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Biochips: Handheld Labs and Microscopic Sensors

Executive Summary

Replacing vacuum tubes with computer chips enabled computers to evolve from room-sized machines run by technicians to handheld devices used by ordinary people. Replacing test tubes with tiny channels promises to do the same for biology, chemistry and medicine.

The potential rewards including saving a large portion of the hundreds billions of dollars spent every year on medical testing, drug development and genetics research, speeding the tests from hours or days to minutes or seconds, and enabling them to take place in the field.

In the past couple of years researchers have constructed highly intricate channels as small as 100 nanometers in diameter and have found ways to control tiny amounts of liquid coursing through them, including the key ability of mixing.

Researchers are also working to incorporate staples like biomolecules, optics, micromechanics, and electronics into various types of labs-on-a-chip.

Major research thrusts include using DNA and proteins to sense chemicals, enabling microscopic optics, making tiny channels and devices like valves, and finding ways to mix, pump and manipulate tiny amounts of fluids despite physics working differently at such small scales.

There are also efforts under way to use electricity to push around, carve up and mix liquids on chips without walls. Researchers are also looking to tap microelectromechanical systems and laser tweezers to manipulate and measure individual cells and even molecules.

Challenges include making labs-on-a-chip gentle enough not to disturb delicate samples, finding ways to eliminate cross-contamination, and ensuring that reactions happen quickly.

Though all-purpose handheld biochip devices won't be practical for decades, researchers have begun to build devices that perform specific lab tests in the field. Embedded biochips could eventually power sensors scattered around smart homes, battlefields and toxic waste sites.

What to Look For

Sensors:

Sensor capable of testing for 100 substances at once
Sensor capable of testing for 1,000 substances at once
Microscope built into a biochip

Microfluidics:

Biochip that uses electricity to control droplets
Unpowered biochip that uses hydrophilic surfaces and hydrogels
Implantable biochip that uses particle-based pumps and valves
CD-based microfluidic device for home DNA testing
Bacteria harnessed for pumping fluids
Hybrid biological/artificial device for drug making/delivery

Manipulators:

Biochip that includes laser-driven micromachines
Microfluidic device that includes laser tweezers
Device that injects substances into individual cells
Microrobotic surgical tools

Tiny labs

Computer chips have worked out quite well. Using arrangements of microscopic transistors to carry out logic operations has made it possible to make computers that carry out several billion operations per second.

There is an air of deja vu about the emerging field of biochips, where researchers are devising methods of making tiny, intricate channels in chips and coaxing minuscule amounts of liquid through them.

Replacing vacuum tubes with computer chips enabled computers to evolve from room-sized machines run by technicians to handheld devices used by ordinary people. Replacing test tubes with tiny channels promises to do the same for biology, chemistry and medicine.

Wet chips

The effort to make workable biochips has been ongoing for the past decade or so, and in the past few years researchers have devised ways to construct highly intricate channels as small as 100 nanometers in diameter and have found ways to control tiny amounts of liquid coursing through them, including the key ability of mixing.

This is no trivial matter. In such small amounts liquids behave differently than they do in test tubes. The viscosity of water flowing through a channel the size of a human hair, for instance, is close to that of honey flowing through a straw. And at very small scales turbulence disappears, making mixing more like kneading dough than stirring coffee.

A standard lab is equipped with much more than test tubes, plumbing and mixers. Researchers are working to incorporate staples like biomolecules, optics, micromechanics, and electronics into various types of labs-on-a-chip.

The challenge is making labs-on-a-chip gentle enough not to disturb delicate samples. Electric fields, heat, and chemicals can warp molecules and kill cells.

Though all-purpose handheld biochip devices won't be practical for decades, researchers have begun to build devices that perform specific lab tests in the field.

Anatomy of a biochip

Biochips are amalgamations of computers, plumbing and chemistry. Samples enter biochips through input ports. Samples and chemical reaction agents, or reagents, are guided through channels by some means of propulsion. Samples interact with reagents, biomolecules or other test mechanisms in tiny chambers. The results are sensed and recorded. Used samples, reagents and cleansers are expelled through output ports.

Several forms of biochips are under development, including networks of miniature plastic pipes and chambers that mix fluids, patches of DNA on electronic chips that sense biological material, and electronic circuits under glass surfaces that mix droplets of fluids without channels.

There are several challenges to making smaller, more intricate biochips:

- Incorporating biomolecules into chips
- Incorporating optics into chips
- Creating smaller, more intricate channels or even virtual channels
- Moving, mixing, manipulating and containing samples
- Eliminating cross-contamination
- Incorporating micromechanical devices

How It Works

Molasses and dough

Shrinking pipes and test tubes to the scale of computer chips promises to dramatically improve how people diagnose illnesses, monitor the environment and make medicine. But it's not enough to simply make tiny pipes. The minuscule amounts of fluid that flow through those pipes behave differently than the larger flows we're used to seeing in the everyday world.

Viscosity, for instance, becomes a relatively large force, making pumping water more like pumping molasses. This happens because different portions of flowing liquid travel at different speeds. Fluid very close to pipe walls, for instance, moves more slowly than fluid at the center of the pipe, and the effect is amplified in smaller channels. Viscosity can be thought of as a type of friction between fluids traveling at different speeds.

And when viscosity is high, turbulence disappears. The phenomenon responsible for bumpy airplane rides also causes liquids to easily mix at the macro scale. A few swirls generates enough turbulence to thoroughly mix a teaspoon of cream into a cup of coffee, for instance. At the small scales that lack turbulence, however, mixing liquids becomes very like kneading dough.

Pumping and mixing

Several traditional pumping methods have been scaled down for use in microfluidics, including pneumatics, peristalsis and mechanics. Pneumatics methods release compressed air or another gas through tiny pins inserted into microfluidic channels. The pressurized gas expands in the channels, pushing fluids ahead of it.

Peristalsis, which is how the heart pumps blood and the intestines move food, involves compressing a chamber to expel the fluid it contains. A micromechanical actuator or a series of actuators can compress the walls of a channel to push fluids through.

Mechanical pumps are popular at the large-scale, but it has proven difficult to make microscale versions of them because they're generally powered by motors.

The simplest methods of microfluidic mixing draw on geometry. The shapes and orientations of channels in microfluidics systems can induce the necessary kneading action. Just sending fluids around a sharp been increases the rate of mixing.

Using electricity

Microelectronics provide another avenue for moving and mixing fluids at the microscale. Electricity can move and mix fluids in several ways:

- Electroosmosis

- Ensuring that reactions take place quickly

What it all adds up to

The potential rewards are great. Hundreds of billions of dollars are spent every year on medical testing, drug development and genetics research.

Biochips promise to bring down the cost of medical and chemical laboratory testing by lowering the cost of equipment and decentralizing testing facilities in the same manner that computer chips made computers cheaper and widespread. The substantially smaller volumes of reagents needed in biochips alone has the potential to greatly reduce the cost of tests, making more of them possible.

Biochips also have the potential to greatly speed tests. Currently most tests for the presence of chemicals or pathogens take place in a lab and often take hours or days. Quick, in-the-field tests would be welcome in many contexts — any number of medical, environmental and biowarfare scenarios come to mind.

Cheap, disposable sensors could also be placed in the field to constantly monitor for many substances, acting as technological sentries on watch for disease and harmful chemicals.

Detecting with DNA

One of the most versatile sensors is the most complex molecule known: DNA. It contains the instructions all biological organisms use to make the proteins that carry out life's varied processes.

