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Science **321**, 1795 (2008);
DOI: 10.1126/science.1154533

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.

Assembling Materials with DNA as the Guide

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DNA's remarkable molecular recognition properties and structural features make it one of the most promising templates to pattern materials with nanoscale precision. The emerging field of DNA nanotechnology strips this molecule from any preconceived biological role and exploits its simple code to generate addressable nanostructures in one, two, and three dimensions. These structures have been used to precisely position proteins, nanoparticles, transition metals, and other functional components into deliberately designed patterns. They can also act as templates for the growth of nanowires, aid in the structural determination of proteins, and provide new platforms for genomics applications. The field of DNA nanotechnology is growing in a number of directions, carrying with it the promise to substantially affect materials science and biology.

Today, we can chemically synthesize complex molecules such as palytoxin, vitamin B12, or Taxol with remarkable angstrom-scale precision and fabricate intricately designed micron-scale electronic components at the rate of billions per second. These advances may suggest that we have conquered most major frontiers of chemical construction. Yet, nature illustrates that we are nowhere near the limit of exquisite control over organization; it possesses an extraordinary capacity to assemble complex nanostructures with active and specialized functions. Our ability to precisely position components on the nanometer scale the way nature does, and to do so in a parallel rather than a serial manner, is still limited and is a key goal in nanotechnology and materials science.

Self-assembly, the spontaneous association of components into organized structures using noncovalent interactions, is the chief method that nature uses to achieve complexity. Of the natural self-assembling molecules, DNA is arguably the most remarkable. A cooperative interplay of hydrogen-bonding, π-stacking, electrostatic, and hydrophobic interactions drives one DNA strand to assemble with its complement into a double helix according to extremely precise base-pairing rules. Additional attributes, such as rigidity on the nanoscale, a diameter of ~2 nm, and a near-infinite number of potential sequences, extend DNA's reach beyond a genetic blueprint for life. DNA is emerging as an attractive tool for nanoscience as well; it is a highly promising template for organizing nanomaterials in a programmable way. Research in this area promises to allow us to use DNA to dictate the precise positioning of materials and molecules into any deliberately designed structure, thus approaching the effortless manner in which nature generates complexity and function.

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Structural DNA Nanotechnology

By exploiting DNA's structural features and powerful base-pairing rules, the field of structural DNA nanotechnology aims to generate nanopatterned materials and to control motion at the nanoscale. Its initial challenge was to convert the one-dimensional (1D) DNA molecule into 2D and 3D structures. Seeman and his research group looked to nature's branched DNA structures (for example, the Holliday junction) to meet this challenge. By assembling four DNA strands into a stable four-way junction and incorporating single-stranded "sticky ends" at the periphery for hybridization, Seeman developed an artificial branched DNA "tile" (Fig. 1A, top) (*1*). The second major challenge of DNA nanotechnology was to generate more rigid junctions, which are essential to achieve well-defined 2D DNA assemblies. By joining two DNA double helices with a single strand that begins on one helix and switches onto an adjacent helix, Seeman generated tiles that have "crossovers" and addressable sticky ends at their edges and are of greater rigidity (Fig. 1B, left). The group used these tiles to construct well-defined 2D lattices with predesigned periodicity (*2*).

These principles of construction have since been used, adapted, and developed to generate systems with very fine control over design and function (*2*). A number of basic structural motifs have been designed that can be classified as planar tiles, branched junctions, or helix bundles. Planar tiles are formed from several parallel helices joined by crossover junctions (Fig. 1B, left) and were used to synthesize linear arrays, 2D lattices, and DNA nanotubes. Branched junctions are constructed with multiple DNA arms that radiate from a focal point and are held together with crossover junctions to minimize flexibility (Fig. 1B, middle). They have been used to generate 2D arrays with square, hexagonal, and compound cavities. Helix bundles are tiles constructed by joining parallel DNA helices that are not coplanar (that is, they cooperatively produce a curvature) by using multiple crossover junctions (Fig. 1B, right). They have been assembled into extended 2D arrays and well-defined DNA nanotubes. These structural motifs (*2*) collectively provide a toolbox to rationally access a rich number of 2D DNA architectures and refine DNA materials assembly. It is of note that in structural DNA nanotechnology, DNA is used to provide all the parameters for self-assembly: connectivity, structural features, and programmability.

