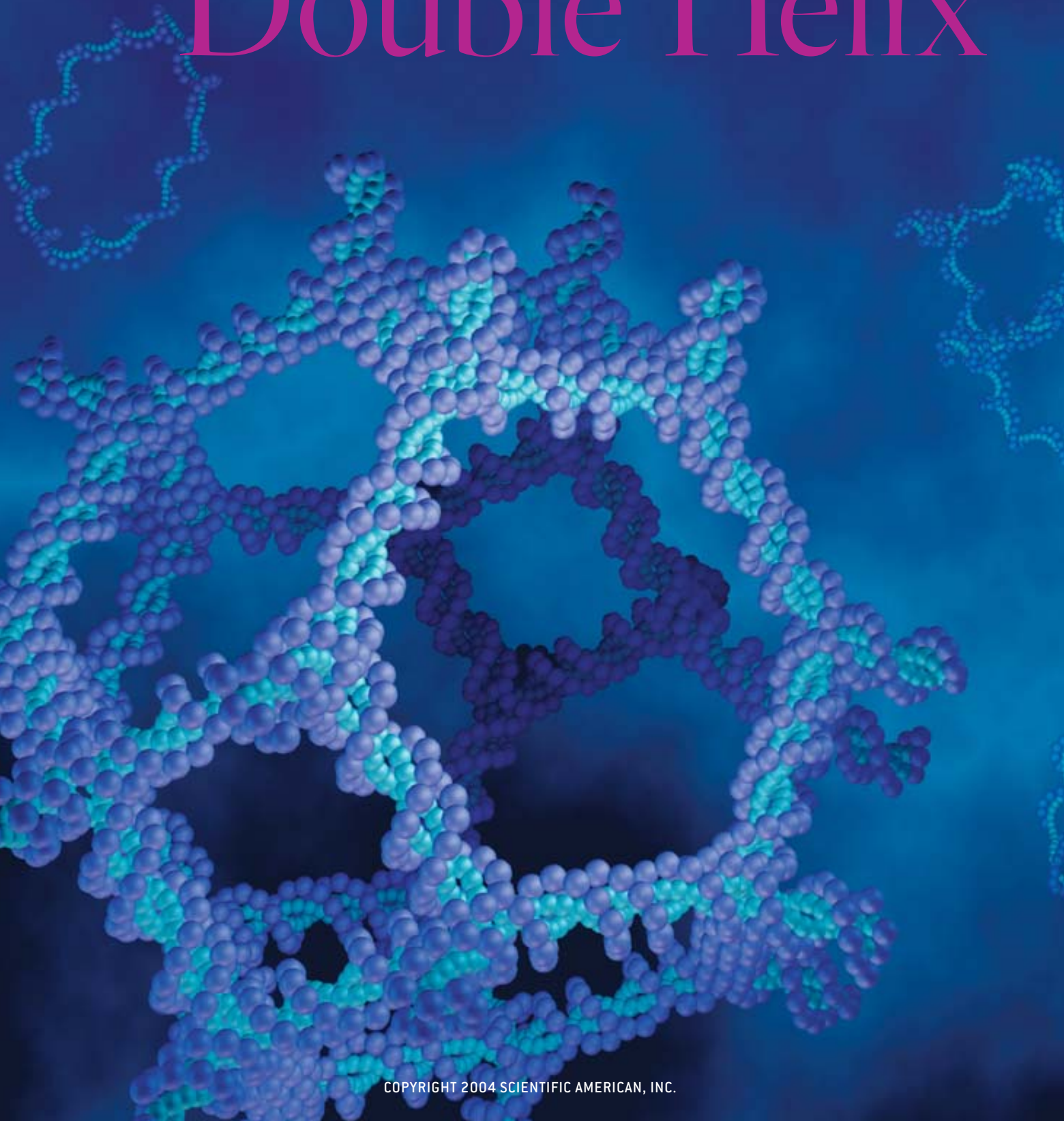


Nanotechnology and the Double Helix



COPYRIGHT 2004 SCIENTIFIC AMERICAN, INC.

DNA is more than just the secret of life—it is also a versatile component for making nanoscopic structures and devices

By Nadrian C. Seeman

The year 2003 witnessed the 50th anniversary of the discovery of DNA's double-helix structure by James D. Watson and Francis H. Crick. Their discovery reduced genetics to chemistry and laid the foundations for the next half a century of biology. Today thousands of researchers are hard at work deciphering the myriad ways that genes control the development and functioning of organisms. All those genes are written in the medium that is DNA.

Yet this extraordinary molecule has other uses in addition to those of biochemistry. By employing the techniques of modern biotechnology, we can make long DNA molecules with a sequence of building blocks chosen at will. That ability opens the door to new paths not taken by nature when life evolved. In 1994, for example, Leonard M. Adleman of the University of Southern California demonstrated how DNA can be used as a computational device [see "Computing with DNA," by Leonard M. Adleman; *SCIENTIFIC AMERICAN*, August 1998]. In this article I will discuss another nonbiological use of DNA: the building of structures and devices whose essential elements and mechanisms range from around one to 100 nanometers in size—in a word, nanotechnology.


Such structures have many potential applications. Regular lattices made of DNA could hold copies of large biological molecules in an ordered array for x-ray crystallography to determine their structure, an important step in the "rational" design of drugs. Alternatively, the lattices could serve as scaffolding for nanoelectronic components, either as a working device or as a step in the manufacture of a device. Materials could be constructed—either made of the DNA or made by it—with structures precisely designed at the molecular level. DNA machines with moving parts could be employed as nanomechanical sensors, switches and tweezers as well as for more elaborate robotic functions.

