21. STEADY-STATE PATTERNS IN A REACTION DIFFUSION SYSTEM WITH MIXED BOUNDARY CONDITIONS

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A number of models for pattern formation and regulation are based on the hypothesis that a diffusible morphogen supplies positional information that can be interpreted by cells. Such models fall into two main classes: those in which pattern arises from distributed sources and/or sinks of the morphogens, and those which can spontaneously produce pattern via the interaction of reaction and transport. In source–sink models, specialized cells maintain the concentration of the morphogen at fixed levels, and given a suitable distribution of sources and sinks, a tissue can be proportioned into any number of cell types with a threshold interpretation mechanism. However, the spatial pattern established is strongly dependent on the distances between the sources and sinks, and additional hypotheses must be invoked to ensure that the pattern is invariant under changes in the scale of the system. This is most easily seen in a one-dimensional system with a source at one end and a sink at the other. If the ends are held at c_0 and c_1 respectively, then the morphogen distribution is given by $c(x) = (c_1 - c_0)(x/L) + c_0$, and so the flux through the system must vary as $1/L$. Thus the homeostatic mechanism that maintains the boundary concentrations at fixed levels must be able to vary the production or consumption of morphogen over a wide range.

Turing models (Turing 1952) are an example of systems in which the pattern can arise spontaneously. These involve two or more morphogens that react together and diffuse throughout the system. In Turing's analysis no cells are distinguished *a priori*; all cells can produce or degrade the morphogens. Moreover, Turing only considered periodic systems or closed surfaces, in which case no boundary conditions are needed. More generally, we call any system of reaction-diffusion equations for which the boundary conditions are of the same type for all species, and such that the elliptic system which governs the steady state admits a constant solution, a Turing system. For an appropriate choice of parameters, it is well known that a spatially–homogeneous stationary state of a Turing system can become unstable with respect to small non–uniform disturbances. Such instabilities, which Turing called symmetry–breaking because the homogeneous locally-isotropic stationary state becomes unstable and therefore physically inaccessible, can lead to either a spatially non–uniform stationary state or to more complicated dynamical behavior. Such transitions from uniform stationary states to spatially– and/or temporally-ordered states might in turn lead, via an unspecified 'interpretation' mechanism, to spatially–ordered differentiation. For mathematical simplicity most

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analyses of Turing models deal with instabilities of uniform stationary states, since numerical analysis is generally required for more general reference states. However, Turing himself recognized the biological unreality of this in stating that 'most of an organism, most of the time is developing from one pattern to another, rather than from homogeneity into a pattern'.

Reaction diffusion systems have been proposed to account for spatial pattern formation in several other biological systems and in chemical systems, but in many of these cases experimental evidence is lacking. Recently, however, Turing-type structures have been found in the chlorite-iodide-malonic acid reaction (Castets *et al.* 1990; Ouyang & Swinney 1991). Aside from the difficulty of identifying morphogens and the reactions in which they participate in a biological context, there are several general properties of Turing systems that limit their applicability.

- The spatial patterns in a Turing system typically arise via an instability, and thus the parameters must be tightly controlled to obtain the onset of the instability at the desired point in parameter space. In particular, for a given kinetic mechanism, the diffusion coefficients must have the proper relative magnitudes.

- Because the instabilities result from the interaction of reaction and diffusion, the patterns that arise are sensitive to the overall scale of the system. As a result, it is difficult to obtain the degree of scale-invariance that is observed in various biological systems. However, modifications of Turing's model can circumvent this difficulty (Othmer & Pate 1980).

- Frequently there are multiple stable solutions that coexist in a Turing system, which raises the problem of pattern selection. Generally tight control of the initial conditions is needed to select the desired pattern.

