it is not easily used to make intrinsically three-dimensional objects.

Douglas and colleagues' work[1] represents a third revolution in DNA nanotechnology. They have extended the DNA origami technique by showing how a DNA scaffold strand can form layers of helices arranged in a honeycomb lattice, thus providing a general-purpose, crystalline material from which three-dimensional objects can be constructed. In principle, any shape can be made from this DNA material, as long as it can be 'carved out' from a block of the honeycomb lattice.

To design their nanostructures, the authors devised a computer-aided process that begins with a template block composed of tubes (Fig. 1); each tube becomes a DNA duplex in the final structure. Once a target shape has been defined by removing sections of the block, a single-stranded scaffold DNA (the M13 virus genome, as in flat DNA origami) is routed through every part of the structure, and complementary 'staple' strands are designed to bind to the scaffold and thus create duplexes. Finally, strand-exchange points are defined between neighbouring double helices. Enough of these junctions must be used to stabilize the overall structure, while still maintaining enough flexibility in the system to allow the desired shape to assemble. Having drawn up plans for their target structures, Douglas *et al.*[1] heated, then very slowly cooled, a solution of the scaffold DNA and its hundreds of staples. Under these conditions, the staples directed the folding of the scaffolds into the desired shapes.

Douglas and colleagues' approach can be compared with a recently published procedure for three-dimensional DNA origami[7], in which a hollow box ($42 \times 36 \times 36$ nanometres) was assembled. Two-dimensional DNA origami was used to construct all six flat walls of the box on a single scaffold strand, and then inter-wall staple strands directed the assembly of the final three-dimensional form. The box design is highly innovative — it even includes a lid that can be opened and closed — but the box gains its three-dimensionality by orienting intrinsically two-dimensional subunits against one another in space. By contrast, the honeycomb lattice technique[1] is inherently three-dimensional from the start of the design process.

Of course, the primary goal of DNA nanotechnology is not to create aesthetically pleasing sculptures, but to make functional devices and materials. For practical applications, structures generated using Douglas and colleagues' method will probably need to be integrated with other nanomaterials that have electronic, photonic or catalytic properties superior to those of DNA. There are currently also other limitations to the technique. For example, the self-assembly process results in low product yield (providing only about 7–44% of the theoretical yield), proceeds very slowly (taking about a week), and generates products that have an unfavourably high charge density (because the charged DNA backbone is packed tightly in space). Furthermore, the upper limits on the total size of the products and the lower limits on their feature resolution have yet to be determined. The shapes that have been made so far are also somewhat blocky (see Fig. 2 on page 416); the sculpture depicted in Fig. 1b of this article would require either a larger scaffold strand than is currently used, or several such strands.

Nevertheless, the potential of Douglas and colleagues' technique is clear. Hierarchical structures, constructed from several repeating subunits, are a much-sought-after goal of nanotechnology, and the authors present three examples in their paper, including a stunning icosahedron assembled from three M13 genome scaffolds (see Fig. 4 on page 418). This successful move into three dimensions heralds a new era for the field of structural DNA nanotechnology. ■

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COMPUTATION

The edge of reductionism

P.-M. Binder

Research at the frontier between computer science and physics illustrates the shortcomings of the reductionist approach to science, which explains macroscopic behaviour using microscopic principles.

In his 1972 paper "More is different", Philip Anderson[1] claimed that multi-component physical systems can exhibit macroscopic behaviour that cannot be understood from the laws that govern their microscopic parts — a feature known as emergent or complex behaviour. Anderson's position is at odds with that of Stephen Hawking, who once suggested[2] that, as soon as all fundamental laws of the Universe are understood, we will in principle be able to explain all macroscopic phenomena. Writing in *Physica D*, Gu and colleagues[3] provide a beautiful illustration of a physical system that cannot be easily 'reduced', and of the developing symbiosis between theoretical physics and computer science[4].

To address 'the understandable', Stephen Wolfram[5] examined the relation between computation and the unfolding of the physical world. He defined as reducible those systems for which there is a computational shortcut that allows their behaviour to be efficiently predicted rather than reproduced step by step. For example, the motion of a simple pendulum is described by a cosine function that can be computed using a rapidly converging mathematical series, rather than simulating each and every pendulum oscillation. Such shortcuts do not usually exist for chaotic systems, for example.

Wolfram made an additional, important point. Many systems are irreducible, but among them only a few are undecidable: they have properties that cannot be formally calculated, as stated in Kurt Gödel's and Alan Turing's theorems[6]. Undecidability is a property of universal computers or Turing machines. Macs, PCs and DNA computers[7] with unlimited memory would qualify as such machines. And this is where the notion of 'different' (or complex) systems can be made more precise — those with undecidable global properties despite having well-understood local (microscopic) governing laws.

