A Conversation with Prof. Ned Seeman: Founder of DNA Nanotechnology

I met with Prof. Ned Seeman in Snowbird, Utah, at the 2008 Foundations of Nanoscience Meeting (FNANO08),[1] which we both helped organize. Prof. Seeman is a pioneer in the area of structural DNA nanotechnology, and he shared some of his early experiences in the field.

PSW: What made you think of making nanostructures with DNA?

Ned Seeman: I was trained as a crystallographer. When I went off to get my first independent position at Albany, I was unsuccessful at growing any crystals. So, what does a crystallographer do who cannot get crystals? The answer is, he writes code to try to solve some problem, because you can always write code.

I wound up worrying about branch migration in DNA.[2] This is a phenomenon that involves the relocation of the branch point in naturally occurring branched DNA structures in the process of genetic recombination. I was doing this with Bruce Robinson, who is now on the faculty at the University of Washington. What I realized during our effort (which took 2 or 3 months) was that we were really engaged in a scholastic enterprise rather than a scientific enterprise because there was no way that we could test any hypothesis that we came up with.

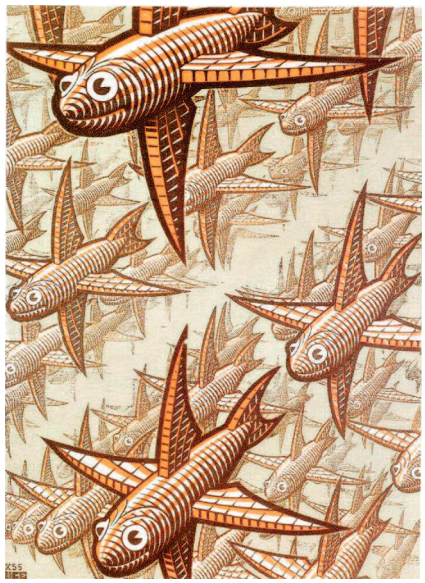

Figure 1. M.C. Escher's *Depth*. Copyright 1955, The M.C. Escher Company—Holland (http://www.mcescher.com/). All rights reserved. Used with permission.

One day, I was talking to an undergraduate student in my laboratory and I suddenly realized, "Wow, if I had synthetic branched molecules, I could study these things and test various hypotheses," because with the branched molecules, if they were synthetic, I could trash the symmetry that was responsible for the branch migration that gave you a polydisperse system. I was really excited about that, and I told everybody I knew. One visitor came by and he said, "Four arms—can you make them with different numbers of arms?" And I said, "You know, I hadn't thought about that!" I thought about it and realized that we could go up to at least eight.

One day, I went over to the campus pub to think about six-arm junctions. When I was thinking about six-arm junctions, I suddenly thought about Escher's woodcut *Depth* [Figure 1]. This is the one with the flying fish that are organized like the molecules in a molecular crystal: periodicity front to back, up and down, right and left. The flying fish were just like the six-arm junction!

I said, "Maybe I could use this concept to make crystals, to get crystals to self-associate rather than simply to try to crystallize them in the usual method of throwing stuff in a pot and invoking one deity after another to get the crystals." Of course, I needed some way to do this, something to get them to come together.

I was in a biology department and I had been listening to other people's students (since I had none of my own at the time) talking about how they made a series of constructs. I was familiar with so-called "sticky ends"—single-stranded overhangs that cohere with each other when they're put in the same pot. That struck me as the

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Prof. Ned Seeman at the Cliff Lodge at the 2008 Foundations of Nanoscience Meeting in Snowbird, Utah.

To hear Prof. Seeman's advice to nanoscientists, please visit us at the podcast page of http://www.acsnano.org/.

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way to get things to associate. So, that was sort of the birth of the whole notion.

Now, at the time, I was a crystallographer. The last time I had even thought about making a molecule was when I was an undergraduate taking organic chemistry. There was a long way to go between having this notion of getting branched DNA molecules to associate and actually getting there. In fact, although we have been reasonably successful in making 2D crystals, it is only recently that we had some success in making 3D crystals. We have yet to solve any of those structures, but we believe we're close.

