NEWS & VIEWS

NANOTECHNOLOGY

Another dimension for DNA art

Thomas H. LaBean

Many of nature's intricate nanostructures self-assemble from subunits. Efforts to mimic these assembly processes enter a new phase with a method to design and build three-dimensional DNA nanostructures.

Through the ages, some of the most iconic and lasting artefacts of human ingenuity have been sculptures and carvings, created from a wide variety of materials. But until now, a general-purpose material from which nanometre-scale, three-dimensional shapes could be made has been lacking. On page 414 of this issue, Douglas *et al.*[1] introduce a clever method for fabricating nanometre-scale objects from DNA, and report the construction of several such objects. The authors describe their method as "analogous to sculpture from a porous crystalline block", except that the structure of their block consists of tubes — DNA double helices — arranged in a regular honeycomb lattice. The desired shapes are not literally carved into the starting material, but instead form from DNA that has been designed to self-assemble into a supramolecular complex.

The use of DNA as a construction material for making nanometre-scale objects began more than 25 years ago[2], and has since developed into the field of structural DNA nanotechnology[3,4]. The field relies on the fact that molecular recognition and assembly of DNA can be programmed so that it forms designed nanostructures. Such programming is enabled by our understanding of Watson–Crick base pairing: for any DNA base sequence, we can immediately determine the complementary sequence, and know that the two molecules will find and bind to one another in water under appropriate conditions. Well-developed synthesis techniques allow DNA strands of any desired base sequence to be easily prepared.

In 1998, DNA nanotechnology was transformed by the introduction of the 'tile and lattice' strategy[5]. Tiles are nanometre-scale building blocks that fold independently, and typically contain domains of DNA double helices tethered by 'strand-exchange points'. These points model naturally occurring junctions that form in genetic-recombination complexes when DNA strands are traded between helices. Short, single-stranded DNA segments hang off the tiles at strategic locations. On cooling in solution, the single-stranded segments on different tiles bind to each other, so that the tiles assemble into larger, predominantly two-dimensional lattices.

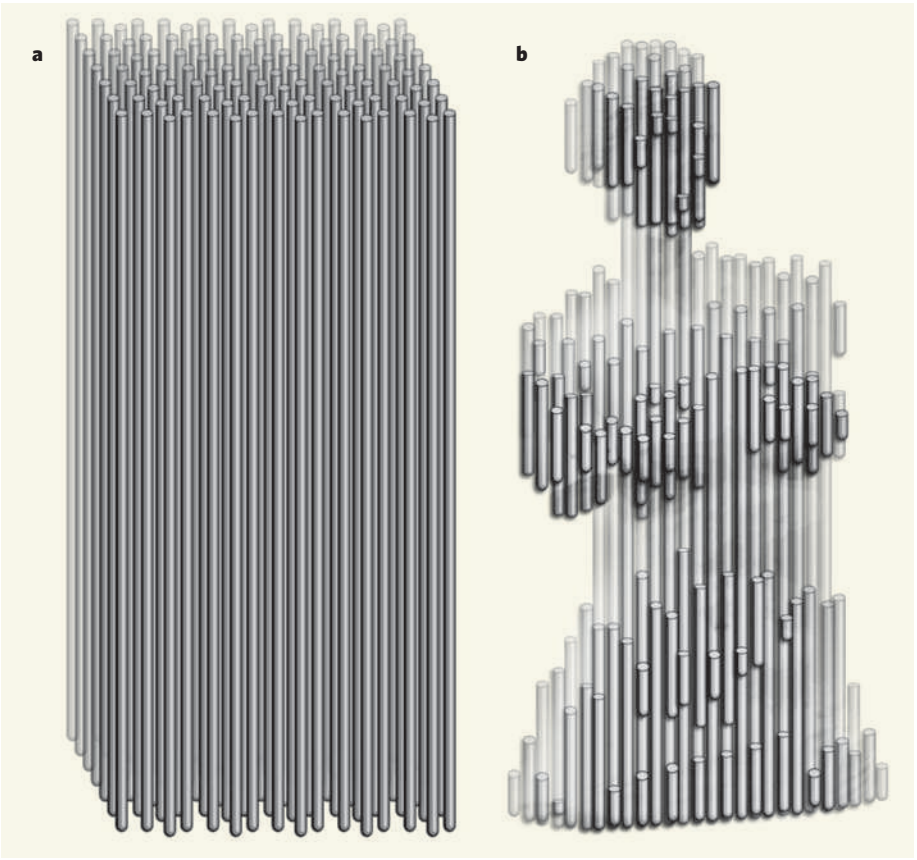

Figure 1 | DNA sculpture. Douglas *et al.*[1] report a method for designing and constructing three-dimensional nanostructures from DNA. **a**, The computer-aided design process begins with a block of tubes arranged in a honeycomb lattice. **b**, A template for the desired DNA structure is designed by removing sections of the tubes, just like carving a sculpture from a block. The remaining tubes will become DNA duplexes in the final object. The DNA structure is designed by routing a single-stranded scaffold DNA (a virus genome) through every section of the tube template. Hundreds of short strands of DNA are then designed to bind to the folded scaffold, cross-linking between different tubes and 'stapling' together the overall structure. When the staple molecules are synthesized and mixed with the scaffold DNA in solution under appropriate conditions, they direct the folding of the scaffold into the desired nanostructure. The structure shown here is more complex than those prepared by the authors (see Fig. 2 on page 416).

Another conceptual leap occurred in 2006, with the demonstration of DNA 'origami'[6]. This strategy uses a long, single-stranded DNA — for example, the genome of the M13 virus — as a scaffold molecule that is folded back and forth on itself to form a planar raft of double helices. The resulting structure is knitted together by a few hundred short, synthetic DNA molecules that act as staples, linking together the helices at appropriately spaced strand-exchange points. The raster-like routing of DNA scaffolds through origami structures provides a general system for making nanometre-scale, two-dimensional sheets of any shape, and with any desired surface pattern. But given the flat raft architecture,

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

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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