Branched DNA

THE NANOSCALE is the scale of molecules. A typical bond between two atoms is about 0.15 nanometer long. (A nanometer is a billionth of a meter.) The helix of DNA has a diameter of about two nanometers, and it twists full circle once every 3.5 nanometers or so, a distance of about 10 base pairs, which form the "rungs" of DNA's ladder [see *upper illustration on page 67*]. A short piece of DNA has highly specific interactions with other chemicals, depending on its sequence of base pairs. One can imagine using such pieces to recognize particular molecules or to control the composition of a material by acting as a catalyst. And for many years biologists have used DNA for its recognition properties, especially exploiting the "sticky ends" in genetic engineering. A sticky end occurs when one strand of the helix extends for several

DNA STRANDS SELF-ASSEMBLE into a complicated structure when their base sequences are designed to pair up with specific partners. Here a stick model of a truncated octahedron, which has six square faces and eight hexagonal faces, has formed. The edges are about 20 nanometers long. A short "hairpin" of DNA sticks out from each corner. The hairpins could be modified to link truncated octahedra together to form a regular three-dimensional scaffold.

KEN EDWARD BioGrafX (strands, left); ALICE Y. CHEN (helix, right)



unpaired bases beyond the other [see lower illustration on opposite page]. The stickiness is the propensity of the overhanging piece to bond with a matching strand that has the complementary bases in the corresponding order—the base adenine on one strand pairs with thymine on the opposite strand, and cytosine binds with guanine. [For another application using the stickiness of DNA, see “The Magic of Microarrays,” by Stephen H. Friend and Roland B. Stoughton; SCIENTIFIC AMERICAN, February 2002.]

At first sight, it does not appear that DNA can lead to interesting structures. Naturally occurring DNA forms a linear chain, like a long piece of twine, so that all one can envision making

that of the numeral “69”) in the base sequences that flank it. This symmetry means that each strand can pair up with either of two other strands. In 1979 I was working with Bruce H. Robinson, now at the University of Washington, to describe the nature of this motion when I recognized that synthetic DNA molecules lacking this symmetry could form branched molecules whose branch points do not move. To design such a junction, one would make four strands of DNA. For each strand, the sequence along half of the strand would match half of a second strand and the remaining half would match half of a third strand [see lower illustration on opposite page].

DNA’s favorite structure is the conventional double helix

STRANDS OF DNA interact in the most programmable way. Their enormous variability provides ample scope for DESIGNING MOLECULES.

from it is lines or circles, perhaps snarled up or knotted in one way or another. But a linear chain is not the only form that DNA takes. During certain cellular processes, DNA exists briefly as a branched molecule. This branching occurs when DNA replicates (in preparation for cell division) and during recombination (when genetic material is swapped between matching pairs of chromosomes, as happens when sperm and eggs are produced).

The branches form when the double helix partially unravels into two strands. In replication, each strand is made into a new double helix by the addition of complementary nucleotides all along its length. (A nucleotide is the combination of a base and the corresponding section of the backbone of the helix.) More interesting is the crossover that occurs in recombination, in which two pieces of DNA break and partially unravel and the resulting four strands join up somewhat like the intersection where two highways cross.

In recombining DNA, the branch point occurs where each of the four strands switches from one partner to another. The branch point moves around because of twofold symmetry (like

identified by Watson and Crick. A quantity called free energy determines which structure is favored. In general, free energy determines whether a chemical reaction proceeds in the forward or reverse direction; it also determines the conformation—the folds and joins—of large molecules such as DNA, RNA and proteins. A chemical system always tends to change toward the state that has the lowest free energy. For two complementary strands of nucleotides, the free energy is minimized when they pair up to form a double helix.

The four strands of our immobile junction can come together and form the maximum amount of conventional DNA double helices only by forming a branched molecule. In general, a branch point is not favored—it increases the free energy of the molecule—but this increase is outweighed by the much greater energy saving in the four arms made of ordinary double-helix DNA. Today it is simple to synthesize such strands and implement this idea of a stable branched DNA molecule, but in 1979 it was state-of-the-art chemistry and I was a crystallographer, not an organic chemist, so mostly I just thought about the system. (It was not until 1982 that I learned how to make DNA.)

Overview/DNA Nanotech

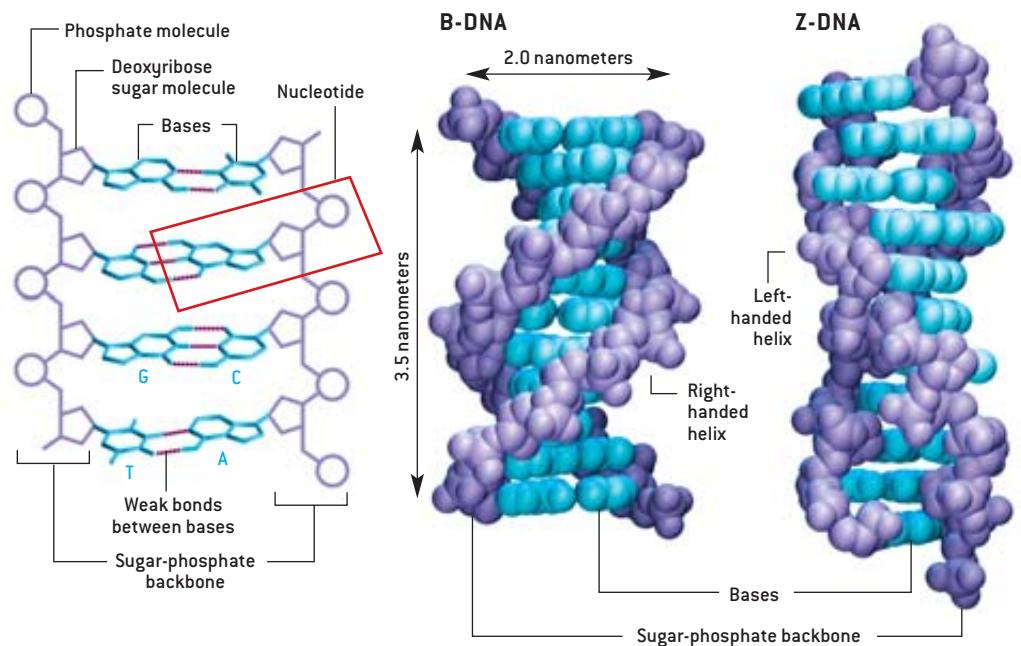
- DNA is an ideal molecule for building nanometer-scale structures. Strands of DNA can be programmed to self-assemble into complex arrangements by producing the strands with the appropriate combinations of complementary bases, which preferentially bond together to form stretches of double helices.
- DNA scaffolds could hold guest molecules in orderly arrays for crystallography. They could also hold molecule-size electronic devices, or be used to build materials with precise molecular configurations.
- Nanometer-scale DNA machines can function by having parts of their structure change from one DNA conformation to another. These movements can be controlled by chemical means or by the use of special DNA strands.