That was the start of it. Of course, if the first thing you think of is making a crystal, that does not mean it is the first thing that you try. You have to start off slowly. So, we learned how to make DNA. Then, after learning how to make DNA, we learned how to get these things to associate, usually by ligation, which we really hate—at least, enzymatic ligation, because it does not work well with branched molecules, not in our hands and not in anybody else's hands that I'm aware of.

It took quite a while to get there; I had this notion in the fall of 1980 and it was not until 1990 that Junghuei Chen in the laboratory actually put together a DNA cube [Figure 2].[3,4] That was the first nontrivial thing that we made in this way, the first multiply connected object, a three-connected object. I almost threw in the towel at that point because, in order to make the cube, we had to throw out all the beautiful logic of DNA sticky ends to form the various edges of the polyhedron (it was a stick figure). Then, I sat back and I said, "We've got to be able to rescue this somehow." We went through a bunch of tricks to make the cube; it was basically a reconstitution of single-stranded species. It was a nightmare!

PSW: Did you imagine it was only topologically a cube, or did you think it would be a real-space structure?

Ned Seeman: We thought of it as a cube, but we knew we only had control over the topology, both the branching and the linking topologies. We could characterize that. We could not control the other [geometries], so it could have been rhombohedral-looking or whatever. We were never able to characterize any aspect of it that way. We started off with a belt, and then we closed the belt. We never were able to establish even which way the belt had closed. The two ways are not quite equivalent; we did not know.

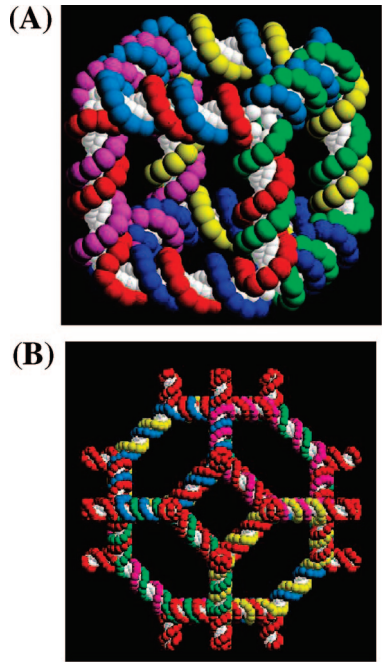

Figure 2. Topologies of (A) a DNA cube and (B) a DNA truncated octahedron. Adapted with permission from ref 5. Copyright 2003 American Chemical Society.

PSW: What were the major stepwise advances?

Ned Seeman: We rescued the notion by putting together a solid-support-based methodology.[6] This was done by Yuwen Zhang, who then made a truncated octahedron [Figure 2][7]—again, only with control over topology. He made this thing on something like the 1 pmol scale, and there were three intermolecular coupling steps with the starting units we had and something like seven intramolecular ones, one of which did not go well. We wound up with about 10 fmol of material (the cube had been about 4 fmol of material).

I realized at that point that we had to back off and have simpler components. We spent a few years trying to find something that would assemble easily in high yield and be stiff. Eventually, we came up with the DX molecule.

PSW: Would you define the terms "DX", "B-Z", and "PX-JX$_2$"?

Ned Seeman: "DX" [double-crossover] refers to two parallel helices that are connected twice by crossovers, and the crossovers can be between strands of the same polarity or the opposite polarity. Opposite polarity works better for us [Figure 3]. The double-crossover molecule is very closely related to the Holliday junction.[8] In fact, we make just two DXs, relatively simple ones—there are five different flavors. One of those flavors, when the separation between branch points is maybe 100 turns or 1000 turns, is a meiotic intermediate in biology.[9] But, we were working with one to two turns between branch points, and those molecules were not well-behaved. So, we stuck with two of the other flavors; they are differentiated by where the crossovers are relative to the polarity of the strands.

We've done a lot with DX molecules and their extensions, TXs [triple-crossovers; Figure 3]. That has really been the basis for most of what many people have done in terms of structural DNA nanotech.[10] If you think about it, even the DNA origami from Paul Rothemund[11] is basically just an extended DX structure, or TX, or multi-X.