As a first example of undecidability, consider a cellular automaton (CA) — a lattice of cells, each of which can take on a finite number of values (states) and evolves over time according to the configuration of a set of neighbouring cells. This is the microscopic transition rule. For the one-dimensional CA known as 'elementary rule 110', two states are allowed ('0' or '1'), and any cell will evolve to 0 if either its state and that of its right-neighbour cell are 0, or if its state and those of both its immediate neighbours are 1 — otherwise it will evolve to 1. Thus, the local governing law is fully understood.

But the global dynamics of a CA is a different matter, as can be seen in Figure 1. Each row displays the lattice at a different time step, thus providing a full spatiotemporal record of the dynamics of the system. Cells far apart act in concert to sustain 'particles'[8]: structures that move and interact, and in doing so, compute. The result is an intricate and undecidable global dynamics.

It is not easy to demonstrate that rule 110 can simulate a universal computer[9]. Such proofs often involve the construction of a few logic gates and information channels that allow universal computation to be implemented, and could well be argued to be reductionist. But once these elements have been constructed, the step that shows that a system has undecidable

DAVID J. ECK

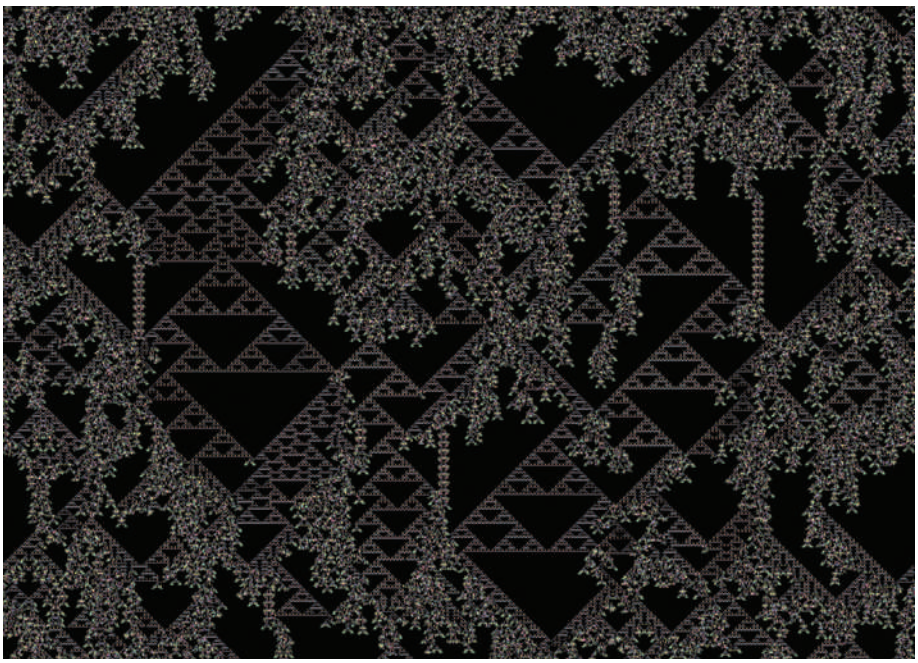

Figure 1 | Evolution of a cellular automaton. A cellular automaton is a lattice of cells that evolves through a number of time steps according to a predefined rule, which stipulates the next state of a cell on the basis of its current state and that of its immediate neighbours. In this example, each row represents the same lattice, 1024 pixels across, at a different time step, for a total of 768 steps. The colour of each pixel denotes one of the eight possible states of the cell. The initial condition (top row) was randomly chosen. As time proceeds, patterns ('particles') can be identified that move to the left or right and interact with each other, leading to complex and formally undecidable global dynamics. Gu and colleagues' findings[3] are based on the interpretation of this image as a two-dimensional spatial array of spins at a fixed time.

properties involves proof by contradiction rather than constructive proof: a higher level of abstraction. When Gu *et al.*[3] write "the understanding of macroscopic order is likely to require additional insights", they may have in mind procedures such as proofs by contradiction that transcend mere reductionism.

The authors focused on the Ising model: a lattice of spins that interact with one other and with an external magnetic field. The individual spin states can be 0 or 1 (corresponding to 'up' or 'down' magnetization), just like those of elementary CA. The main difference is in the dynamical rule: spins tend to align with their neighbours (and with the external field, if one is applied to the system), whereas thermal fluctuations counteract and randomize their state. Therefore, the microscopic transition rules are probabilistic. Ising models in more than one dimension exhibit phase transitions: at sufficiently low temperatures, the tendency of spins to align overcomes thermal jiggling, and the system becomes and remains ordered. Perhaps not surprisingly, the physics and mathematics immediately around the disorder-to-order phase transition are rich, and have been well studied.

