1. De'ath, G., Fabricius, K. E., Sweatman, H. & Puotinen, M. *Proc. Natl Acad. Sci. USA* **109,** 17995–17999 (2012).
2. Babcock, R. C. *et al. PLoS ONE* **11,** e0169048 (2016).
3. Hall, M. R. *et al. Nature* **544,** 231–234 (2017).
4. Vogler, C., Benzie, J., Lessios, H., Barber, P. & Wörheide, G. *Biol. Lett.* **4,** 696–699 (2008).
5. Savolainen, O., Lascoux, M. & Merila, J. *Nature Rev. Genet.* **14,** 807–820 (2013).
6. Bockaert, J. *et al. Biochem. Soc. Trans.* **32,** 851–855 (2004).
7. Hock, K., Wolff, N. H., Condie, S. A., Anthony, K. R. N. & Mumby, P. J. *J. Appl. Ecol.* **51,** 1188–1196 (2014).
8. Allendorf, F. W., Hohenlohe, P. A. & Luikart, G. *Nature Rev. Genet.* **11,** 697–709 (2010).
9 Kirk, H., Dorn, S. & Mazzi, D. *Evol. Appl.* **6,** 842–856 (2013).
10. Platt, J. R. *Sci. Am.* **314,** 16 (2016).

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DEVELOPMENTAL BIOLOGY

How the lizard gets its speckled scales

Can a reptile compute? In one species of lizard, *Timon lepidus*, the colour and pattern of its scales evolve in a manner akin to a discrete rule-based computation called a cellular automaton. SEE LETTER P.173

LEAH EDELSTEIN-KESHET

In 1902, Rudyard Kipling wrote the *Just So Stories*, which provided fanciful accounts of how, for example, the leopard got its spots. More than 80 years later, the mathematician James D. Murray suggested a mathematical mechanism that could explain this spotted pattern formation[1]. On page 173, Manukyan *et al.*[2] tell an even more intriguing tale. The authors describe a strikingly beautiful biological pattern-forming system that spans the development of the ocellated lizard (*Timon lepidus*), which changes from a drab brown youngster with white polka dots (ocelli) to an adult whose skin is a rich black and green tapestry (Fig. 1). The authors call this patterning system a living cellular automaton.

Originally conceived in the 1940s, a cellular automaton[3,4] is a system of spatially discrete but interconnected units that switch between different states depending on their own state and the states of their neighbours. Cellular automata have been used to probe theoretical concepts in computer science (such as a universal Turing machine[5]), study complex patterns in nature[6], produce startling moving patterns based on simple rules (the 'Game of Life'[7]) and model biological systems[8] and a panoply of discrete systems that are too numerous to list.

The quest to understand pattern-forming biological systems has spanned more than half a century. It originated with the seminal work of Alan Turing, who published a much-cited paper[9] on the chemical basis of morphogenesis — the developmental emergence of shape and form in living organisms. Similar ideas were proposed two decades later[10], and have since been popularized in many papers and books. These theories established that interacting and diffusing chemicals can create spontaneous patterns of concentration: mountains and valleys in a chemical landscape. Such an uneven chemical distribution can direct morphogenesis. This concept has led to new scientific fields in mathematics, biology, chemistry and physics.

How patterns form in living systems remains hotly debated and much discussed. The chemical signalling that underlies morphogenesis is fully understood in just a few systems. Moreover, tracking the fates of individual microscopic cells in a living tissue is a difficult problem that has been addressed only in the past two decades, albeit in various systems, including the transparent zebrafish embryo[11,12].

Enter the team of Manukyan and colleagues. The authors present a case study in which a living pattern can be observed in detail as it unfolds. The skin pattern of *T. lepidus* is mesoscopic (a length scale between microscopic and macroscopic) and involves microscopic interactions of single pigment cells. These cells collectively give rise to the colour of the skin scales, and therefore the speckled pattern of the adult lizard's skin.

The authors devised a remarkable way to track the skin pattern of an individual lizard over 3–4 years of its growth, matching skin-scale for skin-scale as the lizard's length

A, FLPA/ALAMY; B, IAN WATT/ALAMY

Figure 1 | The ocellated lizard. Manukyan *et al.*[2] track the skin colour and pattern of the ocellated lizard (*Timon lepidus*) over 3–4 years of its growth and a fourfold increase in its length. **a,** The juvenile's skin is brown and has white polka dots (ocelli). **b,** Conversely, the adult's skin has a labyrinthine pattern, in which each scale on the lizard's back is either black or green. The authors demonstrate that these changes are governed by a pattern-forming system that they call a living cellular automaton.

increased fourfold. They used 3D scans of the lizard's skin and corrected for the curvature of its body and irregular surface texture to identify the centres of its scales. They then used a slight but sophisticated adjustment to map these points to the centres of hexagons; the resulting hexagonal array becomes a flattened 'tiling pattern', in which each tile represents one scale. The authors were able to track the skin scales because their number and relative position are maintained throughout the reptile's growth. The level of detail achieved by Manukyan *et al.* makes this study innovative in terms of providing empirical data with which to drive a theory of pattern formation.

At the macroscopic scale, pattern formation is usually described as a smooth process that is continuous in space and time, and it is modelled by a set of reaction–diffusion equations — mathematical equations that describe how chemicals redistribute over space and time. The authors follow this convention, but with a key difference: they show that the boundaries between *T. lepidus* scales constrict during morphogenesis, and argue that this creates partial barriers to the diffusion of cells and chemicals between adjoining scales. As a result, the scales form discrete spatial units that each take on a uniform colour (black or green on the lizard's back) in a way that depends on the states of their neighbours. Formally, then, the biological pattern-forming system resembles the output of a cellular automaton. The scale pattern evolves by obeying a set of rules that transform one configuration of scale colours into another, with certain probabilities. It is in this sense that the authors describe *T. lepidus* as a 'living' cellular automaton.