The "PX-JX$_2$" was a device that we built;[12] the "PX" motif consists of having a crossover at every possible position where two double helices would juxtapose and the strands are of the same polarity (those are stable). A "JX$_2$" means that you have two juxtapositions [Figure 3]. If you get rid of two of those juxtapositions in a PX molecule, one of the two ends rotates with respect to the other by about a half-turn. So, you get a rotary device.

"B-Z" DNA is normally in the so-called B conformation, the form of DNA that is virtually iconic in society, with the bases perpendicular to the helix axis; it is a right-handed double helix. In 1979, Alex Rich first described Z-DNA,[13] where the repeating unit is in fact a dinucleotide and it is a *left-handed* molecule. It has sort of a zigzag backbone, hence the name Z-DNA. It is left-handed, and

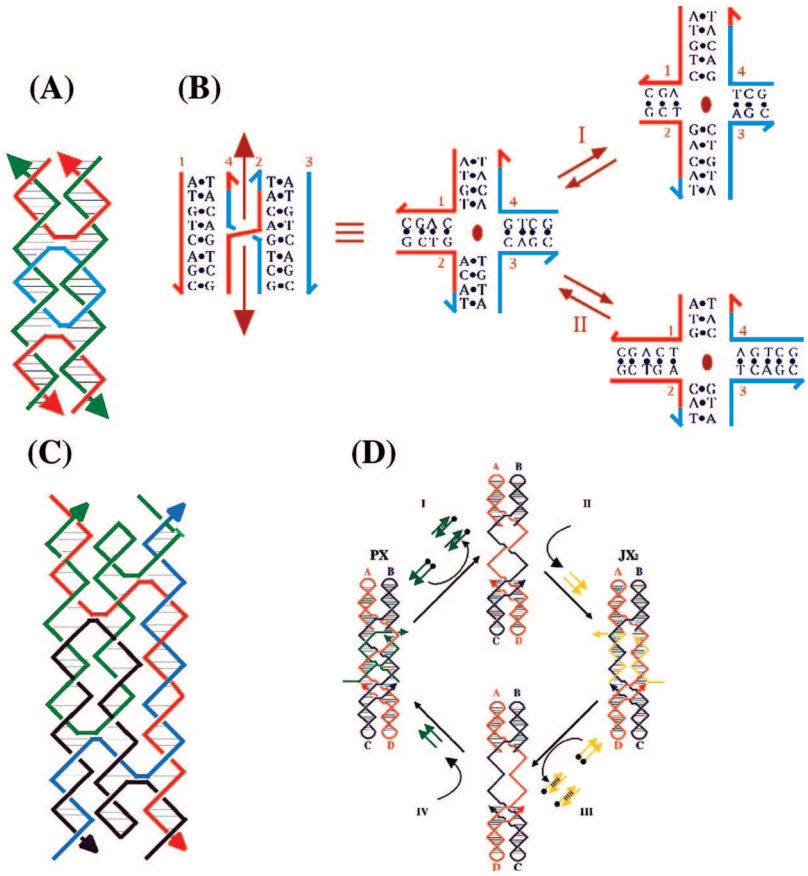

Figure 3. Topology of DNA junctions (see text): (A) double-crossover (DX), (B) Holliday, (C) triple-crossover (TX), and (D) PX-JX_2. Adapted with permission from ref 5. Copyright 2003 American Chemical Society.

there's a different twist involved (−60° instead of +34−36°); it is a different molecule. You can use that structural transition for different purposes.

PSW: And these different DNA junctions allowed you to construct different geometries?

Ned Seeman: There was the cube, then there was the truncated octahedron, and then we spent time working on getting a stiff component. When we got a stiff component, we had two breakthroughs right away (when I say right away, I mean a couple of years because that is the time constant when it is one laboratory and you are making mistakes): (1) the DX lattice that we did with Erik Winfree,[14] and (2) the B-Z nanomechanical device[15]—that was the first robust nanomechanical device. It was 12 years from the conception of that device to the publication of the device. It was finally built by Chengde Mao; he was about the fourth person in the laboratory to work on it. Chengde is a superb scientist, but one of the reasons that he was successful was because we finally had the DX robust motif. Then, we were able to get a FRET [Förster resonance energy transfer] signal that we could believe (before that, we had other species that were not stiff enough to give a reliable FRET signal). Those two breakthroughs came from the DX molecule.