In this approach, DNA tiles are typically made using strands with different sequences to prevent the formation of undesired structures. In practice, however, this requires synthesizing a large number of components and mixing these in exact stoichiometric ratios for successful assembly. By incorporating identical sequences (sequence symmetry) in DNA strands, Mao found that a stable four-way junction can be constructed from three strands instead of nine and that it assembles into the desired square grid array with an increased long-range order (*2*). Yan used sequence symmetry to tackle the problem of constructing finite arrays, rather than extended 2D assemblies, from a small number of DNA tiles (*2*). Thus, judicious incorporation of sequence symmetry in DNA strands merely used as architectural elements, such as struts and junctions, can simplify tile-based assembly. Winfree proposed the concept of "algorithmic DNA self-assembly" to increase complexity in DNA assembly. This was achieved by designing a set of DNA building blocks that represent "Wang tiles." Conceptually, Wang tiles contain a single color on each of their four sides and assemble so that the adjacent sides of each square are of the same color. This requirement necessarily means that each tile can fit in a specific manner within the assembly. Winfree adapted this methodology to construct rectangular-shaped DNA tiles, with four addressable sticky ends at each side as Wang tiles, and demonstrated the feasibility of assembling these according to a set of algorithmic rules initiated by a nucleating strand. Impressively complex fractal patterns can be generated using this approach, from a minimal set of DNA tiles (*3*).

In addition to tiles created by simple Watson-Crick base-pairing of DNA, many other nucleic acid motifs have been developed. For example, Jaeger showed that folded RNA molecules could be assembled together like a jigsaw puzzle (Fig. 1C) (*4*); Willner synthesized a polycatenated DNA ladder as a mechanically interlocked system onto which proteins, nanoparticles, and dyes were fixed with precise control (Fig. 1D) (*5*); and Sen demonstrated the "synapsing" together of two DNA duplexes into a ladderlike structure through guanine-quadruplex formation (Fig. 1E) (*6*).

Two-dimensional DNA templates provide the opportunity to template the positioning of materials with nanoscale precision. For example, nanoparticle assemblies are promising components for functional devices. Their collective properties, such as electron transport, optical coupling, and magnetic interactions, depend on their relative arrangement; thus, the DNA-mediated control of nanoparticle organization promises to greatly affect the fields of nanoelectronics and nanooptics, among others. Sequence-specific DNA-templated 1D organization of gold nanoparticles was demonstrated by Alivisatos by labeling gold nanoparticles with DNA strands that determined their exact position onto complementary single-stranded DNA templates (*7*). Kiehl (*8*), Seeman (*9*), and Yan (*10*) showed the sequence-encoded organization of gold nanoparticles into well-defined rows on a number of 2D DNA lattices, demonstrating remarkable control over periodicity and arrangement. In addition to nanoparticles, the organization of proteins on DNA templates can possibly lead to "enzyme factories" and substrates for proteomics and can also shed light on the nature of protein-protein interactions. The biotin-avidin interaction was used by LaBean and Yan to generate an alternating assembly of streptavidin molecules onto a 2D square DNA array (Fig. 1F) (*11*). Antigen-antibody interactions enabled Mao (*12*) and Yan and Chaput (*13*) to organize antibodies to fluorescein and c-*myc*, respectively, on antigen-modified DNA arrays. Aptamer-protein interactions are particularly interesting because it is possible to discover aptamers for any protein by using the systematic evolution of ligands by exponential enrichment (SELEX), which means that these interactions can potentially be adapted to organize any protein. For example, Yan used a 2D DNA array, modified with two different aptamers, to assemble two proteins into alternating lines with no unwanted cross-talk (Fig. 1G) (*14*). Although the previous examples require labeling the DNA array with molecules that recognize the materials to be patterned (for example, DNA strands, biotin, antigens, and aptamers), unmodified DNA arrays can also be used to template materials assembly. The Dervan lab developed a class of polyamides that sequence-selectively bind the minor groove of DNA. These molecules can selectively bind to 2D DNA arrays and, when modified with biotin, they mediate the organization of streptavidin into lines with control over sequence and periodicity (*15*).