DNA is made up of four bases – adenine, cytosine, guanine and thymine — connected to a sugar-phosphate backbone. The two strands of double-stranded DNA are like a mirror image, with adenine on one side connecting to thymine on the other and cytosine pairing up with guanine.

Biological processes use a single DNA strand that has unzipped from its pair as a template to replicate DNA strands, and use portions of the rows of bases as templates to make proteins.

Researchers have co-opted this ability in order to make artificial DNA strands that connect to biological DNA and other chemicals. The DNA strands sense minute amounts of these target substances.

Using DNA as a sensor is tricky, however. The molecule is delicate, small and has a tendency to coil up. It must be protected, but in order to detect anything it must be in contact with the environment. DNA-based sensors must also have some way to communicate readings to the outside world.

Standard laboratory DNA tests require a replication step that makes millions of copies of particular DNA strands in order to make it possible to read the test results. The tests use fluorescent dyes whose molecules attach to the target DNA strands, and once enough DNA molecules fluoresce, the results can be observed. Skipping the replication step would enable simpler, faster tests on much smaller samples. To do this, many research teams are turning to the stuff of computer chips — electricity.

Researchers from the University of Wisconsin at Madison, Argonne National Laboratory and the Naval Research Laboratory have found that it is easier to attach DNA to diamond and form

- Magnetohydrodynamics
- Electrowetting
- Electrocapillary Pressure

Electroosmosis is a flow resulting from the combination of electric voltage and the chemical reaction between a solid surface and a liquid. At the boundary between a liquid and a solid, a negative charge builds up on one side and a positive charge on the other. Putting a pair of electrodes some distance apart in the fluid and applying a voltage causes the charged atoms, or ions, in the liquid to move in the direction of the oppositely charged electrode, and friction drags the rest of the fluid along. Using arrays of electrodes, researchers can make fluids flow in patterns that enhance mixing.

Magnetohydrodynamics is the interaction between electrically conductive fluids and magnetic fields. Applying a magnetic field to a portion of a channel causes a charged fluid to flow toward or away from that portion of the channel, depending on the polarities of the fluid's electric field and the magnetic field. Causing fluids to flow in patterns can enhance mixing.

Surface tension

A network of electric circuits beneath a glass surface can move droplets in precise patterns and merge and split droplets. The key is surface tension, the effect responsible for droplets holding their shapes rather than spreading out.

Surface tension has to do with cohesive forces between liquid molecules. Molecules at the surface of a liquid behave differently than molecules in the bulk of the liquid because surface molecules do not have molecules on all sides of them.

Molecules are attracted to neighboring molecules on all sides. Because molecules on the surface are not subject to an attractive force above them, they are pulled into the interior. This makes the surface of the liquid rearrange until the least number of molecules possible are present on the surface. Liquid naturally forms into drops, or spheres because the shape has the minimum surface area for a given volume. The surface molecules are also pulled more closely together than the rest of the molecules in the liquid, to form a film-like surface.

Electric fields affect the forces between molecules and therefore can be used to manipulate liquids.

Electrowetting is the technique of using an electric field to modify the wetting behavior of a droplet. Applying an electric field to one side of a droplet lowers the surface tension on that side, causing the droplet to flow in that direction.

Electrocapillary pressure taps electricity to change the surface tension between the inner wall of a channel and the fluid within. Applying an electric charge to the surface reduces the surface tension. Reducing

electrical connections between DNA and diamond than with DNA and the silicon used in ordinary computer chips. (See "DNA Prefers Diamond", page 10.)

Northwestern University researchers have made a device that contains a single DNA strand stretched between gold electrodes. The current running through the electrodes changes when the DNA strand combines with another strand. (See "Handheld DNA Detector near", page 12.)

Researchers from Delft University of Technology in the Netherlands, Leiden University in the Netherlands, and Princeton University have found a way to stretch and pin down DNA molecules that takes advantage of an affinity the ends of DNA molecules have for polystyrene. (See "Plastic Pins DNA Molecules in Place", page 13.)

Researchers are also looking for orderly ways to pack many DNA strands together in order to enable single chips that are capable of them of carrying out many different tests.

Researchers from them the University of California at Davis and Wayne State University have devised a method for attaching DNA strands to a gold surface so that the molecules stand up straight like a forest of branchless trees. The method promises to give DNA good access to surrounding chemicals and could incorporate DNA strands that sense different chemicals. (See "Biochip Sprouts DNA Strands", page 11.)

Researchers are also using protein molecules as sensors. Antibodies, for instance, use the lock-and-key method to capture harmful microorganisms.

Purdue University researchers have shown it is possible to use a computer chip studded with the egg white protein avidin to pick up bioten molecules in a solution. (See "Proteins-Coated Chip Sniffs Out Bacteria", page 14.)

It will take 5 to 15 years for University of California at Davis/ Wayne State University DNA microarray method to be ready for commercial use. The other DNA sensor methods could be ready for practical use within a year.

Microscopic optics

Light has many uses in biomedical and chemical testing. It is used to make images of samples, to trigger or inhibit reactions, and to analyze a sample's chemical composition. Researchers are working to bring various types of optical devices to biochips.

Researchers from the State University of New York at Buffalo have made a light-based sensor that contains 100 or more elements in the space of a thumbtack and so can detect 100 or more different substances in a single sample. (See "Porous Glass Makes Minuscule Sensor", page 15.)

Sandia National Laboratories researchers have made a microscopic laser that measures and identifies microorganisms and cell types without inhibiting biological processes. (See "Plastic Coating Makes Chips Biofriendly", page 16.)

Researchers from the University of California at Berkeley have built a confocal microscope-on-a-chip that promises to give scientists the surface tension in one portion of the channel causes the fluid to flow toward that portion of the channel.

Temperature and surfaces

Temperature also affects surface tension, and researchers have used tiny heating elements to move droplets across a surface.

Liquids can also be moved by using electricity to change the surface properties of a film from hydrophobic, or water repelling, to hydrophilic, or water-attracting. This process causes a droplet to bead or spread out on the surface.

Who to Watch

Microfluidics

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the means to observe the inner workings of cells in the cells' native habitats. (See "Speck-Sized Microscope Nears", page 16.)

The Sandia and Berkeley methods could be practical in three to five years.

Plumbing

Microscopic plumbing — microfluidics — is key to getting samples to the right place at the right time.

Researchers from California Institute of Technology have made a pair of rubber biochip prototypes. Their storage chip contains channels that measure 100 by 9 microns, 3,574 microvalves, and 1,000 chambers that each hold about one 80th of a drop. The chip contains fluid multiplexers that address, or control, the 1,000 chambers via twenty-two connections. The second chip, a comparator, has 2,056 microvalves and 256 chambers and can mix two fluids in any number of chambers. (See "Integrated Biochips Debut", page 18.)

Researchers from the University of Illinois at Urbana-Champaign have found a way to fashion tiny mechanisms like valves from hydrogels, which are soft polymers that change size by absorbing or expelling water when the pH or temperature around them changes. (See "Gels Make Micro Plumbing", page 30.)

Researchers from Cornell University have fabricated flexible tubes that are 100 nanometers in diameter, which is 50 times smaller than the width of a red blood cell. (See "Nanoscale Rubber Hoses Debut", page 17.)

These microscopic plumbing methods could be practical in one to three years.

