The Turing model comes of molecular age

Philip K. Maini,[1,2,*] Ruth E. Baker,[1] Cheng-Ming Chuong[3]

[1]Centre for Mathematical Biology, Mathematical Institute, 24-29 St Giles', Oxford, OX1 3LB, UK.
[2]Oxford Centre for Integrative Systems Biology, Department of Biochemistry,
South Parks Road, Oxford, OX1 3QU, UK.
[3]Department of Pathology, University of Southern California, Los Angeles, California 90033, USA.

[*]To whom correspondence should be addressed; E-mail: maini@maths.ox.ac.uk.

One of the most fascinating questions in science is "what are the underlying mechanisms that give rise to complex patterns in biology?" Despite the huge advances in biotechnology and mathematical modelling that have occurred recently, this still remains a largely open question. In their paper "WNT and DKK determine hair follicle spacing through a reaction-diffusion mechanism" (*1*), Sick et al. have made a major advance towards answering this question for the regular patterning of hair follicles by identifying key molecular players in perhaps the most well known mathematical model for biological pattern formation.

In his seminal paper, Alan Turing proposed that spatial patterns arise due to a phenomenon he termed "diffusion-driven instability" (*2*). He showed, using mathematical analysis, that small spatial fluctuations in an otherwise well-mixed system of reacting and diffusing chemicals could become unstable, and that amplification of such fluctuations could lead to a spatial pattern of chemicals which he termed morphogens. He proposed that this spatial arrangement could serve as a pre-pattern for development. This work was ground-breaking conceptually because the mathematical nature of the solutions is wholly counter-intuitive: since their discovery, they have motivated much mathematical research. However, the search for potential molecular players in

model biological systems has either been ignored or is often the subject of controversy, because the model has been deemed to be too simplistic. Moreover, while the phenomenon of diffusion-driven instability has been shown to be present in chemistry, in the fruit fly Drosophila, there is substantial evidence to refute the model. The paper by Sick et al., by providing the first compelling biological evidence for the Turing model, is thus a landmark publication.

In this issue, Sick et al. investigate the regulation of hair follicle patterning in developing murine skin (*1*). They propose that WNT and its inhibitor DKK are morphogens acting in the Turing sense. Expression of Dkk1, which inhibits WNT, is actually controlled by secreted WNTs, and both WNTs and DKKs are secreted into the extracellular space where they diffuse, so that their action is felt over long distances. Given that the WNT proteins are substantially larger than the DKKs one would expect them to diffuse much more slowly than the latter. Therefore, we have the possibility of the classical "short-range activation, long-range inhibition" phenomenon that underlies Turing-driven instability (*3*).

Since hair follicle patterning occurs in waves, the authors use a reaction-diffusion model to set up an initial pattern of follicles. Then, along the same lines as Mooney and Nagorcka (*4*), they assume these follicles are chemical sources. This leads to a second wave of hair follicle formation on a larger domain (due to the growth of skin). The model predicts that moderate over-expression of activator (WNT) increases follicular density, while moderate over-expression of inhibitor (DKK) during the initial inductive wave increases the inter-follicular spacing. These predictions are verified experimentally, providing strong evidence for a genetic underpinning of a Turing reaction-diffusion model.

The formation of skin appendages (hairs, feathers, *etc.*) is an excellent paradigm for patterning because these systems are amenable to experimental manipulation. Nagorcka was the first to propose the Turing model to explain hair pattern formation (*5*), but at that stage the molecular biology was lagging behind the theory. It was only in 1998 that Jung et al. made

the first efforts to link known molecular morphogens with a reaction-diffusion mechanism for feather germ formation (*6*). They showed how the size, number and distribution of appendages could be modulated by altering morphogen concentrations (*7*). Similarly, Sick et al. show this for hair follicles. Together these papers demonstrate that skin progenitors are stem cells, in that they are multi-potent and may assume appendage or inter-appendage fates depending on the local chemical environment at the time of specification. In this sense, the molecular components identified by these experiments appear to be acting as morphogens in the true Turing sense.