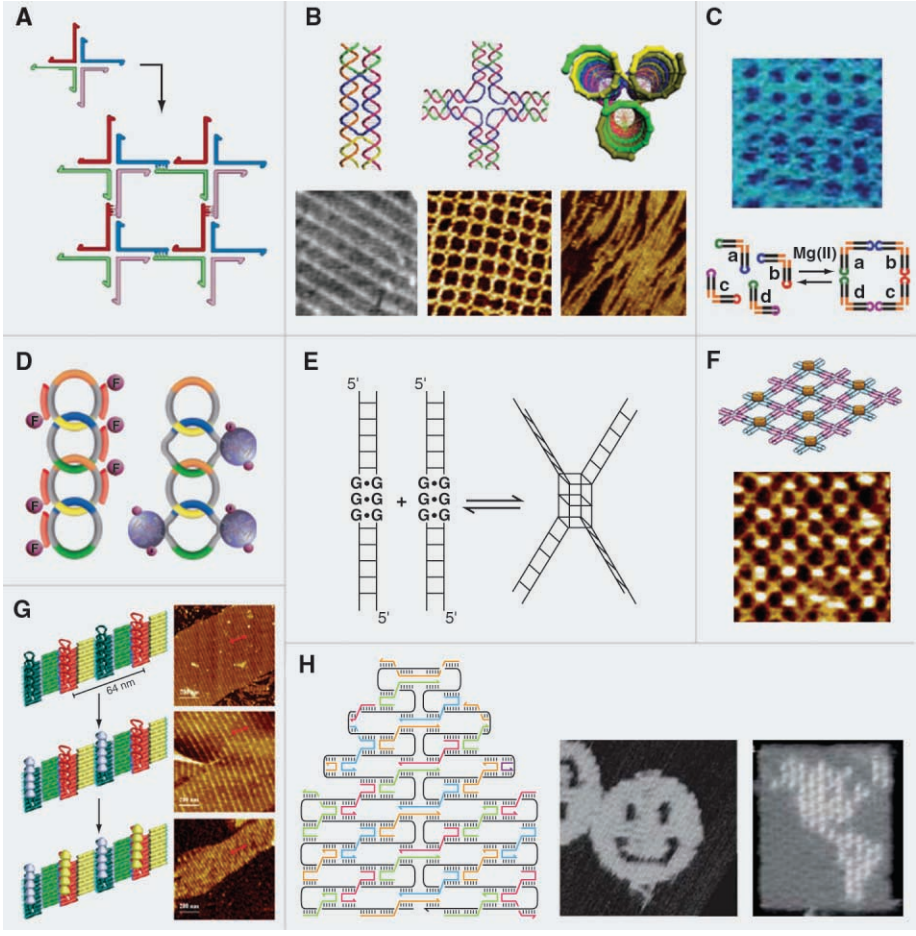

Fig. 1. (**A**) Four DNA strands assemble into a four-way junction with sticky ends, which can further assemble into 2D structures. (**B**) Motifs in structural DNA nanotechnology. Tiles (left) can assemble into periodic 2D arrays; junctions (middle), such as this four-way junction, can result in a 2D square lattice; and helix bundles (right), such as this triple bundle, can generate a 1D DNA nanotube. (**C**) Folded RNA molecules are used to selectively construct extended RNA arrays with different cavity sizes and shapes. (**D**) Interlocked DNA circles form catenated ladder-assemblies, containing single-stranded sides for molecule organization (left) or for protein binding when folded into aptamers (right). F, fluorophore. (**E**) Guanine tracks incorporated into duplexes can be used to snap four strands into a four-way junction composed of a guanine quadruplex. (**F**) A four-arm junction modified with biotin is used to organize streptavidin onto a periodic square array. (**G**) Four tiles are assembled into a 2D array with alternating rows of two different aptamers to organize two different proteins into alternating lines. (**H**) In DNA origami, a long DNA strand is folded into the desired structure and is held into shape using many stapling strands (left). This approach is used to access different 2D architectures (middle) and to draw 2D shapes, such as the map of the Western Hemisphere (right).

A number of applications of materials assembled by structural DNA nanotechnology are already starting to emerge in both biotechnology and materials science. Precisely positioned 2D DNA and protein nanoarrays (rather than conventional microarrays) can be useful in many areas of genomics, proteomics, diagnostics, and tissue engineering. By assembling different DNA tile arrays, each with a specific recognition molecule and "bar-coded" with a specific dye, Yan developed a platform that allows the simultaneous detection of multiple biological analytes. This method may be simpler than DNA or protein microarrays for small-scale profiling of bioanalytes (*16*). Mao employed a 2D DNA array as a reusable "mask" to create 2D gold nanopatterns via vapor deposition into the array's cavities (*17*). This method is promising for controlling topography in the nanoscale regime at a much higher resolution than conventional photolithography. Turberfield showed the binding of the protein RuvA to the four-way junctions of a DNA 2D lattice. This resulted in a 2D crystalline array of this protein, which allowed for its structural elucidation by using cryogenic transmission electron microscopy with a resolution of 30 Å. Interestingly, this DNA-binding protein was found to dramatically modify the geometry of the DNA motif by changing the structural features of these junctions when bound to them (*18*).

DNA Origami

In "DNA origami," a single continuous strand of DNA is systematically folded using a large number of smaller DNA strands. This approach was first reported by the group of Joyce, who synthesized a single continuous DNA strand that is 1.6 kb long and, in a single step, annealed it in the presence of five smaller strands to generate a DNA octahedron (*19*). Ingeniously, Rothemund

generalized this approach to fold naturally occurring genomic DNA into any 2D shape (*20*). In his DNA origami approach, the long strand is folded into the desired shape by a number of smaller strands ("stapling strands") (Fig. 1H, left). The sequences of these strands are computationally designed. Rothemund was able to assemble the same initial long strand of DNA into squares, rectangles, stars, smiley faces (Fig. 1H, middle), and many other 2D shapes. The power of this approach lies in its addressability: Because each stapling strand is a unique sequence, each strand is also a spatially addressable bit. Hairpins were incorporated into stapling strands to write words, such as "DNA," and to draw complex objects, such as the outline of the Western Hemisphere (Fig. 1H, right). DNA origami will be useful for accessing larger DNA shapes with highly addressable surfaces. In a recent application, Yan constructed origami-based DNA nanoarrays for label-free RNA detection of the three genes *Rag*-1, c-*myc*, and β-*actin* (*21*). Shih, Chou, and Douglas synthesized DNA nanotubes by "rolling" a DNA origami array and used the alignment made by these liquid crystalline materials to measure nuclear magnetic resonance parameters in transmembrane proteins (*22*), a powerful way to use DNA organization in protein structure determination.

