The Impact of Turing's Work on Pattern Formation in Biology

Philip K. Maini FIMA, Centre for Mathematical Biology, Mathematical Institute, Oxford, OX1 3LB

Introduction

In 1952, Alan Turing wrote his seminal paper: *The Chemical Basis of Morphogenesis* (Turing, 1952) in which he suggested that a system of chemical substances (which he termed *morphogens*) reacting and diffusing together could be driven unstable resulting in spatially varying profiles (patterns) of chemical concentrations. If these chemicals determined cell fate, or were growth hormones, then they would underly the morphogenetic patterns that we actually see. For example, he considered an isolated ring of cells and showed that, if one of the chemical morphogens was a growth hormone, then the chemical pre-pattern set up by the reaction-diffusion system would lead to patterned cell growth accounting for branched structures. By approximating as a sphere, the blastula stage of early development, when the embryo is a hollow ball of cells, he proposed that a reaction-diffusion system could account for a symmetry-breaking which may lead to gastrulation (the process by which complex cell movements begin to shape the embryo). By considering the system on a two-dimensional spatial domain, he showed that the model exhibited dappled patterns. In this case, if the morphogen coded for the production of pigmentation, this could account for animal coat markings.

Turing's model essentially took the form:

$$\frac{\partial \mathbf{c}}{\partial t} = D\nabla^2\mathbf{c} + \mathbf{f}(\mathbf{c}) \qquad (1)$$

where $\mathbf{c}(\mathbf{x}; t)$ is a vector of chemical concentrations, D is the diagonal matrix of diffusion coefficients, $\mathbf{f}$ the vector of reaction kinetics, $\mathbf{x}$ space and t time. Typical boundary conditions could be periodic or zero flux.

Remarkably, he showed that under certain conditions on D and the forms of the kinetic terms in $\mathbf{f}$ such a system could exhibit spatially uniform steady states which were stable in the absence of diffusion, but which were driven unstable by diffusion. This is a highly counterintuitive result because basically it says that one can take a system which has stabilising reaction kinetics, add to it diffusion (which we also think of as stabilising) and the resultant system is unstable! This is an example of an *emergent property* and what it shows is that complex phenomena can arise as the result of the *integration* of fundamental units. This phenomenon is now well-known but the Turing system was one of the first to illustrate it.

Alan Turing - one of the first systems biologists?

In the last two decades there have been huge technological advances in molecular biology resulting in, for example, the determination of the whole genome of many species. This has led already to enormous and very important advances in medical treatment. However, biologists are now beginning to realise that identifying the individual components is not enough and that in order to understand the process of development it is essential to see how these individual components interact. This has led, in the present post-genomic era, to the almost hysterical interest in *systems biology*, yet it is as Turing predicted over 50 years ago. Moreover, Turing's work showed that an instability could arise solely due to the interaction of a number of stablising components. This is a profound result, because it means that a search to find the de-stabilising component in such a system would be fruitless as the instability arises due to the integration of the individual processes.

Turing's work has inspired a huge amount of mathematical biology but has been dismissed to a large extent by experimental biologists. This has proved to be premature because, as well as illustrating the importance of integration, he was the first to properly formalise the idea that cells responded to chemical concentrations and differentiated depending on the concentration of chemical. He coined the term *morphogen* and it has now been shown that morphogens exist. He also predicted *diffusion-driven instability* as a mode of pattern formation and this phenomenon has now been found in chemistry (for references, see Maini, et al., 1997, and Figure 1).

