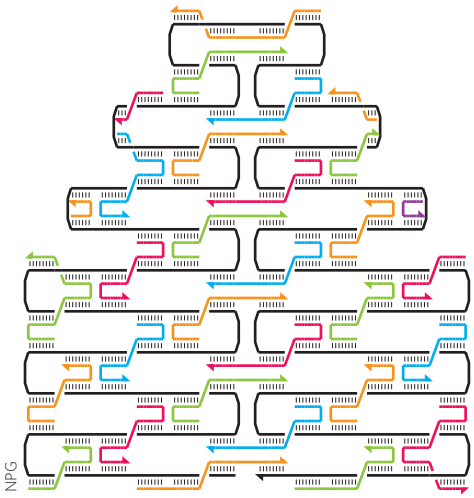
Returning to the fold

This month marks ten years since the general principles of DNA origami were established, a technique that changed the field of DNA nanotechnology and that promises new physical and biomedical applications.

It was a bold leap for Nadrian Seeman to suggest, over 30 years ago, that nucleic acids could be used to synthesize new and complex DNA-like constructs. The range of 2D and 3D DNA nanostructures that were soon fabricated, such as a planar lattice and a hollow cube, demonstrated the scientific and technological potential of harnessing the power of Watson–Crick base pairing, and heralded the arrival of DNA nanotechnology.

With time, the synthesis of increasingly complex nanostructures put significant demands on traditional fabrication techniques, which typically relied on the stoichiometric combination of many short DNA strands. Intricate structures required many reactions with intermediate purification steps, which inevitably extended synthesis time frames and reduced product yields. These limitations prompted researchers to devise easier synthesis methods that could increase the structural complexity of DNA nanostructures. Works by Hao Yan[1], William Shih[2] and their colleagues offered potential solutions: rather than relying on the bottom-up assembly of short DNA strands, they showed that lattices of DNA tiles could be assembled by means of a scaffold DNA strand encoding the desired pattern[1], and that a linear DNA chain could be designed to fold into a predetermined shape[2].

These preliminary findings paved the way for Paul Rothemund's pivotal work, in which he presented the general principles of 'scaffolded DNA origami' and how it can be applied to the fabrication of two-dimensional nanomaterials. Published in *Nature* 10 years ago this month[3], the method appeared remarkably straightforward: a long single-stranded DNA scaffold could be designed, with relaxed stoichiometric constraints, to fold into any geometric pattern by means of short 'staple' strands (pictured). Complex shapes and patterns roughly 100 nm in diameter — such as Rothemund's five-pointed star, smiley face and even a map of the Americas[3] — could be made quickly, reliably, in high yield and with a spatial resolution of 6 nm. Rothemund's work gained immediate interest, inspiring others to explore the boundaries of the technique. Increasingly complex 2D and 3D architectures were made — including multilayer lattices[4], polyhedral cages[5] and



a self-assembled DNA nanobox bearing a dynamic and controllable lid[6]. Controlled curvature was achieved in both two and three dimensions to generate shapes such as concentric rings, spheres and ellipsoids[7]. In another variation, 'DNA kirigami' — the folding and cutting of DNA into reconfigurable topological nanostructures — was applied for the synthesis of a Möbius strip and catenated twisted cylinders[8]. In terms of geometry, there were seemingly few limitations to what could be achieved with DNA origami.

Alongside the increasingly impressive demonstrations of shape control, functional applications were being investigated. By modifying frameworks with DNA sequences able to bind other nucleotide polymers (such as RNA), origami-based DNA nanomaterials have been successfully applied in single-molecule biosensing[9], and structures combining origami frameworks with other types of biomolecules have led to applications in sensing devices and biological assays[10], as well as protein structure analysis[11], bioimaging[12], drug delivery[13] and membrane transport[14]. Pairing DNA with metal nanoparticles has afforded DNA nanomaterials potential applications in nanoelectronics[15] and plasmonics[16], and the controllable arrangement of molecular dyes on a DNA scaffold can confer light-harvesting and energy-transfer properties[17]. Moreover, the precise arrangement of reactive species on a DNA framework has provided nanomaterials for the study of complex chemical processes[18] — for example, the functionalization of origami scaffolds, using chemically labile tethers, for imaging single-molecule chemical reactions[19]. DNA nanomaterials possessing dynamic mechanical abilities, such as tweezers[20], walkers[21], and molecular machines[22] were also demonstrated.

These representative examples clearly present the broad appeal of DNA origami and the success it has enjoyed since its introduction. Yet a 'killer application' has yet to emerge from the many proof-of-concept studies that are currently underway. For instance, the reliability and compatibility of DNA nanomaterials with established device technologies are key aspects to be addressed for the deployment of, for example, optoelectronic systems. Also, the eventual use of origami nanomaterials for disease diagnosis and therapy will hinge upon the clinical efficacy and pharmacokinetics, as well as stability and immunogenicity. It is possible that scale-up and cost considerations of producing DNA nanomaterials will also present a significant problem in some applications. Still, continued efforts to understand the DNA folding process[23] should lead to further improvements in structure control and product yield. ❐

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