In their study, Gu *et al.*[3] mapped the dynamics[10] of a certain CA into the lowest-energy (ground) states of Ising models. In this framework, Figure 1 can now be interpreted as a snapshot of a two-dimensional spatial lattice of spins. They grouped spins into blocks that encode the logic operations needed to produce universal computation in the corresponding CA. They then defined the 'prosperity', p, of two-state systems as "the probability that a randomly chosen cell at a random time step is live" (live meaning state 1).

Using the computational properties of the CA, Gu and colleagues were able to show that p is undecidable for infinite, periodic Ising systems. They argued that, as a consequence, many macroscopic properties of an Ising system, including the system's magnetization and degeneracy (number of independent configurations) at zero temperature, depend on p and hence are also undecidable. Because Ising models have been used to describe not only magnetic materials but also neural activity, protein folding and bird flocking, the consequences of Gu and colleagues' results transcend both computer science and physics.

Alas, their results apply only to infinite lattices, and hence seem of limited use. The finite Turing systems one would encounter in real life are decidable. But there are hints that finite objects may, after all, have undecidable properties. One hint comes from certain mappings of a solid square onto itself, which have been shown to be undecidable[11,12]. These procedures slice and rearrange parts of the square in a way that allows computer operations such as shifts to be implemented, and they take advantage of real numbers (which require an infinite number of digits) to pack an infinite computer into a finite region. A second hint comes from a new level of computation[13] that is

50 YEARS AGO

The Neutrino. By Prof. James S. Allen — This small book gives an excellent description of experimental work on the neutrino, which only in the past few years has been shown to have any direct physical property apart from balancing energy, momentum and spin in β-decays. It is a tribute to modern methods of experiment that neutrino-capture in hydrogen has been demonstrated by Reines and Cowan in spite of the fact that a neutrino beam could traverse a thickness of solid material measured in *light years* without appreciable loss ... It has not happened often that so tricky a field of physics has been cleared up so quickly, as a result of brilliant theoretical work, which suggested many key experiments.
From *Nature* 23 May 1959.

100 YEARS AGO

The Problem of Age, Growth, and Death: a Study of Cytomorphosis. By Prof. Charles S. Minot — From the time of Cicero, perhaps before, the problems of longevity and of the cause of old age have again and again been subjects of speculation. Not long ago, Metchnikoff, in his optimistic work, "The Nature of Man," ascribed old age to poisoning by bacterial poisons developed as a result of fermentations occurring in the large intestine ... Prof. Minot develops another conception of the nature of "growing old." Although in old age a condition of atrophy is frequent, and various degenerations of cells and tissue are usually present, in particular of the arterial system, so that it has been said "a man is only as old as his arteries," Prof. Minot combats the view that old age is a kind of disease, and regards it as a necessary consequence of the changes in the cells of the body, which are inevitably progressive from birth to death; this succession of cellular changes is termed "cytomorphosis."
From *Nature* 20 May 1909

more powerful than a Turing machine, and has been proposed as just the right one to simulate natural physical phenomena. One hopes that the work of Gu *et al.*[3], along with these two ideas, will lead to a better understanding of the 'computer' in which we live. ■

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SYSTEMS BIOLOGY

When it is time to die

Philippe Bastiaens

Why do cells of the same population respond differently to external death-inducing stimuli? Individuality seems to originate from non-genetic differences in the levels and activation states of proteins.

Any cell biologist can tell you that individual cells from a clonal cell population respond differently to the same stimulus, some not responding at all. In such cases the percentage of responders is seen as a measure of the experimenter's control over parameters that affect the stimulus, such as uniformity of the cellular environment. Variability in cell response can have grave implications. For instance, some tumour cells refuse to die in response to drugs that trigger programmed cell death (apoptosis), affecting the efficacy of chemotherapy. In this issue, Spencer *et al.*[1] (page 428) show that the non-uniform response of a human cell population to the apoptotic stimulus TRAIL can be ascribed to an intrinsic random factor: the naturally occurring differences in protein-expression levels.

To induce apoptosis, TRAIL binds to the cell-surface receptors DR4 and DR5, triggering specific intracellular signalling pathways. These receptors are therefore attractive targets for the development of anticancer drugs, and several compounds that can activate them have been tested in preclinical and in phase I clinical trials, with some promising results[2]. DR4 and DR5 are expressed in normal as well as cancerous tissues, although there is some indication that tumour cells might have higher levels of these receptors[2]; at least, the compounds tested in the trials selectively induce apoptosis in tumour cells. Nonetheless, significant problems remain, including resistance and differences in sensitivity to TRAIL, and fractional killing — situations in which successive cycles of chemotherapy kill only some of the tumour cells[3].