About the time we published the B-Z transition device, Bernie Yurke published the sequence-dependent device,[16] which we adapted in the so-called PX-JX_2 system. The PX-JX_2 system was developed by Hao Yan.[12] The essence of that was to have a sequence-dependent device as opposed to something predicated on a structural transition of DNA. If I have 10 different flavors of the molecule, except for certain limits of chemical nuance, we have two states. With 10 flavors of B or 10 flavors of Z, maybe I could get one or two of them converted in intermediate Z-producing conditions, but we want to use the *programmability* of DNA to control it. The other thing that was going on while we were trying to make structural things is that we were heavily influenced by topology.

We made the first deliberate DNA knot, and we made the first of any kind of figure-eight knot [see Figure 4].[17] The DNA knot we made was a knot with so-called negative nodes (which means right-handed crossings). Then, by making them both out of potentially Z-DNA, we were able to make from one strand: a circle, a knot that had negative crossings, right-hand crossings, and the figure-eight knot that had two of each [see Figure 4], and then, the positive crossings, the so-called "left-handed" ones, as well.[18] So, we were able to make a collection of knots all from a single strand and characterize them in various ways, but all solution methods.

Although it is really quite simple to design on paper how to make any knot if you have enough different positive node-producing materials, it is not so easy to do that in practice. The characterization of anything where there are knot topoisomers—so, for instance, there are two flavors of five-noded knot, and three flavors of six-noded knot, and by the time you get up to a nine-noded knot, there are 49 flavors—it rises very steeply. I have no idea how many 13-noded knots there are; it is well over 10^4. It goes offscale, and you have to characterize these things structurally. We have been holding off on making anything more complex than that (these are all single-topoisomer knots) until we could characterize them structurally, arguably through the crystallographic system that we're hoping to develop in 3D.

The one other topological thing that we did was to construct a sort of synthetic holy grail from DNA, which was Borromean rings [three concatenated rings in which cutting any single one would make the structure fall apart; see Figure 4].[18] Chengde [Mao] did that; that was his trainer project. It had been a holy grail for about 37 years, and Chengde did it in a year using DNA (which speaks both to Chengde's prowess as a scientist and to the simplicity

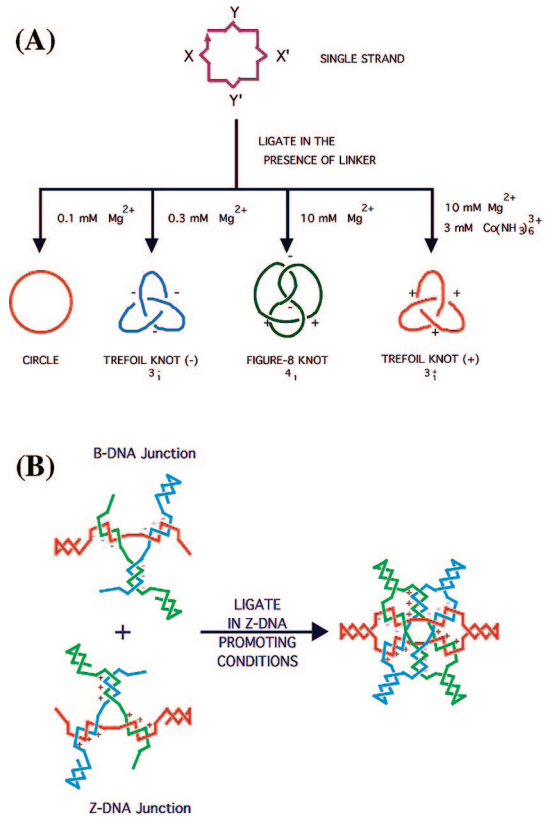

Figure 4. Topology and assembly of (A) DNA knots[17] and (B) DNA Borromean rings.[18] Reproduced with permission from ref 5. Copyright 2003 American Chemical Society.

of using DNA as a topological "synthon").

