The idea of self-organisation in biology and its critics

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Using the example of Alan Turing's paper on morphogenesis, Ute Deichmann at Ben-Gurion University of the Negev explores self-organisation in biology

The availability of large amounts of genomic and other data and the complexity of biological systems have led to increasing collaboration of biologists with mathematicians and computer scientists. However, the use of mathematics in biology differs from that in physics, and problems arise when basic biological principles, such as the genomic control of basic life processes or the specificity of organisms and their biochemistry, are disregarded. I exemplify the importance of mathematics in biology and the problems this can entail, using the example of mathematician and computer scientist Alan Turing's work on morphogenesis, that is, the generation of form in development.

The Chemical Basis of Morphogenesis

Turing's 1952 paper "The Chemical Basis of Morphogenesis" has played a central role in the discussion about self-organisation—the spontaneous emergence of spatio-temporal patterns— in embryological development. The paper has recently inspired embryologists and computational biologists to generate models of pattern formation in development. Turing suggested "that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis" (disregarding that the title and the term "morphogen" – form producer – are misleading because the paper deals with the formation of patterns, not form).

Turing aimed at demonstrating that patterns can be created spontaneously in an originally homogeneous cell by introducing reaction-diffusion equations into the modeling of development. His model showed mathematically that in a system of two or more diffusing reagents, a pattern of high and low concentrations may spontaneously emerge from an initially uniform distribution, and two homogeneously distributed substances within a certain space—one "locally activated" and the other capable of "long-range inhibition"—can produce novel shapes and gradients.

The design of thinking machines and embryological growth

Turing most likely began to work on morphogenesis in the context of his work on the design of thinking machines. Since brains were too complicated to create a simple mathematical model, he decided to study the determination of embryological growth instead. Another reason for Turing to become interested in biology was his desire to "defeat the argument from design" as a proof of the existence of God and to show that form can be explained by chemistry and physics alone (Saunders 1993).

Turing's "mathematical model of the growing embryo" was, as intended, simple and elegant. The "chemical reactions" in his model were not related to any particular type of molecules or their specificities. Most importantly, Turing's concepts of gene and cell were unclear, and the "genes as enzymes" theory that he advocated was long obsolete. Moreover, Turing disregarded the fact that the assumption of enzymes catalyzing the production of other enzymes (catalysts) and so on would lead to an infinite regress, an observation which a few years later led Francis Crick to conclude that the synthesis of enzymes must be radically different from the synthesis of other molecules and that it must logically be based on templates.

The model was hardly cited by biologists for decades

This disregard for biological logic and knowledge shows that Turing was more interested in "mathematical fruitfulness and accessibility" than in the correspondence of his hypothetical reactions to real reactions in the cell (Fox Keller 2002). In contrast, biologists were not interested in whether the interactions could build patterns the way Turing suggested but whether they really do, of which there was no evidence for a long period of time. For this reason, the model was hardly cited by biologists for decades.

In the 1970s, Ilya Prigogine and his school of the irreversible thermodynamics of complex systems made the model popular for some time. Reaction-diffusion studies increased, in particular those regarding pattern formation in butterfly wings and animal coats. Scientists applied updated versions of Turing's model and other mathematical models to simulate pattern formation in a variety of different animal systems, such as the generation of periodic sea shell patterns and body segmentation in Drosophila. However, many of these simulation models did not reflect reality. Like Turing, their authors disregarded genes as causal factors for morphogenesis and development as a whole and also for many biochemical pathways for pattern formation, and they regarded the unfertilised egg as a homogeneous sphere, not as a highly organised structure.

At a meeting on mathematical models of development in 1972, Francis Crick, one of the skeptics about the relevance of Turing's model for development, quoted Turing's remark about the zebra: "Well, the stripes are easy but what about the horse part?" (Hogeweg 2011). Pattern formation can be modelled elegantly and relatively simply, but morphogenesis and development would require modelling of the zebra itself, its body architecture, and organs in a very complex way.

Michael Akam, who has studied the generation of the repeating stripes along the antero-posterior axis of Drosophila, discussed two possible ways of generating the exact periodicity of the stripes: An "elegant mechanism" that was favoured by model builders and that would "use an intrinsically periodic pattern-generating system", and a mechanism in which unique instructions were generated by gene encoded proteins to define the position of each stripe (Akam 1989). He showed that the latter mechanism was more likely to take place in the organism and that "the apparent simplicity of the repeating segment pattern" might be deceptive.

The strongest critic of mathematical simulation models without underlying experimental perturbation was Eric Davidson. According to him, “one of the worst fallacies [in modeling in biology] is the assumption that if you can make a model, which simulates a process, then the model must represent how it works” (Deichmann 2016). Davidson’s causal explanation of the molecular events of early development in sea urchins based on rigorous experimentation, his theory of gene regulatory networks (GRN), and mathematical modelling, were regarded as a logical framework for the description of the transcriptional programs, encoded in the genome, that have to be activated at the right time and place during development (Briscoe 2019). The GRN approach shows the power of experimental data in combination with computation simulation. Its shortcomings, such as a lack of consideration of tissue mechanics and quantitation, have been addressed in recent work, for example by James Briscoe, who combines the GRN theory with dynamical systems approaches.

To conclude, taken alone, methods based on Turing’s model and more recent reaction-diffusion models have been unable to explain the complex developmental program that is brought about by multiple genetic and molecular pathways; they also cannot account for many of the simpler patterns such as stripes. However, physical processes and self-organising events play important roles in biological processes. For example, according to Eric Karsenti, the cell cycle in eukaryotes “can be seen as being based on the principle of self-organization by reaction–diffusion.” But these processes are taking place in the framework of genomic determination: Karsenti showed that genes are required for them and that “none of these processes are true Turing patterns”, because “the symmetry is not broken by spontaneous instabilities, but rather by deterministic effects” (Karsenti 2008).

References

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