Modelling Biological Pattern Formation: The Role of Domain Growth

One of the central puzzles in developmental biology concerns the formation of spatio-temporal patterns during early embryogenesis. Although genes ultimately determine spatial structure and form, the study of genetics alone may not be sufficient to reveal the mechanisms which regulate production of patterns. These must arise due to interaction of underlying physical and chemical processes and, as such, are open to investigation via mathematical modelling. Here, we review some of the most common mathematical models for biological pattern formation and present some recent results from studies that include domain growth.

1 Introduction

The revolution in molecular genetics has led to unprecedented advances in understanding development, leading to the unravelling of mechanisms by which differentiated structures emerge from the interaction of genes and their products. A major question, despite the identification of the genes involved, is to account for spatial organisation, illustrated by the adaptive and regulatory properties of developing organisms. To understand how morphology is determined and regulated it is necessary to postulate mechanisms that may plausibly coordinate the spatio-temporal emergence of structure. In this review we consider various models, based on simple physical principles, which can generate spatial pattern from initial homogeneity, and that have been proposed for biological pattern formation. In particular we will comment on the role of growth of the underlying domain on the pattern formation process.

Comments on Theoretical Biology
2001, Vol. 6, No. 3, pp. 229-249

2 Models for Biological Pattern Formation

In the biological context a *pattern* refers to any instance of a heterogeneous distribution of gene product, differentiated tissue, cell population or spatial distribution of an organism. A multitude of different morphologies in many different areas of biology have been the subject of mathematical modelling. Several biological systems have attained status of paradigm in theoretical work in this field, including the segmentation of the insect embryo [23, 57], limb development [33, 12], the formation of animal coat markings [41, 39, 36], butterfly wing patterns [39, 61, 60] and the arrangement of hair follicles and feather primordia in skin [43, 42]. Certain unicellular organisms have also been studied experimentally and theoretically in the context of pattern formation, for example the generation of whorls in the marine alga *Acetabularia* [17] and the branched and star-shaped morphologies of *Micrasterias* [28, 19, 20]. For these species, where each organism has only one nucleus, it is most apparent that structure must develop through spatially distributed physical processes occurring within the cell. At the other end of the scale, patterns in population density (often called 'patchiness') are studied in ecological settings [59, 38, 46, 34].

These examples raise an important theoretical consideration. For the patterning of animal skins some degree of variability is often displayed between members of the same species and even between closely (genetically) related animals. However, the mechanisms regulating segmentation and limb development, for example, must be able to reliably generate the same number of pattern elements despite normal biological variation, for example in the size or geometry of the region in which the pattern develops. Models whose purpose it is to describe the mechanisms of spatial organisation in a particular biological system must be able to account for whichever of these alternative features is observed.

Two general categories for models of pattern formation have been described, namely cell motility and chemical prepattern models. Cell movement models consider the aggregation of cell populations subject to chemical signals or mechanical forces, where it is supposed that cell differentiation occurs in response to increased cell density (see the book by Murray [39] and references therein). The aggregation of cells may occur in response to a gradient in the distribution of a chemical signal (chemotaxis, [31], see figure 1) or due to mechanical cues: for example the advective forces exerted by motile

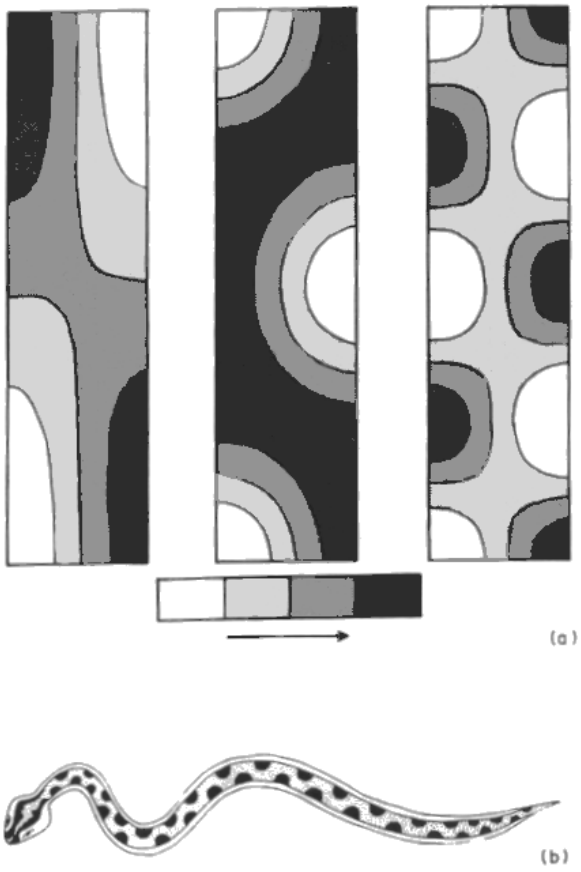


Figure 1: (a) Numerical solutions for a cell-chemotactic model showing the final steady state solution for cell density for three different parameter sets. (b) The regular spot pattern on the leopard snake *Bitis atropos atropos*. Reproduced from [41] with permission.

cells on a substratum or via cellular motion up a gradient in adhesivity of the extracellular material (haptotaxis, [48, 39]).