In principle, a reaction-diffusion model can set up a chemical pre-pattern before we can visualize changes in cell distribution. That is, it determines sites at which cells will cluster: regions of high cell density coincide with those of increased morphogen concentration – although the model does not specify how this rearrangement occurs. On the other hand, it is possible for cellular aggregations to form without such a pre-pattern; via simple chemotactic movement in response to gradients in chemical concentration. By way of illustration, the patterns formed by these two different mechanisms are shown in Figure 1. It is immediately obvious how similar such patterns are.

This highlights one of the difficulties in mathematical modelling: determining which is the "correct" model. What is so crucial about the identification of WNT and DKK as possible morphogens is that it may now allow this issue to be addressed experimentally. Exploration of simulation models allows us to elucidate pertinent biological phenomena, and generate hypotheses which may be tested experimentally. The key requirement then, is that the results of such experiments are used to test and refine models, ruling some out, if the data allows. While the WNT-DKK interaction does appear to be qualitatively of the form necessary for a Turing-type system, it is now imperative that we try to overcome the experimental challenges in measuring key parameters (rates of production, decay, diffusion coefficients, etc.) so that quantitative tests can be performed in order to determine if the system actually is of Turing type. This would then

be the first definitive example of the Turing model in biology.

Turing models have been proposed to describe other types of patterns observed in developmental biology: two applications presently receiving much attention from experimentalists are pigmentation patterning in fish, and skeletal development in the mouse limb. While the evidence for a Turing diffusion-driven instability in these systems is not as strong as that presented by Sick et al., their paper should stimulate further work in biological pattern formation.

References and Notes

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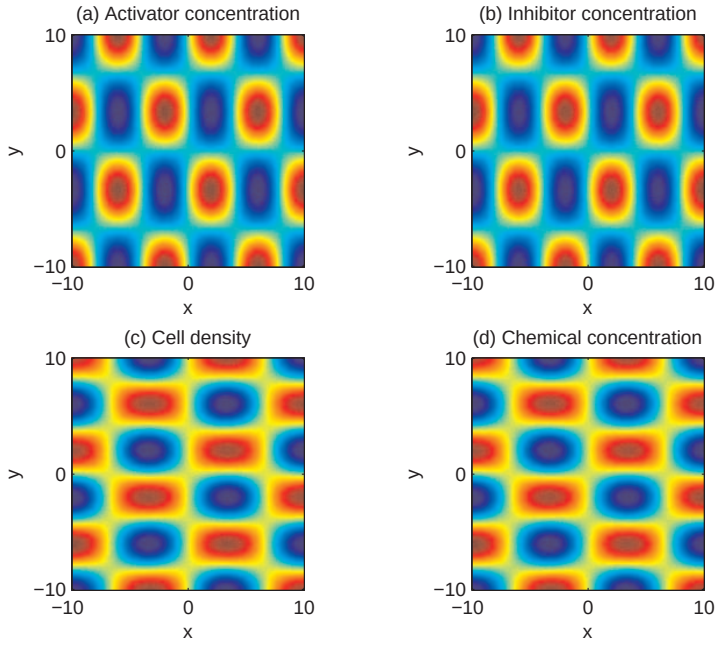

Figure 1: Illustration of pattern formation via two different mechanisms. (a) and (b) show the results of simulation of a reaction-diffusion model with Gierer-Meinhardt kinetics (*3*). Activator and inhibitor react and diffuse on the domain: small random fluctuations in the initial field lead to coinciding spatial patterns of activator and inhibitor concentration. (c) and (d) show the results of simulation of a cell-chemotaxis model of the form used in (*8*). Both cells and chemical diffuse, with cells also moving up gradients in chemical concentration. Cells are produced according to a logistic growth law and themselves produce the chemical. Once again, small random fluctuations in the initial field lead to coinciding spatial patterns in cell density and chemical concentration. In each plot, concentration/density is shown on a scale with blue indicating low levels and red indicating high levels.