DNA Inside

DNA computers may help scientists overcome the limitations of silicon-based machines, leading to new nano-scale products as well as smart drugs that adjust to their biological environment.

By Lori Andrews

Mark Sims is an unusual CEO. Instead of focusing on selling one of his key products, the founder of Bloomfield Hills, Michigan-based Nanorex spends much of his time giving it away. NanoEngineer-1, as it's called, is a computer program that allows scientists to model DNA nanostructures. The software, Sims reckons, could hasten progress in DNA computing, a once obscure field that is of growing intrigue to the entrepreneur as well as to other scientists and venture capitalists. Once focused on attempts to outdo silicon-based computers at mathematical problems, DNA computing is now looking to use DNA self-assembly to create new biological and nano-electronic products.

First developed in the mid-1990s, DNA computing is increasingly concentrating on a central tenet of the biotech industry: mimicking the complex activities of nature to create new processes and products. Because of its interdisciplinary nature, the field brings together computer scientists, physicists, chemists, and biologists in cutting-edge research. Sims has high hopes for the work. One day, he envisions, even high school students could build novel structures out of DNA. Dr. Yaakov Benenson, a researcher at the Harvard Center for

WEIZMANN INSTITUTE OF SCIENCE

Molecular Automata, shares his enthusiasm. "Each genetic cell already has all of the tools to build biocomputers on its own," says Benenson. "All that must be provided is a genetic blueprint of the machine and our own biology will do the rest."

As is the case with many advances in computing, the development of DNA computing began when researchers were looking for ways to create computers that run faster and have greater memory. Adding urgency to the exploration is the eventual obsolescence of silicon chips. The number of components that can be etched on a silicon chip has been doubling about every 18 months, but that will max out in the next decade. At that point, the chips won't be able to shrink further without electron leakage or other problems.

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> *Mark Sims, Founder, Nanorex*

The space between each base pair in a genetic sequence is 1 billionth of a meter, allowing for a denser packing of information than in silicon. But beyond the expansion in capacity it can provide, DNA computing offers a unique advantage in biological environments. In cells or in the bloodstream, DNA computers can take advantage of their ability to interact directly with a biological environment.

Computers were once room-sized calculating machines, but DNA computers may be able to function as "smart drugs" that can detect abnormalities in the environment to indicate a particular disease, and then, ultimately, adjust that environment to offset the disease process. DNA can also be used to create machines and structures other than computers, such as tiny motors or miniaturized circuitry.

In 1936 Alan M. Turing, the renowned British mathematician, invented a "toy" computer which is now called the Turing Machine. The machine stored information as sequences of letters on tape and used a finite control to manipulate that information. What began as a conceptual device to explore mathematical computations ended up being a universal tool to store and manipulate data.

A half-century later, University of Southern California computer scientist Leonard Adleman, realizing that DNA and enzymes also store information and manipulate it, set out

Computer in a tube: Professor Ehud Shapiro *(standing)* of the Weizmann Institute of Science in Israel holds a test tube containing 1 trillion biomolecular computing machines. Yaakov Benenson holds eight test tubes containing eight software molecules.

IBM CORPORATE ARCHIVES

Friendly dinosaur: IBM's Model 168 of 1972 was designed for the needs of the large database and data communications user. A single 168 could provide up to 8 megabytes of monolithic processor (main) storage.

to create the first DNA computer. His work at the intersection of computer science and molecular biology inspired research to find an approach for DNA to replace silicon chips. Along the way, companies such as Olympus, Gentel Biosciences, Nanorex, and CDF have funded and fabricated components to harness DNA, not just to replace certain computer functions but to venture where traditional computers do not tread.

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Richard Feynman once said, "The inside of a computer is dumb as hell, but it goes like mad." The speed of silicon-based computers comes from their being able to quickly solve problems one step at a time. DNA is potentially much faster. This biological raw material replicates exponentially and each of the strands can be working on a different aspect of the problem at the same time. And rather than needing a multimillion-dollar dust-free factory to make thousands of silicon chips, the creator of a DNA computer could use a single bacteria cell in a flask in a lab to produce billions of cells with the same DNA.

Silicon-based computers store information using the binary code and manipulate that information with a microchip. Adleman realized that he could store information in DNA

and manipulate that information utilizing the process by which a sequence of nucleotides binds to a complementary strand.