In this review we will be primarily concerned with models of the chemical prepattern type. Here it is argued that a pattern is first established in the concentration of certain chemicals (termed *morphogens*), and subsequent cellular differentiation into different tissue types occurs according to whether or not the local concentration exceeds some threshold. It is implicitly assumed that the chemical pattern is established on a faster timescale than the response of the cellular machinery, so that the formation and interpretation of the pattern decouple.

The idea of threshold-mediated response to morphogen concentration gradients is developed in Wolpert's notion of positional information [65, 66]. Much of this work considers cellular response to (possibly multiple) simple gradients. Crick [8] established that gradients could form on realistic timescales over distances of a millimetre or less under the mechanism of passive or facilitated diffusion of morphogen from a localised source.

Theoretical approaches may also be divided into discrete (cellular) and continuum descriptions. Diffusive coupling between cells is by no means the only mechanism of cellular communication found in biology. Much is known at the molecular level about intercellular signalling. Cells can demonstrate active regulation of signals and passage of substances, which are ignored in diffusion-based models. In some instances, known as juxtacrine signalling, signalling molecules are held in the cell membrane and bind to receptors on adjacent cells only. Lateral inhibition, for which ligand binding down-regulates ligand and receptor expression, generates fine-grained patterns where the wavelength is typically around two cell diameters (on a one-dimensional array of cells high and low expression levels of the ligand are found on alternate cells) (see figure 2). This mechanism is observed in the *Delta-Notch* signalling pathway [6], and typically selects a subset of cells from an initially equivalent field which adopt a different cell fate.

A recent model due to Owen *et al.* [51, 52] considers lateral induction, where signalling results in up-regulation of ligand and receptor expression (positive feedback), and its analysis has demonstrated that longer wavelength patterns may be generated in a mechanism with only nearest-neighbour cell communication. In two dimensions spot and stripe patterns may be generated by this model.

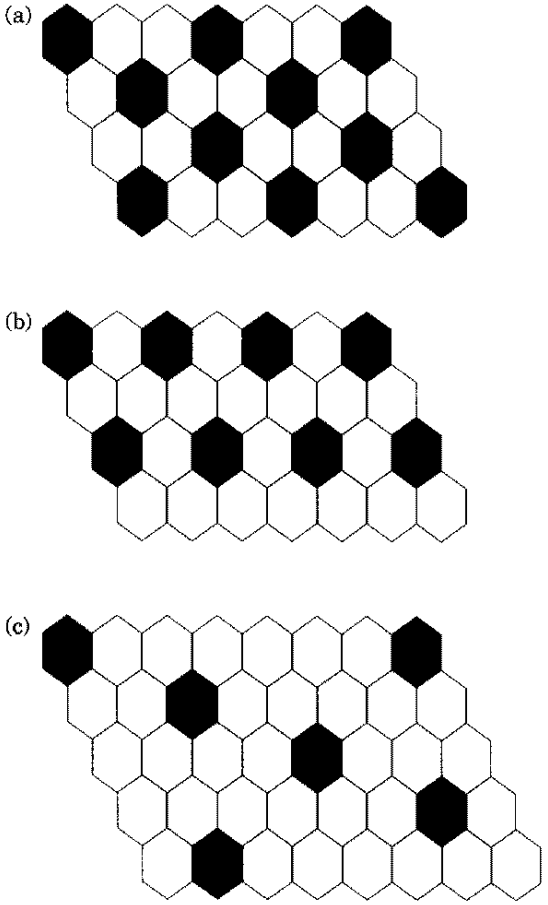


Figure 2: Examples of periodic steady-state patterns of cells in the *Delta-Notch* model of [6]. Black denotes cells that adopt primary fate (low *Notch* activity), white denotes cells which adopt secondary fate (high *Notch* activity). With permission.