Supramolecular DNA Assembly

Supramolecular chemistry exploits intermolecular forces to control the organization of organic and inorganic assemblies. After 40 years of research, it has generated a toolbox of molecular components that assemble with a high degree of control (*23*). These components are structurally rigid, geometrically diverse, and intrinsically functional (for example, are photoactive or redox active or possess magnetic properties), in contrast to the more passive DNA branch points. Now a new research area is evolving that brings the tools of supramolecular chemistry and DNA nanotechnology together. "Supramolecular DNA assembly" blends rationally designed DNA building blocks with synthetic organic and inorganic molecules, which give structural and functional advantages both to the initial self-assembly process and to the final construct.

One exciting potential of incorporating synthetic molecules into DNA is that they can dramatically influence the structure of assemblies and introduce different motifs in DNA nanotechnology. Bergstrom (*24*), Shchepinov (*25*), and von Kiedrowski (*26*) presented branched DNA structures with organic corner units that self-assemble into well-defined nanostructures. Because these structures contained identical DNA strands, however, mixtures of DNA assemblies were obtained. Sleiman developed DNA building blocks, containing two arms of different sequences, and a rigid organic corner unit, which selectively assembled into a discrete DNA hexagon (*27*). This approach was used to organize six gold nanoparticles into a hexagon (Fig. 2A), thus providing model systems to study single-electron transport and optical coupling in gold nanoparticle assemblies.

Synthetic molecules can bring a number of additional interactions into DNA nanotechnology. For example, replacing the DNA bases with supramolecular building blocks can expand the genetic alphabet: self-complementary isoguanines, with two hydrogen-bonding faces that are oriented at an angle that forms a pentameric assembly, result in a higher-order DNA pentaplex rather than the classical duplex (*28*). Incorporating extended aromatic molecules as connectors of DNA strands allows folding of these strands through π-π stacking (DNA "foldamers") (Fig. 2B) (*29*), and replacing the termini of DNA strands with ligands allows metal coordination to override base-pairing and loop DNA into a cycle (*30*). Attaching a polymer to the end of DNA can cause microphase separation, resulting in DNA micellar aggregates (Fig. 2C) (*31*). Synthetic molecules can also covalently link DNA structures. They have been used to create, for example, parallel DNA helix bundles with porphyrins at their cores (*32*) and to "snap" together DNA-modified organic conjugated modules into tailor-made conjugated assemblies (*33*).

Another important impact of incorporating synthetic molecules (for example, transition metals) is that they can give much needed function to the passive DNA scaffolds. Metal complexes can be photoactive and electroactive and can possess magnetic and catalytic properties. In contrast to growing materials on the exterior of a DNA strand, incorporating transition-metal complexes into DNA can create pure and monodisperse DNA structures with preserved self-assembly capabilities. Two approaches have been investigated. The first designs nucleobases for complexing transition metals. Shionoya incorporated five consecutive copper-DNA base pairs into a DNA duplex to create a copper stack likened to a self-assembling DNA nanomagnet (Fig. 2D) (*34*) and later, with Carell, created DNA multimetallic stacks with two selectively incorporated transition metals (*35*).

The second approach, which uses metal complexes as vertices, has allowed for coordination geometries, bond angles, and functionalities unavailable to carbon compounds. Sleiman reported the synthesis of metal-linked branched-DNA building blocks, and assembled a cyclic metal-DNA nanostructure with luminescent metal vertices and DNA arms (*36*). Han constructed a DNA triangle with three iron-corner units and three DNA arms (*37*), and McLaughlin showed the synthesis of a ruthenium complex with six DNA arms (*38*). However, because these approaches require using a small subset of completely unreactive metal complexes, very few additional metals have been incorporated as vertices. Sleiman recently incorporated a range of reactive transition metals into DNA junctions, using a method that allows the DNA duplexes and transition metal complexes to synergistically stabilize each other (Fig. 2E) (*39*). Many applications can be expected for metal DNA nanostructures in such areas as multimetallic catalysis, sensing, artifi-