We've made a "translation" system. We reported the PX-JX_2 device in 2002.[12] In 2004, Shiping Liao was able to make a translation device where we could translate DNA signals into a series of polymer instructions so that we could make a prototype of DNA—a series of different molecules depending on how we program the system.[19]

Another breakthrough was made by Baoquan Ding, who figured out how to make arrangements (lattices that are periodic in 2D) that were not a series of parallel helices but had triangles and what-not in them.[20] Baoquan's main project was to build a cassette that would have this device and it would insert into another DNA array. I did not even know he was doing the 2D lattice; about three other students had failed with that at first. For his main project, in order to know he had been able to change the state of the device within the cassette, he built a little arm on it so that we could actually watch the arm flip with AFM [atomic force microscopy]. We could see before and after (you cannot watch as they happen) [Figure 5]. That was exciting!

The other thing in which we got involved *a little bit* was DNA computation.[21,22] I'm not a leader in that field; I am sort of a spear-carrier, collaborating with other people. One thing that we were able to do collaboratively with John Reif was to build a cumulative XOR device.[23] That was also built by Chengde. It was not a device; it was a system.

We had a series of things that we did that were all landmarks, but we were really alone in what I call structural DNA nanotech, where we are using DNA, as a friend of mine has put it, "both as the bricks and the mortar." There are people that use DNA as "smart glue", so it is like mortar; those systems do not have as high resolution inherently and people started doing that around 1995 or 1996.[24,25] Probably until Erik [Winfree] set up his own laboratory, there was nobody else doing what I call "structural DNA nanotech," where the structure of the system is really central to its essence and to its function.

PSW: Have you tried exploiting some of the other structures of DNA-triple-stranded, quartet-G, and other structures?

Ned Seeman: No, others have done that. We've stayed away from that; we did the B-Z because we just wanted to make a DNA device, but we realized then (and we were kind of scooped by Bernie [Yurke]) that the programmability of a DNA sequence is really the long suit of DNA; that is what you want to be able to exploit.[14,15] So, all of the other devices that we have made and all of the other systems that we have made in terms of devices have all been based on that same type of arrangement.

There are others who have done things with the G-4 state or the i-motif, which is pH-dependent,[26] and they have made sensors and things out of that, and that is all exciting. We tend to stay away from that because there is no diversity there. I always like the system where I can create *more* states rather than fewer states. There, fundamentally, you have got two states and you have a sensor that tells you if you are in this one or that one.

By the way, I just gave you a list of *our* breakthroughs; I did not give you a list of anybody else's breakthroughs.

PSW: What do you see as the biggest challenges ahead?

Ned Seeman: The biggest challenges coming up are 3D. When I say 3D is a challenge, I should be very clear about what is challenging about 3D. In 2D, we assay everything with AFM. The inherent resolution with AFM (in our hands and in sort of every garden-variety investigator's hands) is something like 4−7 nm on a good day, and we do not always have good days. As a result, the 2D lattices that we make have long distances in between them and we make pretty pictures.

However, in 3D, you do not use AFM, you use X-rays. There, the inherent resolution is on the order of an Ångstrom, and when we see something that is ordered to 10 Å resolution, we are disappointed. We do not expect 1 Å resolution data, but 2−3 Å is sort of what you should get from a good macromolecular crystal. Not necessarily nucleic acid crystals, they tend to be about an Ångstrom worse than protein crystals, but 2−3 [Å], in that ballpark. Now, we do not know that our 2D crystals are any better than our 3D crystals, but the point is that we are pushing toward a few Ångstroms resolution rather than a few nanometers resolution, which is all we needed in 2D to call ourselves successful. That is the key difference, one of the key challenges in going to 3D.