Inspiration from Escher

I FIGURED OUT that it ought to be possible to make branched DNA junctions with many arms, not just four. One day, in the fall of 1980, I went over to the campus pub to think about six-arm junctions. For some reason, I thought about Dutch artist M. C. Escher’s woodcut *Depth* [see illustration on page 68]. I realized that the center of each fish in that picture was just like an idealized picture of the branch point of a six-arm junction. Six features extend from that center point on the fish: a head and a tail, a top fin and bottom fin, a left fin and a right fin. The fish are organized in the same way as the molecules in a molecular crystal, with regular repeats forward and back, up and down, left and right. It struck me that if I held junctions together using sticky ends, I might be able to organize matter on the nanometer scale in the same way that Escher held his school of fish together using his imagination.

THE STRUCTURE OF DNA

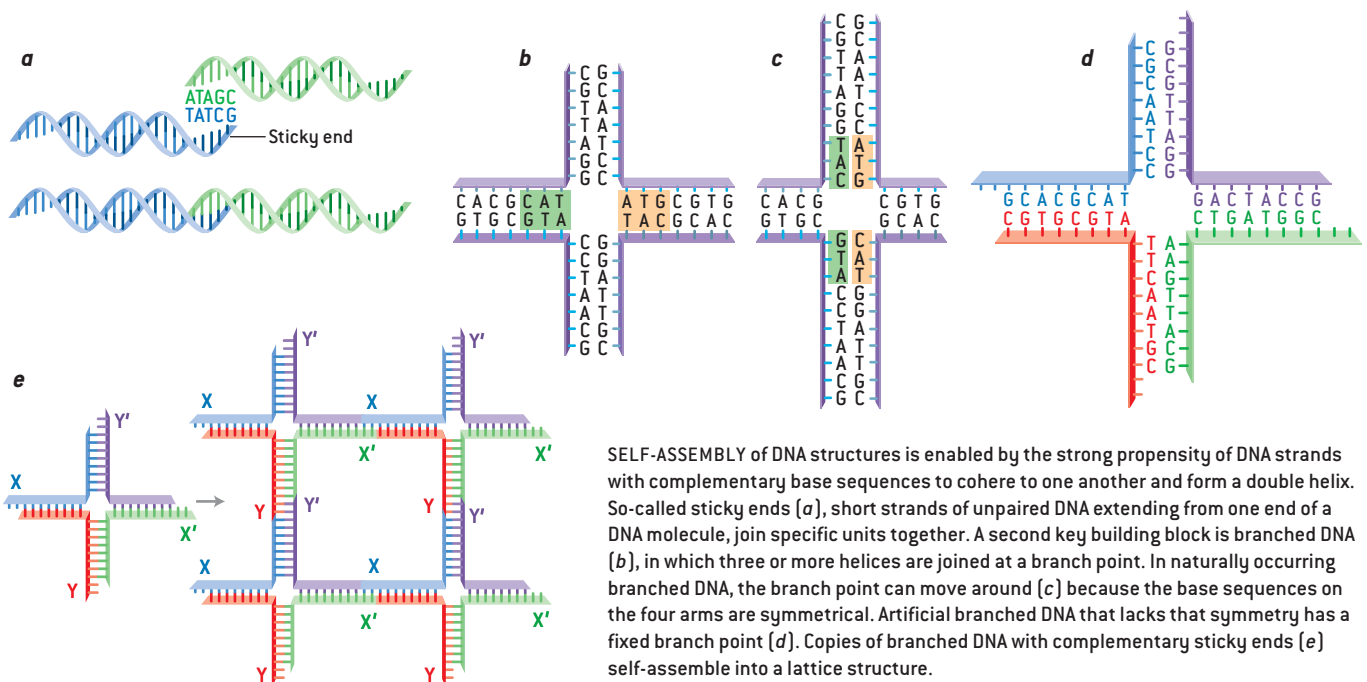
DNA is a nanoscale structure, consisting of a double backbone of phosphate and sugar molecules between which complementary pairs of bases (A and T; C and G) are connected by weak bonds (*left*). DNA's most common conformation is B-DNA (*center*), which twists in a right-handed double helix about two nanometers in diameter. One full turn of the helix is about 3.5 nanometers, or 10 to 10.5 base pairs long. In special circumstances DNA can form a left-handed double helix called Z-DNA (*right*).



