Art as a Stimulus for Structural DNA Nanotechnology

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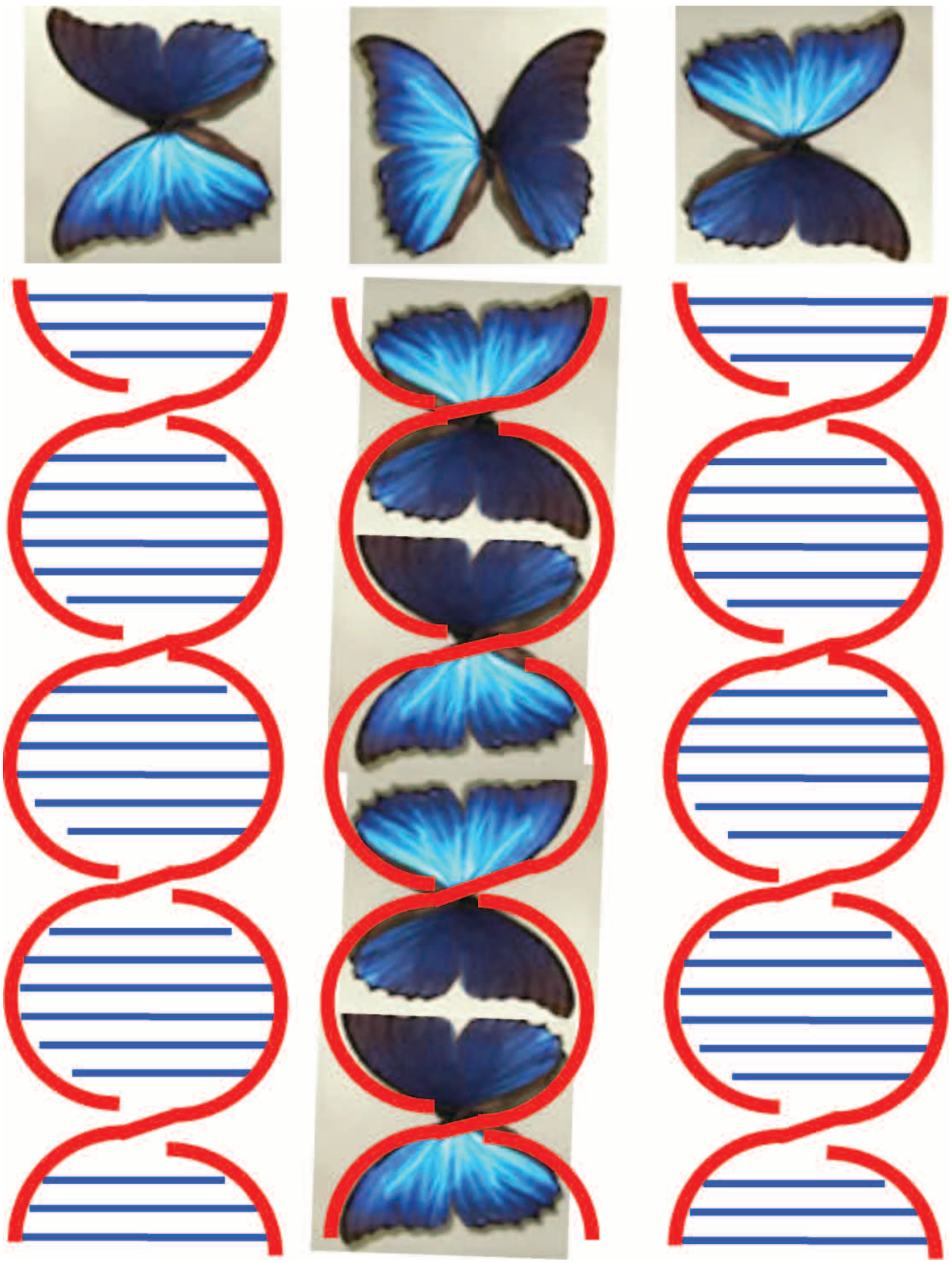

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Nadrian C. Seeman

ABSTRACT

The linear, double-helical structure of DNA was initially recognized as beautiful, as well as being informative about the mechanism of heredity. Recently, branched DNA molecules have been used to produce nanoscale objects, crystals and machines, all the products of a new field: structural DNA nanotechnology. The inspiration for much of this work has been art, starting from the notion that Escher's woodcut *Depth* was analogous to a molecular crystal of branched DNA. The article describes how connecting branched molecules together with the "sticky ends" used by genetic engineers has led to 3D crystals, and how Dalí's *Butterfly Landscape* illuminates the relationship between wrappings of DNA and the crossings in knots or links. Disparate aesthetic patterns are related to branched DNA motifs and constructions.

You see things and you say "Why?"
I dream things that never were and I say, "Why not?"

—George Bernard Shaw

This quote from the serpent in *Back to Methuselah* characterizes much of the scientific enterprise. Most practicing scientists are either asking "Why?" about various phenomena or trying to think up new things and asking "Why not?" Where can new ideas in the "Why not?" category arise? In my own experience, the answer is often from thinking, perhaps just momentarily, that two different things are actually the same. The two things typically are analogs of one another, things that in some aspect are the same, although overall they are not. For example, two objects can look similar in one projection, but from another viewpoint would never be mistaken for one another. In another type of mistaken identity, Figure 1a shows a picture by Arcimboldo, who was a master of images that can be interpreted in a dual fashion; here the face of a person seems to emerge from a collection of fruit (or vice versa). Indeed, art can often supply useful analogs of the systems we ponder.