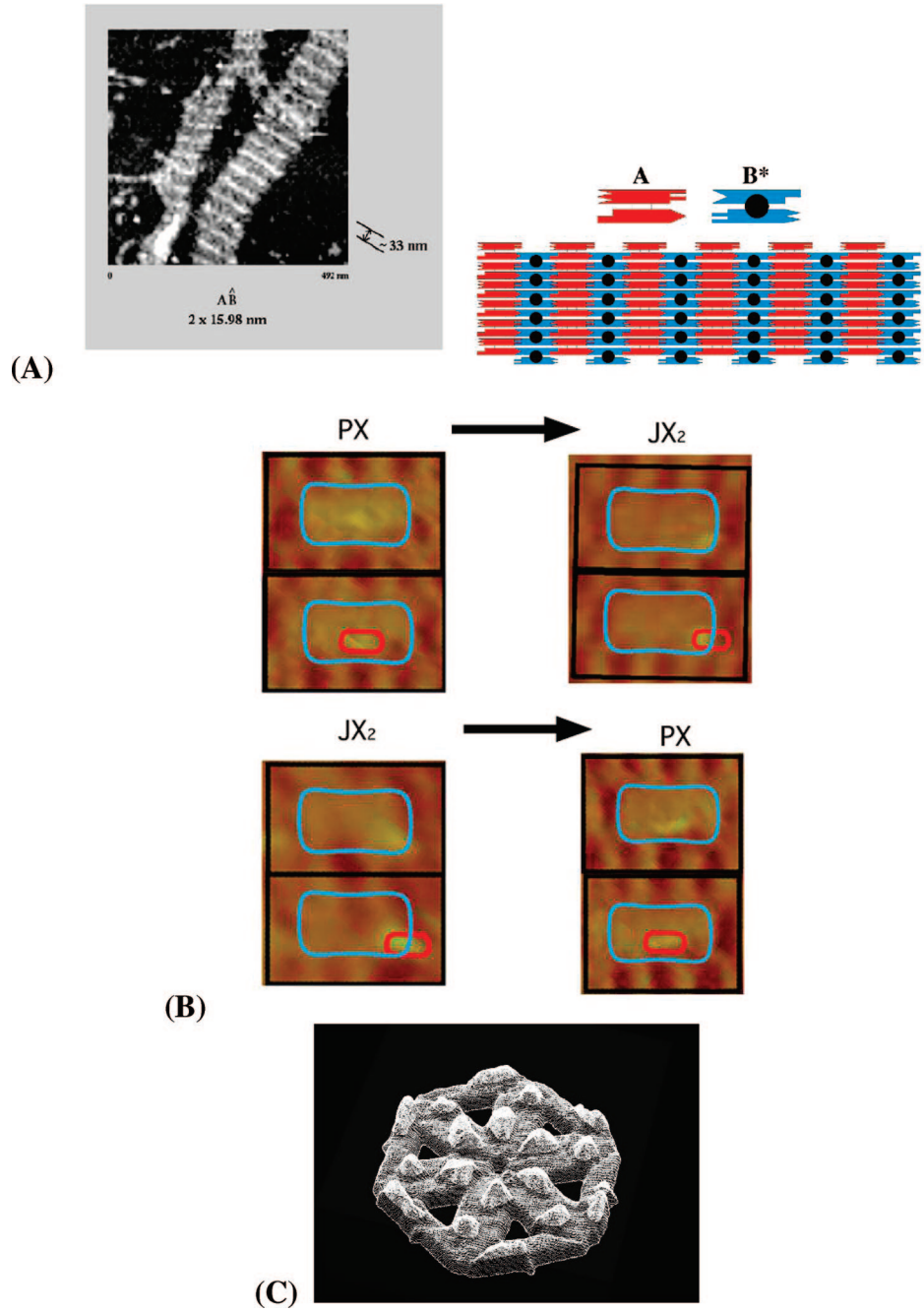

Figure 5. Atomic force microscopy images of DNA on mica: (A) a self-assembled two-dimensional (2D) lattice of DNA (schematic right frame shows tile assembly), each tile is 16 nm long, and every "B" tile has the feature that led to the striped appearance;[21] (B) before and after flipping DNA arm in 2D structure;[20] (C) 2D DNA origami[11] (image courtesy Dr. Paul Rothemund). [(A) and (B) used with permission from refs 21 and 20, respectively). (A) Reproduced with permission from ref 5. Copyright 2003 American Chemical Society. (B) Reproduced from ref 20. Reprinted with permission from AAAS.