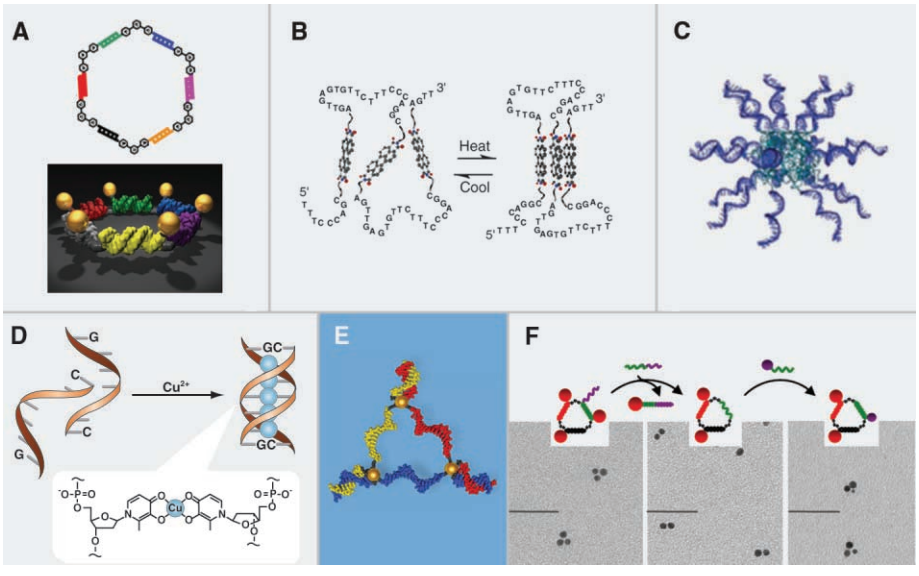

Fig. 2. (**A**) A cyclic DNA hexagon is selectively assembled from building blocks composed of two DNA arms and an organic junction and is used to organize six gold nanoparticles into a 2D discrete hexagon. (**B**) Incorporating extended aromatic molecules into DNA creates folded structures through π-stacking. (**C**) DNA strands attached to polymers result in block copolymers that assemble into micelles via microphase separation of the incompatible blocks. (**D**) Replacing DNA bases with coordinating hydroxypyridone ligands generates copper stacks within DNA strands. (**E**) A metal-DNA nanostructure: a DNA triangle with iron bis(terpyridine) vertices. (**F**) A write/erase experiment using discrete gold nanoparticle assemblies from single-stranded and cyclic DNA templates with organic vertices. A single particle is selectively removed using a fully complementary strand and is replaced with a differently sized particle.

cial photosynthesis, data storage, nanooptics, and nanoelectronics.

In supramolecular DNA assembly, synthetic molecules can contribute to the connectivity and the structure of the final molecule, and DNA is used as the programmable component. One direct consequence of this is that the structures no longer need to be double-stranded and interwoven with crossover units but can now be single-stranded and dynamic. Sleiman reported the synthesis of single-stranded and cyclic DNA structures with rigid organic corners and used them as dynamic scaffolds to organize gold nanoparticles (*40*) with the ability to write/erase and structurally switch these assemblies upon addition of added specific DNA strands (Fig. 2F). The group then constructed 3D DNA cages capable of switching and changing their size between three predefined states (*41*). There have been many elegant designs for DNA nanomachines that respond to specifically added DNA strands or other molecules (*42*). All these examples have led to the development of molecule-responsive DNA materials. In contrast to other environmentally responsive materials (for example, materials that change with pH, light, or oxidation), these allow for the selective control of different parts within the same device and for the incorporation of many molecular triggers to cause individual changes, thus increasing our ability to communicate and externally manipulate structures.