I am neither an artist nor an expert in art. What I discuss in this article is the ability of art to stimulate or reflect interesting things about the DNA molecule. Many artists, ranging from scientific illustrators to Salvador Dalí (Fig. 1b), have depicted this central molecule in biology. One can learn a vast amount about a molecule from staring at an accurate model of it. However, that is not the point here. What I want to talk about is looking at things that are not DNA, but could generate or help illustrate structural ideas—possibly new structural ideas—about DNA.

I am a fairly visual person and I look for inspiration in visual art, particularly paintings and mosaics. Clearly, a hand-crafted picture of a molecule is not the same as the object itself. Rather, it is our interpretation of the data. For instance, virtually every crystal structure publication shows molecules in typical chemical-formula representations, where the bonds connecting atoms are the most prominent features. However, only in very special structure determinations are bonding electrons visible. The bonds are our interpretation of short distances

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Article Frontispiece. The relationship between a butterfly and a half-turn of DNA. (a, top row) A butterfly is shown in three orientations, each rotated a quarter-turn from its neighbors. (<http://en.wikipedia.org/wiki/Morpho>. Photo: Didier Descouens. Image source: <Wikipedia.org>. Creative Commons CC-SA 3.0 License.) (b, below) The columns on the sides are two DNA double helical representations that have equal-sized grooves, unlike real DNA, which has a major and a minor groove. (© Nadrian C. Seeman) The two butterfly orientations on the edges shown at the top left and top right are used to build up two turns of DNA shown in the central column of 7b, where they are flanked by double helical backbones that are the same as those on the flanking DNA duplexes.

(a) **(b)**

Fig. 1. (a) Giuseppe Arcimboldo, *Summer*, oil on linden wood, 67 × 50.8 cm, 1563. Arcimboldo (1527–1593) was well known for portraits created entirely from objects. (b) Salvador Dalí, *Butterfly Landscape (The Great Masturbator in a Surrealist Landscape with D.N.A.)*, oil on canvas, 1957. This painting is an early artistic representation of the DNA molecular structure. It captures some of the subtle features, such as the major and minor grooves of the double helix. The butterflies are suggestive of a simplified and subtle features of the molecule (see Fig. 7). (© Salvador Dalí, Fundació Gala-Salvador Dalí, Artists Rights Society [ARS], New York 2013)

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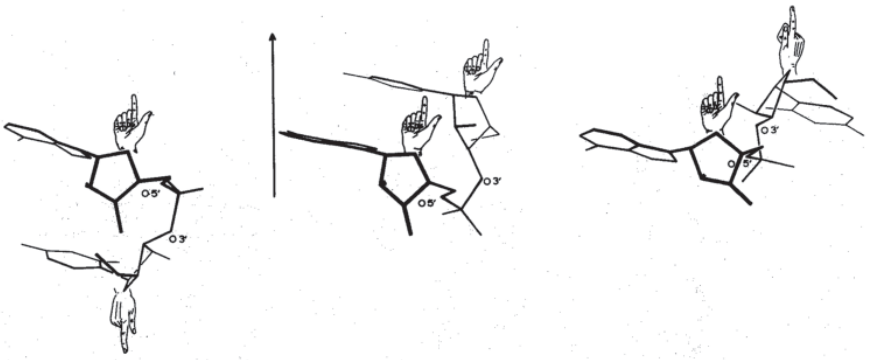
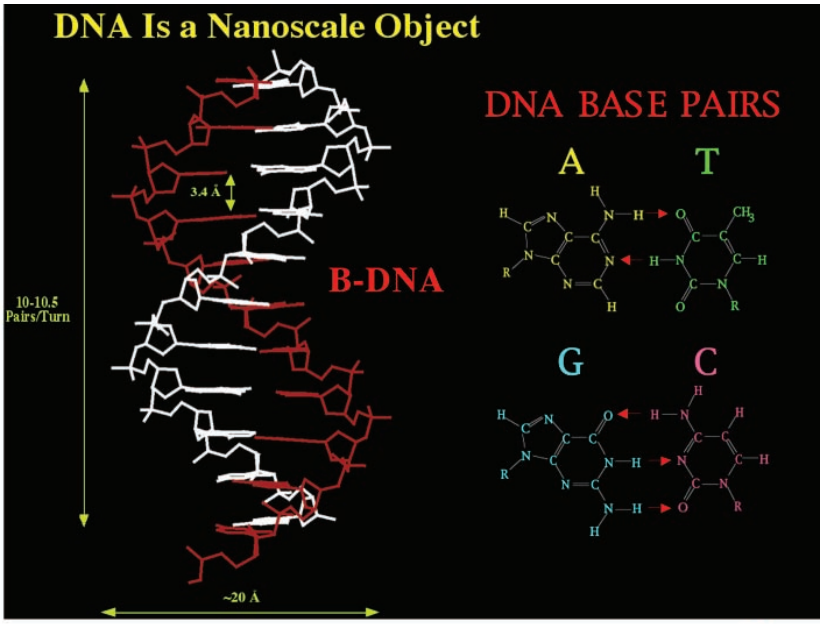


Fig. 2. The crystal structure of UpA. This crystal structure contained two molecules of the RNA dinucleoside phosphate UpA in the asymmetric unit of the crystallographic repeat. One molecule is shown on the left and the other on the right. They are compared with a standard RNA-11 double helix at the center, drawn with its helix axis indicated. The hands that have been added to the furanose oxygen atoms indicate the direction in which a standard helix pointing in the same direction as that nucleoside would point. (© Nadrian C. Seeman. Originally published in Nadrian C. Seeman et al., "Nucleic Acid Conformation: Crystal Structure of a Naturally Occurring Dinucleoside Phosphate (UpA)," *Nature New Biology* 233, Nos. 90–92 [15 September 1971].)

