

where $J(\mathbf{X}, t)$ is the Jacobian for the transformation

$$J = \begin{vmatrix} \frac{\partial x_1}{\partial X_1} & \frac{\partial x_1}{\partial X_2} & \frac{\partial x_1}{\partial X_3} \\ \frac{\partial x_2}{\partial X_1} & \frac{\partial x_2}{\partial X_2} & \frac{\partial x_2}{\partial X_3} \\ \frac{\partial x_3}{\partial X_1} & \frac{\partial x_3}{\partial X_2} & \frac{\partial x_3}{\partial X_3} \end{vmatrix}$$

and $V(0)$ is the volume of the flowing fluid element at time $t = 0$. The computation of the derivative $\mathrm{D}J/\mathrm{D}t$ is achieved using Euler's identity

$$\frac{\mathrm{D}J}{\mathrm{D}t} = J(\nabla \cdot \mathbf{a}) \tag{B.4}$$

which is proved in the following section. This allows us to write

$$\frac{\mathrm{D}G}{\mathrm{D}t}J + G\frac{\mathrm{D}J}{\mathrm{D}t} = \left[\frac{\mathrm{D}G}{\mathrm{D}t} + G(\nabla\cdot\mathbf{a})\right]J \tag{B.5}$$

which on substitution into equation (B.3) and transforming back into coordinates $(\mathbf{x}, t)$ gives the transport theorem (B.2). Using the definition of the material derivative (B.1) this may be written as

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_{V(t)} G(\mathbf{x},t)\,\mathrm{d}\mathbf{x} = \int_{V(t)}\left[\frac{\partial G}{\partial t} + \nabla\cdot\mathbf{a}\,G\right]\mathrm{d}\mathbf{x}. \tag{B.6}$$

B.2 Euler's Identity

The material derivative of the Jacobian determinant $J(\mathbf{X}, t)$ may be reduced to a simple form by the following considerations. Starting from the definition of the material derivative, we have

$$\frac{\mathrm{D}J}{\mathrm{D}t} = \left(\frac{\partial J}{\partial t}\right). \tag{B.7}$$

We use the multilinearity of the determinant to write

$$\begin{aligned}
\frac{\partial J}{\partial t} &= \begin{vmatrix} \frac{\partial^2 x_1}{\partial t\partial X_1} & \frac{\partial^2 x_1}{\partial t\partial X_2} & \frac{\partial^2 x_1}{\partial t\partial X_3} \\ \frac{\partial x_2}{\partial X_1} & \frac{\partial x_2}{\partial X_2} & \frac{\partial x_2}{\partial X_3} \\ \frac{\partial x_3}{\partial X_1} & \frac{\partial x_3}{\partial X_2} & \frac{\partial x_3}{\partial X_3} \end{vmatrix} + \begin{vmatrix} \frac{\partial x_1}{\partial X_1} & \frac{\partial x_1}{\partial X_2} & \frac{\partial x_1}{\partial X_3} \\ \frac{\partial^2 x_2}{\partial t\partial X_1} & \frac{\partial^2 x_2}{\partial t\partial X_2} & \frac{\partial^2 x_2}{\partial t\partial X_3} \\ \frac{\partial x_3}{\partial X_1} & \frac{\partial x_3}{\partial X_2} & \frac{\partial x_3}{\partial X_3} \end{vmatrix} + \begin{vmatrix} \frac{\partial x_1}{\partial X_1} & \frac{\partial x_1}{\partial X_2} & \frac{\partial x_1}{\partial X_3} \\ \frac{\partial x_2}{\partial X_1} & \frac{\partial x_2}{\partial X_2} & \frac{\partial x_2}{\partial X_3} \\ \frac{\partial^2 x_3}{\partial t\partial X_1} & \frac{\partial^2 x_3}{\partial t\partial X_2} & \frac{\partial^2 x_3}{\partial t\partial X_3} \end{vmatrix} \\
&= \begin{vmatrix} \frac{\partial a_1}{\partial X_1} & \frac{\partial a_1}{\partial X_2} & \frac{\partial a_1}{\partial X_3} \\ \frac{\partial x_2}{\partial X_1} & \frac{\partial x_2}{\partial X_2} & \frac{\partial x_2}{\partial X_3} \\ \frac{\partial x_3}{\partial X_1} & \frac{\partial x_3}{\partial X_2} & \frac{\partial x_3}{\partial X_3} \end{vmatrix} + \begin{vmatrix} \frac{\partial x_1}{\partial X_1} & \frac{\partial x_1}{\partial X_2} & \frac{\partial x_1}{\partial X_3} \\ \frac{\partial a_2}{\partial X_1} & \frac{\partial a_2}{\partial X_2} & \frac{\partial a_2}{\partial X_3} \\ \frac{\partial x_3}{\partial X_1} & \frac{\partial x_3}{\partial X_2} & \frac{\partial x_3}{\partial X_3} \end{vmatrix} + \begin{vmatrix} \frac{\partial x_1}{\partial X_1} & \frac{\partial x_1}{\partial X_2} & \frac{\partial x_1}{\partial X_3} \\ \frac{\partial x_2}{\partial X_1} & \frac{\partial x_2}{\partial X_2} & \frac{\partial x_2}{\partial X_3} \\ \frac{\partial a_3}{\partial X_1} & \frac{\partial a_3}{\partial X_2} & \frac{\partial a_3}{\partial X_3} \end{vmatrix}.
\end{aligned} \tag{B.8}$$

