

BE.342/442 Tuesday, November 17, 2005
Topic: DNA Molecular Machines

Administrative: Take-home midterm due today.

DNA has become a scaffold material with applications beyond genetics and nanotechnology.

Many biological materials have self-similarity at multiple length scales, or *fractal* character. This idea might inspire you to conjure up your own ideas about nanotechnology. Don't worry about what other people think about your idea! A book that might inspire you: Michael Gross, *Travels to the Nanoworld: Miniature Machinery in Nature and Technology*.

Richard Feynman predicted that nanotechnology would be the next wave in science after his time.

Gene Chips

Affymetrix, a company located near Intel in the Silicon Valley, has combined semiconductor industry technology with DNA nanotechnology to build a GeneChip™ in which 50-square-micron areas are coated with oligonucleotides that hybridize with fluorescently labeled DNA and RNA fragments. These biochips are able to identify the presence of genes through over 50,000 different probed complementary to the genetic information of interest. A number of companies have mimicked this technology – a sort of “me, too” wave in the biotech industry.

DNA Origami

Two-dimensional paper can be folded into complex 3-D patterns. Can this idea be applied to DNA? Part of your midterm examination was to find all the possible hydrogen bonds to the nucleic acids. What structures can be achieved by these bonds?

Ned Seeman was a postdoc with Alexander Rich here in Building 16 of MIT. He solved early x-ray diffraction patterns of various forms of DNA, which gave him a deep understanding of DNA bonding. After working in Albany, NY, he went to NYU, where he revolutionized DNA nanotechnology through his approach to “DNA origami.”

Reference: Junghuei Chen and Nadrian C. Seeman. “Synthesis from DNA of a molecule with the connectivity of a cube.” *Nature*, 18 April 1991.

Seeman combined cyclized L and R forms of DNA and hybridized them into shapes that look like chains with square links. Once these constructs grew to three links, the ends could be ligated to form a cube shape.

Seeman originally analyzed these structures by sorting them by molecular weight and shape using gel electrophoresis. Knowing the molecular weight of each nucleotide (330 Da per base, 660 Da per base pair), he could calculate the number of bases involved in each structure. Additionally, the shape of the structure influences how quickly the structure travels in a gel. Even before analyzing the shapes with electron microscopy or

force microscopy, Seeman was able to hypothesize about the structures that were separated across the gel. Knowledge of the lengths of the base pair bonds was key to solving the structures formed by DNA. Every hydrogen bond had to be accounted for, either in binding between the base pairs or in a bond to water.

Since the initial discoveries, DNA origami has become more and more elaborate, including formation of knots and interlocked rings.

DNA switches

Seeman was also involved in designing a DNA switch based on the transition between the B-form and the Z-form of DNA.

Reference: Chengde Mao, Weiqiong Sun, Zhiyong Shen, and Nadrian C. Seeman. "A nanomechanical device based on the B-Z transition of DNA." *Nature* 14 Jan. 1999. Only the junction switches from the B-form to the Z-form.

DNA crystals

Later, Erik Winfree, a Caltech grad student communicating with Zeeman, designed DNA crystals.

Erik Winfree, Furong Lin, Lisa A. Wenzler, and Nadrian C. Seeman. "Design and self-assembly of two-dimensional DNA crystals."

DNA was ordered into 2-dimensional crystals in an A-B-A-B or A-B-C-D pattern. Computer simulations were used to select the appropriate base pairs to avoid aggregation and control the length of the loop areas. Loop areas were restricted to 4 base pairs, since the "tetraloop" is the most stable loop form in DNA.

DNA tiles

Nature 6 August 1998.

Regular ladder systems of DNA exhibit a banding structure. These structures are now of interest to semiconductor chip manufacturers, who want to use them to control small features on chips. These bands are different from the banding found in collagen; here, a single piece of DNA forms ridges along the length of the crystal. Unfortunately, these crystals have not been grown for very long stretches – not even to tens of microns.

DNA computing

Stan Williams of UCLA was featured on the cover of MIT's Technology Review believes that computers will someday self-assemble in beakers!