We have several good reasons for wanting to build such structures. First, we are aiming to fabricate macroscopic pieces of matter made of designed molecules joined together in a structure that is controlled with nanoscopic precision. This procedure could result in materials having novel properties or novel combinations of properties. For example, materials with designed optical properties, such as photonic crystals, could be made by constructing precisely defined arrays with specific re-

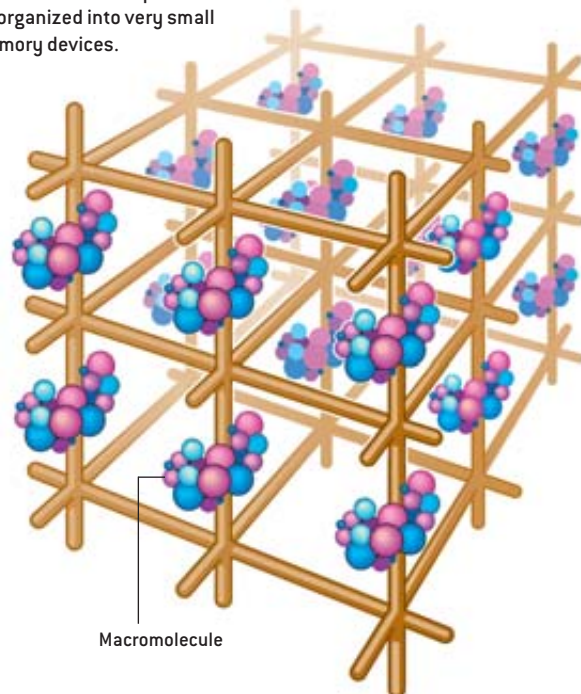
peat distances [see “Photonic Crystals: Semiconductors of Light,” by Eli Yablonovitch; *SCIENTIFIC AMERICAN*, December 2001].

Another goal is to use DNA as scaffolding to hold other molecules in arrays, including those that do not form a regular crystalline structure on their own. In this way, one could make crystals for use in crystallography experiments by making DNA cages that contain large biological molecules such as proteins within them [see *right illustration on next page*]. Such cages





ESCHER'S WOODCUT *DEPTH* (left) inspired the author to consider an array of six-arm junctions connected together to form a three-dimensional molecular crystal (below). The center of each fish is just like the branch point of a six-arm junction. Instead of arms, six features extend from that center point: a head and a tail, a top and bottom fin, and a left and right fin. Molecular scaffolding could hold other molecules in regular arrays. For example, DNA cages containing oriented biological macromolecules as guests could be used in crystallography experiments. In a similar fashion, nanoelectronic components could be organized into very small memory devices.



would enable crystallographers to determine the three-dimensional structures of the enclosed molecules—a key procedure in the rational design of drugs that mesh precisely with specific parts of a targeted molecule. (This crystallographic application is the one that most strongly motivates my interest in this field.) Currently many of the receptor molecules that could be excellent drug targets do not lend themselves to conventional crystallography. In a similar fashion, one could organize nanoelectronic components into very small memory devices, as Robinson and I suggested in 1987. My group has not used DNA as scaffolding yet, but we have had many other successes that are steps on the way to achieving this goal.

Why use DNA for these purposes? The chief reason is that strands of DNA interact in the most programmable and pre-

dictable way. A sticky end that is N bases long has one of 4^N possible sequences of bases. This enormous variability and the propensity of the end to bond to only a closely matching sequence provide ample scope for designing molecules that consist of a large number of DNA strands joined to one another in a completely specified manner. Furthermore, we know that two sticky ends form the classic helical DNA structure when they cohere, and these helical stretches of DNA are relatively stiff. Thus, we know not only which strands link to which other strands but also the detailed shape of the joined segments. We do not have such specific information for proteins or antibodies, which are other candidates for working elements. Those also have tremendous variability, but determining what shape a protein will take and how two proteins or antibodies will join together are laborious problems that would have to be solved anew for each example.

Another reason for working with DNA is the simplicity of its synthesis with the tools of the biotechnology industry. We can manipulate DNA with many enzymes, such as restriction enzymes (which cleave DNA at particular sites) or ligases (which catalyze the joining of two molecules by covalent bonds—sturdy chemical bonds that involve the sharing of pairs of electrons between atoms). These tools can be used to make and manipulate conventional DNA, as well as exotic derivatives, in which different bases from the usual four are incorporated or in which

THE AUTHOR

NADRIAN C. ["NED"] SEEMAN trained in crystallography, but his frustrations with a macromolecular crystallization experiment led him to the idea that DNA junctions could be used in a new approach to crystallization. Ever since then, he has been trying to implement this concept and its spin-offs. For the past 16 years, Seeman has worked in the department of chemistry at New York University. When told in the mid-1980s that what he was doing was nanotechnology, his response was similar to that of M. Jourdain, the title character of Molière's *Bourgeois Gentilhomme*, who was delighted to discover that he had been speaking prose all his life.



additional molecules are attached on the outside of the DNA's backbone (the sides of the DNA ladder). Medical researchers hoping to use nucleic acids (DNA and RNA) for therapy have made many such variants. DNA is extremely well suited to making such derivatives because every nucleotide along the helix has sites where molecules can be attached.

Finally, as we will see below, DNA can be induced to form structures different from the standard double helix. We can build nanomechanical devices whose parts move—such as closing tweezers or a rotating shaft—when there is a transition from one DNA structure to another. One drawback is that DNA ob-

dividual truncated octahedra, instead we built them using four-arm junctions. We intended that the extra arm sticking out at each corner could be used to connect truncated octahedra together in a larger structure, but in the end we did not continue in this direction. We had created only a very tiny quantity of truncated octahedra—enough to characterize their structure but too few to attempt to join them together—and even that minute sample had taken us to the limits of what we could do without overhauling our procedures (for example, by robotizing repetitive steps). Instead we turned to simpler components.

Another reason for changing direction was that along the

THE POLYHEDRA we had built were rather like structures made of toothpicks stuck into BLOBS OF MARSHMALLOW at the corners.

jects must be constructed in an aqueous solution. It is no problem, however, to dry the resulting structures (on mica, for instance) as we do to make microscopic images of our results.