Now $a_i = a_i(x_1, x_2, x_3)$ and by the chain rule

$$\frac{\partial a_i}{\partial X_j} = \frac{\partial a_i}{\partial x_1}\frac{\partial x_1}{\partial X_j} + \frac{\partial a_i}{\partial x_2}\frac{\partial x_2}{\partial X_j} + \frac{\partial a_i}{\partial x_3}\frac{\partial x_3}{\partial X_j}. \tag{B.9}$$

Hence we may write the first term of (B.8) as

$$\frac{\partial a_1}{\partial x_1}\begin{vmatrix} \frac{\partial x_1}{\partial X_1} & \frac{\partial x_1}{\partial X_2} & \frac{\partial x_1}{\partial X_3} \\ \frac{\partial x_2}{\partial X_1} & \frac{\partial x_2}{\partial X_2} & \frac{\partial x_2}{\partial X_3} \\ \frac{\partial x_3}{\partial X_1} & \frac{\partial x_3}{\partial X_2} & \frac{\partial x_3}{\partial X_3} \end{vmatrix} + \frac{\partial a_1}{\partial x_2}\begin{vmatrix} \frac{\partial x_2}{\partial X_1} & \frac{\partial x_2}{\partial X_2} & \frac{\partial x_2}{\partial X_3} \\ \frac{\partial x_2}{\partial X_1} & \frac{\partial x_2}{\partial X_2} & \frac{\partial x_2}{\partial X_3} \\ \frac{\partial x_3}{\partial X_1} & \frac{\partial x_3}{\partial X_2} & \frac{\partial x_3}{\partial X_3} \end{vmatrix} + \frac{\partial a_1}{\partial x_3}\begin{vmatrix} \frac{\partial x_3}{\partial X_1} & \frac{\partial x_3}{\partial X_2} & \frac{\partial x_3}{\partial X_3} \\ \frac{\partial x_2}{\partial X_1} & \frac{\partial x_2}{\partial X_2} & \frac{\partial x_2}{\partial X_3} \\ \frac{\partial x_3}{\partial X_1} & \frac{\partial x_3}{\partial X_2} & \frac{\partial x_3}{\partial X_3} \end{vmatrix} \tag{B.10}$$

for which the second and third terms are identically zero as two rows of the determinant are repeated. Similarly computing the other terms of (B.8) we find

$$\begin{aligned}
\frac{\mathrm{D}J}{\mathrm{D}t} &= \left(\frac{\partial J}{\partial t}\right) \\
&= \frac{\partial a_1}{\partial x_1}J + \frac{\partial a_2}{\partial x_2}J + \frac{\partial a_3}{\partial x_3}J \\
&= (\nabla\cdot\mathbf{a})J
\end{aligned} \tag{B.11}$$

which is Euler's identity.

Bibliography

[1] D. J. Acheson, *Elementary Fluid Dynamics*, Clarendon Press, Oxford, 1990.

[2] M. Akam, *Making stripes inelegantly*, Nature, 341 (1989), pp. 282–283.