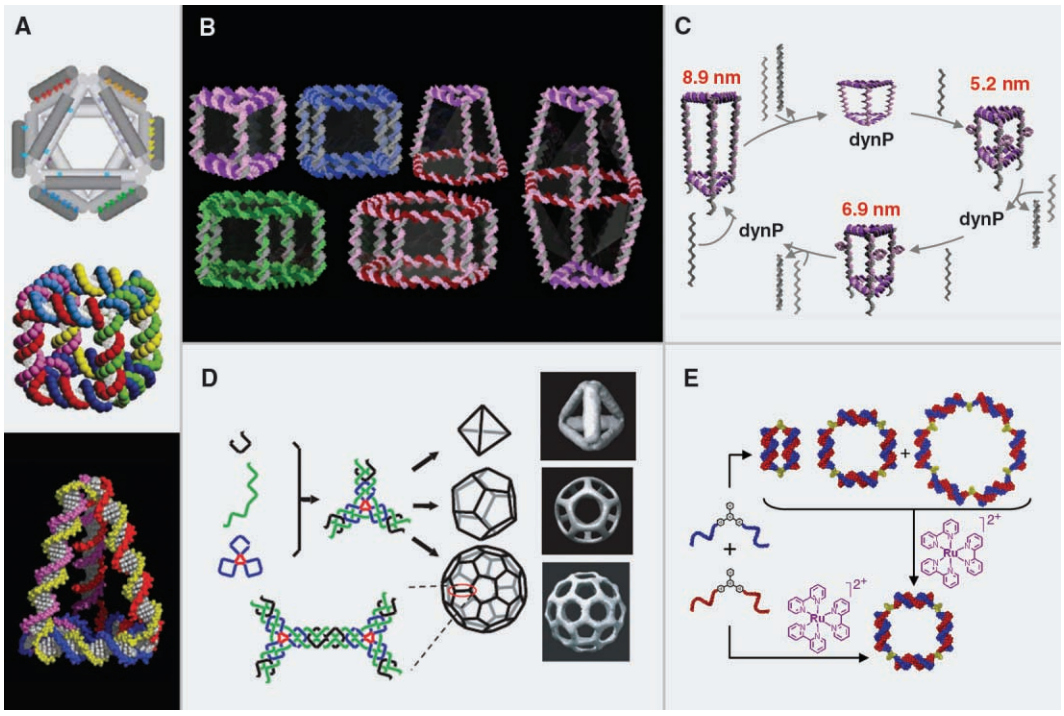

Fig. 3. (**A**) A DNA octahedron (top), cube (middle), and tetrahedron (bottom). (**B**) Single-stranded and cyclic DNA triangles, squares, pentagons, and hexagons with organic vertices as their corner units are assembled into 3D triangular prisms, cubes, pentameric and hexameric prisms, a heteroprism, and a biprism. (**C**) 3D DNA assemblies generated using this approach can also be dynamic. A triangular prism is switched between three predefined lengths using a series of strands capable of rigidifying and erasing. dynP, dynamic prism. (**D**) A symmetric three-arm junction assembles into a 3D tetrahedron, octahedron, or buckyball. Access to the desired structure is determined by the flexibility and concentration of the symmetric junction. (**E**) The molecule $Ru(bpy)^{2+}$ affects the self-assembly outcome of two symmetric DNA building blocks and selectively mediates the assembly of a single product, a DNA square.

Three-Dimensional Assembly

Three-dimensional structures made of DNA have tremendous potential to encapsulate and release drugs, regulate the folding and activity of encapsulated proteins, selectively encage nanomaterials, and assemble 3D networks for catalysis and biomolecule crystallization. Seeman reported early examples of 3D DNA objects with the topology of a cube (*43*) (Fig. 3A, middle) and a truncated octahedron. Joyce reported the synthesis of an octahedron (*19*) (Fig. 3A, top), and Turberfield generated a rigid and chiral DNA tetrahedron (Fig. 3A, bottom), in which the group encapsulated the protein cytochrome c (*44*). More recently, new methods that increase the range of 3D structures and their ease of synthesis have been reported. Sleiman developed a face-centered approach to 3D DNA construction (Fig. 3B). By breaking down 3D objects into discrete 2D DNA shapes, such as triangles, squares, pentagons, and hexagons with organic vertices, a large number of 3D DNA cages were quantitatively accessed. These include a triangular prism, a cube, a pentameric and hexameric prism, a heteroprism, and a biprism (*41*). The approach also allowed for the construction of the first dynamic 3D DNA capsule, whose size was switched reversibly between three different lengths (Fig. 3C) (*41*). Mao adopted the rules of symmetry to access 3D assemblies from building blocks with identical arms. By controlling the flexibility within a symmetric three-arm junction, the group synthesized a tetrahedron, a dodecahedron, and a buckyball from a minimal set of building blocks (Fig. 3D) (*45*). Turberfield also showed dynamic switching of a DNA tetrahedron (*44*), and von Kiedrowski reported the synthesis of a DNA dodecahedron with organic vertices (*46*).

In a different approach, Mirkin (*47*) and Gang (*48*) created 3D gold nanoparticle crystals with long-range order without using a preassembled DNA template. Instead, they modified gold nanoparticles with single-stranded DNA, which allowed them to control the interparticle distances and packing dynamics, and induced crystallization.

Current Challenges

These examples illustrate the power and promise of DNA as a template to precisely position materials on the nanoscale. In order to move this research forward, two challenges need to be addressed: the correction of errors that arise in DNA assembly, and the replication and scale-up of DNA nanostructures.

As the complexity of DNA assemblies increases, so will the number of the DNA sequences required to form them. This will necessitate using overlapping, degenerate strands that may assemble into undesirable products. Biological systems have developed a number of elegant strategies to proofread and remove errors during and after assembly. Inspired by these systems, Lu used an approach in which deoxyribozymes (DNAzymes) specifically locate and cleave misassembled structures in gold nanoparticle assemblies (*49*). In the presence of the "correct" DNA strands, the DNAzyme is not properly folded and is inactive; however, in the presence of the "incorrect" DNA strands, the DNAzyme is properly folded and proceeds to cleave and remove the errors. Using the rules of dynamic combinatorial chemistry, Sleiman used an external molecule to proofread and correct for errors (*50*). DNA building blocks with identical arms initially generated a library of many assemblies, but adding the small molecule $Ru(bpy)_3^{2+}$, an electrostatic binder of DNA, forced the library to converge to only one member, a DNA square (Fig. 3E). Pierce generated a number of metastable folded intermediates that systematically

interact with each other in a cascading approach to generate the final product (*51*). By programming the biomolecular pathway leading to the final assembly, and not just the final product, Pierce's approach prevents error formation.

To enable practical applications, it is necessary to develop techniques that copy, amplify, and scale up the synthesis of these structures. Assemblies generated using DNA origami are constructed from a single long DNA strand and, in principle, could readily be amplified using the already existing biological machinery. Seeman and Yan recently reported the successful enzymatic amplification of a building block found in classical DNA nanotechnology: a branched DNA tile containing several double cross-over motifs (*52*).