Fig. 3. (a) A standard DNA double helix. A single turn of DNA is shown on the left, with the two strands in different shades. The image indicates that the width and helical repeat of the B-DNA double helix are on the nanoscale. The base pairs are viewed edge-on. The molecular structures of the base pairs are indicated on the right, with the hydrogen bonding interactions drawn as red arrows. (b) Branch migration. The molecule in the center is a two-fold symmetric 4-arm branched junction. Owing to this symmetry, the junction can undergo the branch migration isomerization. These isomerizations can continue until the branched molecule resolves into two duplex molecules. (© Nadrian C. Seeman)

(a)



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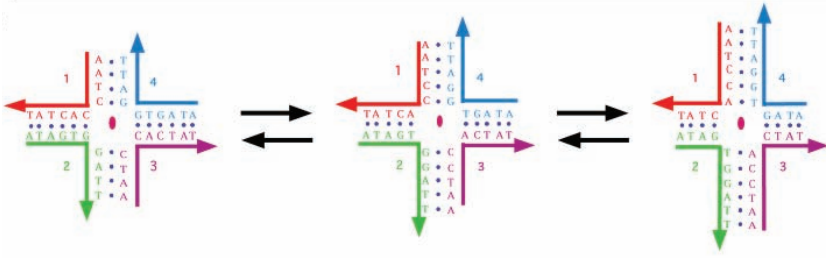


between the positions of atomic nuclei. In another example, from one of my early crystal structures [1], my coauthors and I added hands to a molecular structure to indicate the directions in which RNA helices would extend if they were attached to particular components of the molecule (Fig. 2).

We all know that artists interpret what they see around them through their art, adding to the objects features that enhance the meaning of the representation. Nevertheless, their representations are not atom-for-atom identical with what they are representing (assuming that they are representing an object at all). Most of us tend to think of reality as more closely resembling photographs than paintings or sculptures. If we look at non-photographic art, it is often a little different from the mental image we may have had of the subject before we looked at the artwork. Sometimes those differences lead to ideas, because they force us to think of the images differently. As a structural scientist, I have found that these differences can lead to interesting notions and experiments.

Let me give a concrete example that is central to the genesis of my own research program. I work to make interesting and useful molecular structures and topologies from DNA, using its chemical information to control the structure in three dimensions. All of us are aware of the double-helical structure of DNA (Fig. 3a). The helix axis may bend but it is unbranched. By contrast, my structural DNA nanotechnology lab usually works with branched DNA molecules. Structural DNA nanotechnology began with art and it continues to be informed and inspired by art. To tell this story, I should indicate that naturally branched DNA is formed by combining two DNA double helices to make a structure that can be drawn like an intersection where two highways cross; this structure is called a Holliday junction [2] and it is an intermediate in genetic recombination.

Naturally occurring Holliday junctions have twofold symmetric sequences. This symmetry enables the junctions to undergo a spontaneous rearrangement called branch migration, whereby their branch points move around (Fig. 3b). This mobility makes it difficult to study the structural features of junctions, because any solution will be a mixture of Holliday junctions with different branch points. As a crystallographer, I wanted to crystallize uniform molecules because the best crystals have the same matter or forces at every position. In the spring of 1979, I realized that it