Stick Models

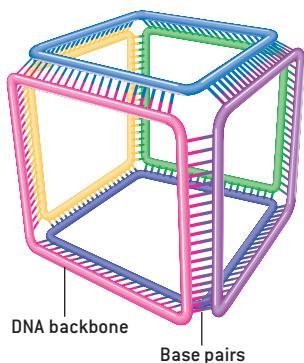
THE FIRST STEP in any new scientific research program is to establish the basic feasibility of the project. In 1991 Junghuei Chen, now at the University of Delaware, and I did this by building a DNA molecule shaped like a cube formed from sticks [see illustration below]. Each edge of the cube is a stretch of double-helical DNA; each corner is a three-arm junction. Each corner is connected to three other corners; it is said that the cube's connectivity is three. Genetic engineers had made many linear DNA constructs, but this was the first DNA molecule with connectivity greater than two. The cube self-assembles from pieces of DNA designed to adhere to one another, but the ends of each piece do not join up. Ligases can connect these free ends, resulting in six closed loops, one for each face of the cube. Because of the helical nature of DNA, each of these loops is twisted around the loops that flank it, so the cube cannot come apart, even if all the bonds joining the base pairs together were somehow broken.

Yuwen Zhang, now at Baxter Healthcare, and I built another shape called a truncated octahedron, which is similar to but more complicated than a cube [see illustration on page 64]. Although three-arm junctions would have sufficed to make in-

way we realized that the stick polyhedra we had built were not rigid. DNA is a stiff molecule: a stretch of DNA that is two or three turns long (the lengths we use for the polyhedra edges) can wiggle around its helix's axis no more than a piece of cooked spaghetti two or three millimeters long can wiggle around its central axis. That inflexibility ensured that the edges of our stick figures were rigid, but we learned that the angles at each corner were quite variable. The polyhedra we had built were rather like structures made of toothpicks stuck into blobs of marshmallow at the corners. Such structures might have uses, but building a regular lattice is not one of them. It is much easier to self-assemble an orderly, crystallike piece of matter from bricklike components than from marshmallows.

To solve this problem, my group examined another branched motif found in biological recombination systems, the DNA double-crossover (DX) molecule. The DX molecule consists of two double helices aligned side by side, with strands crossing be-

STICK CUBE [far right] made out of six loops of DNA demonstrated that three-dimensional structures can be built. The backbone of each DNA strand is depicted as colored spheres (a different color for each strand) and the bases as white spheres. Each edge of the cube comprises 20 nucleotide pairs, or about two complete turns of the double helix. Each corner is a three-arm junction. Simplified schematic (near right) depicts how the DNA strands are connected but omits the helical twists.

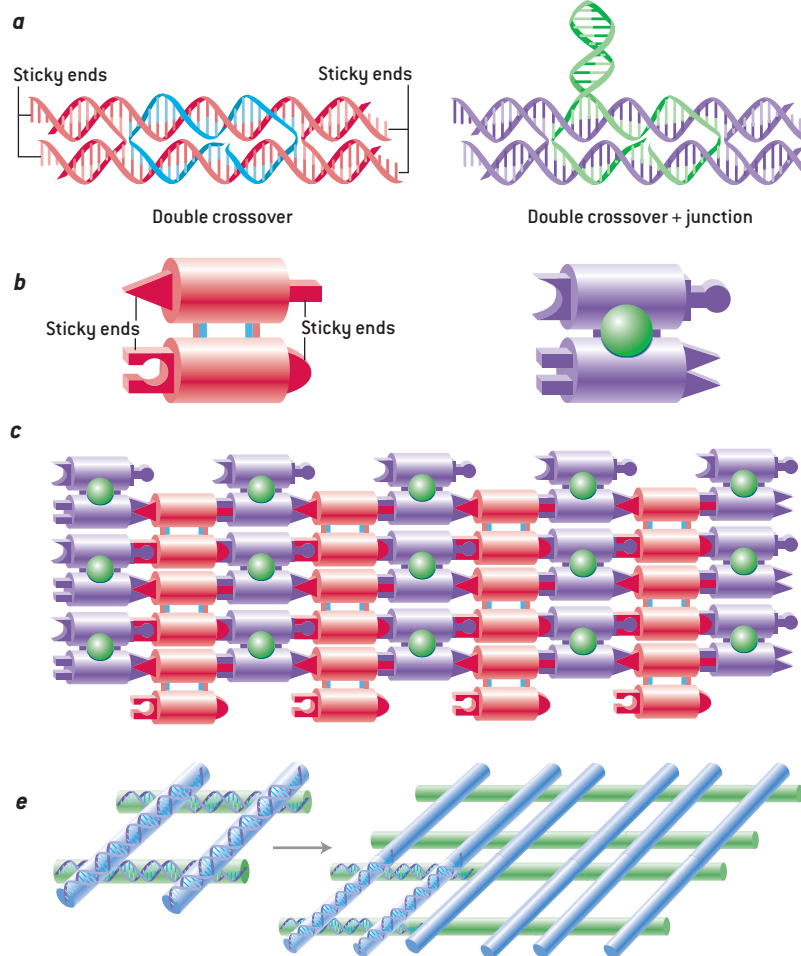


STIFF DNA ARRAYS

Two-dimensional crystals can be made out of stiff bricks of DNA. The bricks (a) are double-crossover (DX) and double-crossover-plus-junction (DX + J) units, which cannot flop around at their joining

points the way that multiarm junctions can. Each brick has four distinct sticky ends for joining bricks together. The extended green strand of the DX + J unit sticks out of the plane. Each unit is about

4 by 16 nanometers in size. For simplicity, the DX and DX + J units are shown schematically, with geometric shapes at their ends representing the sticky ends (b). In a solution, the sticky ends cohere and the units self-assemble in a two-dimensional pattern (c). The striped pattern shows up in an atomic-force microscope image of the crystal (d) (which is deposited onto a flat mica surface for the microscopy). The bright stripes, spaced about 32 nanometers apart, are the lines of DNA protruding from the DX + J units. Parallelograms of DNA have also been self-assembled into two-dimensional patterns (e, f).



tween the helices, yoking them together [see box above]. We characterized this molecule and established that it is stiff. We also demonstrated that a DX molecule containing another small double helical region (called a DX + J molecule) is very stiff. This additional double helical region creates a bump on the top of the DX molecule, which serves as a marker—a nanotech equivalent of a dab of paint.