Assemblies generated using supramolecular chemistry can also be amplified. Von Kiedrowski showed the chemical copying of a molecule composed of three single-stranded DNA arms that branch out from a single organic vertex (*53*). Ultimately, today's materials are synthesized in large amounts using chemical approaches. It is therefore worthwhile to further investigate chemical methods to economically amplify these molecules. In principle, as long as the base-pair information within DNA is preserved, different backbones could also be used. Lynn copied the information from DNA into a daughter molecule, with preserved base sequence and a synthetic oligomeric backbone (*54*). The development of economically feasible amplification methods will allow for the structures developed by DNA nanotechnology to be widely used in materials science.

Conclusions and Outlook

DNA's simple code forms our genetic blueprint for life. But the field of DNA nanotechnology has invited us to look at the code in a whole new way: as a means to precisely position materials. This code can now help dictate the specific location of materials and the structure of assemblies, creating linear, 2D and 3D assemblies. It can also control motion, creating capsules that expand and contract, molecular "walkers" that move directionally along a track, and tweezers that grab desired targets (*55*). The DNA code can even dictate specific mechanistic pathways, enabling DNA origami to fold and DNA hairpins to open each other sequentially.

Nature builds complexity in a hierarchical way. It progressively increases length scales and relies on a number of noncovalent interactions, including DNA base-pairing, to drive assembly. Supramolecular DNA assembly is a means to weave in principles of hierarchical complexity and new interactions into DNA nanostructures, and opens the door to assembling more diverse functional structures with greater ease.

The next step will be to investigate the possibilities for making practical materials with DNA nanotechnology. DNA's ability to guide patterning of transition metals, nanoparticles, and proteins into deliberate designs gives it tremendous potential for answering many important challenges in science. For instance, is it now conceivable to assemble an artificial photosynthesis system, create a multienzyme catalytic "factory," or access complex nanoelectronic circuitry, using DNA? Can DNA be employed to generate combinatorial patterns of precisely positioned small-molecule ligands that probe cooperative binding and allosteric interactions in proteins and aid in the discovery of new multivalent drugs? Can DNA cages be used as biodegradable and molecule-responsive materials for the specific on-demand delivery of drugs to diseased cells? Can 3D DNA crystalline arrays be created and used as designer molecular hosts to template protein crystallization, as initially anticipated by Seeman, or to induce catalysis and new chemistry within their cavities?

These are only a handful of the opportunities created by our remarkable control over the organization of materials using DNA. It is by identifying the important challenges of biology, chemistry, physics, engineering, and medicine that we can put these patterned nanomaterials to the test and evolve this exciting field into an applied, central area of research.