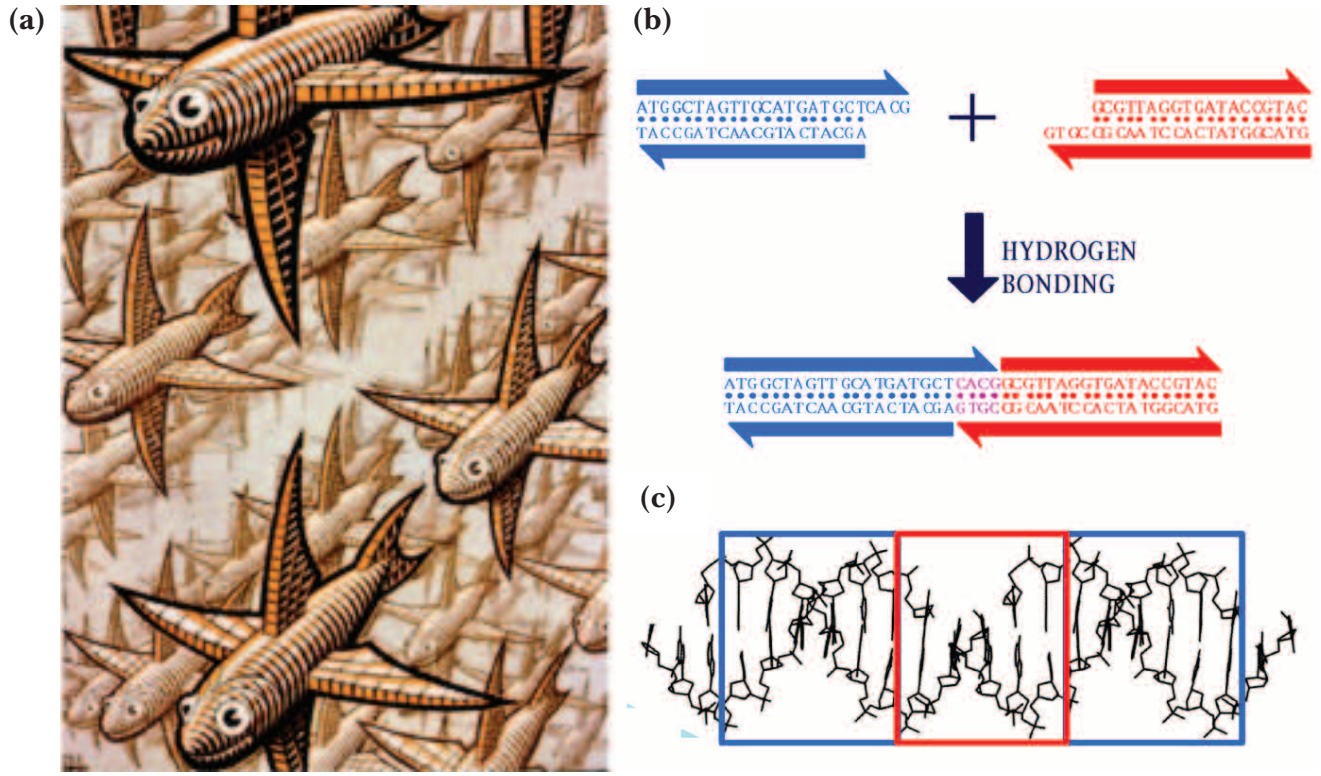


Fig. 4. (a) M.C. Escher, *Depth*, woodcut, 1955. Each fish is analogous to a 6-arm junction, with a head, a tail and four fins. The fish are organized like the molecules in a molecular crystal, with periodicity front to back, left to right and top to bottom. (© 2013 The M.C. Escher Company–The Netherlands. All rights reserved. <www.mcescher.com>). (b) An example of sticky-ended cohesion. The two strands of the two molecules are not quite the same length, creating 4-nucleotide overhangs. These overhangs are complementary, so the two molecules can cohere to produce a single molecular complex. (© Nadrian C. Seeman) (c) The local product structure resulting from sticky-ended cohesion. This crystal structure consists of DNA decamers that are held together in the horizontal direction by two-nucleotide sticky ends. The central box surrounds the sticky ends and flanking nucleotides, as is evident from the gaps in the backbone. The end boxes are crystallographically repeating segments of the rest of the decamers and are a half-turn away from the sticky ends and hence upside down from them. (© Nadrian C. Seeman)

would be possible to use synthetic DNA to build immobile non-symmetric branched molecules [3]. Shortly thereafter, I realized that it is possible to build branched junctions with many arms, not only four [4].

In September 1980, I went to the SUNY/Albany campus pub to think about 6-arm junctions. When I went in, I was thinking of 6-arm junctions as planar objects with 6-fold symmetry—sort of like a snowflake. Suddenly, Escher's woodcut *Depth* (Fig. 4a) flashed into my mind, and I recognized that the fish in the picture were analogous in their branching to a 6-arm junction: Starting from the middle of each fish, there is a head, a tail, a top fin, a right fin, a bottom fin and a left fin: a total of six protrusions that are not planar, but are 3-dimensional. Far more important to me was that the fish are organized like the molecules in a molecular crystal: They are arranged in repeating arrays from front to back, from left to right and from top to bottom. I had been hired at SUNY/Albany as a macromolecular crystallographer and until then (the start of the fourth year of my five-year probationary assistant professorship) I had managed to crystallize nothing of interest to myself or to others. I was facing a fatal progression: No crystals. No crystallography. No crystallographer.

When I realized that by analogy I could think of the extremities of the fish as nucleic acid double helices, it was a short step to imagine their intermolecular associations being directed by "sticky ends." Sticky ends are short single strands that extend beyond the ends of double helices when one strand is a little longer than the other. Figure 4b shows two (unwound) double helices that cohere because their sticky ends are complementary. Genetic engineers had used this technique since the early 1970s [5]. Thus, the idea was to take immobile branched junctions and put sticky ends on them and then get them to self-assemble into crystals. Programmed self-assembly of crystals is different from the way macromolecules are normally crystallized, which entails letting the molecules establish their contacts by trial and error.

Sticky ends are special interactions in several respects. First, they are programmable intermolecular interactions. If I have a sticky end with a given sequence, say CAGC, it is simple to program its complement, GCTG. Although there are plenty of affinity interactions in biological systems, the local product structure is known in advance only for the sticky ends. Figure 4c shows the crystal structure of a DNA molecule in the well-known B-structure that is held together in the horizontal direction by sticky ends [6]. The structure in the middle box, containing the sticky ends (delimited by the discontinuities in the structure), is very similar to the continuous structures in the end boxes. Of course, the structures in the end boxes are rotated upside down, because they are half a double-helical turn away. To program the structure of matter in 3D, it is crucial to be able to program both affinity and the local product structure of intermolecular interactions. Sticky ends provide this capability.