The authors determined empirically the probabilities of scales changing colour for distinct colour configurations of scales and their nearest neighbours. They then linked the reaction–diffusion and cellular-automaton approaches in a theoretical model. They found good agreement between the patterns that evolve over years on their reptilian subjects and the solutions to their model based on neighbourhood-dependent rules obtained from empirical data. This agreement is surprising and adds to the novelty of the authors' approach.

What underlying mechanism drives this pattern formation? According to the authors, a system consisting of pigment cells (melanophores and xanthophores) interacting with a long-range, rapidly diffusing chemical suffices to explain the pattern formation — taking into account the partial diffusion barriers between adjoining scales that form during morphogenesis. The authors' model, which is modified from a pre-existing zebrafish pigmentation model[13], reproduces the black and green labyrinthine pattern of the adult lizard's skin. Future work in which the chemicals and cellular interactions are identified in more detail (possibly in related but simpler *in vitro* experimental systems, such as cells and chemicals interacting in a tissue culture) would provide an opportunity for manipulating the patterns experimentally, and therefore allow us to learn more about the underlying cellular and molecular pattern-forming mechanisms.

As the authors conclude, a cellular automaton is not just an abstract concept, but corresponds to a process generated by biological evolution. Nearly 80 years after its conception, the cellular automaton has come of age — it has matured from an abstract concept in the 1940s to *in silico* realizations since the 1960s and, finally, to a pattern-forming mechanism that has biological relevance and can be observed *in reptilio*. ■

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1. Murray, J. D. *Sci. Am.* **258,** 80–87 (1988).
2. Manukyan, L., Montandon, S. A., Fofonjka, A., Smirnov, S. & Milinkovitch, M. C. *Nature* **544,** 173–179 (2017).
3. Ulam, S. *Bull. Am. Math. Soc.* **64,** 1–49 (1958).
4. Shannon, C. E. *Bull. Am. Math. Soc.* **64,** 123–129 (1958).
5. Cook, M. *Complex Syst.* **15,** 1–40 (2004).
6. Wolfram, S. *Nature* **311,** 419–424 (1984).
7. Gardner, M. *Sci. Am.* **224,** 112–117 (1971).
8. Ermentrout, G. B. & Edelstein-Keshet, L. *J. Theor. Biol.* **160,** 97–133 (1993).
9. Turing, A. M. *Phil. Trans. R. Soc. Lond. B* **237,** 37–72 (1952).
10. Gierer, A. & Meinhardt, H. *Biol. Cybern.* **12**(1), 30–39 (1972).
11. Keller, P. J., Schmidt, A. D., Wittbrodt, J. & Stelzer, E. H. K. *Science* **322,** 1065–1069 (2008).
12. Keller, P. J. *Science* **340,** 1234168 (2013).
13. Nakamasu, A., Takahashi, G., Kanbe, A. & Kondo, S. *Proc. Natl Acad. Sci. USA* **106,** 8429–8434 (2009).

BIOMEDICINE

Human genes lost and their functions found

Individuals who lack a functional copy of a gene — gene knockouts — can reveal the gene's role. Most knockout research has used model organisms, but now a comprehensive catalogue of human knockouts is in sight. SEE LETTER P.235

ROBERT M. PLENGE

In the nineteenth century, Charles Darwin and Gregor Mendel studied natural genetic variation. But by the twentieth century, scientists did not have to rely on natural variation to investigate gene function because they could delete genes in genetically tractable model organisms such as the fruit fly *Drosophila melanogaster* and inbred mouse strains. Since then, research using model organisms has provided many fundamental biological insights. On page 235, Saleheen *et al.*[1] describe approaches to identifying and studying people who lack functional copies of specific genes and who are therefore natural human 'knockouts' for those genes.

Many sophisticated tools are available for investigating human biology. Genomic engineering of human cells can be performed *in vitro* using the gene-editing approach known as CRISPR–Cas9. The biology of complex tissues can also be studied *in vitro* using populations of human cells. In biobanks, clinical samples can be linked to data from electronic health records, enabling investigation of the relationship between genetics and disease. Saleheen and colleagues' work adds to the growing set of experimental resources for understanding human biology.

The authors studied mutations — known as nonsense, frameshift and splice-site mutations — that cause a copy of a gene to be non-functional because it encodes a highly abnormal or truncated protein. As a result of selective evolutionary pressure, these mutations are extremely rare in human populations[2], or if present, usually occur on only one of the two parental chromosomes; such mutations are said to be heterozygous. The functional copy of the gene on the other parental chromosome is often sufficient to fulfil the gene's normal function. If this is the case, an individual who is heterozygous for the gene is unaffected by the mutant copy.

When, as happens occasionally, both inherited parental chromosomes contain non-functional copies of a specific gene, this results in a gene knockout called a homozygous null mutation. If a gene has a key role in human physiology, its loss might cause disease or abnormal function. But if the gene is not essential, an individual lacking it will have normal function. Knowing the effects of not having a functioning copy of a specific gene provides useful information about the gene's role.

The frequency with which homozygous null mutations occur depends on the relatedness of an individual's parents. In outbred populations, where the genetic relationship between the two parents will be slight, it is unlikely that both will have a mutation in the same gene.