Egg Yolks and CDs

Researchers from the Chalmers University of Technology and Göteborg University in Sweden have found a way to form networks of tiny containers and tubes using liposomes derived from egg yolks or soybeans. (See "Artificial Cells Make Mini Lab", page 22.)

Researchers have also found ways to adapt CD players to lab work. Although not as tiny as chips, CD players are relatively small, readily available, and already possess several abilities useful in a lab. The players use removable media, contain optical sensors, and are capable of spinning at different speeds, a force that can be used to shunt liquids around. Research teams have devised methods to carve channels and reservoirs into compact disks.

Advancing the effort, researchers from Ohio State University have developed a method of calibrating a CD's optical sensor so it can be used to measure variables like pH. (See "Lab-on-a-CD Corrects Itself", page 20.)

Puny pumps

Another important aspect of biochips is a means to move and mix samples. Several research teams have fashioned very tiny pumps and mixers.

Researchers from the Colorado School of Mines have constructed a pair of microscopic valves and a pair of microscopic pumps. The pumps, which are about twice the size of a red blood cell, move about one 20th of the volume of a drop of water per hour. (See "Biochips Get Pumped", page 25.)

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Researchers from Harvard University, the University of California at Santa Barbara, and the School of Industrial Physics and Chemistry in France have developed channels that have a herringbone pattern that directs the flow of a liquids moving through them to twist and thereby mix. (See "Labs-on-a-Chip Gain Micro Mixer", page 26.)

Scientists from Philips Research have made fluid flow through 20-millimeter-long channels as quickly as several centimeters per second. (See "Electricity Moves Fluids", page 29.)

Researchers from Texas A&M University are harnessing the swimming mechanisms of bacteria to control fluid flow in tiny devices. (See "Bioengineers Aim to Harness Bacterial Motion", page 27.)

Harnessing bacterial motion may take as long as a decade. The other moving and mixing methods could become practical in one to four years.

Virtual channels

It is also possible to contain, control and mix liquids without using physical channels.

Researchers from Duke University and Nanolytics are using electricity to push around, carve up and mix tiny droplets of liquid on a chip. The method has the potential to produce simple, reprogrammable chips. (See "Chip Juggles Droplets", page 23.)

University of Illinois and University of Wisconsin researchers have developed microchannel networks of hydrogel that direct water using a combination of materials that are hydrophilic, or attract water, and hydrophobic, or repel water. (See "Surfaces Channel Liquids", page 19.)

Researchers from Princeton University are using heat to move, mix and split droplets of liquid along interconnected networks of hydrophilic strips on a hydrophobic surface. (See "Biochip Moves Liquids with Heat", page 23.)

These methods could be practical in two to four years.

Getting a grip

In addition to containing, moving and mixing liquids, biochips must be able to manipulate and measure individual cells and even molecules. An obvious mechanism is microelectromechanical systems.

Researchers from Sandia National Laboratories have fashioned a set of nearly microscopic silicon jaws that rapidly open and close in order to trap and release red blood cells one at a time. The prototype proves that it will eventually be possible to puncture and inject substances into single cells. (See "Tiny Jaws Snatch Cells", page 35.)

Researchers from the University of Linköpings in Sweden have produced tiny robot arms that work in saltwater. The researchers' prototype has picked up and moved a glass bead that measures 100 microns, or about the size of a human egg cell. (See "Tiny Robot Flex Their Muscles", page 36.)

Cornell researchers have connected a biological motor to a tiny metal propeller. The device produces about 120 piconewtons, or trillionths of a newton, of power per nanometer — enough to move a piece of human hair that is several times as long as it is wide. (See "Biomotor Powers Propeller", page 37.)

These technologies could become practical in five to ten years.

Researchers from Harvard University have found a way to sort particles that are moving through fluid. The method employs a magnet, the natural curvature of liquid, and the Poiseuille effect, which slows the flow of liquid near channel walls. (See "Magnets Channel Biomatter", page 32.)

The Harvard method is ready for use now.

By the force of light

Another means of manipulating objects contained in or passing through biochips is light. A stream of photons can affect minuscule objects much like wind turning a windmill, and researchers regularly use pairs of laser beams, or laser tweezers, to manipulate small objects.

Researchers from the University of Glasgow in Scotland have found a way to use light to rotate an object in three dimensions, turning it like a ball rather than a wheel. (See "Lasers Tweeze Every Which Way", page 38.)

Researchers from the Mexican National Institute of Optical Electronic Astrophysics and the Universities of St. Andrews and Edinburgh in Scotland have found a way to use lasers to manipulate several particles at a time. The method allows them to arrange microscopic particles into three-dimensional structures, and to rotate those structures. (See "Laser Patterns Particles and 3D", page 38.)

A team of researchers from the Universities of Tokyo, Tokushima and Toyohashi in Japan are using laser beams to aggregate clusters of extremely small plastic beads near a DNA molecule in such a way that they can transport, stretch or keep the DNA molecule in place. (See "Lasers Snatch Free-Floating DNA", page 40.)

Researchers from Kyoto University in Japan have devised a way to use infrared laser beams to handle liposomes, which are water-balloon-like microscopic sacs. (See "Lasers Grasp Cell-Size Water Balloons", page 41.)

Laser tweezers could be used in practical applications within a few years, and could be used in conjunction with biochips in two to five years.

Researchers are also building microscopic mechanical manipulators that are driven by lasers. Researchers from the Hungarian Academy of Sciences have constructed tiny resin rotors powered by light. The rotors could eventually be used to measure the viscosity of microscopic samples or twist macromolecules. (See "Light Spins Resin Rotors", page 33.)

Researchers from Nagoya University in Japan have employed light to drive a pair of resin nano tweezers and a minuscule needle whose tip is 20 times smaller than a red blood cell. (See "Lasers Drive Tiny Tool Set", page 35.)

These methods could be practical within one or two years.

Issues and wrinkles

A big challenge for researchers who are attempting to make chip-size laboratories is scaling down the power sources that drive the plumbing and mechanics involved. Many biochips use pneumatics to force fluids through microscale channels, but there isn't much that can be done to miniaturize tanks of pressurized gases. Biochips also use significant volumes of fluids to purge channels and chambers between tests.

Another problem, particularly for biochips that move droplets on surfaces, is figuring out how to avoid cross-contamination. Moving samples and reagents through intersecting channels or on overlapping paths leaves plenty of opportunity for unwanted residues from one portion of a test to ruin another. Some biochips also face the risk of samples and reagents diffusing through thin polymer walls that make up channels and chambers.

Another challenge is integrating laser tweezers into biochips. Although lasers can be made small enough to fit on a computer chip, the instruments used to control laser tweezers usually take up laboratory bench tops. Researchers are aiming to make portable laser tweezers; in February, 2002 a team from East Carolina University to step in that direction by making a device that uses a single laser to both trap and analyze living cells. But laser tweezers built into biochips in handheld devices are at least a decade away.

These are engineering challenges rather than fundamental roadblocks, and they should be straightforward to solve for specific applications like chemical sensors and home medical diagnostic kits. Building a universal biochip, however, is a different story.

Getting to the Tricorder

The ultimate biochip would be a sensor capable of detecting and identifying any substance or life form. Star Trek provides a model for this device in the Tricorder, a handheld scanner that — in the fictional television shows — is capable of instantly diagnosing illnesses and injuries, mapping the physiological, biochemical and genetic makeup of unknown organisms, and identifying where individuals have been by sensing traces of DNA left behind days before.

Building a universal, Tricorder-like device would require much more than highly integrated, multifunctional biochips.