In collaboration with Erik Winfree of the California Institute of Technology, Furong Liu and Lisa A. Wenzler of my group at New York University used combinations of DX and DX + J molecules as tiles to make two-dimensional crystals with defined patterns. The tiles are joined together by sticky ends on each helix. One arrangement, with columns of DX tiles alternating with columns of DX + J tiles, produces a pattern of stripes separated by about 32 nanometers. We deposited the arrays on

a flat mica surface and examined them with an atomic-force microscope to confirm that the structure had the correct dimensions. We established that the pattern was not accidental by making a second crystal with modified tiles that link together with three DX columns for each DX + J column, to produce stripes with double the separation.

Recently John H. Reif's group at Duke University demonstrated "DNA bar codes" made using such patterns. In these tilings, the positions of stripes were programmed to occur in a pattern representing the number "01101" (with molecules analogous to our DX and DX + J serving as 0 and 1, respectively). The pattern was programmed using an input DNA strand whose sequence encoded the 01101 pattern. The analogues of the DX and DX + J bricks self-assembled on the sections of the DNA strand corresponding to 0 and 1, respectively. Many such

five-brick sequences then joined up in parallel, generating the 01101 pattern of stripes. The stripes were about 15 nanometers apart. By examining the stripes with an atomic-force microscope, one is effectively using the bar code to read out the data that were encoded on the input DNA strand. This visual means of reading out the DNA sequence could greatly speed up the readout stage of DNA-based computing and might also be used for mapping mutations.

Chengde Mao, now at Purdue University, and I have made two-dimensional patterns from DNA parallelograms similar to our stick polyhedra. Copies of this unit can be joined to form a

quirement lets us control *when* the transition (and hence the machine action) occurs.

My N.Y.U. colleagues Weiqiong Sun and Zhiyong Shen, Mao and I built a device consisting of two DX molecules connected by a shaft of double-helical DNA [see illustration below]. In the middle of the shaft is a sequence of 20 base pairs that can adopt the Z-structure in the appropriate conditions. In ordinary conditions, every part of the device will form B-DNA and the two DX molecules will both be on the same side of the shaft's axis. When cobalt hexamine is added to the solution, the central part of the shaft converts to Z-DNA and one DX molecule ro-

A CRUCIAL GOAL for nanotechnology based on DNA is to extend the successes in two dimensions TO THREE DIMENSIONS.

crystal that extends like a waffle in two dimensions. One can tune the sizes of the cavities in the array by changing the dimensions of the parallelograms. Although individual branched junctions are floppy, arranging four of them at the corners of a parallelogram results in a well-behaved unit in a parallelogram array.

Nanomachines

CENTRAL TO NANOTECHNOLOGY are molecular-scale machines. DNA has proved to be very useful for constructing these machines. We have built several devices from DNA, but here I will focus on two that have well-defined structures. In both cases, the mechanism is based on a structural transition of DNA molecules—a change from one conformation (such as the usual double helix) to another.

Conventional DNA is a right-handed helix. Imagine walking up a spiral staircase with your left hand on the inner banister and your right hand on the outer one. Such a staircase is a right-handed helix. Conventional right-handed DNA is called B-DNA and is the most energetically favored structure in typical aqueous conditions.

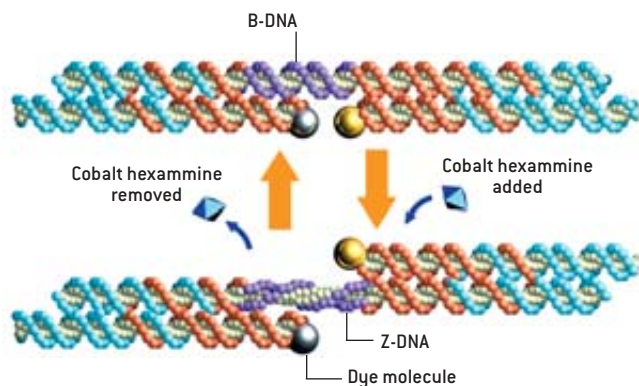
Double-helical DNA can also assume a number of different structures depending on its base sequence and the chemical species present in the solution in which it is immersed. One is Z-DNA, whose structure was first characterized in 1979 by Alexander Rich and his colleagues at the Massachusetts Institute of Technology [see upper illustration on page 67]. Z-DNA is a left-handed DNA structure.

To make Z-DNA typically requires a stretch of alternating cytosine and guanine bases. The DNA backbone includes negatively charged phosphate groups, and these come close together in the Z-DNA structure. This formation is favored only if the charges of the phosphates can be screened from one another by an aqueous environment containing either a high concentration of salt or a special “effector” species, such as cobalt hexamine, $\text{Co}(\text{NH}_3)_6^{+++}$, that does the same job at a much lower concentration. The cytosine-guanine sequence requirement lets us control *where* on a DNA molecule the B-Z transition takes place (and hence *what* our machine does), and the environmental re-

tates about 3.5 turns relative to the other; the odd half-turn means that they are now on opposite sides of the shaft's axis. Removal of the cobalt hexamine reverts the device back to its original structure. We demonstrated that the motion was taking place by using spectroscopy involving two colored dyes attached to the DX molecules.

This B-Z device is quite robust, but it suffers from a flaw. Were a bunch of different B-Z devices incorporated into a larger superstructure (for example, one of the two-dimensional lattices discussed earlier), the entire structure would have only two states: every machine in the B state or every one in the Z state. To control a collection of machines individually requires devices with independent triggers. With DNA, of course, there is a natural way to do this, by using DNA strands as the triggers and having a different base sequence trigger each machine.

