

# DNA Nanotechnology at 40

Nadrian C. Seeman

Cite This: <https://dx.doi.org/10.1021/acs.nanolett.0c00325>

Read Online

ACCESS |



Metrics &amp; More



Article Recommendations

We are approaching the 40th anniversary of the conceptualization of DNA nanotechnology. I was inspired in a bar in 1980 by the topological isomorphism between 6-arm DNA branched junctions and the crystalline arrangement of fish in Escher's *Depth*: the notion presented itself that branched DNA motifs could be connected in crystalline or other network arrangements by single-stranded sticky ends. The importance of using DNA and sticky ends is that motif topologies and structures, and particularly intermolecular contacts, could be specified simply by programming DNA sequences.<sup>1</sup> As a bonus, the structure of paired sticky ends is B-DNA so that in addition to affinity the product structures are also predesigned. Control of nanostructures by using DNA information is now sometimes termed Semantomorphic Chemistry.

The first designed self-assembled diffraction-grade crystals were eventually reported in 2009,<sup>2</sup> 29 years after the inspiration from Escher. They were based on the tensegrity triangle motif, designed by the Chengde Mao laboratory. The initial goal of using designed self-assembled DNA crystals to organize biological macromolecules automatically as guests in high-resolution crystals remains to be achieved. However, that goal is a bit like the 16th–20th century attempt to find a Northwest Passage: unsuccessful but with lots of interesting spinoffs.

The key development in the early 21st century has been Paul Rothemund's invention of DNA origami.<sup>3</sup> DNA origami typically combines a long circular viral single-stranded scaffold with a group of 200–250 short staple strands that fold it into a two-dimensional (2D) or three-dimensional (3D) shape. This approach revolutionized DNA nanotechnology in several ways: [1] It vastly increased the size of DNA constructs from 100 to 300 nucleotide pairs to over 7000. [2] DNA nanotechnology was suddenly available to a much larger community because, with certain exceptions, the DNA did not need to be purified but just ordered from a supplier. [3] Owing to the fact that everyone was using M13 single-stranded form as the scaffold, much of the time wasted previously optimizing DNA sequences was eliminated, because sequence selection proved to be unimportant. A second advance in the early 21st century was Peng Yin's development of DNA bricks.<sup>4</sup> These are short single-stranded pieces of DNA that bind with each other. Gigadalton assemblies have been built from bricks. Both origami and bricks owe their success to the cost of DNA dropping dramatically: The DNA oligonucleotides purchased to demonstrate the first immobile branched junction in 1983 cost \$312/nucleotide, whereas oligonucleotides today cost

pennies per nucleotide. This is not merely a quantitative change; it changes the constructs that can be imagined and built, as well as the uses to which they can be put. For example, DNA nanomechanical devices were reported at the end of the 20th century, and they have been combined with 2D and 3D crystalline arrays. The 2D array accommodated a single device in an array containing eight small tiles; by contrast, a single origami (about 3 times as big) was able to act as a programmable factory behaving as a three-stage assembly line.

An enterprise that has served as a valuable concomitant to DNA nanotechnology has been DNA-based computation, first demonstrated experimentally by Leonard Adelman in 1994, when he solved a Hamiltonian path problem using DNA strands.<sup>5</sup> The most important upshot of this development was that a whole community of computer scientists and mathematicians suddenly became aware of DNA nanotechnology, and they have become major contributors to it. Rather than the crystallographer-based thinking of “we will build a unit or a unit cell using tiles with sticky ends”, this community realized that tiles could be treated as logic units. Erik Winfree suggested that DNA tiles could be treated as Wang tiles and ultimately went on to build a Sierpinski triangle (a fractal pattern) from DNA tiles. Recently, he and his colleagues have used this approach, “Algorithmic Assembly”, to build tubes with highly reliable computed surface structures.<sup>6</sup> In a more mundane vein, numerous investigators have built AND, XOR, and NOT gates and the like to control the operation of various DNA devices.

So what is it all good for? This writer and his colleagues have encountered the viewpoint that “It has been 40 years and they have not made their crystalline hosts successfully yet, so let us flush the entire enterprise and its practitioners with it.” In response, I think I should point out that there are nearly 500 laboratories worldwide engaged in DNA nanotechnology. Very few of these investigators are even working on the crystalline scaffold problem but are instead employing DNA nanotechnology in a wide variety of applications. DNA is often used as a system for organizing other materials than DNA to somewhat lower resolution than the crystallographic ideal. Gold nanoparticles, proteins, viruses, and other nanoscale species have all been organized, usually by origami. These



experiments have been used as the basis for exploiting the positions of the heteromaterials for research or therapeutic purposes. DNA origami has apparently been used to get various macromolecular drugs into cells. This is a viewpoint, not a review article, so I will not expand further on the uses to which DNA nanotechnology has been put, nor will I describe the huge branch of DNA nanotechnology based on nanoparticles initiated by Chad Mirkin and Paul Alivisatos. A more complete list of references is available in ref 7.

So where is the field going? The short answer is “I DON’T KNOW”. However, there are some obvious things that can be exploited. First, the term “DNA” above has to be read to include RNA, TNA, and all the many other modified backbones and bases that exist for information-bearing nucleic-acid-like molecules. In addition, the beauty of nucleic acids is that they provide a great starting point to modify the molecule, but there are plenty of other variants that are readily imagined. My own laboratory is today engaged in using DNA nanotechnology in studies of self-replication and the organization of nanoelectronics. New 3D materials are an interesting route, and many laboratories are working in that direction. Every day I open a journal and I’m surprised by another unit of progress in the nanoscale control of the structure of matter that DNA nanotechnology offers. I like being surprised that way.

## ■ AUTHOR INFORMATION

### Author

Nadrian C. Seeman – Department of Chemistry, New York University, New York, New York 10003, United States;

[orcid.org/0000-0002-9680-4649](https://orcid.org/0000-0002-9680-4649)

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acs.nanolett.0c00325>

### Notes

The author declares no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the following grants: CCF-1526650 and CHE-1708776 from the National Science Foundation, MURI N00014-19-1-2506 from the Office of Naval Research, DE-SC0007991 from the Department of Energy for partial salary support, and RGP0010/2017 from the Human Frontiers Science Program.

## ■ REFERENCES

- (1) Seeman, N. C. Nucleic Acid Junctions and Lattices. *J. Theor. Biol.* **1982**, *99*, 237–247.
- (2) Zheng, J.; Birktoft, J. J.; Chen, Y.; Wang, T.; Sha, R.; Constantinou, P. E.; Ginell, S. L.; Mao, C.; Seeman, N. C. From Molecular to Macroscopic *via* the Rational Design of a Self-Assembled 3D DNA Crystal. *Nature* **2009**, *461*, 74–77.
- (3) Rothmund, P. W. K. Scaffolded DNA Origami for Nanoscale Shapes and Patterns. *Nature* **2006**, *440*, 297–302.
- (4) Wei, B.; Dai, M. J.; Yin, P. Complex Shapes Self-Assembled from Single-Stranded DNA Tiles. *Nature* **2012**, *485*, 623–627.
- (5) Adleman, L. M. Molecular Computation of Solutions to Combinatorial Problems. *Science* **1994**, *266*, 1021–1024.
- (6) Woods, D.; Doty, D.; Myhrvold, C.; Hui, J.; Zhou, F.; Yin, P.; Winfree, E. Diverse and Robust Molecular Algorithms using Reprogrammable DNA Self-Assembly. *Nature* **2019**, *567*, 366–372.
- (7) Seeman, N.C. *Structural DNA Nanotechnology*; Cambridge University Press: Cambridge, U.K., 2015.