3 Reaction-Diffusion Theory

In 1952, Turing [62] proposed that pattern formation during morphogenesis might arise through an instability in systems of reacting chemicals, driven by diffusion. The resulting chemical prepatterns would be subsequently interpreted as positional information by competent cells, with cell fates determined via prepattern-dependent differentiation. A set of two or more chemicals is required to interact in a well defined manner in order that heterogeneous patterns may arise in their concentrations. Significantly, for the spatially homogeneous state to be stable in the absence of diffusion yet unstable to spatial perturbations of particular wavelengths (diffusion-driven instability) a disparity is required between the diffusivities of the chemicals. The pattern forming interaction between two such chemicals has been described in terms of short range auto-catalytic activation and long range (lateral) inhibition [16]. The model equations for two such interacting chemicals, $u(x,t)$ and $v(x,t)$, are given by

$$\frac{\partial u}{\partial t} = D_u \nabla^2 u + f(u,v) \tag{1}$$

$$\frac{\partial v}{\partial t} = D_v \nabla^2 v + g(u,v) \tag{2}$$

where the kinetic functions f and g describe the nonlinear reaction between the chemicals. Linear stability analysis [39] of the homogeneous steady state of the equations (u^*, v^*), where $f(u^*, v^*) = g(u^*, v^*) = 0$, shows that the inhibitory chemical must have larger diffusivity than the self-activating one. The problem is completed by specifying initial data and boundary conditions on the solution domain.

This mechanism for spatial and spatio-temporal pattern formation is of great theoretical interest as it represents a spontaneous spatial symmetry-breaking phenomenon in a simple physical system. Any thermodynamically closed system, where there is no transfer of matter or heat into or out of the system, must evolve towards thermodynamic equilibrium. Pattern formation in such systems can be only transient. However, Nicolis and Prigogine [44] showed that if nonequilibrium (or far-from-equilibrium) thermodynamic conditions are maintained in an open reactor, e.g. by providing a constant supply of reactant, then heterogeneous patterns may be

sustained. In the mechanism described by Turing these patterns have an intrinsic wavelength which does not depend on the physical size of the reactor (unlike the bouyancy-driven instability in the Rayleigh-Bénard system or the Taylor-Couette flow instability for a rotating fluid [9]), and Turing patterns tend to demonstrate periodicity. Turing's theory has found application in fields far removed from developmental biology—see for example the book by Walgraef [64].

Turing's ideas have been applied to a wide variety of pattern formation problems in biology. The model can exhibit a wide range of steady-state spatial patterns depending on the parameter values, domain size and geometry, and the form of the nonlinearities in the kinetics f and g (for example, quadratic nonlinearities favour the selection of spots over stripes, which are the dominant pattern for the case of cubic nonlinearity [15]). It has been used to account for many of the paradigm model examples mentioned in the Introduction. The model also exhibits propagating spatial patterns initiated by a localised perturbation. Such patterns arise in reptilian coat markings and can also be reproduced by the chemotactic mechanism [40].

However, the theory has received important criticism on several fronts. Firstly, although many molecules have been identified which appear to act as diffusive signals, some of which may act as morphogens in the Wolpertian sense, no set of chemicals has been demonstrated conclusively to operate in the manner that Turing described in a biological system. In fact, it is only relatively recently that Turing patterns have been realised under controlled conditions in artificial chemical systems (discussed in the following section).

We have already hinted at a second major difficulty for Turing's theory of pattern formation in biology. In many situations the number of pattern elements (for example the number of wavelengths generated in one dimension) is critical. Turing patterns have been shown to display strong sensitivity to the size and geometry of the solution domain. This criticism, which has come to be known as the *robustness* problem, was first brought to light concerning the segmentation of *Drosophila*. Kauffman [24] suggested that periodic gene expression patterns observed during the early development of insects could be explained by a reaction-diffusion model, which appeared to give qualitatively similar patterns on spatial domains of regular and symmetric geometry. Subsequent work [3] showed that patterns which do not resemble those occurring naturally are obtained for minor perturbations of the size

and shape of the domain. In fact it was later discovered that the segmentation of the *Drosophila* embryo is achieved in a rather different manner, in that each individual element of the apparently periodic pattern is separately controlled and regulated, and the pattern is generated in a cascade of gene switching [1].

The root of this problem is in the fact that for domains of anything but very small aspect ratio (the ratio of domain size to intrinsic pattern wavelength) there are many different patterns which may be admitted as solutions, the number increasing as the domain size is increased, and the selection between these different patterns depends sensitively on initial data and domain geometry. Bard and Lauder [2] drew the same conclusion, finding in a series of numerical experiments that patterns in discrete cellular simulations are sensitive to the number of cells, concluding that only unpredictable *mosaic* patterns are possible. More recently Saunders and Ho [57] have considered segmentation of growing systems, concluding once again that reaction-diffusion does not constitute a reliable pattern generation mechanism. Dillon *et al.* [12] have shown that the multiplicity of solutions may be reduced by varying the boundary conditions. Recently we have suggested that the consideration of domain growth during pattern formation may have important consequences for the robustness issue [7].