[3] P. Arcuri and J. D. Murray, *Pattern sensitivity to boundary and initial conditions in reaction-diffusion models*, J. Math. Biol., 24 (1986), pp. 141–165.

[4] M. Ashkenazi and H. G. Othmer, *Spatial patterns in coupled biochemical oscillators*, J. Math. Biol., 5 (1978), pp. 305–350.

[5] J. F. G. Auchmuty and G. Nicolis, *Bifurcation analysis of nonlinear reaction-diffusion equations—I. Evolution equations and the steady state solutions*, Bull. Math. Biol, 37 (1975), pp. 323–365.

[6] J. Bard and I. Lauder, *How well does Turing's theory of morphogenesis work?*, J. theor. Biol., 45 (1974), pp. 501–531.

[7] D. L. Benson, *Reaction Diffusion Models with Spatially Inhomogeneous Diffusion Coefficients*, D. Phil. Thesis, University of Oxford, 1994.

[8] D. L. Benson, P. K. Maini, and J. A. Sherratt, *Analysis of pattern formation in reaction diffusion models with spatially inhomogeneous diffusion coefficients*, Mathl. Comput. Modelling, 17 (1993), pp. 29–34.

[9] P. Borckmans, A. De Wit, and G. Dewel, *Competition in ramped Turing structures*, Physica A, 188 (1992), pp. 137–157.

[10] B. Bunow, J.-P. Kernevez, G. Joly, and D. Thomas, *Pattern formation by reaction-diffusion instabilities: Applications to morphogenesis in* Drosophila, J. theor. Biol., 84 (1980), pp. 629–649.

[11] G. J. Butler and G. S. K. Wolkowicz, *A mathematical model of the chemostat with a general class of functions describing nutrient uptake*, SIAM J. Appl. Math., 45 (1985), pp. 138–151.

[12] T. K. Callahan and E. Knobloch, *Pattern formation in three-dimensional reaction-diffusion systems*, Physica D, 132 (1999), pp. 339–362.

[13] V. Castets, E. Dulos, J. Boissonade, and P. De Kepper, *Experimental evidence of a sustained Turing-type nonequilibrium chemical pattern*, Phys. Rev. Lett., 64 (1990), pp. 2953–2956.

[14] M. A. J. Chaplain, M. Ganesh, and I. G. Graham, *Spatio-temporal pattern formation on spherical surfaces: Numerical simulation and application to solid tumour growth.* University of Bath Preprint 99/12, June 1999.

[15] Y. Y. Chen and M. C. Cross, *Pattern formation in finite-size nonequilibrium systems and models of morphogenesis*, Nonlinearity, 7 (1994), pp. 1125–1132.

[16] A. J. Chorin and J. E. Marsden, *A Mathematical Introduction to Fluid Mechanics*, Springer-Verlag, Berlin, 3rd ed., 1993.

[17] J. R. Collier, N. A. M. Monk, P. K. Maini, and J. H. Lewis, *Pattern formation by lateral inhibition with feedback: A mathematical model of Delta-Notch intercellular signalling*, J. theor. Biol., 183 (1996), pp. 429–446.

[18] E. D. Conway, *Diffusion and predator-prey interaction: Pattern in closed systems*, in Partial Differential Equations and Dynamical Systems, W. E. Fitzgibbon III, ed., no. 101 in Research Notes in Mathematics, Pitman, London, 1984, pp. 85–133.

[19] E. J. Crampin, E. A. Gaffney, and P. K. Maini, *Pattern formation through reaction and diffusion on growing domains: Scenarios for robust pattern formation*, Bull. Math. Biol., 61 (1999), pp. 1093–1120.

[20] F. Crick, *Diffusion in embryogenesis*, Nature, 225 (1970), pp. 420–422.

[21] M. C. Cross and P. C. Hohenberg, *Pattern formation outside of equilibrium*, Rev. Mod. Phys., 65 (1993), pp. 851–1112.

[22] P. W. Davies, P. Blanchedeau, E. Dulos, and P. De Kepper, *Dividing blobs, chemical flowers and patterned islands in a reaction-diffusion system*, J. Phys. Chem. A, 102 (1998), pp. 8236–8244.