It would also require some form of comprehensive scanning ability. The current candidate is terahertz radiation, which falls between infrared light and microwaves in the electromagnetic spectrum. Unlike x-rays, terahertz radiation can provide detailed images of biological material without causing damage. Sources of terahertz radiation are relatively new and are only just beginning to be used to develop a new generation of medical imaging technology. Terahertz radiation sources are also relatively large, however, and operate at very low temperatures.

It would also require sophisticated software and large amounts of compute power to process, interpret and present the huge amounts of data the scans would collect. Though technology like this exists, the large databases and artificial intelligence software are a long way from fitting on handheld computers.

The biochip component, too, is imaginable but a long way from reality. Being able to identify any one of the vast number of biological molecules is challenging enough. But researchers are only beginning to come to grips with the significance of protein folding, which controls how proteins carry out the basic processes of life. It is clear that for many molecules, shape is at least as important as composition. Using lock-and-key molecular recognition techniques to identify biological molecules will require a vast array of individually-addressable probe molecules, and fitting such an array in a handheld device is likely to require well-developed molecular electronics.

Though research into the component technologies of a Tricorder-like device is underway, a universal scanner/diagnostic tool is still beyond the scope of even the most optimistic research project.

Fantastic voyage

One of the more fanciful images associated with nanotechnology is that of swarms of robots, each hundreds of times smaller than a blood cell, coursing through arteries and navigating through tissues to repair damage, hunt for cancer cells and scavenge environmental toxins. The body comes equipped with countless cells and molecules that handle many of these tasks, however. In vivo nanobots could also prove a health hazard in and of themselves.

But sending small, though far larger than nanoscale, devices into the body could be useful. Shrinking biochips enough to send a sensor to a sample in vivo could eventually prove possible, and sending such probes to examine diseased or damaged tissue could reduce the need for biopsies and exploratory surgeries. And perhaps, as a natural progression from today's endoscopic procedures, hybrid biochip-microelectromechanical systems equipped with cameras could be used to perform surgery.

Pipes in the walls

Still, biochips are more likely to end up in the environment than in the body. As with the evolution of the computer chip, biochips could also be used as embedded systems: small, specialized computer chips that control machines rather than run computers.

Embedded biochips could power sensors scattered around battlefields and toxic waste sites. And they could also play a role in the smart home of the future. Imagine what biochip-enabled toilets could do for home medical diagnostics. It's an area flush with possibilities.

Recent Key Developments

Advances in DNA-based sensors:

- Diamond as a material for DNA chips (DNA prefers diamond, page 10)
- A biochip that contains lines of vertical DNA strands (Biochip sprouts DNA strands, page 11)
- A method for linking DNA strands to semiconductor nanoparticles, Argonne National Laboratory
- A microscale device that detects tiny amounts of specific DNA molecules (Handheld DNA detector near, page 12)
- A method for stretching and pinning DNA molecules onto a surface (Plastic pins DNA molecules in place, page 13)

Advances in other biological sensors:

- A method for putting organic molecules on gold-coated semiconductors, Purdue University
- A biochip that uses protein molecules to identify pathogens (Protein-coated chips sniffs out bacteria, page 14)
- A small glass chip that senses 100 different substances (Porous glass makes minuscule sensor, page 15)

Advances in optical sensors:

- A tiny, biocompatible laser that identifies cells and bioorganisms (Plastic coating makes chips biofriendly, page 16)
- A tiny optical microscope for observing cells in biochips or in the body (Speck-sized microscope nears, page 16)

Advances in microfluidic channels:

- A method for making flexible, 100-nanometer-diameter tubes (Nanoscale rubber hoses debut, page 17)
- A biochip with 1,000 chambers (Integrated biochips debut, page 18)
- A tubeless method for channeling fluids (Surfaces channel liquids, page 19)

- A method for calibrating a CD-based microfluidic system (Lab-on-a-CD corrects itself, page 20)
- A room-temperature silicon biochip fabrication process (Sandia speeds microbe to chipmaking, page 21)
- A network of chambers and tubes made from artificial cells (Artificial cells make mini lab, page 22)

Advances in microfluidic control:

- A method for channeling and controlling droplets using heat and surface tension (Biochip moves liquids with heat, page 23)
- A method for channeling and controlling droplets using electric fields and surface tension from the University of Rochester
- A set of tiny spinning magnetic bars for stirring small amounts of fluids, University of Illinois, October 2002
- A method for channeling and controlling droplets using electric fields and surface tension (Chip juggles droplets, page 23)
- A passive pumping technique that uses surface energy, the University of Wisconsin
- A pair of microscopic pumps for biochips (Biochips get pumped, page 25)
- A passive mixer for microfluidics (Labs-on-a-chip gain micro mixer, page 26)
- A plan to use bacteria as microscopic turbines (Bioengineers aim to harness bacterial motion, page 27)
- A method for controlling flow using electrically-controlled capillary pressure (Electricity moves fluids, page 29)
- Microvalves made from pH-sensitive hydrogels (Gels make micro plumbing, page 30)

Advances in structural manipulators:

- An artificial cell-membrane-like ion channel (Tiny hole guides atoms against tide, page 31)
- A micro nozzle for immobilizing and testing individual cells, Swiss Federal Institute of Technology and Evotec OAI in Germany
- A surface with pores that trap individual cells for testing ion channels, Ludwig Maximilians University in Germany
- A method for sorting biomolecules using magnetism and geometry (Magnets channel biomatter, page 32)

Advances in mechanical manipulators:

- Laser-produced, laser-driven microscopic rotors (Light spins resin rotors, page 33)
- A microscopic pair of tweezers and needle for manipulating individual cells (Lasers drive tiny toolset, page 35)
- A set of mechanical jaws for trapping individual cells (Tiny jaws snatch cells, page 35)
- A tiny robotic arm that operates in fluids (Tiny robots flex their muscles, page 36)
- A biomolecular motor that spins a nanoscale metal propeller (Biomotor powers propeller, page 37)

Advances in optical manipulators:

- A laser tweezer that rotates objects around any axis (Lasers tweeze every which way, page 38)
- An artificial light-triggered ion membrane, Arizona State University and the National University of Rio Cuarto in Argentina
- A non-diffracting laser tweezer for manipulating particles in different chambers, the University of St. Andrews in Scotland
- A laser tweezer that arranges particles in three-dimensional patterns (Laser patterns particles in 3D, page 38)
- A laser tweezer that uses microscopic beads to trap DNA strands (Lasers snatch free-floating DNA, page 40)
- A laser tweezer that manipulates artificial cells (Lasers grasp cell-size water balloons, page 41)

DNA-Based Sensors

DNA Prefers Diamond

By Kimberly Patch, Technology Research News
December 11-25, 2002

Scientists have shown that DNA is an extremely useful molecule — it can sense other substances and can automatically arrange itself into microscopic structures.

Tapping the talents of the largest known molecule to sense pathogens like those used in bioterrorism, however, means solving a couple of problems. In order to operate in the field, the delicate molecule needs a stable portable environment and a connection to electronics that will reveal immediately what the DNA has sensed.

Both challenges would be solved by physically and electronically attaching biological molecules to the silicon wafers computer chips are made from, but that has proved difficult.

A research team from the University of Wisconsin at Madison, Argonne National Laboratory and the Naval Research Laboratory has found that DNA prefers diamond.

What's more, there's electricity involved. The researchers found that when DNA is attached to diamond, it is possible to electronically detect the changes in DNA that mark its connection with another molecule.