An alternative way of viewing the robustness problem is to argue that the simple reaction-diffusion mechanism fails to demonstrate the regulatory properties that we described earlier. While for given initial conditions it may be possible to select the desired pattern by judicious choice of domain size, in general, biological systems are subject to natural variation in such parameters and reliable pattern generation requires a certain degree of scale invariance. To achieve this regulatory property, various modifications to the theory have been proposed, requiring some form of feedback from the domain size to the parameters in the function describing the reaction rates [49, 21]. Gierer and Meinhardt have shown that patterns may be orientated by a gradient in parameters appearing in the kinetic functions (which they call source density), exploited in a model for the regenerative properties of Hydra [16, 35]. Before turning to consider domain growth we discuss the realisation of chemical patterns in laboratory experiments.

4 Chemical Pattern Formation

Travelling waves in chemical systems have been known for some time in the Belousov-Zhabotinsky reaction, however, reactions demonstrating the stationary patterns predicted by Turing have only been discovered within the last decade. General reviews of spatio-temporal phenomena in chemistry can be found in Epstein and Showalter [14] and Johnson and Scott [22] and, for spatial patterns, Maini *et al.* [32].

The experimental realisation of Turing patterns was precipitated by the development of gel reactors where reactants undergo diffusive transport through an aqueous gel, which serves to suppress any convective motion. First introduced by De Kepper and Boissonade in Bordeaux, the Gel Strip reactor has two reservoirs containing chemically inert sets of reactants which are allowed to diffuse into a thin rectangular ribbon of gel from opposite sides. In the middle of the ribbon both sets of chemicals are present and may react. The concentrations in the two reservoirs can be held constant to maintain nonequilibrium conditions. The first unambiguous experimental observation of Turing patterns was reported by this group in the Chlorine-Iodide-Malonic-Acid (CIMA) reaction [4, 11], see figure 3. Here the gel was loaded with starch primarily to aid visualisation. Starch, a large molecule with low mobility in the gel matrix, forms a complex with iodide, one of the reacting species, effectively reducing its diffusion coefficient to provide the necessary conditions for Turing patterns to form. Subsequent observations were reported by Ouyang and Swinney [50] using a variation on the design, the Gel Disk reactor, where patterns form in the plane perpendicular to the concentration gradients so that larger patterned domains can be observed. A vast amount of theoretical work has been done to develop analytical models of these complicated reactions, the aim being to reproduce the phenomena and to calculate phase and bifurcation diagrams describing the chemical systems.

Stationary patterns have also been recorded in the Ferrocyanide-Iodide-Sulfite (FIS) reaction when initiated with sufficiently large perturbation away from equilibrium. Here pattern formation is achieved by propagating chemical (redox) fronts which halt when they approach each other. In this case labyrinthine patterns [29] have been observed as well as self-replicating phenomena [30], where a localised spot grows, divides and separates, repeating to fill domain. Other phenomena include breathing spot patterns, where

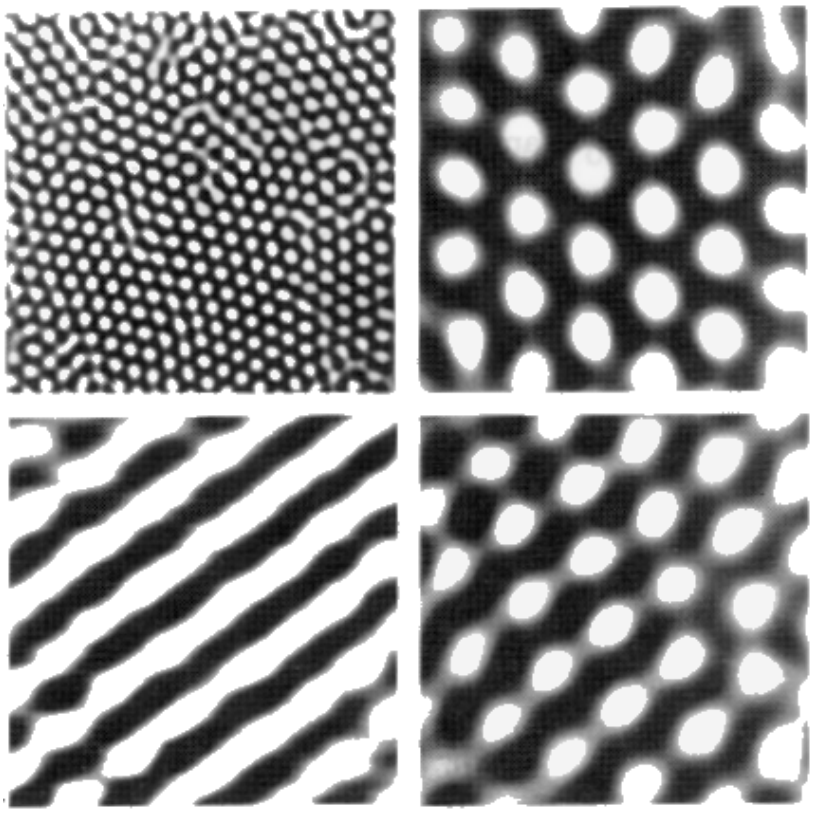


Figure 3: Different types of Turing patterns in the CIMA reaction (see [50] for full details). With permission.

the spot radius oscillates [18]. Recently, similar structures have also been reported in the CIMA reaction [10].

