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Living Machines

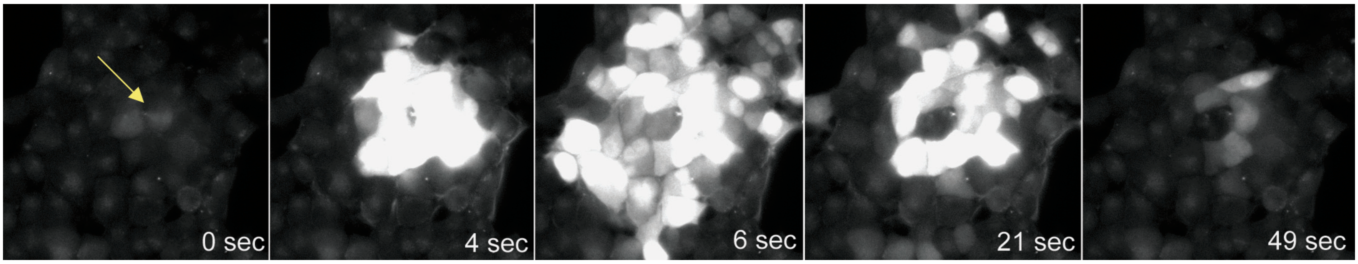
Researchers of molecular computing and communication are focusing on the type of breakthroughs needed to make the vision of ultrasmall, biocompatible computers a reality.

PHYSICISTS HAVE LONG postulated the idea that machines would become so sophisticated one day that scientists would be able to build increasingly smaller and more sophisticated devices until, at an advanced stage, entire computational systems would be able to operate inside the boundaries of a device no larger than a single cell. One early example of this type of speculation was a landmark 1959 lecture titled "Plenty of Room at the Bottom." In the lecture, delivered at the California Institute of Technology (Caltech), Nobel laureate Richard Feynman talked about engineering circuits at the molecular level, with the idea being to build a tiny set of tools that would be able to build an even smaller set of tools, and so on, until scientists reach the point at which they can create circuits consisting of a mere seven atoms.

Feynman's lecture has been credited many times for inspiring researchers working in nanotech and quantum computing. "The principles of physics, as far as I can see, do not speak against the possibility of maneuvering things atom by atom," said Feynman. "It is not an attempt to violate any laws; it is something, in principle, that can be done; but in practice, it has not been done because we are too big." Science hasn't yet realized Feynman's vision of an atomic- or even a molecular-scale computer, but it has been steadily moving in that direction for the last 50 years. Much research has focused on moving beyond the speed limitations of traditional semiconductors with quantum computing, using bulky machines that rely on atoms themselves as bits and bytes, but another branch of research, molecular computing and communication, has focused on the type of breakthroughs needed to make the fantastic vision of ultrasmall computers a reality.

Researchers working in molecular computing and communication—the inspiration for which can be traced, in part, to John von Neumann's theory of cellular automata and Alan Turing's work in autonomous self-structuring—seek to provide fundamentally new methods of solving challenging computational problems at microscale sizes. Currently, nanomachines created from biological materials are capable only of simple functions, such as detecting molecules, performing chemical reactions under certain conditions, and generating motion. While simple, these functions translate into sensing, logic, and actuation, respectively, each of which is a key element in any computing or communication system. But as with any advanced science, several major challenges in molecular computing must be overcome for the technology to make its way from lab to industry.

One of the challenges facing researchers working in this area, which requires advanced expertise in multiple disciplines, is to develop new languages



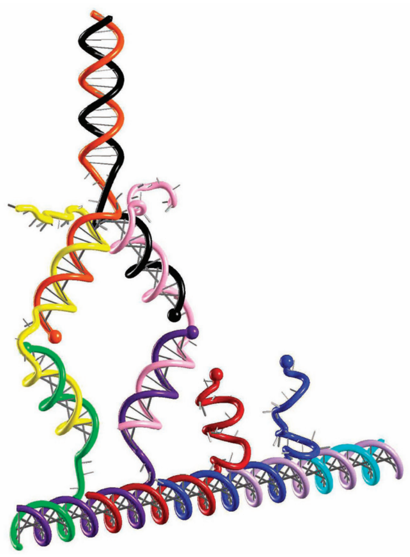
In an experiment on cell-to-cell communication conducted by Tadashi Nakano and colleagues at Caltech, a mechanically induced calcium wave propagates through several cells. The networked cells, behaving much like nodes on a LAN, propagate signals in all directions.

and methodologies so members of a team understand each other. “What a protocol means to computer scientists is communication procedures, while it means to biologists experimental procedures,” says Tadashi Nakano, a professor of computer science at the University of California, Irvine (UCI). “This is a trivial example, but in order to communicate with biologists, I first needed to learn a set of vocabularies that they use in daily conversation; and I needed to explain computer science vocabularies to them.” Nakano’s research in the Molecular Communication Group at UCI in-volves cell biology, nanotechnology, and communications engineering, with the ultimate goal of the work being to integrate these disciplines and establish molecular communication as a science.