It is often easier to understand two-dimensional systems. Figure 5a illustrates a 2D version of this concept. On the left is a 4-arm branched junction with sticky ends, X and its complement X', along with Y and its complement Y'. If the 4-arm junction were shaped this way, and if it

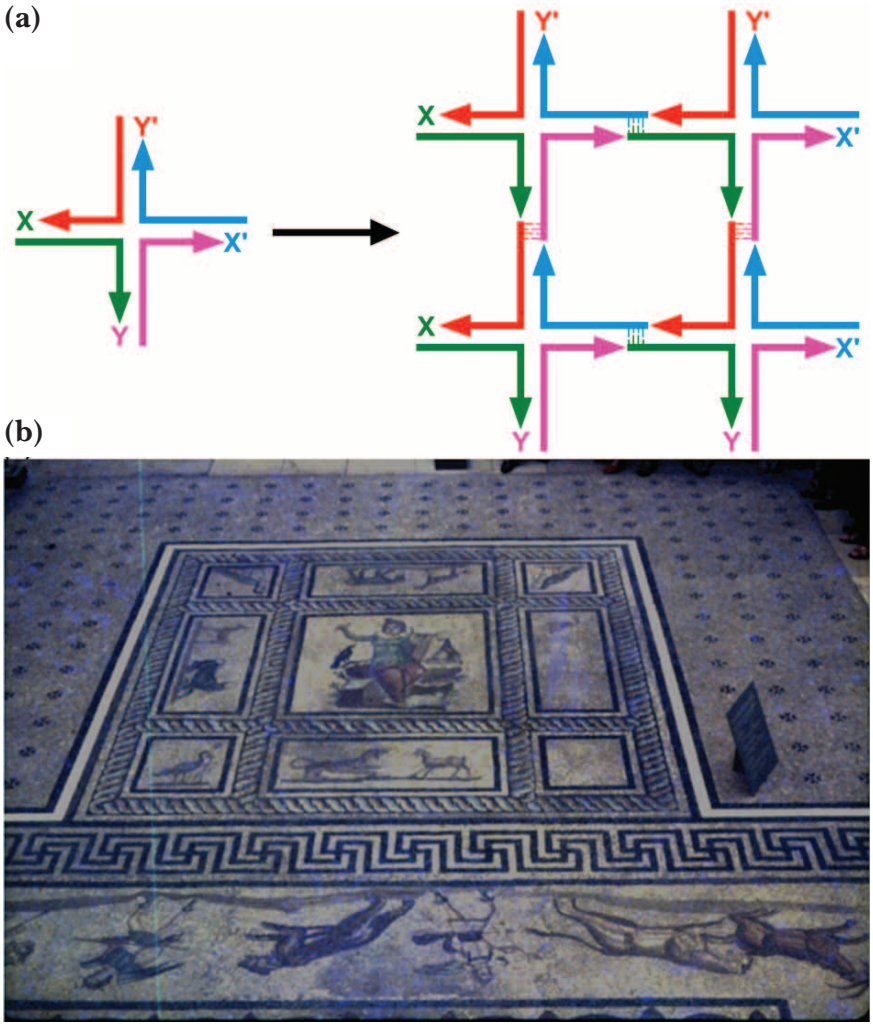


Fig. 5. Two-dimensional branched-DNA quadrilaterals. (a) A self-assembled DNA quadrilateral. The DNA branched junction on the left has four sticky ends, divided into two complementary pairs. When they self-assemble according to the rules of complementarity, they form a quadrilateral that has many sticky ends on its perimeter, so it could be extended into a 2D lattice. (© Nadrian C. Seeman) (b) A mosaic on the floor of the Pergamon museum in Berlin. This Roman mosaic shows a product similar to the product in panel (a). There are four branch points, the components are double helices and the sense of the helices is right-handed. Ironically this image is closer to an accurate image than the schematic in panel (a). (Photo: Nadrian C. Seeman)

were rigid (it is neither), the junctions would self-assemble to form the quadrilateral shown on the right of the panel. However, there are several sticky ends on the outside of the quadrilateral, so the arrangement could be expanded to form a 2D lattice. Compare this notion with a Roman mosaic on the floor of a temple in Berlin's Pergamon Museum (Fig. 5b). The resemblance is remarkable. Ignoring the border, the center consists of four 4-arm branched junctions joined to form a larger object. Each arm of each branch is a double helix, which is evident from the mixed shading. It is even right-handed, just like B-DNA (Figs 1b and 3a).

I should point out that it took 29 years to make the leap from the notion suggested by Escher's *Depth* to the actual self-assembly of a 3D crystal structure [7]. The motif that was finally used to achieve this goal is a triangular arrangement of DNA double helices that spans 3-space. Its developer, Chengde Mao, called it a "tensegrity triangle" [8], although it is somewhat different from the tensegrity structures described below. Artistic renderings of this triangle and its rhombohedral crystalline lattice are shown in Fig. 6.

A curious point about Dalí's DNA molecule (Fig. 1b) is that it is surrounded by butterflies. A half-turn in a double helix is often used to produce a node (a crossing) in DNA topological constructs, like knots or linked rings (catenanes) [9]. This equivalence is the foundation of synthetic single-stranded DNA topology and has been the basis for the synthesis from DNA of deliberate knots [10,11], specific catenanes [12], a Solomon's knot [13] and even Borromean rings [14]. The Article Frontispiece shows that the equivalence of a crossing and a half-turn of DNA is readily visible if one considers a butterfly to represent the projection of a half-turn of DNA. An example of this equivalence principle is illustrated with a trefoil knot in Fig. 7a. Each of the three nodes in this knot is represented by a half-turn of DNA. Of course, we cannot know whether the half-helix represented by the butterfly was part of Dalí's motivation for incorporating them in his painting. Another example of the interpretation of art as DNA components can be seen in the *kolam* design from the floor of the Meenakshi Temple in Madurai, shown in Fig. 7b. The complex arrangement of half-turns and hairpins could represent a DNA pattern.