5 Domain Growth

During development, pattern formation in the embryo is often accompanied by growth and movement of tissue, motivating consideration of domain growth in models of developmental patterning. What may not be immediately clear is whether underlying growth, which is expected to take place

over much longer timescales than the generation of pattern via reaction and diffusion, can be considered to decouple from the pattern formation mechanism, as are other cellular processes. Furthermore, the incorporation of domain growth may influence pattern selection; how the final pattern obtained will depend on the manner in which the domain grows [9].

We now review several examples where growth is thought to play an important role in the pattern formation process, investigating the basic properties of reaction-diffusion models under two types of underlying domain growth.

5.1 Apical Growth

In many developmental systems tissue growth is restricted to a region towards a tip or boundary region (rather, growth in this region is much greater than elsewhere). Patterning takes place behind the advancing tip. Examples of such apical growth include the vertebrate limb bud, where rapid cell proliferation is maintained in the progress zone, a region of undifferentiated mesenchyme beneath a bounding ridge (the apical ectodermal ridge) at the tip of the limb bud. The progress zone is thought to be maintained by signals produced in specialized regions of the tissue (from the apical ectodermal ridge and the zone of polarizing activity, a region at the posterior margin of the limb bud), and the rapid proliferation remains localised close to the border of the limb bud during outgrowth. Similarly, in plants growth typically occurs at the apex of an outgrowing shoot (at the shoot apical meristem), from which organs such as leaves and flower buds originate.

For a proliferating region that retains a constant cell population the rate of outgrowth will be determined by the proliferation rate and the cell population size. In one dimension this results in linear outgrowth of the apical region, and can be modelled as a moving boundary phenomenon. Thus for the reaction-diffusion mechanism, described above, equations (1)-(2) are defined on the spatial domain

$$x \in [0, \ell + rt] \tag{3}$$

where ℓ is the initial length and r is the product of the proliferation rate and the spatial extent of the proliferating region. Boundary conditions, for example no-flux conditions, are prescribed at $x = 0, \ell + rt$. We may

transform to a stationary spatial domain, $\xi = x/(\ell + rt) \in [0,1]$, giving for $u(\xi,t)$ and $v(\xi,t)$

$$\frac{\partial u}{\partial t} = \frac{D_u}{(\ell+rt)^2}\frac{\partial^2 u}{\partial \xi^2} + \frac{r\xi}{(\ell+rt)}\frac{\partial u}{\partial \xi} + f(u,v) \tag{4}$$

$$\frac{\partial v}{\partial t} = \frac{D_v}{(\ell+rt)^2}\frac{\partial^2 v}{\partial \xi^2} + \frac{r\xi}{(\ell+rt)}\frac{\partial v}{\partial \xi} + g(u,v). \tag{5}$$

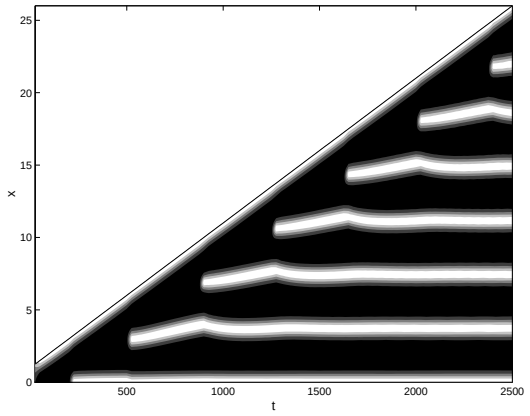
Under the assumption that domain growth is slow in comparison to the diffusion and rate of reaction of the chemicals, the domain growth rate parameter r is small. Solution behaviour under these conditions is shown in figure 4. The reaction schemes have been chosen to illustrate both the generic behaviours observed for two-component reaction-diffusion systems, splitting and insertion of new peaks in the activator solution, depending on the nonlinearities of the kinetic functions.

Meinhardt [37] has considered a similar model in two spatial dimensions for the generation of the arrangements of leaves found on plant stems (phyllotaxis). In computer simulations the growing plant stem is idealised as a cylindrical domain with the addition of cells parallel to the axis of the cylinder. Various of the commonly observed morphologies for leaf primordia may be generated by varying the diffusion constants and the growth rate r. A similar model has also been developed for the pigmentation patterns of some sea shells, which also grow from a narrow region near the leading edge of the shell [36].