The combination of a very stable diamond-DNA interface and direct electronic readout could lead to real-time biosensors, including devices that continuously monitor for pathogens, said Robert Hamers, a chemistry professor at the University of Wisconsin at Madison.

Diamond wasn't the obvious choice. The researchers first worked out, with limited success, chemistry for attaching DNA to silicon. "We always found that there was some slow degradation of the interfaces that we reasoned was intrinsic to the chemistry of silicon," said Hamers.

Today's gene chip technologies already commonly attach biological molecules to silicon dioxide, or glass, a method that works well in the lab, but is less appropriate for the field. "Glass is slightly soluble in water, and so when exposed to water for some time, the outermost layer of glass and the biological... layer that it is attached to simply fall off into solution," Hamers said.

Glass works well for biomedical applications because they tend to use molecules just once, said Hamers. "However, our target application is more along the lines of real-time, continuous monitoring," he said.

Gold is another common surface for attaching biological molecules, but "the molecules have sulfur atoms on the end that bond weakly to the gold surface. This makes nice layers, but again they're not stable for long periods of time," Hamers said.

Biological, or organic, molecules contain carbon, which is the sole atomic ingredient of diamond. "Since carbon-carbon bonds are stronger than silicon-carbon or silicon-silicon bonds we reasoned that diamond surfaces would be more stable," said Hamers. "We decided to see if the chemistry we developed for modifying silicon with DNA would work with diamond," he said. With some modifications, it worked.

The research group developed a method to chemically modify the diamond surface with organic chemical groups that served as good attachment points for biomolecules, said Hamers. "Once that was in place, the rest was reasonably straightforward," he said.

The researchers used ultraviolet light to chemically bond amine molecules to the diamond. Amine is similar to ammonia, and is a product of decomposing biological material. The researchers used a layer of cross-linker molecules to attach DNA to the amine layer.

The carbon-carbon bonds between biological molecules and diamond are extremely strong and are not subject to the degradation processes that plague other materials, said Hamers. The key was "simply recognizing the carbon-carbon bonds are very strong and very stable, and that if we could link biological materials to something like diamond, it would probably be incredibly stable," he said.

Diamond has a couple of other advantages for real-time field applications like biological sensors, said Hamers. Diamond, like silicon, is a semiconductor, meaning it conducts electricity in a way that can be controlled to make useful electronics. Diamond can also be grown in extremely thin layers, and can be easily integrated with silicon, said Hamers. "You could make an integrated microelectronic device with silicon and diamond," said Hamers.

The drawback to using diamond is that it takes longer to process than silicon, glass or gold; researchers have made recent progress, however, in efficiently producing very thin diamond films. The diamond surface the researchers used to attach DNA was 500 nanometers thick, which is 150 times thinner than a human hair. A nanometer is one millionth of a millimeter.

Just as important as the physical connection is the electronic one. "Using diamond, we have recently been able to sense DNA hybridization and protein binding entirely using electronic means," said Hamers. "We can make the diamond surface part of an electrical circuit, and when DNA binds to it we can sense that electrically."

The common alternative is optical sensing, which uses light to measure changes in DNA. Optical sensing is expensive and requires a lot of power, said Hamers.

In contrast, electrical sensing is inexpensive, requires little power, and integrates well with existing electronics, Hamers said. "By going to electronic detection, one has the possibility of leveraging all the power of microelectronics—high degrees of parallelization, integration, small size, on-board signal

amplification and processing, and [even] build-in communications," he said.

The method is ready now to apply to practical devices, said Hamers.

The researchers are working to make miniaturized versions of the system with all the electronics on the same chip, said Hamers. This would provide "a complete biosensor system on a chip [including] the sensor itself [and] all the fluid handling and signal processing," components, he said.

Eventually, the method could be used for a sort of bio-cell phone, Hamers said. Such a device could be "carried around or placed in high-traffic areas to continuously monitor for chemical or biological pathogens," he said. Because the sensing DNA can be read electronically, when the device encountered a pathogen it could immediately generate a warning signal, he said.

Because the diamond surfaces appear to be very stable they could be very useful, said Robert Corn, professor of chemistry at the University of Wisconsin at Madison.

Corn has teamed up with Hamers in a project to use the method to make better DNA arrays for biological and computing applications. "The robust surface chemistry will allow us to perform many enzymatic... reactions on the DNA monolayers without degradation," said Corn. "The electronic sensing abilities of DNA hybridization of diamond are also potentially very useful for the sensing of DNA in both [biological and computing] applications," he said.

Hamers' research colleagues were Wensha Yang, Wei Cai, Tanya Knickerbocker, Tami Lassiter and Lloyd M. Smith of the University of Wisconsin at Madison, Orlando Auciello, John A. Carlisle, Jennifer Gerbi and Dieter M. Gruen of Argonne National Laboratory, and James E. Butler and John N. Russell, Jr. of the Naval Research Laboratory.

They published the research in the November 24, 2002 issue of *Nature Materials*. The research was funded by the Office of Naval Research (ONR), the Wisconsin Alumni Research Foundation (WARF), and the National Science Foundation (NSF).

Timeline: < 1 year
Funding: Government; University
TRN Categories: Biology; Biotechnology;Materials Science and Engineering; Nanotechnology
Story Type: News
Related Elements: Technical paper, "DNA-Modified Nanocrystalline Diamond Thin-Films As Stable, Biologically Active Substrates," *Nature Materials*, November 24, 2002

TRN

Biochip Sprouts DNA Strands

By Kimberly Patch, TechnologyResearch News
November 13/20, 2002

In addition to DNA's natural role of manufacturing the proteins that drive many of life's rocesses, the molecule has serious potential as a scientific tool. Researchers have found it invaluable for sensing and identifying microbes and chemicals, and there are many possibilities that involve using DNA to construct structures molecule by molecule.

The key to expanding DNA's sensor function is being able to quickly expose DNA molecules that contain different sequences of nucleotides to a solution containing substances to be tested. And the key to using DNA to build molecular structures is finding efficient ways to position and connect the molecules.

Researchers from the University of California at Davis and Wayne State University have addressed both issues with a method for attaching DNA strands to a gold surface so that the molecules stand up like a thick forest of branchless trees.

The method also allowed the researchers to precisely position lines of vertical DNA strands in patterns as narrow as 10 nanometers, or about 100 times the width of a hydrogen atom. "We succeeded in grafting DNA molecules with nanometer precision at desired positions on surfaces," said Gang-yu Liu, an associate professor of chemistry at the University of California at Davis. A nanometer is one millionth of a millimeter.

Because the molecules are standing up, chemicals introduced into a surrounding solution would have access to the full strands, which stretch to heights of around 700 nanometers. This makes the method a good candidate for making biological microarrays that would use different types of DNA to test very small samples of many different substances at the same time.

Such closely packed, miniature arrays could speed gene identification, disease diagnoses, drug discovery and toxicological research, said Liu. "Further miniaturization could provide [better] performance in a shorter time," she said. For instance, larger portions of an organism's genome could be incorporated into a single chip.

The ability to control exactly where DNA molecules attach also makes the method useful for producing molecular-scale devices for applications like quantum computing, she said. Many quantum computing schemes, which exploit the traits of particles like atoms and electrons to store and manipulate information, require devices small enough to direct small numbers of particles, or even single atoms or electrons.

The researchers made their DNA patterns using chemistry and an atomic force microscope that directly manipulates molecules using an extremely sharp tip as narrow as one nanometer.