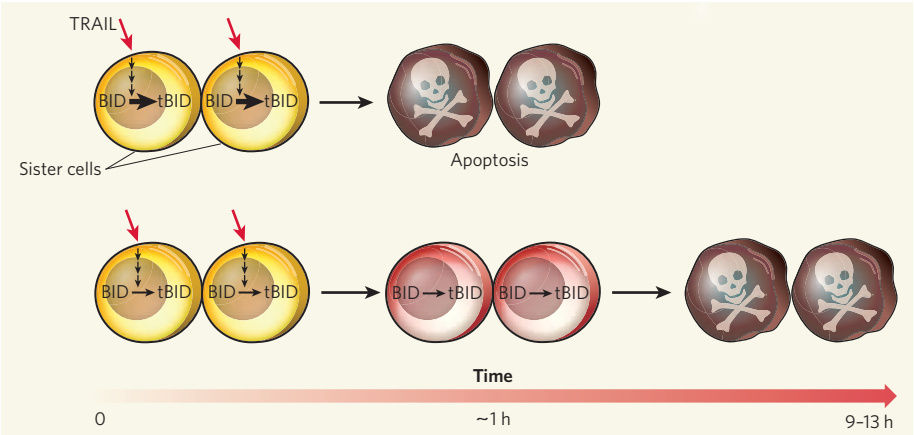

Figure 1 | Non-genetic factors contribute to the rate of apoptosis. Spencer *et al.*[1] find that different sets of sister cells respond differently in the time they take to die after exposure to the apoptotic stimulus TRAIL. The rate of response to TRAIL depends on the rate of proteolytic conversion of the pro-apoptotic protein BID to its active form tBID, which itself is affected by variance in the expression levels of several proteins in the early apoptotic machinery (vertical black arrows). The protein levels are inherited by daughter cells (which become neighbouring sister cells) causing them to behave similarly in response to TRAIL.

Spencer *et al.*[1] show that, in a cancer cell line, TRAIL induces a non-uniform response: some cells die within 45 minutes, some 8–12 hours later, and yet others do not die at all. Intriguingly, following exposure to TRAIL, recently born sister cells die after a similar period of time, suggesting that variability in the population arises from inherited cell differences before treatment with TRAIL (Fig. 1). The authors also find that, on inhibition of protein synthesis, the 'sisterhood' memory persists for longer, an observation that relates a non-genetic factor — protein expression — to variability in cell responses. Finally, they use computer simulation of a biochemical reaction model for apoptosis[4]. The stimulation used as input differences in the levels of proteins mediating apoptosis and the range in 'death times' the authors detect using this method match those they observed experimentally[1].

To investigate the molecular basis of variable cellular responses to TRAIL, Spencer and colleagues grouped the apoptotic protein machinery into three tiers: those occurring before, during and after the process of mitochondrial outer-membrane permeabilization (MOMP), which is crucial for apoptosis. In the first reaction tier, TRAIL binds to its receptors and leads to their association; the death-inducing signalling complexes (DISCs) assemble; and the proteolytic initiator-caspase enzymes become active to trigger MOMP. In the second reaction tier, during MOMP, mitochondrial proteins such as cytochrome *c* and SMAC are released into the cytoplasm. There, they activate effector caspases in the post-MOMP third reaction tier, causing cell death. The authors could microscopically image the activity of these mediators from each of the three tiers in single cells with genetically encoded fluorescence indicators[5] for both caspases and MOMP.

They find that variability in the time to death was almost exclusively determined by differences in the reaction rate of the initiator caspases, which convert a pro-apoptotic protein called BID into its truncated active form (tBID) in the first reaction tier (Fig. 1). tBID then induces the self-assembly of two pore-forming proteins, BAX and BAK — an activity that is normally prevented by its interaction with the anti-apoptotic proteins of the BCL2 family — into mitochondrial pores, thereby initiating MOMP. The authors therefore conclude that time to death is set by the rate of approach to a threshold in the levels of activated tBID at which mitochondrial pores form.

Spencer *et al.* argued that the levels of proteins functioning in the first reaction tier (DR4, DR5, DISC components, the initiator caspases 8 and 10, and BID) should determine the reaction rate for BID activation. But the authors' computer-simulation data show that the level of any one protein in the first tier does not determine time to death. Only on increased expression of one of these components did the