PSW: What would you like to be able to do in three dimensions?

Ned Seeman: First, I would like to be able to know that I made what I made, and that requires crystallography of a *moderately* good quality to be able to see the major and the minor grooves of DNA. I do not quite know what it takes, but 4 or 5 Å would be a minimum to be able to feel confident that you are seeing what you are supposed to be seeing. Maybe better. . . I'm just *hoping* it is 4 or 5 Å because we have some 4 or 5 Å crystals!

What we'd like to be able to do with it, the original idea that I had at that pub back in 1980, is to use the DNA as a host lattice for macromolecular-scale guests—basically, to solve the crystallization problem of macromolecular crystallography in a general way. Make boxes, although they cannot look like boxes, because they are not robust structures, but make box-like things that are connected by sticky ends; make that lattice. If the boxes are filled with an ordered material, then the whole system will be ordered and you can do your crystallography and be happy.

If you can imagine organizing biological macromolecules, you can also imagine organizing other things. Back in 1987, Bruce Robinson and I published a suggestion on how to use DNA to organize nanoelectronics.[27] So, those are two of the goals of organizing things. We have organized gold nanoparticles in 2D,[28,29] and we and others are working on other components for those systems. So, you can make things smaller, faster, whatever.

The other things that we would like to be able to do would be to generate systems. Others are now working on all of these things. Control of structure and topology in other *species* is something that we are working on. My colleague Jim Canary and I some years ago published a very short prototype of a ladder polymer based on DNA, the idea being to impose the topology of the DNA molecule (which is such a great topological synthon) on another molecule (in that case it was nylon).[30] So far, we have not gotten there. We have been working on this for about a dozen years, but we are just at the very beginning stages of trying to impose topology on another polymer.

Other things that we would like to be able to do would be make a kind of ribosome-like molecule for polymers.[19] Instead of *di*-block or *tri*-block, you could have *n*-block and have the same diversity and specificity that a ribosome has when it makes proteins. I'm not quite sure where that would lead but it would certainly be able to make interesting things.

> It is all chemistry of one sort or another, just moving atoms around, whether they are in large groups, small groups, whatever—it is just chemistry.

In general, much of our nanomechanical device program is directed at nanofabrication and nanorobotics. A little walker that Bill Sherman designed and put together in the laboratory basically uses the Yurke chemistry again to act like a little inchworm.[31,32] At almost the same time, Niles Pierce did some things very similar that actually moves more like kinesin with a foot-over-foot type of step.[33]

We are thinking about self-replicating systems. As soon as you have self-replicating systems, then the next challenge is to see if you can evolve them. It is very hard to include any kind of combinatorial chemistry into this work because the combinatorial elements have to be structural elements. It is not just changing an "A" for a "G" because then you just get mispairs.

We are also looking at ways to get things to self-weave so as to make polymers that will actually make rather interesting topologies in the future.

PSW: Do you see applications outside of the scientific enterprise for DNA nanostructures?

Ned Seeman: I think self-weaving polymers are likely to be an outside application, and all the usual stuff that everybody thinks about will probably eventually be done using components of structural DNA nanotechnology (drug delivery, cell identification, and so forth). There are lots and lots of little problems out there, all of which can probably be solved on the nanometer scale using these systems or systems derived from them.

So, when I say DNA, I do not necessarily mean garden-variety DNA. I have a 10-year-old paper that lists 200 variants of DNA,[34] and I'm sure by now the number is well over 1000! The generation of variants of DNA, that is another challenge, to make DNA-like molecules that behave properly in *other environments*—with DNA we are limited to not terribly hot temperatures, but there are hydrophobic environments and so forth. The odds are that we are going to have to derivatize DNA to make it less polar and happier in those environments. Then there would be other things that we could do with it. Part of it is DNA and getting DNA to form interesting and exciting and useful shapes, and the other part of it is to modify DNA. That is *real* chemistry, and that is really *hard*. What we do is easy on that scale; we just plug a sequence in the synthesizer and out it comes. But to do things with modified DNA is very hard—that takes a lot of work by talented people.