Currently, Nakano and colleagues are focused on engineering cell-to-cell communication through calcium signaling. The photograph on page 11 shows a series of images captured as a mechanically induced calcium wave propagates through several cells. To monitor the waves, Nakano’s team loaded cells with calcium-sensitive fluorescent dyes, then used a micropipette to mechanically stimulate a cell and a fluorescence microscope to capture the images. Nakano says the project, which is in an early stage, is focused on designing the key components, such as amplifiers and switches, that are necessary to build a cell-based network. To realize some of the promises of molecular communication, says Nakano, the field’s understanding of cellular communication must be expanded and engineering techniques for modifying cell functions must be advanced. “Our current attempt is like designing systems using black boxes or components whose behavior is not completely predictable,” he says. “Our hope here is being able to reveal what’s inside the black boxes—that is, answering unknown questions in cell biology.”

DNA Walkers

Most molecular communication projects—such as Nakano’s work and projects under way at other research labs around the world—share a focus on sender nanomachines, receiver nanomachines, carrier molecules, and the environment in which these tiny objects operate. Senders and receivers include biological and biologically derived nanomachines that are capable of emitting and capturing carrier molecules, such as proteins, ions, or even DNA. Several research teams, for example, have built DNA walkers that operate much like kinesins, which are motor proteins that use ATP hydrolysis to move along microtubules. The goal of these projects is to construct a synthetic transport device that mimics the linear movement of motor proteins and can be used not only to carry a signal but also to carry out nanoscale computations.

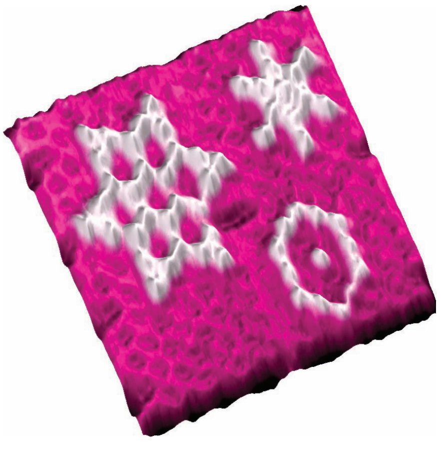


A DNA walker created by Caltech chemists Jong-Shik Shin and Niles A. Pierce. The vertical strands form the walker’s body and legs, which walks on the horizontal track.

Niles Pierce, a Caltech professor of applied and computational mathematics and bioengineering, and his colleagues have created a walker that can move along a DNA track. The first DNA walker that Pierce created several years ago was not autonomous—it required external control over the fuel strands—but his colleagues and him have built on the initial work and have created a microscale system that powers itself. “The key innovation in moving from nonautonomous to autonomous motors (both powered by the formation of DNA base pairs) was to develop conformation-changing molecules that could bind to one molecule and then change structure to deliver energy to the system,” says Pierce.

Currently, Pierce and his colleagues are working on the algorithms needed to create what he calls “a compiler for molecular computing” that will take as input a high-level abstraction of the desired function for a molecular system and produce as output molecular sequences that can be synthesized to execute the function in a test tube or cell. Pierce is also working to develop both nanomechanical instruments that use molecules to detect and regulate signals in living cells and nanomechanical drugs designed to kill diseased cells while leaving healthy cells untouched. “It is a huge scientific challenge to model the cellular environment in which our synthetic molecular systems must operate in living systems,” he says. “It remains to be seen how significant the resulting uncertainties are in thwarting our engineering efforts.”

At present, molecular programming is a research topic, and Pierce says science is far from creating general solutions to these design challenges. Pierce estimates that it will take a minimum of three to five years to achieve practical nanomechanical instrumentation and 10 to 15 years before there are nanomechanical drugs. “But there are already some systems,” he says, citing Caltech researcher Paul Rothemund’s “DNA origami” method for constructing shapes and patterns, “where high school students can program molecules using a simple CAD interface to specify nanoscale details of the self-assembling structures.” Other notable research includes John Reif’s work at Duke University, which is focused on self-assembling nanostructures; Tom Knight’s work at MIT, which is oriented toward standardizing DNA components for synthetic biology; and the work of Caltech’s Erik



An example of Caltech researcher Paul Rothemund’s “DNA origami” method for constructing shapes and patterns.