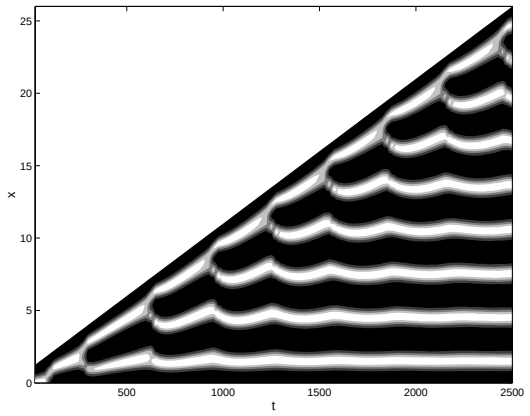
5.2 Domain Expansion

In general, all cells within a tissue may undergo proliferation producing deformation and expansion of the tissue. Domain expansion has previously been considered in reaction-diffusion models for the branching morphology of growing *Micrasterias* [28] and for the emergence of tooth primordia in the alligator [27]. Here experimental evidence suggests that the spatial positioning and order of appearance of tooth primordia is determined in part by tissue growth throughout the jaw. Recently it has been suggested that reaction-diffusion prepatterns may be important in the growth and development of growing solid tumours [5].

New impetus was recently provided by Kondo and Asai [26], who sug-



(a)



(b)

Figure 4: Patterns in the activator chemical obtained under apical growth for (a) (rescaled) Gierer-Meinhardt kinetics [16] where $f(u,v) = v^2 - u$ and $g(u,v) = v^2/u - 0.5v + 0.1$ showing insertion of new activator peaks and (b) Schnakenberg kinetics [58] where $f(u,v) = 0.9 - uv^2$ and $g(u,v) = 0.1 + uv^2 - v$ showing splitting of activator peaks. In both cases $D_u = 1.0$, $D_v = 0.025$, $\ell = 1.0$ and $r = 0.01$. Numerical solutions are computed using NAG library routine D03PCF. Grayscale is from low (black) to high (white) concentration.

gested that a reaction-diffusion mechanism could be responsible for the dynamic changes in pigmentation patterns of the marine angelfish *Pomacanthus*. Unlike mammalian coat markings, the pattern in the skin of these fish changes dynamically during growth of the animal, rather than simply enlarging in proportion to the body size. Juvenile *P. imperator* display concentric stripes and *P. semicirculatus* have a regular array of vertical stripes which increase in number during growth. Juvenile *P. semicirculatus* of less than 2cm in length display three vertical stripes which separate until the length of the fish is approximately 4cm, at which point new stripes appear between the original ones. Similarly at around 8-9cm in length new stripes again appear between the existing ones. In this manner the pattern changes by insertion of new stripes as the animal roughly doubles in length, to preserve the wavelength of the pattern. In *P. imperator* this behaviour is maintained in the adult fish, where horizontal stripes maintain an average spacing. This dynamic regulation of the pattern is quite unlike the static pattern selection previously discussed.

A simple model of such a tissue supposes that uniform tissue density is maintained, so that the expansion of the tissue may be described kinematically, with cell proliferation considered as a distributed source of volume. The equations for reaction and diffusion on such a domain are given by [7]

$$\frac{\partial u}{\partial t} + \nabla \cdot (\underline{a} u) = D_u \nabla^2 u + f(u,v) \tag{6}$$

$$\frac{\partial v}{\partial t} + \nabla \cdot (\underline{a} v) = D_v \nabla^2 v + g(u,v) \tag{7}$$

where $\underline{a}(\underline{x},t)$ is the velocity field generated by the distributed source term $S(\underline{x},t)$ such that

$$\nabla \cdot \underline{a} = S(\underline{x},t). \tag{8}$$

If all cells have the same rate of proliferation then $S(\underline{x},t) = r$ is constant over the domain, and in one spatial dimension the domain length is given by $L(t) = \ell e^{rt}$. Transforming to a fixed interval, $\xi = xe^{-rt} \in [0,\ell]$ we recover, for $u(\xi,t)$ and $v(\xi,t)$,

$$\frac{\partial u}{\partial t} = D_u e^{-2rt} \frac{\partial^2 u}{\partial \xi^2} + f(u,v) - ru \tag{9}$$

$$\frac{\partial v}{\partial t} = D_v e^{-2rt} \frac{\partial^2 v}{\partial \xi^2} + g(u,v) - rv \tag{10}$$

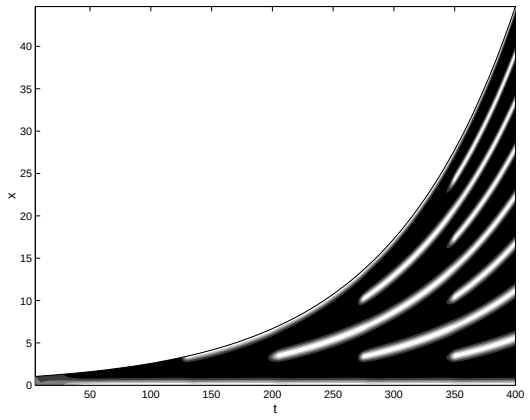
Again, we assume that $r \ll 1$, the slow domain growth limit. The two generic solution behaviours, splitting and insertion of new peaks in the activator solution, are illustrated in figure 5.