[23] P. De Kepper, V. Castets, E. Dulos, and J. Boissonade, *Turing-type chemical patterns in the chlorite-iodide-malonic acid reaction*, Physica D, 49 (1991), pp. 161–169.

[24] A. De Wit, G. Dewel, P. Borckmans, and D. Walgraef, *Three-dimensional dissipative structures in reaction-diffusion systems*, Physica D, 61 (1992), pp. 289–296.

[25] G. Dewel and P. Borckmans, *Effects of slow spatial gradients on dissipative structures*, Phys. Lett. A, 138 (1989), pp. 189–192.

[26] R. Dillon, P. K. Maini, and H. G. Othmer, *Pattern formation in generalized Turing systems I: Steady-state patterns in systems with mixed boundary conditions*, J. Math. Biol., 32 (1994), pp. 345–393.

[27] R. Dillon and H. G. Othmer, *A mathematical model for outgrowth and spatial patterning of the vertebrate limb bud*, J. theor. Biol., 197 (1999), pp. 295–330.

[28] E. J. Doedel, *Lecture notes on numerical analysis of bifurcation problems.* Short Course on Numerical Bifurcation Analysis with AUTO, 1997. Montreal 97 Summer School.

[29] E. J. Doedel, A. R. Champneys, T. F. Fairgrieve, Y. A. Kuznetsov, B. Sandstede, and X. Wang, *AUTO97: Continuation and Bifurcation for Ordinary Differential Equations*, 1997. FTP from `pub/doedel/auto` at `ftp.cs.concordia.ca`.

[30] E. J. Doedel, H. B. Keller, and J.-P. Kernevez, *Numerical analysis and control of bifurcation problems I: Bifurcation in finite dimensions*, Int. J. Bifurcation and Chaos, 1 (1991), pp. 493–520.

[31] ———, *Numerical analysis and control of bifurcation problems II: Bifurcation in infinite dimensions*, Int. J. Bifurcation and Chaos, 1 (1991), pp. 745–772.

[32] A. Doelman, R. A. Gardner, and T. J. Kaper, *Stability analysis of singular patterns in the 1D Gray-Scott model: A matched asymptotics approach*, Physica D, (1998), pp. 1–36.

[33] A. Doelman, T. J. Kaper, and P. A. Zegeling, *Pattern formation in the one-dimensional Gray-Scott model*, Nonlinearity, 10 (1997), pp. 523–563.

[34] E. Dulos, P. Davies, B. Rudovics, and P. De Kepper, *From quasi-2D to 3D Turing structures in ramped systems*, Physica D, 98 (1996), pp. 53–66.

[35] J. C. Eilbeck, *Pattern formation and pattern selection in reaction-diffusion systems*, in Theoretical Biology: Epigenetic and Evolutionary Order from Complex Systems, B. C. Goodwin and P. T. Saunders, eds., Johns Hopkins, London, 1992, pp. 31–41.

[36] I. R. Epstein and K. Showalter, *Nonlinear chemical dynamics: Oscillations, patterns and chaos*, J. Phys. Chem., 100 (1996), pp. 13132–13147.

[37] B. Ermentrout, *Spots or stripes? Nonlinear effects in bifurcation of reaction-diffusion equations on the square*, Proc. R. Soc. Lond. A, 434 (1991), pp. 413–417.

[38] P. C. Fife, *Boundary and interior transition layer phenomena for pairs of second order differential equations*, J. Math. Anal. Appl., 54 (1976), pp. 497–521.

[39] ———, *Pattern formation in reacting and diffusing systems*, J. Chem. Phys., 64 (1976), pp. 554–564.

[40] ———, *Stationary patterns for reaction-diffusion equations*, in Nonlinear Diffusion, W. E. Fitzgibbon III and H. F. Walker, eds., no. 14 in Research Notes in Mathematics, Pitman, London, 1977, pp. 81–121.

[41] A. GIERER AND H. MEINHARDT, *A theory of biological pattern formation*, Kybernetik, 12 (1972), pp. 30–39.

[42] M. G. M. GOMES, *Black-eye patterns: A representation of three-dimensional symmetries in thin domains*, Phys. Rev. E, 60 (1999), pp. 3741–3747.

[43] B. C. GOODWIN, S. A. KAUFFMAN, AND J. D. MURRAY, *Is morphogenesis an intrinsically robust process?*, J. theor. Biol., 163 (1993), pp. 135–144.