DNA scaffolds for nanotechnology

DNA scaffolds are no longer news, but the pioneers of early work on DNA scaffolds are good sources of ideas for emerging nanotechnology.

Chad A. Mirkin, Lobert L. Letsinger, Robert C. Mucic, and James J. Stornhoff. "A DNA-based method for rationally assembling nanoparticles into macroscopic materials." *Nature*, 15 August 1996.

Recall that thiol groups (-SH) bind to gold. Here, unpaired DNA strands bound to gold nanoparticles via thiol groups were used as "sticky ends" to organize the nanoparticles into colloidal nanocrystals. The crystal formation is reversible, simply by heating to break apart the base-paired DNA strands. The investigators demonstrated that alternating temperatures of 0°C and 80°C reversibly formed and dissolved the gold colloidal structures. This technology has been applied to instruments such as sensors.

A. Paul Alivisatos, et al. "Organization of 'nanocrystal molecules' using DNA." *Nature*, 15 August 1996.

This study, published in the same magazine, used a completely different approach to organize gold nanocrystals. Here, single-stranded DNA was reacted with just one gold nanoparticle per strand and allowed to assemble into double-helices spaced apart precisely by the lengths of the strands: 34Å per 10 bases per turn. This way, the spacing in the crystal could be controlled with nanoscale resolution.

DNA nanowires

Erez Braun, Yoav Elchen, Uri Sivan, and Gdalyahu Ben-Yoseph. "DNA-templated assembly and electrode attachment of a conducting silver wire." *Nature*, 19 February 1998.

DNA was used to fill gaps between electrodes spaced microns or nanometers apart. Then, metal clusters were deposited on the DNA to form nanowires. AFM and fluorescence microscopy show the arrangement of the DNA; I-V curves show the conductivity of the metal-coated DNA.

In this example, DNA is no longer used as a genetic material, but instead as a material for nanotechnology. This group has published two interesting papers since releasing this work, showing progress in the use of DNA as nanowires.

Paul S. Weiss. "Molecules join the assembly line." *Nature* Vol 413, 11 October 2001.

Another approach to DNA nanowires is the use of functionalized porphyrins that are coated with gold and allowed to self-assemble into well-ordered nanowires.

Nature Vol 413, 6 September 2001.

Yet another approach involved formation of aurophilic chains (linked by attractive forces between gold nanoparticles) that cause the gold-bound molecules (here, Cl-Au-C-B-CH₂-CH₂-CH₃) to form a structure similar to a beta-sheet.

Finally, Angela Belcher's research at MIT uses a virus (M13 phage) to select and align nanoparticles of inorganic materials such as ZnS.

As you can see, a fair amount of research is going on in this area! Today, gold nanoparticles are commercially available in 0.8 nm (11 atom) or 1.4 nm (55 atom) sizes to support this research! The nanoparticles are stabilized by ligands that make their effective sizes larger – 5 nm and 10 nm, respectively.

Nanomachines powered by DNA

Reference: Bernard Yurke, Andrew J. Turberfield, Allen P. Mills Jr., Friedrich C. Simmel, and Jennifer L. Neumann. "A DNA-fueled molecular machine made of DNA." *Nature* Vol 406, 10 August 2000.

How would you build a molecular machine? Start by building the parts, which will stick together by DNA hybridization. Here, five complementary DNA molecules assemble into "molecular tweezers" that can cycle through several stable types of pairings, including "open" and "closed" forms. To observe the cycle, DNA was labeled with fluorescent proteins that can be quenched depending on which strands are bound to each other.

On the horizon

Sir John Maddox, "The Unexpected Science to Come."

"The most important discoveries of the next 50 years are likely to be ones of which we cannot now even conceive." It's true – who can predict where nanotech will take us?

Francis Crick, *What Mad Pursuit*, 1998.

"In nature, hybrid species are usually sterile, but in science the reverse is often true. Hybrid subjects are often astonishingly fertile, whereas if a scientific discipline remains too pure, it usually wilts."