They prepared a surface for the DNA to attach to by making a sandwich of mica, a thin layer of gold and a single layer of organic molecules. They added a solution containing short, single-stranded segments of DNA that were thiolated, meaning they contained a segment on one end capable of adsorbing, or chemically attaching to, the gold.

When the researchers used an atomic force microscope to etch patterns into the molecule layer, exposing the gold, strands of DNA attached to the exposed areas. "Molecules in selected regions of the surface are shaved away [and] the resist molecules are removed, [DNA molecules] immediately adsorb onto these newly exposed areas following the scanning track of the AFM tip," said Liu.

Using the same microscope tip, but less pressure, the researchers were able to confirm that the DNA had attached by sensing the height of the molecules on the surface. "DNA molecules are densely packed in, and adopt a standing-up configuration," said Liu.

The ability to construct patterns of DNA and examine the results as the patterns are being constructed is unusual, said Liu. It makes the process easier by allowing patterns to be extended without the need to change masks or repeat the entire fabrication process, said Liu.

The DNA the researchers used, in contrast to the variety found in living beings, was single-stranded and very short, containing between 12 and 35 of the four bases that make up the bulk of DNA. Biological DNA stored in the nuclei of cells contains billions of bases and is wound into a double-stranded helix; the two strands separate to access segments of bases that act as blueprints for building proteins.

There are two challenges to using the method practically, said Liu. The first is to stabilize the DNA nanostructures over time. This is a necessary step in being able to produce nano-sized features without the structures deforming, she said.

The second is to make the structures more quickly and efficiently by making the fabrication process parallel and more automatic. The current scanning probe lithography process is "serial... with relatively low throughput," she said.

The researchers are looking to eventually use the method to form complicated two- and three-dimensional nanostructures, said Liu. At the same time, they will determine how the DNA nanostructures react to various agents, she said. "Our ultimate goal is to construct designed nanostructures of DNA, and to demonstrate their unique physical and biochemical reactivities," she said.

The technique is potentially useful, and could allow for smaller bioarrays that are around 10,000 times more complex than those made using conventional processes like robotic spotting and photolithography, said Linette Demers, a chemist at NanoInk, Inc.

In contrast to the 10-nanometer-thick lines produced by the researchers, robotic spotting equipment cannot currently make dots smaller than several hundred thousand nanometers, said Demers. At the same time, the most advanced commercial photolithography processes cannot make feature smaller than 130 nanometers.

Bioarrays—patterns of DNA spots arranged on chips—are widely used to study gene structure and expression in basic research areas like oncology, toxicology, neurology and pharmacogenomics.

The technique could also be used to improve on-the-spot diagnosis, said Demers. Even "modest improvements in understanding and implementation of DNA patterning and readout technologies... have an impact in biomedicine," she said.

There is work to be done before the researchers' technique can be implemented in widely used real-world applications, Demers added. In its present form, nanografting is a serial technique and thus inherently very slow. "Speed, and the ability to lay down tens of thousands of different DNA sequences on a chip" are needed to use the technique to miniaturize genetic arrays, she said.

However, even slow nanografting is potentially useful for niche applications like examining the effects of nanoscale confinement of protein molecules, investigating new readout methods for miniaturized bioanalysis devices, and preliminary research into bioelectric circuits, she said.

It is difficult to predict when the method could be ready for use because of the rapid pace of change in nanotechnology development, said Liu. "We hope to have it ready in five to fifteen years," she said.

Liu's research colleagues were Christine S. Chow of Wayne State University, and Maozi Liu and Nabil A. Amro of the University of California at Davis. They published the research in the August 14, 2002 issue of *Nano Letters*. The research was funded by the National Science Foundation (NSF) and the University of California at Davis.

Timeline: 5-15 years
Funding: Government, University
TRN Categories: Chemistry; Nanotechnology
Story Type: News
Related Elements: Technical paper, "Production of Nano Structures of DNA on Surfaces," *Nano Letters*, August 14, 2002

TRN

Handheld DNA Detector Near

By Kimberly Patch, Technology Research News
February 27, 2002

Pathogens like anthrax and botulism, as well as garden variety bacteria, can be identified by their DNA signatures. Finding a way to quickly and easily read telltale DNA sequences could lead to a convenient and lifesaving tool for doctors' offices and emergency workers in the field.

Researchers at Northwestern University have identified tiny amounts of DNA in a sample by catching a particular pathogen's DNA between tiny gold electrodes, then using electric current to identify whether the electrodes have picked up the target DNA.

The method could eventually be used in a hand-held device sensitive enough to quickly identify pathogens in the field, said Chad Mirkin, a chemistry professor at Northwestern University. "It addresses a very important need in the detection arena, a hand-held device which offers the sensitivity and selectivity necessary for point-of-care applications," he said.

The researchers' device contains single-stranded DNA stretched between tiny gold particles that act as microelectrodes.

The familiar double helix of biological DNA contains long strings of paired bases attached to sugar-phosphate backbones. The single strand of DNA contains sequences of bases that can pair up with the target DNA. If the target DNA is present it is essentially caught by the DNA strand spanning the electrodes.

Once this happens, a strand of probe DNA that has a metal nanoparticle in tow binds to another portion of the captured DNA. The particles are 13 nanometers in diameter, or about one millionth of the thickness of a dime. "If enough binding events take place, an electronic bridge [of nanoparticles] is formed between the two electrodes," said Mirkin.

To make the device more sensitive, the electrical signal can be strengthened by treating the device with photographic developing solution, Mirkin said. "When the gaps with particles are exposed to the solution, silver is played out on the particles, increasing the conductivity between the microelectrodes, and therefore the signal associated with the detection process."

The researchers were able to detect DNA molecules in concentrations as low as 500 femtomolars, which is equivalent to about 15 million DNA molecules in a sample the size of a drop of water. A water drop contains trillions of water molecules.

The researchers also developed a new method for differentiating molecules that nearly match, but do not bind fully with the captured DNA string, from perfect matches. Instead of using the usual heating method to differentiate mismatched strands from perfectly matched samples, the researchers found a way to use a salt solution, according to Mirkin.

The tricky part of developing the method was making the tiny probes, said Mirkin. "The development of the nanoparticle probes was not trivial. They must be stabilized and made highly specific for the DNA targets," he said.

The researchers' next step is to make the device smaller, which should make it more sensitive, according to Mirkin. "The sensitivity of the device should be inversely proportional to gap size," he said.

The researchers' prototype device contained four electrode pairs. Because the device is essentially a computer chip, this number could be greatly expanded, according to Mirkin. DNA identification chips can eventually be designed with thousands of electrode pairs with different DNA strands between them, each designed to detect different types of DNA, he said.

The technology is currently being commercialized by Nanosphere, Inc. "They expect to have a product within two years," said Mirkin.

Mirkin's research colleagues were So-Jung Park and T. Andrew Taton. Teton is now at the University of Minnesota. They published the research in the February 22, 2002 issue of *Science*. The research was funded by the Defense Advanced Research Projects Agency (DARPA), the Army Research Office (ARO), Air Force Office of Scientific Research (AFOSR) and the National Science Foundation (NSF).

Timeline: 2 years
Funding: Government
TRN Categories: Biology; Biotechnology
Story Type: News
Related Elements: Technical paper, "Array-Based Electrical Detection of DNA with Nanoparticle Probes," *Science*, February 22, 2002.