[44] B. C. GOODWIN AND L. E. H. TRAINOR, *Tip and whorl morphogenesis in* Acetabularia *by calcium-regulated strain fields*, J. theor. Biol., 117 (1985).

[45] P. GRAY AND S. K. SCOTT, *Autocatalytic reactions in the isothermal, continuous stirred tank reactor: Oscillations and instabilities in the system* $A + 2B \rightarrow 3B$, $B \rightarrow C$, Chem. Eng. Sci, 39 (1984), pp. 1087–1097.

[46] P. GRINDROD, *The Theory and Applications of Reaction-Diffusion Equations: Patterns and Waves*, Oxford University Press, 2nd ed., 1996.

[47] D. HAIM, G. LI, Q. OUYANG, W. D. MCCORMICK, H. L. SWINNEY, A. HAGBERG, AND E. MERON, *Breathing spots in a reaction-diffusion system*, Phys. Rev. Lett., 77 (1996), pp. 190–193.

[48] L. G. HARRISON AND M. KOLÁŘ, *Coupling between reaction-diffusion prepattern and expressed morphogenesis, applied to desmids and dasyclads*, J. theor. Biol., 130 (1988), pp. 493–515.

[49] M. HERSCHKOWITZ-KAUFMAN, *Bifurcation anaylsis of nonlinear reaction-diffusion equations—II. Steady state solutions and comparison with numerical simulations*, Bull. Math. Biol., 37 (1975), pp. 589–636.

[50] D. M. HOLLOWAY AND L. G. HARRISON, *Algal morphogenesis: modelling interspecific variation in* Micrasteras *with reaction-diffusion patterned catalysis of cell surface growth*, Phil. Trans. R. Soc. Lond. B, 354 (1999), pp. 417–433.

[51] A. HUNDING AND R. ENGELHARDT, *Early biological morphogenesis and nonlinear dynamics*, J. theor. Biol., 173 (1995), pp. 401–413.

[52] A. HUNDING AND P. G. SØRENSEN, *Size adaptation in Turing prepatterns*, J. Math. Biol., 26 (1988), pp. 27–39.

[53] D. IRON AND M. J. WARD, *The dynamics of boundary spikes for a nonlocal reaction-diffusion model.* submitted, 1999.

[54] D. IRON, M. J. WARD, AND J. WEI, *The stability of spike solutions to the one-dimensional Gierer-Meinhardt model.* to be submitted, 1999.

[55] M. J. JENKINS, *Pattern Formation Through Self-Organisation in Diffusion-Driven Mechanisms*, D. Phil. Thesis, University of Oxford, 1990.

[56] B. R. JOHNSON AND S. K. SCOTT, *New approaches to chemical patterns*, Chem. Soc. Rev., 25 (1996), pp. 265–273.

[57] H.-S. JUNG, P. H. FRANCIS-WEST, R. B. WIDELITZ, T.-X. JIANG, S. TING-BERRETH, C. TICKLE, L. WOLPERT, AND C.-M. CHUONG, *Local inhibitory action of BMPs and their relationships with activators in feather formation: Implications for periodic patterning*, Dev. Biol., 196 (1998), pp. 11–23.

[58] S. A. KAUFFMAN, *Pattern formation in the* Drosophila *embryo*, Phil. Trans. R. Soc. Lond. B, 295 (1981), pp. 567–594.

[59] S. A. KAUFFMAN, R. M. SHYMKO, AND K. TRABERT, *Control of sequential compartment formation in* Drosophila, Science, 199 (1978), pp. 259–270.

[60] J. P. KEENER, *Principles of Applied Mathematics: Transformation and Approximation*, Addison-Wesley, Reading, Massachusetts, 1988.

[61] E. F. KELLER AND L. A. SEGEL, *Initiation of slime mold aggregation viewed as an instability*, J. theor. Biol., 26 (1970), pp. 399–415.

[62] B. S. Kerner and V. V. Osipov, *Autosolitons: A New Approach to the Problem of Self-Organisation and Turbulence*, Kluwer, Dordrecht, 1994.

[63] I. G. Kevrekidis and H. S. Brown, *Predicting pattern formation in coupled reaction-diffusion systems*, Chem. Eng. Sci., 44 (1989), pp. 1893–1901.