6 Discussion and Outlook

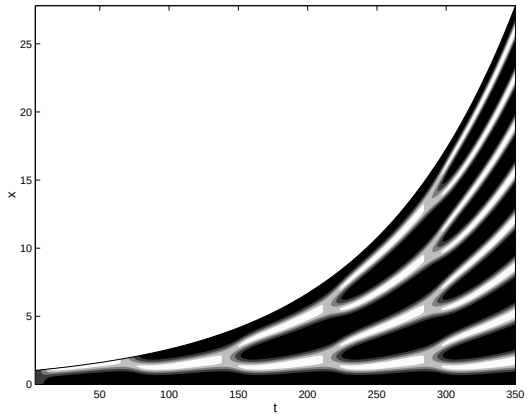
The insertion of new peaks shown in figure 5(a) was compared by Kondo and Asai [26] to the regular insertion of stripes on the growing angelfish. Subsequent work [63, 53] has shown that stripe-forming equations on two-dimensional domains may exhibit similar behaviour. We have found that domain growth can stabilise parallel stripes, as well as giving rise to stripe splitting or insertion, and Painter *et al.* [53] have demonstrated that a population of cells responding chemotactically to the dynamic chemical prepattern can lead to the insertion of initially narrow stripes in the cell population, which broaden with age, as observed on the fish. While this is seemingly good circumstantial evidence that a mechanism such as reaction-diffusion is at work in the fish, it is important to note that these experimental observations may also be consistent with any other mechanism which generates patterns with an intrinsic wavelength.

Many more patterning phenomena have been observed in the growing fish, including the formation and movement of Y-shaped branching points where one stripe divides into two. A wider range of behaviours, such as these, are possible in the reaction-diffusion model in two spatial dimensions, and with nonuniform domain growth, although the full range of possibilities for pattern formation under nonuniform domain growth remains to be determined.

One important feature of growth and form that we have overlooked is curvature of the domain. The bowing and folding of sheets of tissue are as important in developmental systems as their migration and expansion. Translation without changing geometry (curvature or size) has no influence on the reaction-diffusion mechanism within a tissue, however, curved surfaces and in particular curvature changing with growth may be an important factor in pattern formation. To our knowledge there is, at present, little work discussing the interaction of curvature and domain growth in pattern for-



(a)



(b)

Figure 5: Patterns in the activator chemical obtained on the expanding domain for (a) Gierer-Meinhardt kinetics, showing regular insertion of new activator peaks, and (b) Schnakenberg kinetics, showing peak splitting. Kinetic functions and parameters as for figure 4. For domain expansion the patterns change regularly through frequency or mode doubling behaviour. Grayscale is from low (black) to high (white) concentration.

mation. One notable exception is the paper by Chaplain *et al.* [5] in which the results of a simulation of reaction-diffusion on the surface of a radially growing sphere are reported, however, there are not sufficient data presented to ascertain whether or not similar phenomena are observed in their system. This warrants further investigation.

Thus far we have considered models for growing tissue, however, it has been suggested that a similar model may represent tissue in which a region that is competent to form pattern enlarges with time, for example in response to the passage of a wave of maturation. In this *simulated growth* model the changes in pattern are similar to the moving boundary problem described for apical growth, and such a model has been proposed for the periodic patterning of feather primordia in chick [25]. A further possibility is that the local rate of domain growth (cell proliferation) is determined by chemical signals, and may be controlled by the morphogens themselves. Such *reactant-controlled* growth has been proposed for the outgrowth of the limb bud, where the progress zone is maintained by the morphogens [13].

There are many aspects of pattern formation on growing domains which remain unresolved. Mathematical analyses of the dynamic pattern formation process suggest that the periodic doubling of the number of peaks occurs as a result of a symmetry in the bifurcation structure of the model, however as yet no detailed stability analysis of the model has been attempted. Furthermore, there is a clear link between the behaviour of the equations on the growing domain and spot and wave-splitting phenomena that have been reported and analysed in bistable reaction-diffusion systems (on stationary domains) [54, 55, 56, 45].

It has also been suggested that the regular doubling of the number of peaks on the domain can provide a mechanism for reliable pattern selection [7]. In one dimension the number of peaks in the pattern can be selected by growing the pattern from an initially simple one, and in two spatial dimensions regular periodic patterns can be obtained, and the orientation of striped patterns controlled by the domain growth. Furthermore, between the splitting or insertions, the pattern remains unchanged as the domain size changes, providing a degree of regulatory invariance to the domain size. The set of possible behaviours under domain growth is severely limited. Such results may prove useful when trying to identify which biological pattern formation events might arise as a consequence of the reaction-diffusion

mechanism, and where it may be more prudent to seek alternative explanations.