We have analyzed the spatial pattern formation properties of a two-component reaction-diffusion system in one-dimension, in which the two species are subject to different boundary conditions (Dillon *et al.* 1993). For example, one species may be subject to Neumann conditions, whereas the other species may satisfy Dirichlet conditions. We refer to these as non-scalar boundary conditions. We have concentrated on a simplified version of a model for glycolysis, which is obtained from a biochemical model in the limiting case in which the enzymes are far from saturation (Ashkenazi & Othmer 1978). The governing equations are

$$u_t = \nu u_{\zeta\zeta} + \beta - \kappa u - uv^2, \; v_t = \nu\delta v_{\zeta\zeta} + \kappa u + uv^2 - v, \tag{21.1}$$

where $u(\zeta, t)$ and $v(\zeta, t)$ are nondimensionalised chemical concentrations at position ζ and time t; $\nu = D_1/\omega L^2$, $\delta = D_2/D_1$, where D_1 and D_2 are the diffusion coefficients of u and v respectively, ω^{-1} is a typical reaction time scale and L a measure of the domain length; $\zeta \in [0, 1]$, and β and κ are parameters that we set to 1.0 and 0.001, respectively.

The time evolution system is analysed by a combination of linear analysis, which is non-trivial for the case of non-scalar boundary conditions, bifurcation analysis and numerical integration. The steady state system is analysed using the numerical package AUTO (Doedel 1981). In particular, we consider the properties of solutions as the length scale L is varied. We find that for non-scalar boundary conditions, qualitatively new phenomena arise. For example, stable, non-uniform solutions exist for small values of L. It is well known that for Turing systems all solutions converge to a spatially uniform solution for sufficiently small L (Othmer 1977).

Furthermore, patterns are less sensitive to both the length parameter and the initial conditions. In particular, for certain combinations of boundary conditions we find smooth

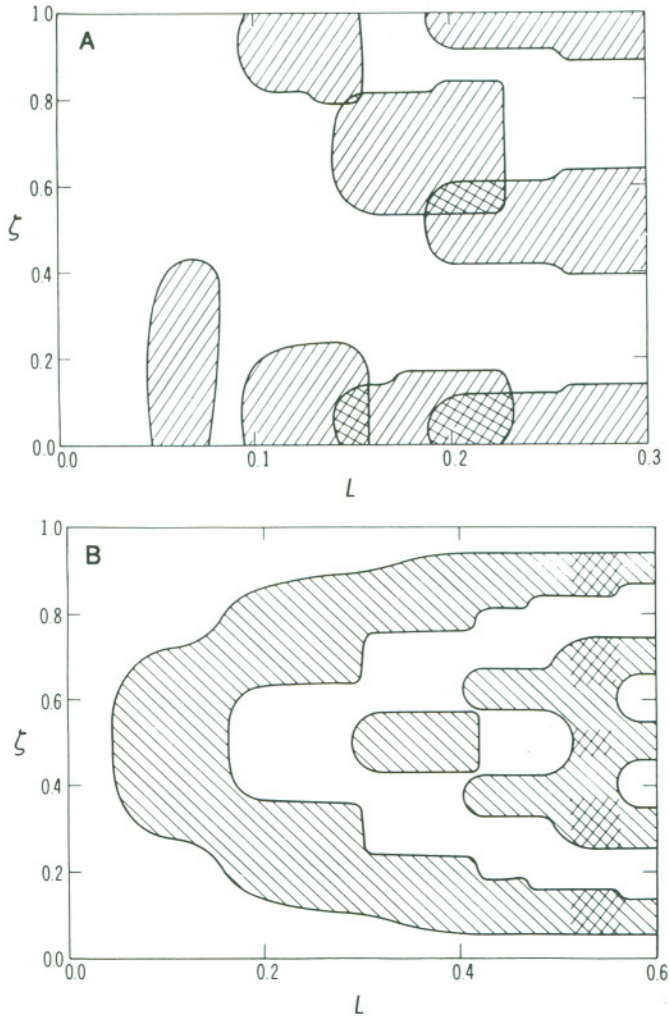

Figure 21.1. Comparison of steady states of the modified glycolysis model for (a) scalar boundary conditions and (b) homogeneous Neumann conditions on u and zero Dirichlet conditions on v (*cf.* Dillon *et al.* 1993).