References and Notes

1. N. C. Seeman, *Nature* **421**, 427 (2003).
2. C. Lin, Y. Liu, S. Rinker, H. Yan, *Chem. Phys. Chem.* **7**, 1641 (2006) and references therein.
3. P. W. Rothemund, N. Papadakis, E. Winfree, *PLoS Biol.* **2**, 2041 (2004).
4. A. Chworos *et al.*, *Science* **306**, 2068 (2004).
5. Y. Weizmann, A. B. Braunschweig, O. I. Wilner, Z. Cheglakov, I. Willner, *Proc. Natl. Acad. Sci. U.S.A.* **105**, 5289 (2008).
6. R. P. Fahlman, D. Sen, *J. Am. Chem. Soc.* **124**, 4610 (2002).
7. A. P. Alivisatos *et al.*, *Nature* **382**, 609 (1996).
8. K. Y. Pinto *et al.*, *Nano Lett.* **5**, 2399 (2005).
9. J. Zheng *et al.*, *Nano Lett.* **6**, 1502 (2006).
10. J. Sharma, R. Chhabra, Y. Liu, Y. Ke, H. Yan, *Angew. Chem. Int. Ed.* **45**, 730 (2006).
11. H. Yan, S. H. Park, G. Finkelstein, J. H. Reif, T. H. LaBean, *Science* **301**, 1882 (2003).
12. Y. He, Y. Tian, A. E. Ribbe, C. Mao, *J. Am. Chem. Soc.* **128**, 12664 (2006).
13. B. A. R. Williams, K. Lund, Y. Liu, H. Yan, J. C. Chaput, *Angew. Chem. Int. Ed.* **46**, 3051 (2007).
14. R. Chhabra *et al.*, *J. Am. Chem. Soc.* **129**, 10304 (2007).
15. J. D. Cohen, J. P. Sadowski, P. B. Dervan, *J. Am. Chem. Soc.* **130**, 402 (2008).
16. C. Lin, Y. Liu, H. Yan, *Nano Lett.* **7**, 507 (2007).
17. Z. Deng, C. Mao, *Angew. Chem. Int. Ed.* **43**, 4068 (2004).
18. J. Malo *et al.*, *Angew. Chem. Int. Ed.* **44**, 3057 (2005).
19. W. M. Shih, J. D. Quispe, G. F. Joyce, *Nature* **427**, 618 (2004).
20. P. W. K. Rothemund, *Nature* **440**, 297 (2006).
21. Y. Ke, S. Lindsay, Y. Chang, Y. Liu, H. Yan, *Science* **319**, 180 (2008).
22. S. M. Douglas, J. J. Chou, W. M. Shih, *Proc. Natl. Acad. Sci. U.S.A.* **104**, 6644 (2007).
23. J.-M. Lehn, *Chem. Soc. Rev.* **36**, 151 (2007).
24. J. Shi, D. E. Bergstrom, *Angew. Chem. Int. Ed. Engl.* **36**, 111 (1997).
25. M. S. Shchepinov, K. U. Mir, J. K. Elder, M. D. Frank-Kamenetskii, E. M. Southern. *Nucleic Acids Res.* **27**, 3035 (1999).
26. M. Scheffler, A. Dorenbeck, S. Jordan, M. Wüstefeld, G. von Kiedrowski, *Angew. Chem. Int. Ed.* **38**, 3311 (1999).
27. F. A. Aldaye, H. F. Sleiman, *Angew. Chem. Int. Ed.* **45**, 2204 (2006) and references therein.
28. J. C. Chaput, C. Switzer, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 10614 (1999).
29. W. Wang, W. Wan, H.-H. Zhou, S. Niu, A. D. Q. Li, *J. Am. Chem. Soc.* **125**, 5248 (2003).
30. M. Goritz, R. Kramer, *J. Am. Chem. Soc.* **127**, 18016 (2005).
31. K. Ding, F. E. Alemdaroglu, M. Borsch, R. Berger, A. Herrmann, *Angew. Chem. Int. Ed.* **46**, 1172 (2007).
32. M. Endo, N. C. Seeman, T. Majima, *Angew. Chem. Int. Ed.* **44**, 6074 (2005).
33. K. V. Gothelf, A. Thomsen, M. Nielsen, E. Clo, R. S. Brown, *J. Am. Chem. Soc.* **126**, 1044 (2004).
34. K. Tanaka, A. Tengeiji, T. Kato, N. Toyama, M. Shionoya, *Science* **299**, 1212 (2003).
35. K. Tanaka *et al.*, *Nat. Nanotechnol.* **1**, 190 (2006).
36. D. Mitra, N. Di Cesare, H. F. Sleiman, *Angew. Chem. Int. Ed.* **43**, 5804 (2004).
37. J. S. Choi *et al.*, *J. Am. Chem. Soc.* **126**, 8606 (2004).
38. K. M. Stewart, J. Rojo, L. W. McLaughlin, *Angew. Chem. Int. Ed.* **43**, 5808 (2004).
39. H. Yang, H. F. Sleiman, *Angew. Chem. Int. Ed.* **47**, 2443 (2008).
40. F. A. Aldaye, H. F. Sleiman, *J. Am. Chem. Soc.* **129**, 4130 (2007).
41. F. A. Aldaye, H. F. Sleiman, *J. Am. Chem. Soc.* **129**, 13376 (2007) and references therein.
42. The development of DNA machines has been an exciting and productive area of research; for a recent review see (*55*).
43. J. H. Chen, N. C. Seeman, *Nature* **350**, 631 (1991).
44. R. P. Goodman *et al.*, *Nat. Nanotechnol.* **3**, 93 (2008) and references therein.
45. Y. He *et al.*, *Nature* **452**, 198 (2008).
46. J. Zimmermann, M. P. J. Cebulla, S. Monninghoff, G. von Kiedrowski, *Angew. Chem. Int. Ed.* **47**, 3626 (2008).
47. S. Y. Park *et al.*, *Nature* **451**, 553 (2008).
48. D. Nykypanchuk, M. M. Maye, D. van der Lelie, O. Gang, *Nature* **451**, 549 (2008).
49. J. Liu, D. P. Wernette, Y. Lu, *Angew. Chem. Int. Ed.* **44**, 7290 (2005).
50. F. A. Aldaye, H. F. Sleiman, *J. Am. Chem. Soc.* **129**, 10070 (2007).
51. P. Yin, H. M. T. Choi, C. R. Calvert, N. A. Pierce, *Nature* **451**, 318 (2008).
52. C. Lin, X. Wang, Y. Liu, N. C. Seeman, H. Yan, *J. Am. Chem. Soc.* **129**, 14475 (2007).
53. L. H. Eckardt *et al.*, *Nature* **420**, 286 (2002).
54. X. Li, Z.-Y. Zhan, R. Knipe, D. Lynn, *J. Am. Chem. Soc.* **124**, 746 (2002).
55. J. Bath, A. J. Turberfield, *Nat. Nanotechnol.* **2**, 275 (2008).
56. F.A.A. and H.F.S. have filed a provisional patent, U.S. 60/960,000, on using DNA nanocapsules for controlled drug and gene delivery.

10.1126/science.1154533