In 1994, Adleman decided to use DNA to solve the directed Hamiltonian Path Problem, also called the Traveling Salesman Problem. He chose a classic computer problem to ensure that he would not be accused of picking a problem to fit the machine. In the Traveling Salesman Problem, a hypothetical salesman must determine the best travel route. For example, the salesman might need to travel from Los Angeles to New York, passing through three other cities—Dallas, Chicago, and Miami—on the way. Specific restrictions are placed on the itinerary. For example, the airline allows a flight from Los Angeles to Chicago, but not from Miami to Chicago. To avoid missing a destination, visiting a city twice, or not making it to the final destination of New York, only one itinerary is possible: beginning in L.A., the salesman flies to Chicago, Dallas, Miami, and then to New York. This problem, while easy with a few cities, becomes problematic for an individual and for a computer when the number of cities increases and the number of possible routes increases exponentially.

Adleman solved this problem with a DNA computer, a clear liquid in a test tube. He assigned each of seven cities a different 20-nucleotide genetic sequence, generated all possible itineraries, and then selected the correct one. This would not be the ideal approach using a silicon computer because it would take too long to search all possible routes one after another. But DNA is well suited to this "shotgun" approach. Enzymes working on many DNA molecules simultaneously favor a massively parallel selection process.

Using gel electrophoresis, which analyzes the size of DNA, Adleman was able to eliminate many routes that would require visiting some cities twice by screening for only DNA sequences that were 140 nucleotides long (seven cities times 20 nucleotides). Then he used affinity purification to separate the DNA molecule containing the correct sequence.

When Adleman announced his breakthrough, scientists from around the world gathered for the first conference on DNA computing. The field is still going strong—the 14th International Conference on DNA Computing took place June 2-6 in Prague. And money continues to flow into the research. Anthony Macula, an associate professor at the State University of New York at Geneseo, is funded by the U.S. Air Force to harness DNA's speed and increase computation capacity. He also has a large National Science Foundation grant to train undergraduates to perform research in biomathematics. At the same time, he is using private funds from CFD Research of Huntsville, Alabama, to create a simulated DNA computer that acts as a tool for understanding disease.

UNIVERSITY OF SOUTHERN CALIFORNIA

Realizing that DNA and enzymes also store information and manipulate it, University of Southern California computer scientist Leonard Adleman set out to create the first DNA computer.

The initial applications of DNA computing solved the types of problems in computation and logic that computer scientists traditionally used to measure their programming skills and the powers of generations of silicon-based computers. DNA computers have attacked the Knight problem in chess (using RNA to compute how to place a collection of knights on a chessboard so that none can attack each other) and the knapsack problem (figuring out how to choose objects for a knapsack to maximize their value within a certain weight limitation). They've even consistently beat human opponents at tic-tac-toe. Researchers at Stanford University and Princeton University have suggested using the parallel processing ability of

JIM DAHLBERG

Shifting focus: University of Wisconsin chemist Lloyd Smith simplified DNA computing by attaching DNA molecules to a surface—a gold-coated glass slide. Between steps of the calculation, the surface of the chip is rinsed and the reagents for the subsequent step are added. "We started out commercializing DNA computing, using IP from our lab," says Smith. "Over time, the company morphed into commercializing antibody arrays. The commonality is the surface chemistry."

a DNA computer to break the United States government's digital encryption standard; while the system might keep data secure from silicon computer decryption, DNA would work like a billion silicon computers at once, each trying a different combination.

As with silicon-based computers, many of the theoretical and practical advances in DNA computing are coming from Japan. In March 2008, a Japanese team from Waseda University reported in *Biosystems* that DNA computing is an appropriate way to solve problems of "clustering"—analyzing concepts and algorithms in huge, heterogeneous data sets to reveal meaningful relationships.

But DNA computers have their own, unique drawbacks. Using Adleman's original DNA computer for a Hamilton path problem with 200 cities would require an amount of DNA that was heavier than the weight of the earth. Plus, DNA replication can introduce errors in the DNA sequence. And even when the DNA itself may contain the right answer, analyzing the DNA to get the answer can be a cumbersome procedure. Adleman's initial DNA computer operated at 100 Teraflops per second at a time when the world's fastest silicon-based computer ran at a mere 35.8 teraflops. But, translating the DNA answer into something people can understand was time consuming. Back in 1994, it took Adelman six days to translate the DNA sequence solution.

These drawbacks led researchers to shift away from trying to develop DNA to solve mathematical problems. Now, many of the researchers are asking: What can DNA computers do that traditional computers cannot? Along the way to answering that question, some researchers developed useful technologies that they have been able to commercialize for other purposes.

Lloyd Smith is typical of the DNA computer researchers whose work has changed focus. In 2002, he advanced the field by moving away from Adleman's approach of having all the reactions of the DNA computer occur in a test tube. Working with $900,000 in funding from the Department of Defense and the National Science Foundation, Smith, a University of Wisconsin chemist, simplified DNA computing by attaching DNA molecules to a surface—a gold-coated glass slide. Between steps of the calculation, the surface of the chip is rinsed and the reagents for the subsequent step are added.