It is easy to be inspired by art if one works with DNA. Any depictions of lines that wrap around each other or that form braided and woven patterns can stimulate an idea. Returning to Roman mosaics for a moment, there are plenty of images that represent the things we have already discussed. The helix is a common motif in those mosaics. However, we do not have to restrict ourselves to helices; the Romans also depicted other relationships of inter-wrapped lines, particularly woven braids. Figure 8 illustrates a mosaic pattern at a restored Roman ruin in Conimbraga, Portugal. We see double-helical images formed into branched molecules at the upper left. However, consider the braided weave seen on the bottom and right. Mosaics like this one led me to wonder if we could make woven structures out of DNA. Remembering the equivalence between nodes and half-turns of DNA, we can indeed imagine forming a woven pattern from DNA. However, nodes can be of two different signs, corresponding to mirror images of the ways two lines can be placed over each other in 3D. In the Conimbraga weave, the node signs alternate between positive and negative. A right-handed DNA double-helical half-turn corresponds to a negative node, and a left-handed DNA double-helical half-turn corresponds to a positive node. Naturally occurring DNA has backbone components (called nucleosides) with handedness (chirality), which leads to its helix being right handed. Nevertheless, it is possible to make left-handed DNA. The primary example of left-handed DNA with conventional nucleosides

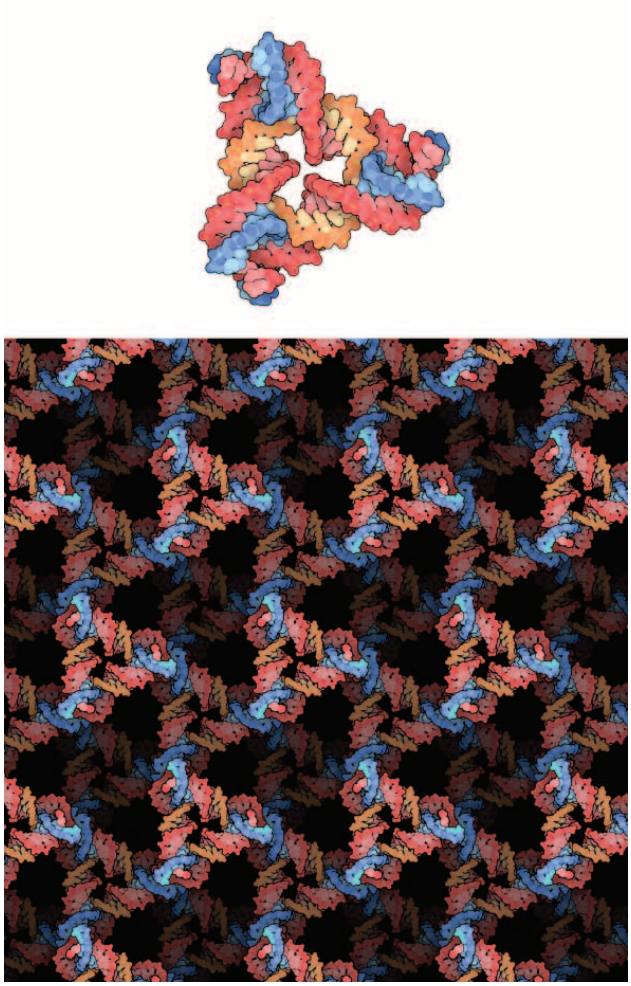


Fig. 6. David Goodsell, drawing of the crystal structure of the tensegrity triangle and of its crystalline lattice, 2009. Three layers of the rhombohedral crystal structure are shown, and the distance from the viewer is indicated by the brightness of the triangle: The dim triangles are furthest from the viewer, the brighter ones are in a plane closer to the viewer and the brightest ones are closest of all. Starting from a bright triangle, it is possible to follow the connectivity of the crystal structure back to the dimmest layers. (© David Goodsell)