This last point raises the question as to whether the behaviour we have described is particular to reaction-diffusion systems or is generic to all global pattern generation mechanisms, such as chemotaxis and mechanochemical models. In terms of the phenomenology of patterns generated on fixed domains, such mechanisms are difficult to distinguish, all having a range of destabilising modes which present the same pattern selection issues and similar robustness problems. As is discussed by Oster and Murray [47], the underlying mathematical structure of these biologically distinct models may be very similar indeed, leading to model predictions that are independent of the detailed underlying biology. If such mechanisms are found to differ then the predicted behaviour on the growing domain will provide a useful means to distinguish between them. Whether these other models exhibit qualitatively different behaviour in response to domain growth is the subject of current investigation.

E.J. CRAMPIN* and P.K. MAINI
Centre for Mathematical Biology,
Mathematical Institute,
24–29 St Giles',
Oxford OX1 3LB,
UK
October 24, 2000

References

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

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

[3] 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.

[4] 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.

[5] 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*, J. Math. Biol, (2000). to appear.

*Author to whom correspondence should be addressed: E.J. Crampin. email: crampin@maths.ox.ac.uk

[6] 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.

[7] 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.

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

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

[10] 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.

[11] 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.

[12] 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.

[13] 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.

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

[15] B. Ermentrout, *Stripes or spots? Nonlinear effects in bifurcation of reaction-diffusion equations on the square*, Proc. Roy. Soc. Lond. A, 234 (1991), pp. 413–417.

[16] A. Gierer and H. Meinhardt, *A theory of biological pattern formation*, Kybernetik, 12 (1972), pp. 30–39.

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

[18] 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.

[19] 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.

[20] 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.

[21] A. Hunding and P. G. Sørensen, *Size adaptation in Turing prepatterns*, J. Math. Biol., 26 (1988), pp. 27–39.

[22] B. R. Johnson and S. K. Scott, *New approaches to chemical patterns*, Chem. Soc. Rev., 25 (1996), pp. 265–273.

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

[24] S. A. Kauffman, R. M. Shymko, and K. Trabert, *Control of sequential compartment formation in* Drosophila, Science, 199 (1978), pp. 259–270.

[25] A. J. Koch and H. Meinhardt, *Biological pattern formation: From basic mechanisms to complex structures*, Rev. Mod. Phys., 66 (1994), pp. 1481–1507.

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

[27] 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.

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

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

[30] 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.

[31] P. K. Maini, M. R. Myerscough, K. H. Winters, and J. D. Murray, *Bifurcating spatially heterogeneous solutions in a chemotaxis model for biological pattern generation*, Bull. Math. Biol., 53 (1991), pp. 701–719.

[32] P. K. Maini, K. J. Painter, and H. N. P. Chau, *Spatial pattern formation in chemical and biological systems*, J. Chem. Soc., Faraday Trans., 93 (1997), pp. 3601–3610.

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

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

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

[36] ———, *The Algorithmic Beauty of Sea Shells*, Springer, Heidelberg, 1995.

[37] H. Meinhardt, A.-J. Koch, and G. Bernasconi, *Models of pattern formation applied to plant development*, in Symmetry in Plants, R. V. Jean and D. Barabé, eds., World Scientific, Singapore, 1998, pp. 723–758.

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

[39] J. D. Murray, *Mathematical Biology*, Springer-Verlag, Berlin, 2nd ed., 1993.

[40] J. D. Murray, D. C. Deeming, and M. W. J. Ferguson, *Size-dependent pigmentation-pattern formation in embryos of* alligator mississippiensis*: time to initiation of pattern generation mechanism*, Proc. Roy. Soc. Lond. B, 239 (1990), pp. 279–293.

[41] J. D. Murray and M. R. Myerscough, *Pigmentation pattern formation on snakes*, J. theor. Biol., 149 (1991), pp. 339–360.

[42] 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.

[43] 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.

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

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

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

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

[48] G. F. Oster, J. D. Murray, and A. K. Harris, *Mechanical aspects of mesenchymal morphogenesis*, J. Embryol. Exp. Morph., 78 (1983), pp. 83–125.

[49] 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.

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

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

[52] 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.

[53] 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.

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

[55] 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.

[56] 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.

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

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

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

[60] T. Sekimura, A. Madzvamuse, A. Wathen, and P. Maini, *A model for colour pattern formation in the butterfly wing of* papilio dardanus, Proc. Roy. Soc. Lond. B, 267 (2000), pp. 851–859.

[61] T. Sekimura, P. Maini, J. Nardi, M. Zhu, and J. D. Murray, *Pattern formation in lepidopteran wings*, Comments in Theoretical Biology, 5 (1998), pp. 69–87.

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

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

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

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

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