Smith formed a company, Gentel BioSurfaces, in Madison, Wisconsin, to commercialize DNA computers. But as the limits of DNA computing became more apparent, the company instead began to commercialize Smith's technology for immunoassays and in 2006 renamed itself Gentel BioSciences. "We started out commercializing DNA computing, using IP from our lab," says Smith. "Over time, the company morphed into commercializing antibody arrays. The commonality is the surface chemistry."

At the Weizmann Institute of Science in Rehovot, Israel, Ehud Shapiro and Benenson, now at Harvard, made a conceptual leap that took the field a step further through a proof of concept experiment in which an in vivo DNA computer not only diagnosed a disorder, but treated it. In a test tube, their molecular creations (made of DNA and proteins) successfully detected the symptoms of prostate cancer and small-cell lung cancer. Because of the possibility that their DNA computer might generate potential errors, Shapiro and Benenson came up with a striking solution. They created multiple copies of two types of molecules, one to release a drug when the cancer was detected and one to release a suppressor of that same drug when the cancer was not detected. "By changing the relative concentrations of the two types of molecules," they wrote in *Scientific American*, "we could have a fine control over the threshold of diagnostic

certainty that would trigger an administration of an active drug."

Duke computer science professor John Reif is similarly concentrating on diagnostics. He formed a company, Eagle Eye, to commercialize his work on DNA detection methods that need no equipment. His goal is to create test kits where a drop of blood on filter paper indicates the presence of HIV or Chlamydia. He's already managed a proof of concept in a test tube. Through the biological application of DNA, he can eliminate costly aspects of tests (such as the need for PCR and thermal cycling), which would allow him to offer tests that now cost hundreds of dollars for mere pennies.

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As the chair of the annual F-NANO (Foundations of Nanoscience) meeting, Reif sees DNA as a more useful tool for self-assembly than carbon nanotubes or other non-biological materials. "DNA is highly programmable, it can create predictable structures, and the scientific methods for manipulating DNA are well understood," says Reif, whose work is funded in part by the Air Force.

DNA can function as a computer, relying on its natural properties. But it can also be used as a building block for other types of tools in ways that it is not used in the body. "The term 'DNA computing' is a historical term," Reif says. "The field has diverged into areas dealing with DNA nanostructures, DNA molecular motors, and so forth."

In 2006, California Institute of Technology computer science professor Paul Rothemund published an article in *Nature* demonstrating that he could use DNA self-assembly to fabricate any two-dimensional shape—a technique he dubbed DNA origami. He envisioned using these structures as scaffolding for medical purposes (to model complex proteins) or to create molecular electronic or plasmonic circuits (by attaching nanowires, carbon nanotubes or gold nanoparticles). Sims, the Nanorex CEO, visited Rothemund's lab and now includes a DNA origami option in his open-source software.

Researchers led by Bernard Yurke at Bell Labs (a division of Alcatel-Lucent) discovered a sequence of DNA that acts like a motor. In their research, they put three specific strands of DNA into a test tube, forming a tweezer-like structure of two strands and a hinge. A specially designed "fuel strand" is added to the test tube, binding to the two ends of the tweezers to bring them closer together. The fuel strand's complementary strand is added to the test tube to open the hinge. The thermodynamic change that occurs is akin to a molecular motor. Yurke is now exploring ways to attach the DNA strands to molecules that conduct electricity as a way of creating superminiaturized circuitry.

Harvard genetics professor George Church, who directs the Center for Computational Genetics, says that DNA computing is now "directed at a practical interface with biomedicine, rather than losing an abstract race with existing computers on their own turf."

Church's interest in DNA self-assembly is proof enough that the field is hot. Along with Walter Gilbert, Church developed the first direct DNA sequencing method in 1984, which launched the Human Genome Project. In 2005, he initiated the Personal Genome Project. Recently, he helped found Codon Devices, a biotech startup in Cambridge, Massachusetts, engaged in synthetic biology. The company is poised to market the first commercial piece of DNA origami—a nanorod for membrane-protein structure determination.

"DNA-directed self-assembly represents a general purpose form of nano-manufacturing technology that could be used across a broad range of markets and applications, including electronics, medicine, energy, sensors, materials, etc.," Sims says. Although he plans for NanoEngineer-1 to remain open source, he anticipates that commercial plug-ins will be developed and sold by Nanorex and other companies. He may also enter into joint ventures with the users of NanoEngineer-1.

Sims' business strategy may sound odd, but his software could turn out to be indispensable for future molecular engineers. His philosophy might be something like this: If you show them how to build it, they will come. TJOLS

Lori Andrews, a Chicago law professor and novelist, chaired the federal ethics advisory commission to the Human Genome Project. In her latest novel, IMMUNITY, *a DNA computer helps solve the crime.*