ILLUSTRATION BY ANDY POTTS

Pattern formation

We are only beginning to see the impact of Turing's influential work on morphogenesis, says **John Reinitz**.

Alan Turing's 1952 paper on the origin of biological patterning[1] solved an intellectual problem that had seemed so hopeless that it caused a great developmental biologist, Hans Driesch, to give up science and turn to the philosophy of vitalism.

In the late nineteenth century, Driesch, and later Hans Spemann, demonstrated that animal bodies develop from a patternless single cell, rather than growing from a microscopic, preformed version of the adult body — in humans, the 'homunculus'. But such self-organization, Driesch realized, could not be understood with the ideas of that century. Before the invention of computers, applied mathematics dealt only with linear differential equations, which can amplify a pattern but not generate it.

In 'The chemical basis of morphogenesis', Turing showed that a pattern can indeed form *de novo*. In considering how an embryo's development unfolds instant by instant from its molecular and mechanical state, Turing was using a modern approach. Developmental biologists today similarly investigate how molecular determinants and forces exerted by cells control embryonic patterning.

Turing's focus was on chemical patterns: he coined the term 'morphogen' as an abstraction for a molecule capable of inducing tissue differentiation later on. This concept will be familiar to any molecular biologist: the protein products of the *HOX* gene cluster, for example, which are essential for body patterning throughout the animal kingdom, are morphogens in Turing's sense. (Confusingly, the term has been more narrowly defined since.)

At the heart of pattern-making is symmetry-breaking. Turing considered an idealized embryo beginning with a uniform concentration of morphogens, which have translational symmetry that is lost as specific tissues emerge. He raised deep questions that are still unsolved, noting for instance that all physical laws known at the time had mirror-image symmetry, but biological systems did not. Turing speculated that the asymmetry of organisms originated from that of biological molecules. His point is still relevant to life's origins.

Turing's argument involved a mathematical trick: he created a nonlinear system by turning on diffusion discontinuously in an otherwise linear system at a specific instant. Without diffusion, the system is stable and homogeneous, but with diffusion, it becomes unstable and forms spatial pattern. The brilliance of the trick is that the nonlinearity is confined to a single point in time, so that at all other times, only the theory of linear equations is needed. Turing cleverly arranged to have diffusion generate pattern, rather than blur it, as it usually does.

The influence of Turing's paper is difficult to overstate. It was a transition point from the era of analytical mathematics to that of computational mathematics. Although his proof was constructed analytically, Turing's paper contains the first computer simulations of pattern formation in the presence of stochastic fluctuations, and is possibly the first openly published case of computational experimentation.

Turing used analytical arguments of the nineteenth century to point the way towards the computational science of the twenty-first century. He was well aware, however, that nonlinear science and developmental biology would require more advanced computational methods. "Most of the organism, most of the time, is developing from one pattern into another, rather than from homogeneity into a pattern," he stated[1]. He realized that even though an embracing theory for such processes might not be possible, individual cases could be modelled with a digital computer.

Yet Turing's work is frequently misinterpreted, perhaps because he died tragically in 1954, before he could correct the record. His analytical arguments are often mistaken for biological predictions, although Turing did not intend them as such. His hypothetical system, based on two substances, was a simplification. For the pattern-forming trick to work, one substance should catalyse synthesis of both substances while diffusing slowly; the other should catalyse destruction of both substances while diffusing rapidly. For patterns that shift over time, three substances would be required. A field of investigation of these models has sprung up[2], but credit or blame for the results rests with those authors, not Turing.

What Turing should receive credit for is opening the door to a new view of developmental biology, in which we deal directly with the chemical reactions and mechanical forces embryos use to self-organize their bodies from a single cell. He was well ahead of his time. It was three decades before the work on *Drosophila* embryos by Lewis[3], Wieschaus and Nüsslein-Volhard[4] led to the discovery of real morphogens. It is the young researchers of today who will benefit most from reading Turing's work — seeing his ideas about morphogenesis not as speculation but as the conceptual framework for concrete problems. ■

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