[64] S. Kondo and R. Asai, *A reaction-diffusion wave on the skin of the marine angelfish* Pomacanthus, Nature, 376 (1995), pp. 765–768.

[65] P. M. Kulesa, G. C. Cruywagen, S. R. Lubkin, P. K. Maini, J. Sneyd, M. W. J. Ferguson, and J. D. Murray, *On a model mechanism for the spatial pattering of teeth primordia in the alligator*, J. theor. Biol., 180 (1996), pp. 287–296.

[66] T. C. Lacalli, *Dissipative structures and morphogenetic pattern in unicellular algae*, Phil. Trans. R. Soc. Lond. B, 294 (1981), pp. 547–588.

[67] T. C. Lacalli, D. A. Wilkinson, and L. G. Harrison, *Theoretical aspects of stripe formation in relation to* Drosophila *segmentation*, Development, 103 (1988), pp. 105–113.

[68] D. C. Lane, J. D. Murray, and V. S. Manoranjan, *Analysis of wave phenomena in a morphogenetic mechanochemical model and an application to post-fertilisation waves on eggs*, IMA J. Math. Appl. Med. and Biol., 4 (1987), pp. 309–331.

[69] K. J. Lee, W. D. McCormick, Q. Ouyang, and H. L. Swinney, *Pattern-formation by interacting chemical fronts*, Science, 261 (1993), pp. 192–194.

[70] K. J. Lee, W. D. McCormick, J. E. Pearson, and H. L. Swinney, *Experimental observation of self-replicating spots in a reaction-diffusion system*, Nature, 369 (1994), pp. 215–218.

[71] K. J. Lee and H. L. Swinney, *Lamellar structures and self-replicating spots in a reaction-diffusion system*, Phys. Rev. E, 51 (1995), pp. 1899–1915.

[72] ——, *Replicating spots in reaction-diffusion systems*, Int. J. Bifurcation and Chaos, 7 (1997), pp. 1149–1158.

[73] S. A. Levin and L. A. Segel, *Hypothesis for origin of planktonic patchiness*, Nature, 259 (1976), p. 659.

[74] M. J. Lyons and L. G. Harrison, *A class of reaction-diffusion mechanisms which preferentially select striped patterns*, Chem. Phys. Lett, 183 (1991), pp. 158–164.

[75] ——, *Stripe selection: An intrinsic property of some pattern-forming models with nonlinear dynamics*, Dev. Dynam., 195 (1992), pp. 201–215.

[76] A. Madsvamuse, *Numerical Solution of Reaction-Diffusion Systems on Growing Domains*, P.R.S. Dissertation, University of Oxford, 1999.

[77] P. K. Maini, D. L. Benson, and J. A. Sherratt, *Pattern formation in reaction-diffusion models with spatially inhomogeneous diffusion coefficients*, IMA J. Math. Appl. Med. and Biol., 9 (1992), pp. 197–213.

[78] P. K. Maini and M. R. Myerscough, *Boundary-driven instability*, Appl. Math. Lett., 10 (1997), pp. 1–4.

[79] P. K. Maini and M. Solursh, *Cellular mechanisms of pattern formation in the developing limb*, Int. Rev. Cytol., 129 (1991), pp. 91–133.

[80] L. Matthews and J. Brindley, *Patchiness in plankton populations*, Dynam. Stabil. Syst., 12 (1997), pp. 39–59.

[81] A. May, P. A. Firby, and A. P. Bassom, *Diffusion driven instability in an inhomogeneous circular domain*, Mathl. Comput. Modelling, 29 (1999), pp. 53–66.

[82] H. Meinhardt, *Models of Biological Pattern Formation*, Academic Press, London, 1982.

[83] M. Mimura and J. D. Murray, *On a diffusive prey-predator model which exhibits patchiness*, J. theor. Biol., (1978).

[84] J. Monod, *Recherches sur la Croissance des Cultures Bacteriennes*, Herman, Paris, 1942.

[85] K. W. Morton and D. F. Mayers, *Numerical Solution of Partial Differential Equations*, Cambridge University Press, 1994.

[86] C. B. Muratov and V. V. Osipov, *Spike autosolitons in the Gray-Scott model*. submitted, October 1998.