TRN

Plastic Pins DNA Molecules in Place

By Eric Smalley, Technology Research News
May 2/9, 2001

DNA molecules are extremely long and are usually coiled up. Getting them to lie flat and straight and stay in place has challenged many a lab technician, whether in studying their role as the blueprints for life or using them as building blocks of nanotechnology.

A research team based at Delft University of Technology has developed a technique to position, stretch out and pin down DNA molecules with nanometer-scale precision.

The technique combines the previously developed process of DNA combing, which stretches out DNA molecules, with photolithography, and also takes advantage of the affinity DNA molecule ends have for polystyrene.

"Single molecules of DNA can be stretched, patterned and directed site-specifically onto an arbitrary surface [when] molecular combing... is used in combination with current lithographic techniques," said Dionne C. G. Klein, a graduate student at Leiden University.

The researchers demonstrated the technique by using electron beam lithography to produce a grid of polystyrene lines two microns wide and 17.5 microns apart on a gold-covered silicon wafer. Polystyrene is used to make hard plastics and Styrofoam.

They submerged the wafer in water containing molecules of the DNA from a bacteria-infecting virus. Because the ends of the DNA molecules are hydrophobic, they bind to the polystyrene, which is also hydrophobic.

The researchers then comb the DNA by slowly drawing the wafer out of the water. The surface tension exerts a strong enough force to pull the loose ends of the DNA molecules straight but not strong enough to pull the fixed ends loose from the polystyrene. "The single-stranded DNA ends bind to the [polystyrene] and the meniscus of the solution forces the coiled DNA to stretch," said Klein.

The free end of each molecule, which can stretch to more than 20 microns long, then attaches to the next polystyrene line in the grid.

The method keeps the DNA molecules lined up. The researchers found that the DNA molecules did not attach both ends to the same polystyrene line.

Source: Delft University of Technology

This atomic force microscope image shows strands of stretched DNA.

The researchers also fixed stretched DNA molecules to unpatterned polystyrene surfaces.

Positioning, stretching and pinning DNA molecules makes it easier for researchers to examine them with atomic force and scanning tunneling microscopes. It is also a step toward eventually using DNA molecules to make integrated circuits much smaller than today's computer chips.

"Patterned DNA on a substrate can serve as a template for wires and for two-and three-dimensional nanoscale devices," said Klein.

Klein's research colleagues were Leonid Gurevich, Jorg W. Janssen and Leo P. Kouwenhoven of Delft University of Technology and Jeffrey D. Carbeck and Lydia L. Sohn of Princeton University. They published the research in the April 16, 2001 issue of the journal Applied Physics Letters.

The research was funded by the Foundation for Fundamental Research on Matter in the Netherlands, the Exploratory Research for Advanced Technology program in Japan and the National Science Foundation.

Timeline: Now
Funding: Government
TRN Categories: Biological, Chemical, DNA and Molecular Computing
Story Type: News
Related Elements: Technical paper, "Ordered stretching of single molecules of deoxyribose nucleic acid between microfabricated polystyrene lines," Applied Physics Letters, April 16, 2001

TRN

Other Biological Sensors

Protein-Coated Chip Sniffs Out Bacteria

By Kimberly Patch, Technology Research News
July 12, 2000

Researchers at Purdue University have created a computer chip that contains just a hint of Star Trek Borg: it combines inorganic silicon, organic protein molecules, and microfluidic channels.

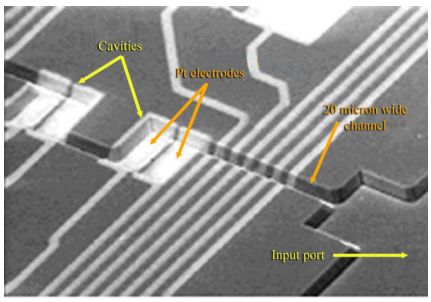
The protein biochip, which uses the proteins to identify specifc molecules, is designed to be used in handheld devices that will quickly detect low levels of harmful or therapeutic chemicals and microbes.

The biochip contains tiny channels that allow fluids to pass by proteins that are attached to the chip using a process that leverages the proteins' naturally occurring electrical charges.

The proteins bind to specific molecules contained in the fluid via the same lock and key mechanism antibodies in organisms use to capture harmful microorganisms.

"The idea is to place the [protein] in the chip, expose a solution containing the cells to the chip, and then if the cells are present they would specifically bind with the [protein] and thereby we would detect them," said Michael Ladisch, Professor of agriculture and biological engineering and biomedical engineering at Purdue.

The researchers proof-of-concept chip, studded with the egg white protein avidin, picked up biotin molecules. In that case researchers verified the capture via florescence microscopy. "We have also shown we can detect the presence of the cells themselves electronically, so the next step is to put everything together," Ladisch said. "Our first target is of course food, and the possibility of the presence of food pathogens."



Source: Purdue University

The cavities in this chip (middle and upper left)are designed to hold proteins that adhere to particular microorganisms

The researchers are working on a chip that would quickly detect very low levels of the bacteria Listeria and show the result electronically. "We apply an electric signal to the chip, we change the frequency of it, and depending on the

spectrum of the frequency we will get a different signal back for a solution containing cells versus a solution not containing cells," said Ladisch.

The researchers have identified a protein in the Listeria membrane that will bind with a specific protein antibody and are working on attaching the antibody to a chip.

"It sounds like they've been successful in bringing together a number of different technologies into an integrated system," said Charles L. Cooney, professor of chemical and biochemical engineering at MIT. And that's the sort of thing that's exciting these days.... miniaturization into chip technologies [is] a convergence of technologies that we're going to see more of," he added.

Microfluidic technology allows the researchers to miniaturize diagnostic tests, which means they need only small amounts of both the attached proteins and the sample to be tested Cooney said. In addition, "because the distances are short on these chip technologies you can do things very quickly."

Eventually the technology could be applied to handheld devices that could be used in the field to probe plant fluids for therapeutic molecules, said Ladisch.

"This is speculative... but one can imagine going out into a forest and having a device that has a receptor for a molecule that might be effective against infection, or against some type of cancer... [and finding] molecules that bind to these receptors [as candidates] for further investigation," said Ladisch.

The Listeria detector could be a viable product within two years; other detectors based on biochips may be available in three years or so, said Ladisch.

In addition to Ladisch and Bashir, the cross disciplinary project involved the following Purdue researchers:

Biomedical Engineering Research Scientist Stephen Badylak, Physics and Materials Engineering Associate Professor Mike McElfresch, Food Science Associate Professor Arun Bhunia, Biomedical Engineering and Immunopharmacology Professor J. Paul Robinson and graduate student Rafael Gomez.

The researchers presented a poster on the subject at NIH on June 25th.

The research was funded by the U.S. Department of Agriculture and by Purdue's Agriculture Research Program's Food Safety Program.

Timeline: < 2 years; > 3 years
Funding: University; Government
TRN Categories: Applied Technology; Integrated Circuits
Story Type: News
Related Elements:

TRN

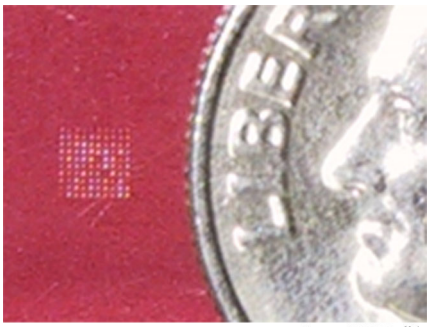
Porous Glass Makes Minuscule Sensor

By Kimberly Patch, Technology Research News
April 3/10, 2002

Being able to sense the presence of small amounts of chemicals is useful in many ways. Although humans have largely lost any natural ability to do so, many animals use their senses of smell to communicate and glean information about their environments like who has been where, when.