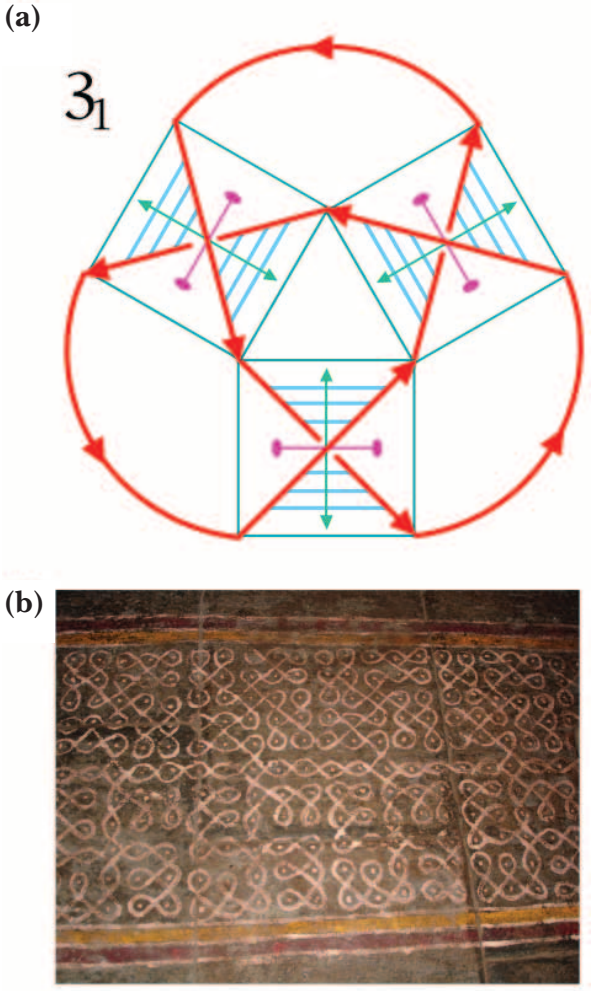


Fig. 7. (a) A trefoil knot that demonstrates the relationship between a half-turn of DNA and a crossing in a knot or a catenane. The backbone strand is drawn with an arbitrary polarity. Its three crossings are flanked by boxes, so that the crossings are the diagonals of the boxes. The crossings divide the boxes into four zones, two between parallel strands and two between antiparallel strands. DNA is antiparallel, so a half-turn's worth of base pairs (about six) are drawn between strands in that direction. The helix axis of the duplex DNA is drawn as a two-headed arrow, and the dyad axis of the DNA crossing is indicated perpendicular to the helix axis with ellipses on its ends. Each half-turn of DNA can supply the crossing necessary to make a trefoil knot. (© Nadrian C. Seeman) (b) A kolam from the Meenakshi Temple in Madurai. Whether or not a DNA molecule can replicate this pattern, we can see the value of thinking of a topological crossing as a half-turn of DNA. (Photo: Nadrian C. Seeman)

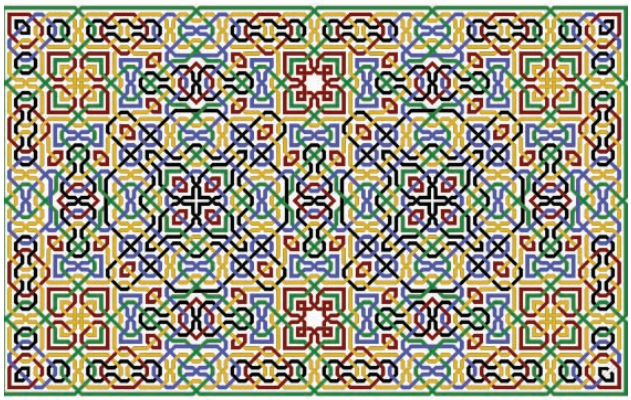
is an unusual conformation known as Z-DNA [15], which was used in most of the topological targets mentioned above. However, it is now possible to synthesize DNA conveniently with the mirror-image backbone components, which has certain chemical advantages. Recently, coauthors and I constructed a 2×2 portion of the woven pattern in Fig. 8 using this approach [13].

Once one starts looking for strands crossing one another, they are all over the place. Since one of my goals is designing periodic matter [7,16], Moorish art is a great inspiration, because it contains examples of interesting topologies in periodic or at least locally periodic patterns. The pattern from the Alhambra mosaic shown in Fig. 9a is a complex catenane with locally periodic features. The pattern shown in Fig. 9b is the strand structure of a 2D DNA crystalline network built from DNA double crossover molecules, related to intermediates in the genetic process of meiosis [17]. The particular double crossover molecule shown in Fig. 9b is not a meiotic intermediate, but it has been used in making 2D DNA arrays [16]. The strands in both arrangements are a mixture of cyclic and infinite strands (although some "infinite" strands in the mosaic are actually cycles, owing to the finite nature of the pattern). The strands in the DNA pattern are shaded differently to differentiate them for ease of viewing. Nevertheless, both patterns suggest that different species of nucleic acids [18] could be mixed to build novel networks with distinct and possibly useful properties.

One of the most interesting DNA motifs with which I have worked is the

Fig. 8. A Roman mosaic in Conimbriga, Portugal. The central part of this mosaic is largely out of view, but some branched junctions are visible. Flanking this portion is a complex braided pattern consisting of six strands, wherein the signs of the nodes alternate. (Photo: Nadrian C. Seeman)

(a)



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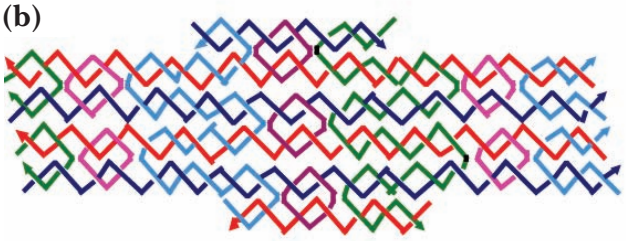

Fig. 9. Periodic catenanes. (a) A locally periodic catenane found in a mosaic from the Alhambra. The structure consists of numerous linked cycles and one set of apparently infinite blue strands. The periodicity is limited by the finite size of the pattern. (b) A periodic DNA pattern. This pattern, known as DAE-O, has been used to produce 2D DNA periodic patterns. It is clear that one could consider using variants of DNA within a given pattern, leading to a system with color symmetry. (© Nadrian C. Seeman)

PX motif [19]. This motif looks like two double helices wrapped around each other, as illustrated in Color Plate C No. 1, part b. The PX motif is a key stage of the machine cycle of a robust programmable nanomechanical device [20]. This device has been used as a component of a machine that directs the programmed assembly of polymers [21], of a robot arm that has been inserted into a 2D DNA array [22], as a programmable unit in a DNA-based capture system [23] and as a programmable component in a nanoscale assembly line [24]. In addition, the PX motif has been implicated in the recognition of homology by double helical DNA [25]. Color Plate C No. 1, part a, shows a Mayan vessel that contains motifs reminiscent of this system with both chiralities. A detail of the right-handed motif is illustrated in Color Plate C No. 1, part c.