[87] J. D. Murray, *Parameter space for Turing instability in reaction diffusion mechanisms: A comparison of models*, J. theor. Biol., 98 (1982), pp. 143–163.

[88] ——, *Mathematical Biology*, Springer-Verlag, Berlin, 2nd ed., 1993.

[89] B. N. Nagorcka, V. S. Manoranjan, and J. D. Murray, *Complex spatial patterns from tissue interactions—an illustrative model*, J. theor. Biol., 128 (1987), pp. 359–374.

[90] B. N. Nagorcka and J. R. Mooney, *The role of a reaction-diffusion system in the initiation of primary hair follicles*, J. theor. Biol., 114 (1985), pp. 243–272.

[91] B. N. Nagorka, *A pattern formation mechanism to control spatial organization in the embryo of* Drosophila melanogaster, J. theor. Biol., 132 (1988), pp. 277–306.

[92] W.-M. Ni, *Diffusion, cross-diffusion, and their spike-layer steady states*, Notices of the AMS, 45 (1998), pp. 9–18.

[93] G. Nicolis, *Introduction to Nonlinear Science*, Cambridge University Press, 1995.

[94] G. Nicolis and I. Prigogine, *Self-Organization in Nonequilibrium Systems*, Wiley-Interscience, New York, 1977.

[95] Y. Nishiura and D. Ueyama, *A skeleton structure of self-replicating dynamics*, Physica D, 130 (1999), pp. 73–104.

[96] A. Okubo, *Diffusion and Ecological Problems: Mathematical Models*, Springer-Verlag, Berlin, 1980.

[97] V. V. Osipov and A. V. Severtsev, *Theory of self-replication and granulation of spike autosolitons*, Phys. Lett. A, 222 (1996), pp. 400–404.

[98] G. F. Oster, *Lateral inhibition models of developmental processes*, Math. Biosci., 90 (1988), pp. 265–286.

[99] G. F. Oster and J. D. Murray, *Pattern formation models and developmental constraints*, J. exp. Zool., 251 (1989), pp. 186–202.

[100] H. G. Othmer and E. Pate, *Scale-invariance in reaction-diffusion models of spatial pattern formation*, Proc. Natl. Acad. Sci. USA, 77 (1980), pp. 4180–4184.

[101] H. G. Othmer and L. E. Scriven, *Interactions of reaction and diffusion in open systems*, I & EC Fundamentals, 8 (1969), pp. 302–313.

[102] H. G. Othmer and A. Stevens, *Aggregation, blowup, and collapse: The ABC's of taxis in reinforced random walks*, SIAM J. Appl. Math., 57 (1997), pp. 1044–1081.

[103] Q. Ouyang and H. L. Swinney, *Transition from a uniform state to hexagonal and striped Turing patterns*, Nature, 352 (1991), pp. 610–612.

[104] M. R. Owen and J. A. Sherratt, *Mathematical modelling of juxtacrine cell signalling*, Math. Biosci., 153 (1998), pp. 125–150.

[105] M. R. Owen, J. A. Sherratt, and H. J. Wearing, *Lateral inhibition by juxtacrine signaling is a new mechanism for pattern formation*, Dev. Biol., 217 (2000), pp. 54–61.

[106] K. J. Painter, *Chemotaxis as a Mechanism for Morphogenesis*, D. Phil. Thesis, University of Oxford, 1998.

[107] K. J. Painter, P. K. Maini, and H. G. Othmer, *Stripe formation in juvenile* Pomacanthus *explained by a generalised Turing mechanism with chemotaxis*, Proc. Natl. Acad. Sci. USA, 96 (1999), pp. 5549–5554.

[108] D. W. Peaceman and H. H. J. Rachford, *The numerical solution of parabolic and elliptic differential equations*, J. Soc. Indust. Appl. Math., 3 (1955), p. 28.

[109] J. E. Pearson, *Complex patterns in a simple system*, Science, 261 (1993), pp. 189–192.

[110] J. E. Pearson and W. Horsthemke, *Turing instabilities with nearly equal diffusion coefficients*, J. Chem. Phys., 90 (1989), pp. 1588–1599.

[111] A. J. Perumpanani, *Phase Differences in Morphogenesis*, P.R.S. Dissertation, University of Oxford, 1993.