To implement this scheme, Hao Yan, now at Duke, Xiaoping Zhang of New York University, Shen and I devised a system that changes shape when different strands bind to it. The



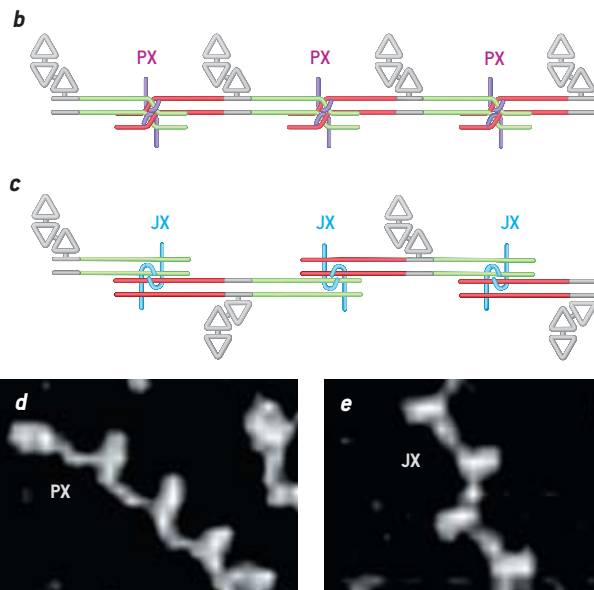
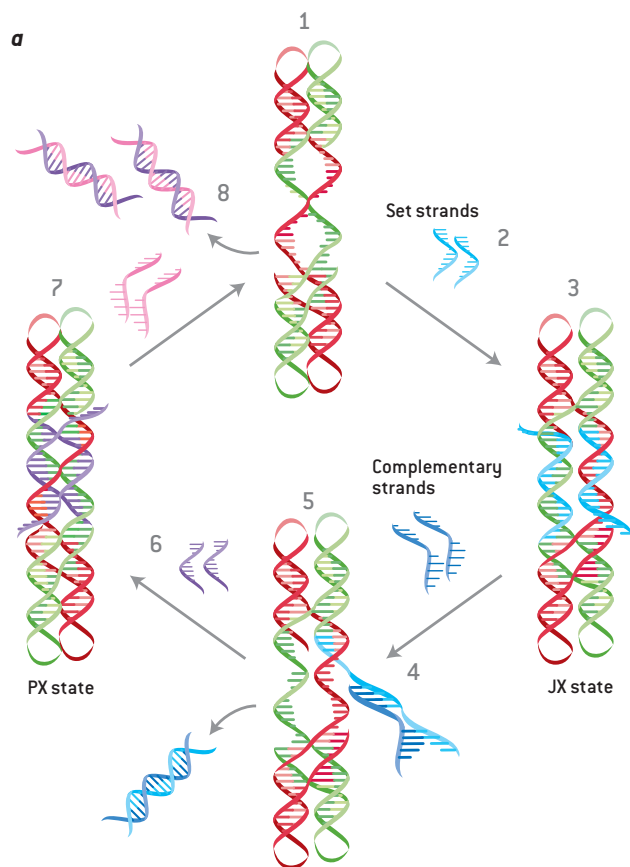
NANOMECHANICAL B-Z DEVICE that demonstrates controlled movement is made of two DX units [blue and orange] joined by a shaft of 20 base pairs [purple]. Two colored dye molecules [silver and gold spheres] highlight the positions of the DX molecules. In the B state (top), the shaft is ordinary right-handed B-DNA and both DX molecules are on the same side. When cobalt hexamine is added to the solution, the shaft converts to left-handed Z-DNA [see upper illustration on page 67] and the DX units rotate through 3.5 turns relative to each other, ending up on opposite sides of the shaft.

USING DNA AS A TRIGGER

Individually controllable DNA device is switched between two states [a, steps 1–8] by the addition and removal of specific stretches of DNA called set strands. The naked device consists of four double helices connected in the middle by two unpaired DNA strands (1). When the light-blue set strands are added (2), they bind to the unpaired strands in a way that forces the device into the “doubly juxtaposed” [JX] state (3). In this state, the red

and green helices are on the same side, top and bottom. The light-blue strands are stripped away when complementary strands are added (4), leaving the device naked again (5). Now the purple set strands are added (6), which bind in a different way, forcing the device into the so-called paranemic crossover [PX] state (7). This rotates the lower part of the device, putting the red and green helices on the opposite sides. The machine’s cycle can continue with the stripping away of the purple strands (8) and the reintroduction of the light-blue strands.

The functioning of this device was verified by connecting copies of it in a chain, with large trapezoid-shaped pieces of DNA attached as markers. When the devices are in the PX state [b, below], all the trapezoids are on the same side. When all the devices are in the JX state [c], the trapezoids alternate sides. Atomic-force microscopy revealed precisely this pattern of behavior [d, e].



system consists of two parallel DNA double helices that each reduce to a single strand in a central crossover region. The crossover region can assume two different states according to which particular strands have been added to the solution to bind to the single-strand sections [see box above]. The two states of the device are called PX (“paranemic crossover”) and JX (“juxtaposed”). When the device is in the PX state, the two helices on one side of the central junction are rotated about a half-turn from their positions in the JX state.

Adding a particular pair of strands (called set strands) to the solution puts the device in the JX state by binding to the central region without crossing over. To change to the PX state, we must first remove these set strands. In 2000 Bernard Yurke and his colleagues at Lucent Technologies showed that a strand can be extracted from DNA by binding the strand’s full complement to it. To implement this process, our set strands have short ends

that remain unpaired with the machine. When we add a full complementary strand to the solution, it begins by joining to the unpaired extension and then strips off the rest of the set strand from the device.

With the first set strands removed from the frame, we can then add different set strands, which bind to the central region and cross over there. That binding turns the two double helices and puts the device in the PX state. The process can be reversed by removing the second set strands and adding back the first ones. In this way, the double helices can be turned back and forth at will. A number of different PX-JX devices can be operated independently by adding and removing set strands designed for their individual binding regions.

We used atomic-force microscopy to verify how our device moved. We made a long chain of these devices and connected a large trapezoid-shape DNA unit to one side of each device.

When all the devices are in the PX state, the trapezoids lie on the same side of the chain. When all are in the JX state, the trapezoids alternate sides, in a zigzag pattern.