Kenneth Snelson originated the concept of tensegrity, a combination of tension and compression; it is visible in many of his artworks. An example of one of these massive structures, at Storm King in Mountainville, New York, is shown in Fig. 10a. Liedl et al. have brought Snelson's inspiration to fruition in the DNA world [26] using the technique of DNA origami, a system originally devised by Paul Rothemund [27]. The electron micrographs shown in Fig. 10b demonstrate that making this type of structure from DNA is well within the realm of feasibility.

I have discussed here the ways in which art and structural DNA nanotechnology can be integrated. The influence of art on DNA chemistry is clearly unlimited. The beauty of macromolecular structure diagrams and sculptures is well known, and many macromolecular species, not just DNA, have been the subjects of artistic exposition [28]. Similarly, it is unlikely that only DNA structural chemistry has been influenced by art. The two realms interpenetrate each other, and it is clear that in the broadest sense, science and art can be thought of as manifestations of similar types of thinking.

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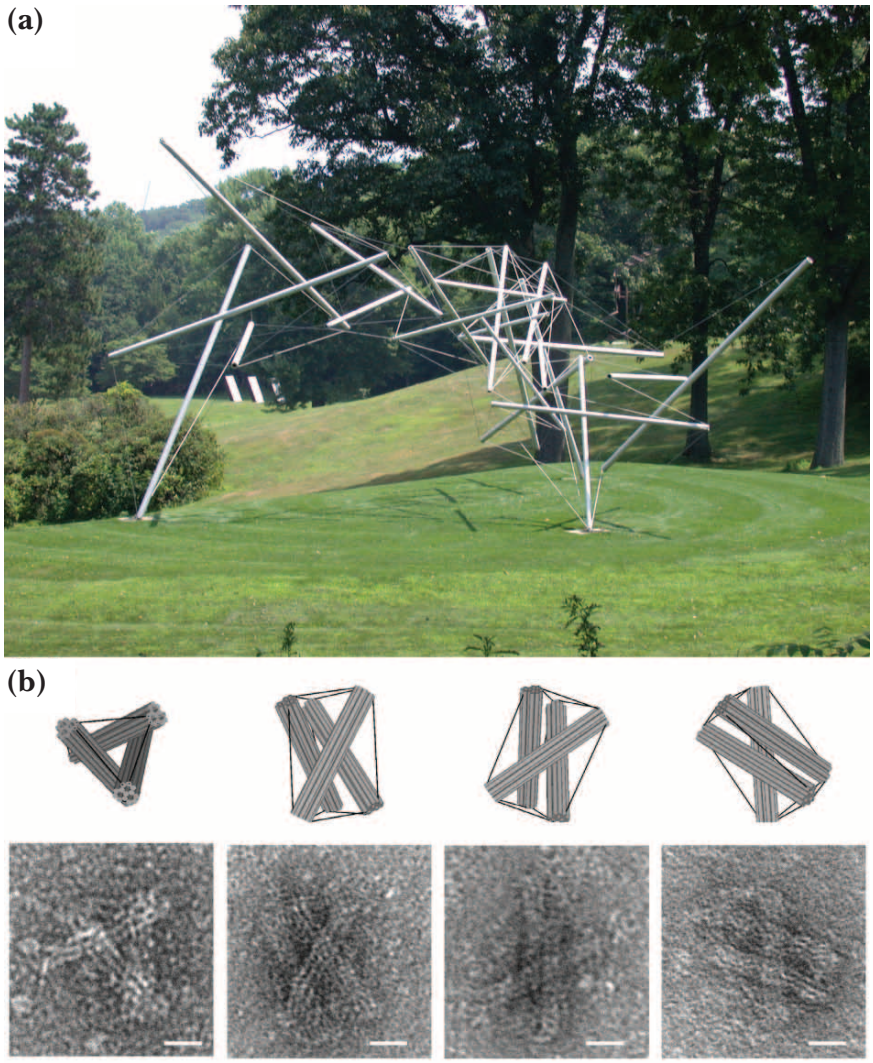

Fig. 10. Tensegrity in art and in DNA nanotechnology. (a) Kenneth Snelson, *Free Ride Home*, Storm King Art Center, Mountainville, NY. (© Kenneth Snelson. Photo: Nadrian C. Seeman.) The tensegrity principles allow the artwork to be large, yet not at all massive. (b) DNA tensegrity structures. (Originally published in Tim Liedl, Björn Högberg, Jessica Tytell, Donald E. Ingber, William M. Shih, "Self-assembly of three dimensional prestressed tensegrity structures from DNA," *Nature Nanotechnology* 5, No. 7, 520–524 [20 June 2010]. © Tim Liedl et al., 2010. Rights Managed by Nature Publishing Group.) The top row shows four schematic views of a tensegrity structure. The bottom row shows electron micrographs of those molecules constructed from DNA.

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