[112] V. Petrov, S. K. Scott, and K. Showalter, *Excitability, wave reflection, and wave splitting in a cubic autocatalysis reaction-diffusion system*, Phil. Trans. R. Soc. Lond., A 347 (1994), pp. 631–642.

[113] W. H. Press, S. A. Teukolsky, W. T. Vetterling, and B. P. Flannery, *Numerical Recipies in FORTRAN*, Cambridge University Press, 2nd ed., 1994.

[114] K. E. Rasmussen, W. Mazin, and E. Mosekilde, *Wave-splitting in the bistable Gray-Scott model*, Int. J. Bifurcation and Chaos, 6 (1996), pp. 1077–1092.

[115] W. N. Reynolds, J. E. Pearson, and S. Ponce-Dawson, *Dynamics of self-replicating patterns in reaction diffusion systems*, Phys. Rev. Lett., 72 (1994), pp. 2797–2800.

[116] W. N. Reynolds, S. Ponce-Dawson, and J. E. Pearson, *Self-replicating spots in reaction-diffusion systems*, Phys. Rev. E, 56 (1997), pp. 185–198.

[117] J. Rinzel and J. B. Keller, *Travelling wave solutions of a nerve conduction equation*, Biophys. J., 13 (1973), pp. 1313–1337.

[118] P. T. Saunders and M. W. Ho, *Reliable segmentation by successive bifurcation*, Bull. Math. Biol., 57 (1995), pp. 539–556.

[119] J. Schnakenberg, *Simple chemical reaction systems with limit cycle behaviour*, J. theor. Biol., 81 (1979), pp. 389–400.

[120] L. A. Segel, *A theoretical study of receptor mechanisms in bacterial chemotaxis*, SIAM J. Appl. Math., 32 (1977), pp. 653–665.

[121] L. A. Segel and J. L. Jackson, *Dissipative structure: An explanation and an ecological example*, J. theor. Biol., 37 (1972), pp. 545–559.

[122] E. E. Sel'kov, *Self-oscillations in glycolysis: 1. A simple kinetic model*, Eur. J. Biochem., 4 (1968), pp. 79–86.

[123] H. L. Smith and P. Waltman, *The Theory of the Chemostat: Dynamics of Microbial Competition*, Cambridge University Press, 1995.

[124] J. Smoller and A. Wasserman, *Global bifurcation of steady-state solutions*, J. Differ. Equations, 39 (1981), pp. 269–290.

[125] D. W. Thompson, *On Growth and Form (Abridged—John Tyler Bonner)*, Cambridge University Press, 1961.

[126] A. M. Turing, *The chemical basis of morphogenesis*, Phil. Trans. R. Soc. Lond. B, 237 (1952), pp. 37–72.

[127] C. Varea, J. L. Aragón, and R. A. Barrio, *Confined Turing patterns in growing systems*, Phys. Rev. E, 56 (1997), pp. 1250–1253.

[128] ———, *Turing patterns on a sphere*, Phys. Rev. E, 60 (1999), pp. 4588–4592.

[129] R. V. Vincent and N. A. Hill, *Bioconvection in a suspension of phototactic algae*, J. Fluid Mech., 327 (1996), pp. 343–371.

[130] D. Walgraef, *Spatio-Temporal Pattern Formation*, Springer-Verlag, New York, 1997.

[131] K. A. J. White and C. A. Gilligan, *Spatial heterogeneity in three-species, plant-parasite-hyperparasite, systems*, Phil. Trans. R. Soc. Lond. B, 353 (1998), pp. 543–557.

[132] G. S. Wolkowicz and Z. Lu, *Global dynamics of a mathematical model for competition in the chemostat: General response functions and differential death rates*, SIAM J. Appl. Math., 52 (1992), pp. 222–233.

[133] D. J. Wollkind, V. S. Manoranjan, and L. Zhang, *Weakly nonlinear stability analyses of prototype reaction-diffusion model equations*, SIAM Review, 36 (1994), pp. 176–214.

[134] L. WOLPERT, *Positional information and the spatial pattern of cellular differentiation*, J. theor. Biol, 25 (1969), pp. 1–47.

[135] ———, *Positional information and pattern-formation in development*, Dev. Genet., 15 (1994), pp. 485–490.