In 2000 Yurke and his colleagues demonstrated nanoscopic “tweezers” made of three strands of DNA. Set strands, which Yurke calls fuel strands, opened and closed the tweezers. Other researchers have used similar methods to switch on the activity of ribozymes—enzymes made of RNA. In 1998 Michael P. Robinson and Andrew D. Ellington of the University of Texas at Austin demonstrated a 10,000-fold enhancement of a ribozyme’s activity by the addition of an appropriate set strand, which bound to the ribozyme, changing its conformation.

The Future

A CRUCIAL GOAL for nanotechnology based on DNA is to extend the successes in two dimensions to three dimensions. When that has been accomplished, we will have demonstrated the ability to design solid materials by specifying a series of DNA sequences and then combining them. If the systems are highly ordered, then the crystallographic experiments involving molecules held within a regularly repeating framework mentioned earlier will be feasible.

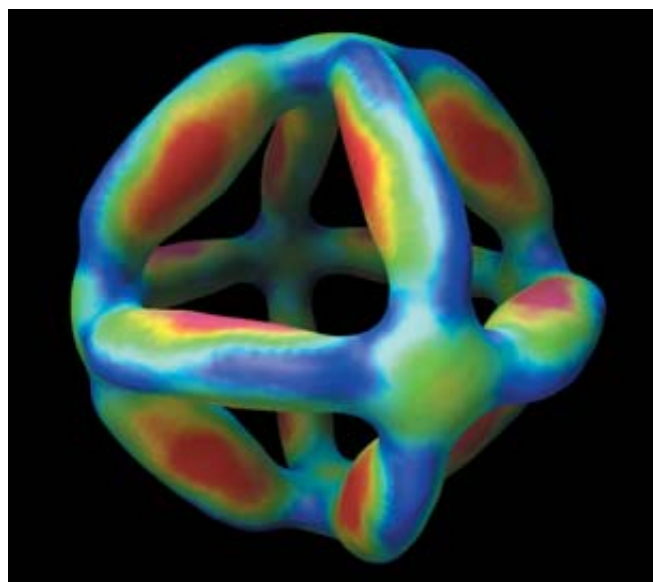
Another goal is to incorporate DNA devices within the frameworks. This accomplishment would be the first step toward nanorobotics involving complex motions and a diversity of structural states, which would enable us to build chemical assembly lines. Using devices similar to the ones described here, we could assemble new materials with high precision. As a prototype, James W. Canary and Philip S. Lukeman of N.Y.U., Lei Zhu, now at the University of Texas at Austin, and I recently assembled a small piece of nylon on a nucleic acid backbone. Someday we expect to be able to make new polymers with specific properties and topologies (such as windings of their backbones).

Achieving these goals primarily entails the use of DNA as a programmable component, but neither crystallography nor nanoelectronics can rely on DNA alone. For instance, nanoelectronic components, such as metallic nanoparticles or carbon nanotubes, will have to be combined with DNA molecules in systems and liquid solutions that are compatible with both the

DNA and the other components. Given the diverse chemical nature of these molecules, achieving this will not be simple. In addition, even if the nanoelectronics can be constructed by DNA self-assembly, the nanomachines ultimately need to interact with the macroscopic world in a manner that is more sophisticated than the addition and removal of set strands from a solution. This challenge is likely to be formidable.

A nanotechnological dream machine is one that can replicate. Unlike linear DNA, however, branched DNA does not lend itself readily to self-replication. Yet late last year William M. Shih, Joel D. Quispe and Gerald F. Joyce of the Scripps Research Institute in La Jolla, Calif., took an exciting first step toward self-replicating DNA objects. They built an octahedron from one long strand of DNA (about 1,700 bases), using five short “helper” strands to complete the assembly [see illustration below]. Each edge of the octahedron is made of two interlinked DNA double helices—a series of DX and PX molecules. The edges were each about 14 nanometers long, or about four turns of a double helix. A folded octahedron cannot reproduce, but in the unfolded state, the long strand is readily cloned millions of times by a standard biotechnology process called PCR (polymerase chain reaction). It is still a far cry from the replication achieved by every living organism, but by the time the Watson-Crick centenary comes around, we should have DNA-based machines that do as well.

SA



DNA OCTAHEDRON shown here was built out of one long strand of DNA and five short “helper” strands. Each strut consists of two parallel, interlinked double helices. The image was reconstructed by combining data from cryo-electron microscope images of more than 600 octahedra. The colors represent relative electron density: red high and blue low.

MORE TO EXPLORE

A DNA-Fuelled Molecular Machine Made of DNA. Bernard Yurke, Andrew J. Turberfield, Allen P. Mills, Jr., Friedrich C. Simmel and Jennifer L. Neumann in *Nature*, Vol. 406, pages 605–608; August 10, 2000.

Logical Computation Using Algorithmic Self-Assembly of DNA Triple Crossover Molecules. Chengde Mao, Thomas H. LaBean, John H. Reif and Nadrian C. Seeman in *Nature*, Vol. 407, pages 493–496; September 28, 2000. [Erratum: *Nature*, Vol. 408, page 750; December 7, 2000.]

A Robust DNA Mechanical Device Controlled by Hybridization Topology. Hao Yan, Xiaoping Zhang, Zhiyong Shen and Nadrian C. Seeman in *Nature*, Vol. 415, pages 62–65; January 3, 2002.

DNA in a Material World. Nadrian C. Seeman in *Nature*, Vol. 421, pages 427–431; January 23, 2003.

DNA as an Engineering Material. Andrew Turberfield in *Physics World*, Vol. 16, No. 3, pages 43–46; March 2003.

A 1.7-Kilobase Single-Stranded DNA That Folds into a Nanoscale Octahedron. William M. Shih, Joel D. Quispe and Gerald F. Joyce in *Nature*, Vol. 427, pages 618–621; February 12, 2004.

Nadrian C. Seeman’s laboratory Web site:
<http://seemanlab4.chem.nyu.edu/>