transitions between different spatial patterns, and these transitions do not involve bifurcations. For example, we find a transition from 1 to 2 to 3 stable pattern elements in a one-parameter family parameterized by the length. This type of transition is similar to that observed in skeletal development in the tetrapod limb. Moreover, these solutions are apparently the only stable solutions. By contrast, for Turing systems a tortuous path in parameter space would be required, because different stable patterns may coexist under certain conditions (see Figure 21.1). In this analysis we have used the domain length L as the bifurcation parameter. However, as this parameter occurs in the model equations as the non-dimensional grouping that involves diffusion coefficients and reaction rate, the sequence of transitions illustrated in Figure 21.1(b) could be generated by changes in the diffusion coefficients. For instance, it is known that the gap junction permeability of cells can be modulated by other species (Mehta *et al.* 1989; Brümmer *et al.* 1991), and such changes would be reflected in the diffusion coefficients in the continuum model used here (Othmer 1983). This is incorporated in the model described by Dillon and Othmer elsewhere in this volume.

Note that our model solutions capture neither the anterior-posterior spatial asymmetries observed in the skeletal elements of the limb nor their temporal sequence of development along this axis. Recently, Benson *et al.* (1992) have shown that a spatially varying diffusion coefficient can produce such spatial asymmetry. The temporal sequence of pattern formation may be due to cells responding to the spatial pattern in a time-specific fashion.

Imposing non-scalar boundary conditions also results in pattern formation occurring over a larger ratio of diffusion coefficients, thereby enlarging the parameter domain over which certain patterns exist and hence lowering pattern sensitivity to small changes in the environment.

Clearly, therefore, boundary conditions have a marked affect on the patterns exhibited by reaction-diffusion models in one-dimension. We would expect this effect to be even more pronounced in two- and three- dimensions, where one has an even wider choice of different types of boundary conditions.

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REFERENCES

Ashkenazi, M., & Othmer, H. G. 1978. Spatial patterns in coupled biochemical oscillators. *J. Math. Biol.*, **5**, 305–350.

Benson, D. L., Sherratt, J. A., & Maini, P. K. 1992. Diffusion driven instability in an inhomogeneous domain. *Bull. Math. Biol.*, **55**, 365–384.

Brümmer, F., Zempel, G., Buhle, P., Stein, J.-C., & Hulser, D. F. 1991. Retinoic acid modulates gap junction permeability: a comparative study of dye spreading and ionic coupling in cultured cells. *Exp. Cell Res.*, **196**, 158–163.

Castets, V., Dulos, E., & Kepper, P. De. 1990. Experimental evidence of a sustained standing Turing-type nonequilibrium chemical pattern. *Phys. Rev. Letts.*, **64**(24), 2953–2956.

Dillon, R., Maini, P. K., & Othmer, H. G. 1993. Pattern formation in generalized Turing systems. *J. Math. Biol.* (To appear).

Doedel, E. J. 1981. AUTO: A program for the automatic bifurcation and analysis of autonomous systems. In *Proc. 10th Manitoba Conf. Num. Anal. and Comp.*, pp. 265–284.

Mehta, P., Bertram, J. S., & Loewenstein, W. R. 1989. The actions of retinoids on cellular growth correlate with their actions on gap junctional communication. *J. Cell Biol.*, **108**, 1053–1065.

Othmer, H. G. 1977. Current problems in pattern formation. In *Lectures on Mathematics in the Life Sciences 9*, pp. 57–85. AMS.

Othmer, H. G. 1983. A continuum model for coupled cells. *J. Math. Biol.*, **17**, 351–369.

Othmer, H. G., & Pate, E. F. 1980. Scale invariance in reaction-diffusion models of spatial pattern formation. *Proc. Natn. Acad. Sciences*, **77**, 4180–4184.

Ouyang, Q., & Swinney, H. L. 1991. Transition from a uniform state to hexagonal and striped Turing patterns. *Nature*, **352**, 610–612.

Turing, A. M. 1952. The chemical basis of morphogenesis. *Phil. Trans. R. Soc. Lond.*, **B237**, 37–72.