IMAGES BY NILES A. PIERCE (TOP) AND PAUL ROTHEMUND, CALIFORNIA INSTITUTE OF TECHNOLOGY

Winfree and New York University's Ned Seeman, which is focused on DNA computing and nanotech.

While these DNA projects have received a great deal of attention in scientific journals and even in the mainstream press, other, less well-known approaches to molecular computing might lead to entirely new computing paradigms, say researchers. One example is the work of Andrew Adamatzky, professor of unconventional computing in the department of computer science at the University of the West of England. Adamatzky's research focuses on reaction-diffusion computing, in particular on a chemical reaction called the Belousov-Zhabotinsky (BZ) reaction, which causes waves of ions to propagate through an environment. By controlling the BZ propagation pattern, Adamatzky has shown it is possible to produce biological logic gates.

Given the proper environment, the BZ reaction can operate much like a parallel processor in which each point on the wave front, mapped to a particular grid, can serve as a point of calculation. To create a Boolean logic gate, for example, Adamatzky represents True and False by the presence or absence of a wave fragment. When two or more wave fragments collide, they fuse, dissipate, generate new wave fragments, or change their trajectory or velocity, representing the Boolean variables and implementing the computation. The trajectories of the traveling wave fragments can be changed dynamically, and adjusted and tuned by colliding other wave fragments against them, making for complex interactions. "The medium can implement such sophisticated tasks as computation of the shortest collision-free path, approximation of Voronoi diagrams of arbitrary geometrical objects, and development of a skeleton of a planar shape," he says. "We proved the computational universality of the BZ medium by constructing a set of functionally complete logical gates in laboratory experiments. Our results indicate that the BZ system is a general-purpose parallel computer."

> **Future applications include environmentally friendly systems that can automatically decompose and drug delivery systems that can be embedded in human bodies.**

But as with other work in molecular computing, several problems must be addressed in reaction-diffusion computing. Sensitivity of the BZ reaction is one of the major issues facing Adamatzky. "We design logical circuits according to principles of collision-based computing, where information is represented by traveling wave fragments," he says. "Unfortunately, these localized excitations are unstable; they collapse or expand after some period of time." But even with unsolved problems and unanswered questions, the experiments are proving to be useful for other fields. The core ideas of reaction-diffusion computing already have spread to those working in massively parallel computing; and even some conventional silicon processors execute wave-based algorithms.

These projects represent a small cross section of the ongoing developments in molecular computing. Unlike quantum-computing projects that require sizeable machinery and clean-room-style environments, the promise of molecular computing is that it can operate in natural environments, without electrical power. Whether scientists are able to achieve Feynman's vision of nanoscale computers consisting of circuits and switches made of a handful of atoms remains to be seen, but researchers today are hopeful that paradigms developed through work in molecular computing will lead to entirely new applications, such as environmentally friendly systems that automatically decompose, energy-efficient machines that generate minimal amounts of heat, and biocompatible communication systems that can be embedded in human bodies.

Based in Los Angeles, **Kirk L. Kroeker** is a freelance editor and writer specializing in science and technology. Tatsuya Suda, National Science Foundation, contributed to the development of this article.

Medicine

Detecting Breast Cancer

A large-scale British study has found that one radiologist aided by a computer is as accurate as two radiologists when it comes to detecting breast cancer in a mammogram, according to an article published online in the *New England Journal of Medicine*.

Mammograms are used to screen women for early signs of breast cancer, but the tests are not perfect. In the U.S. most mammograms are read by a single radiologist, while in Britain, they are read by two radiologists or technicians. The British researchers, led by radiologist Fiona J. Gilbert of the University of Aberdeen, analyzed the results from a randomized study of 31,000 British women. It found that a radiologist aided by a computer detected 198 cancers out of 227, while a pair of radiologists detected 199 cancers.

Computer-aided detection (CAD) systems use computer algorithms to analyze digital mammogram images and to pick out and mark suspicious areas. CAD systems are used in approximately 25% of mammogram readings in the U.S., and this percentage should increase as more medical centers switch from film x-rays to digital images.

"In the United States, it's just not practical in most practices to do double readings by physicians," said Carol H. Lee, a radiologist at Memorial Sloan-Kettering Cancer Center in New York and head of the American College of Radiology's Breast Imaging Commission. "These results are reassuring to me that a single reading with CAD can achieve that same sensitivity."

Double reading is the standard practice in at least 12 European countries. "Up to now double reading has been the gold standard of mammography," said Dr. Marco Rosselli del Turco, president of the European Society of Breast Cancer Specialists. "We have been waiting for a well-designed, prospective, randomized study to establish the role of CAD. This study provides a definitive answer about the value of adding CAD to single reading, and is likely to lead to a change in European guidelines."