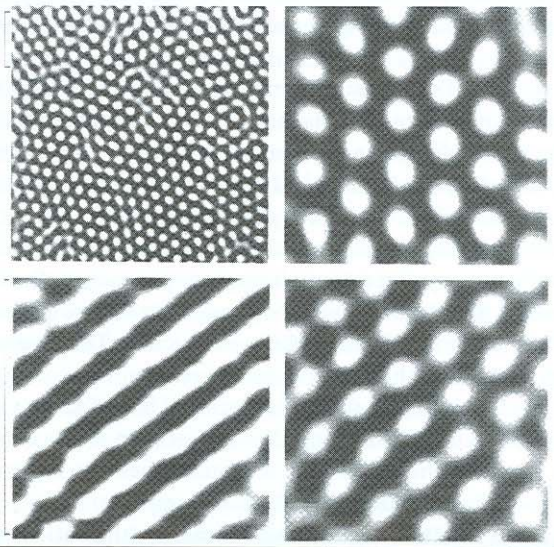

Figure 1 Different types of Turing patterns in the chloride-iodide-malonic-acid (CIMA) chemical reaction.
Reprinted with permission from Ouyang and Swinney, 1991.

A general patterning mechanism

In 1972, Gierer and Meinhardt generalised the ideas of Turing into the patterning principle of *short-range activation, long-range inhibition* or *local activation, lateral inhibition - LALI* (Gierer and Meinhardt, 1972) and applied the model to pattern formation and regulation in Hydra. Since then, Meinhardt has applied extensions of this model to a vast array of biological patterning processes including phyllotaxis, segmentation, veins (Meinhardt, 1982) and, perhaps most colourfully, pigmentation patterns in sea shells (Meinhardt, *et al.*, 2003, Figure 2). Applications of this theory to dissipative structures in chemistry were greatly extended, most notably by Ilya Prigogine, who won the Nobel Prize in chemistry in 1977 for his contributions to nonequilibrium thermodynamics, particularly the theory of

dissipative structures. More recently, the Turing model has been considered on growing domains, where it has been shown to be consistent with the pigmentation pattern transitions (insertion and/or splitting of stripes) observed in certain tropical fish (Kondo and Asai, 1995).

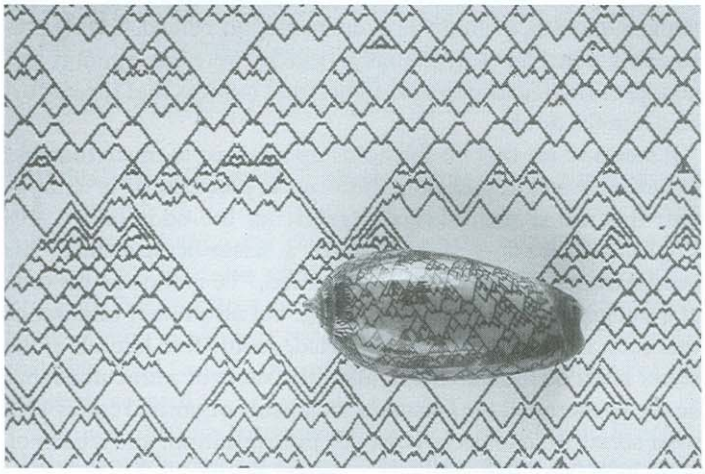

Figure 2 The pigmentation pattern on sea shells is laid down sequentially as the organism grows. In the background is a temporal read out of a one-dimensional spatial pattern exhibited by a reaction diffusion model which, when mapped onto a realistic geometry closely resembles the pattern on an actual shell (foreground). See Meinhardt, et al., 2003 for full detail. Figure reproduced courtesy of H. Meinhardt.

The Turing model for morphogenesis hypothesizes that cells are uniformly distributed and respond to a spatial pattern of morphogen concentration. An alternative view is that the cell density undergoes an instability so that the cells themselves form a spatial pattern, and then cells in high density regions differentiate. This is the mechanochemical theory of morphogenesis first put forward by Oster and Murray (see Murray, 2003, for a review). In this theory, it is assumed that cells move through extracellular material (ECM) exerting large traction forces which deform the ECM and, through the resultant combination of active and passive transport processes, cells form aggregates. Although based on a different biological hypothesis to that of Turing's theory, resulting in a very different form of mathematical model, the underlying LALI patterning principle is still key to the generation of pattern. The mechanochemical theory of morphogenesis has, in turn, served to underly a number of subsequent models proposed to account for certain aspects of abnormal wound healing (see Murray, 2003, for a review).

