Turing's Mathematical Theory of Morphogenesis

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One of the fascinating aspects of the natural world is the diversity of shapes that make up the animal and plant kingdoms: the intricate patterns on a sunflower, the dramatic antlers on a stag, animal coat markings. The list is endless. How these patterns arise is one of the mysteries of science and, despite an enormous amount of research, most of the fundamental questions remain unanswered. Although genes obviously play a role in development, knowing the genetic make-up of an organism does not allow us to understand the mechanisms of development — we may know that certain genes impart particular properties to certain cells, but how this then leads to tissue-level behaviour cannot be addressed by genetics.

The problem that Turing addressed in his seminal paper, "The chemical basis of morphogenesis" (Turing [9]) was precisely this — how can a tissue be patterned? He presented a theory in which he proposed that cells actually respond to a chemical pre-pattern. For example, consider a growing tree. To a good approximation, its horizontal cross-section can be considered to be circular. When a branch begins to bud off the side, this symmetry is broken. Turing proposed that if an underlying pattern of growth hormone went through a symmetry-breaking transition (or bifurcation, as we would now call it) then there would be more hormone in one place than in the others, and this would initiate a bud. He extended this notion to that of a *morphogen*, namely a chemical to which cells respond by differentiating in a concentration-dependent way.

To generate spatial patterns in a chemical system he proposed an ingenious mathematical theory. He considered a system of morphogens reacting and diffusing in such a way that, in the absence of diffusion, they exhibited a spatially uniform steady state which would be stable. He then showed that the introduction of diffusion could lead to an instability (now the well-known *diffusion-driven instability*) resulting in a spatially heterogeneous pattern of chemical concentrations. This was the first example of what is now called an *emergent phenomenon* in the sense that the behaviour of the system, in this case a patterning instability, emerges from the components and is not part of the components. In his system, the reaction kinetics are stabilising and we know that diffusion is stabilising in the sense that it homogenises spatial patterns. Therefore, two stabilising systems interacted to produce an instability. In other words, he recognised that it was the integration of components that gave rise to the structures and behaviours we observe, rather than each behaviour being encoded in its own component. The latter was very much the common view amongst biologists of the time, a view that continued to prevail for many decades thereafter. So, it is no exaggeration to say that in this area, Turing was far ahead of biologists and mathematicians!

Turing's 1952 paper has influenced many biologists and mathematicians. The latter have found that the model, a coupled system of nonlinear parabolic equations, has an enormous richness of behaviours (see, for example, the books by Britton [2], and Murray [7]), while the former have looked for, and found, morphogens. However, the theory was really brought to the attention of mainstream developmental biologists by Hans Meinhardt, in a paper with Alfred Gierer in 1972 (see Meinhardt [5], and references therein). Meinhardt introduced the idea of short-range-activation-long-range-inhibition and this has proved to be a general patterning principle. Briefly, suppose that one morphogen promotes (activates) another morphogen which, in turn, inhibits the first morphogen. One can easily imagine how this could lead to a stable equilibrium state. If now one allows the inhibitor to diffuse more quickly than the activator, then the equilibrium can be broken, leading to a local high concentration of activator, surrounded by a ring of high inhibitor concentration — a spatial pattern. From this rather coarse

verbal "explanation" it is not obvious how very complex patterned structures can arise, but a combination of mathematical analysis and numerical simulation shows that the model can exhibit an enormous range of patterns and it has been applied to regeneration in hydra, limb development, formation of animal coat patterns, shell pigmentation patterns, to name only a few (see, for example, Murray [7] and Meinhardt *et al.* [6]). In fact, most models of biological pattern formation, whether they consider cells interacting with each other and modifying their environment through physical and/or chemical cues to produce cell aggregations, or neurons interacting with each other to lead to ocular dominant stripes, all come under the above patterning principle.

As well as being able to reproduce a vast number of observed patterns, the Turing model can also shed light on why certain patterns display certain features, so-called *developmental constraints*.

However, when it comes to a detailed analysis of pattern formation the original Turing model fares less well. It was proposed to describe the stripe-like patterns of pair-rule genes in *Drosophila* but it was then shown experimentally that each stripe is formed independently of the others, ruling out the Turing mechanism (Akam [1]). It has also been shown that the model can be very sensitive to small changes in parameter values, initial morphogen fluctuations, and geometry, calling into question its ability to robustly reproduce patterns. However, it has been shown that extending the model in a number of ways can overcome this problem. Perhaps the greatest problem facing the Turing model is that, although morphogens have been shown to exist, there is no definitive proof as yet, that they interact and pattern in the way Turing proposed. Turing structures have been shown to occur in chemistry (see, for example, the paper by Horváth *et al.* [4]) and there is now evidence emerging that they may indeed be occurring in some biological systems (Garfinkel *et al.* [3]; Sick *et al.* [8]).

To evaluate the impact of Turing's theory of morphogenesis one really needs to ask the bigger question of how does one evaluate any model. As Turing himself said, "This model will be a simplification and an idealisation, and consequently a falsification. It is to be hoped that the features retained for discussion are those of greatest importance in the present state of knowledge." Or to quote George Box, "All models are wrong, but some are useful". While there is no definitive proof of Turing models operating in nature, he was the first to put forward concisely the ideal of a morphogen (now well accepted) and the first to show how instability could arise from two stabilising processes interacting. Moreover, Meinhardt's extension to the idea of activators and inhibitors now permeates the experimental literature in developmental biology and there have been enormous advances in mathematical and computational approaches motivated by these models. Turing's work in biological pattern formation was well ahead of its time and it continues to motivate and inspire experimentalists and theoreticians alike.

References

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