PSW: How do you differentiate between chemistry, self-assembly, and nanoscience?

Ned Seeman: Frankly, I think it is all chemistry of one sort or another—nanoscience or self-assembly is simply one flavor of it. What's the difference between self-assembly and any other kind of assembly? It is just a matter of whether people are plopping different things in a pot or not.

Presumably, it is "designed self-assembly" we are really talking about here. DNA sticky ends and other kinds of cohesive interactions are very potent, but in fact, it is just a different scale of what a regular chemist does when they put two different species together in a pot and expect some kind of reaction. In our case, the reactions are weak interactions: 5 kcal/mol, instead of forming 80 kcal/mol bonds.

When I was a kid, I used to watch a show on TV that was sponsored by DuPont; you always heard their motto "Better Things for Better Living. . . Through Chemistry"—this was in the 1950s. By the 1960s, the "Through Chemistry" was gone. I think that "nanoscience" or "nanotechnology" is an acceptable way to use the word "chemistry" today. We live in the post-Bhopal world and post-environmental crisis (or continuing environmental crisis) world; we're all aware of it. Most people think of chemistry as being a causal agent in that rather than a curative agent. On the other hand, many of those same people believe (for reasons best known to themselves) that nanotechnology may solve these problems. I'm happy to have any term that makes doing chemistry acceptable.

It is all chemistry of one sort or another, just moving atoms around, whether they are in large groups, small groups, whatever—it is just chemistry.

PSW: You founded an organization called the International Society for Nanoscale Science, Computation and Engineering. Why did you do that, who is involved, and what are your goals?

Ned Seeman: The goal is to promote the fields. There are several constituent parts to the general enterprise, both the nanoscience part of the work and the DNA-based computation part. There are sort of two communities that came together to form this society. We want a place on the scientific horizon. We want to make sure that good work in the field is recognized. Many of us feel that in many organizational contexts we are kind of orphans. We needed a home.

I do not know that we hit upon a very good name for the organization. Perhaps, the people who were really involved in that society (which is represented both by the FNANO [Foundations of Nanoscience] meeting and the DNA Computation meeting [The International Meeting on DNA Computing]) are people who largely, but not exclusively, work with DNA and other informational polymers to do their science. That is a relatively small fraction of all the people involved in nanoscience, and I think it is kind of a special group. Most of us do not feel all that at home in the Biophysical Society. We are tangential, many of us, at MRS [Materials Research Society] or at ACS, or what have you. So, we needed a home and we want to make sure that good work is recognized, that young people are promoted and recognized, and that we have an organization that they feel they can call their own that will look out for their interests. Of course, the essence of any scientific organization is to promote the science.

PSW: Do you have advice for young scientists?

Ned Seeman: I think you have to follow your nose, and if you think what you are doing is interesting and exciting, you have to have the courage to do it, and not go looking around for "what's hot, what's the latest, what is it that everyone else says you should be doing?" In general, I'd say that is what you should *not* be doing. And I think that is true in almost any field, that you have to have enough initiative and enough courage to do what you think is going to be the best and most exciting science for you.

You have to follow your nose, and if you think what you are doing is interesting and exciting, you have to have the courage to do it.

That afternoon—with my little epiphany with the Escher in the pub—did not happen when I was young; I was almost 35 years old! I switched fields when I was an assistant professor! It was not necessarily the smartest move, but it seems to have worked out OK. And I would say that to everybody, that you have just got to do what you think is the most exciting science. If it does not seem like the most exciting science—and realistically speaking, you have to do *something*—all right, keep your eyes out for something that is more exciting to you, and keep thinking about it and see what you can do.

[Literature citations and figures were added after our conversation to assist and to direct the reader to relevant publications.]

— Paul S. Weiss, Editor-in-Chief

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