Models based on neuronal firing patterns to account for stripe formation in the visual cortex, although of integro-partial differential equation type, are also examples of LALI. Thus, there is a whole range of models which are based on very different biological hypotheses but which have the same underlying pattern generating mechanism. On the one hand, this is a problem because it means that they also generate roughly the same pattern, so it is difficult to distinguish between candidate models. On the other hand, it does mean that one can make conclusions which are independent of the details of the biology. An example of this is the notion of *developmental constraints*, that is, the theory that patterns in biology must follow certain rules (Oster *et al.*, 1988). Perhaps the most famous of these is that it is more likely for a spotted animal to have a striped tail, than for a striped animal to have a spotted tail.

Discussion

The Turing model has been generally studied for the case of two interacting morphogens. Even this simplest example gives rise to a bewildering array of spatial and spatiotemporal phenomena and although they have been studied in detail numerically, from the analytical viewpoint there are only limited results, mostly concerning linear stability analysis and pattern formation in the weakly nonlinear case. For the case of three or more morphogens, even the linear stability problem is very challenging and to date has only been solved in a few special cases. It is clear therefore that the Turing model provides interesting and challenging problems for the mathematician, and is arguably one of the most intriguing set of equations ever proposed in applied mathematics. However, what does it say about biology?

One of the earliest applications of the theory was to pattern formation in the developing *Drosophila* fruit fly. However, it has now been shown that this is not the case and that, although the theory is very elegant, the patterning actually occurs due to a rather unweldy cascade of morphogen interactions. This has led to the theory falling into disrepute amongst biologists. However, as mentioned earlier, the notion of morphogen, the importance of emergent properties and diffusion-driven instability are all due to Turing. Although there is as yet no biological example of the latter, the prediction of diffusion-driven instability was shown to be true for chemical systems. There are a number of laboratories all over the world with experimental programs specifically designed to test the Turing hypothesis for pattern formation in biology. This, in itself, is a remarkable achievement.

In his day, the level of detail in the Turing model was totally appropriate because few details of the biology were known. As technology has advanced and more data is generated, mathematical biology has moved on and the theory has become more sophisticated and complicated, involving many different chemicals, kinetics and transport processes. However, the lessons learnt from Turing and how he showed that mathematics could allow us to develop our intuition to understand what at first appears totally counter-intuitive, still live on.

Turing died just two years after the publication of *The Chemical Basis of Morphogenesis*. Had he lived, who knows how far he would have advanced the field of pattern formation in biology and how closer we might now be to solving one of the greatest mysteries in nature?❑

References

Turing, A.M., The chemical basis of morphogenesis, *Phil. Trans. R. Soc. Lond.*, B237, 37-73 (1952)

P.K. Maini, K.J. Painter, H.N.P. Chau, Spatial pattern formation in chemical and biological systems, *Faraday Transactions*, 93(20), 3601-3610 (1997)

Gierer, A. and Meinhardt, H., A theory of biological pattern formation, *Kybernetik*, 12, 30-39 (1972)

Meinhardt, H., *Models of Biological Pattern Formation*, Academic Press, London (1982)

Meinhardt, H., Prusinkiewicz, P. and Fowler, D.R., *The Algorithmic Beauty of Sea Shells*, Springer-Verlag (2003)

Kondo, S. and Asai, R., A reaction-diffusion wave on the marine angelfish *Pomacanthus*, *Nature*, 376, 765-768 (1995)

Murray, J.D., *Mathematical Biology: II. Spatial Models and Biomedical Applications*, Springer- Verlag (2003)

Oster, G.F., Shubin, N., Murray, J.D., and Odell, G.M., Evolution and morphogenetic rules: The shape of the vertebrate limb in ontogeny and phylogeny, *Evolution*, 42, 862-884 (1988)

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