A group of researchers from the State University of New York at Buffalo have made a type of sensor that uses light to detect chemicals in a sample, and can cram many sensors into a space smaller than a thumbtack. "[We] can fit a large number of sensor elements into a small footprint," said Frank Bright, a professor of chemistry at the university.

The scheme could eventually allow for sensor arrays that simultaneously detect 100 or more different substances in a single sample.



Source: SUNY Buffalo

Each of these tiny specks of porous glass contains a different type of molecule that reacts to a specific chemical. Many specks can be printed onto an LED to form a compact sensor array.

The sensor consists of a light source and xerogel, a type of glass that contains chemically-sensitive molecules like protein or dye, but is porous enough to allow chemicals from the environment to diffuse in and interact with the sensitive molecules. Each protein or dye can react with a specific chemical. These interactions change the way the protein or dye emits light.

Once the sensor array is exposed, the light source excites the chemically-sensitive molecules so that they emit light, or fluoresce. The light passes through a filter and goes on to a detector that is something like a very sensitive TV camera. "When we collect the image... we see an... array of sensor elements, each responsive to a given analyte," or environmental chemical, said Bright.

The researchers' prototype devices used molecules that sensed the oxygen content and hydrogen ion concentration, or pH, of a liquid sample.

To make the arrays, the researchers first combined the gel with the chemically-sensitive molecules, then used a pin printer to print each sensor element onto a glass slide. "When the gel material is liquid we mix in the sensing chemistry and the sensing chemistry becomes dispersed within the gel

material. Once the xerogel is formed, the sensing chemistry is entrapped," said Bright.

Pin printers use metallic pins to print spots of liquid onto a surface; the researchers printed the xerogel at the rate of about one sensor per second.

In the past, the group attempted to make sensors by depositing xerogel into tiny wells, but found that printing them was much easier, said Bright. "Filling those small wells was a pain... and we knew we needed to develop a better way," he said.

The key to making the arrays was realizing that they could be printed, said Bright. "The main breakthrough was to recognize that these pin printers can be used to print these... gel materials and form the sensor elements," he said.

Each sensor element measures 100 microns in diameter and is about two microns thick. A micron is one thousandth of a millimeter. The xerogel pores are a few tens of nanometers in diameter, which is more than 100 times smaller than the girth of an E. coli bacterium. A nanometer is one millionth of a millimeter. The sensing elements are reusable, according to Bright.

One advantage of the scheme is the sensing chemistry can be printed right on a light source like an light emitting diode (LED), said Bright. "This makes the whole device much smaller and much more robust," he said. The researchers are currently working on doing this, according to Bright.

The scheme could eventually be used in a hospital where a doctor might take a single, small blood sample and place it on the sensor array, said Bright. "The idea now is that instead of getting a single reading for, say, glucose, our array would allow one to get 100 or more analytes in the sample at the same time," said Bright.

The key challenge now is to find more chemically sensitive materials that can work within the xerogels, said Bright. "The next step for us is to extend the system to more analytes and to gain further understanding of the chemistry that occurs within the small xerogels. We need to always have an understanding of what's going on in the xerogels to use them properly," he said.

The researchers are aiming to detect drugs, agricultural products like pesticides, steroids and antibiotics, and environmental pollutants like polycyclic aromatic hydrocarbons, said Bright. "Our hope is to develop the sensor array where there may be, say, 100 sensor elements designed to detect 100 different chemical species in a single sample simultaneously," he said.

Bright's research colleague was Jeong Cho. The research is slated to be published in the journal Analytical Chemistry in March. The research was funded by the National Science Foundation (NSF).

Timeline: unknown
Funding: Government

TRN Categories: Biotechnology
Story Type: News
Related Elements: Technical paper, "Pin-Printed Chemical Sensor Arrays for Simultaneous Multianalyte Quantification," slated for publication in *Analytical Chemistry* in March

TRN

Optical Sensors

Plastic Coating Makes Chips Biofriendly

March 26/April 2, 2003

Electronics usually don't mix well with biological material.

Sandia National Laboratories researchers have overcome the incompatibility with a microscopic laser designed to quickly measure and identify microorganisms and cell types without inhibiting biological processes.

The device is a tailored stack of materials that includes a light-emitting semiconductor surrounded by a polymer, or plastic material that protects cell membranes from the toxic semiconductor.

The device measures cells by shining light through them and analyzing the light that comes through the other side. The pattern shows the distribution of protein molecules and organelles within a cell. The method can be used to identify cancer cells and distinguish sickle from normal red blood cells; it can potentially identify specific bacteria, including antibiotic-resistant bacteria and different types of anthrax, according to the researchers.

Handheld diagnostic microlaser devices could be used in the field, including areas devastated by war or disaster. The device could also eventually enable surgeons to determine in real-time where a malignant tumor ends and healthy tissue begins, according to the researchers.

Handheld sensors could be practical within three years, according to the researchers. The work appeared in the October 2002 issue of the *Journal of Biomedical Optics*.

TRN

Speck-Sized Microscope Nears

By Eric Smalley, Technology Research News
May 29/June 5, 2002

The '60s sci-fi movie "Fantastic Voyage" featured a team of scientists who were reduced to microscopic proportions along with their submarine and injected into the bloodstream of a man in a coma.

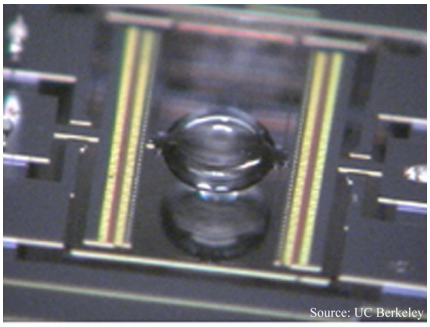
While the notion of shrinking living beings and complicated machinery remains as fanciful as ever, the idea of getting up

close and personal with individual cells inside a living human is firmly within the realm of the technologically possible.

Researchers at the University of California at Berkeley are building a confocal microscope on a chip with the aim of giving physicians and scientists the means to observe the inner workings of cells in their native habitats. Confocal microscopes are tabletop instruments that cost several hundred thousand dollars. They are used to record images of individual cells and cellular components, often from living samples.

The researchers' confocal microscope will be slightly larger than the ball in a ballpoint pen.

"Nanoscopic biophotonic imaging systems can change the... field of quantitative biology," said Luke P. Lee, an assistant professor of bioengineering at the University of with California at Berkeley. The devices could also be used in home diagnostic biochips, and they could eventually serve as vision systems for microrobots, said Lee.



This stacked pair of lenses measures one-third of a millimeter across -- small enough to foster microscopes capable of imaging individual cells working inside the body. The metal strips bracketing the top lens are microactuators that focus the lenses.

Confocal microscopes focus reflected or fluorescent light from a small spot in a sample through one or more lenses to a pinhole. A sensor on the other side of the pinhole records the light coming through. The pinhole blocks out-of-focus light so the microscope captures focused images of small sections of the sample. Moving the lenses or the sample or bouncing the light off movable mirrors produces a scan, or series of images, of the whole sample.

A key advantage of the researchers' design is that the light source shines directly through the lenses, which allows for a more compact device. The lenses move to produce the scan.

The researchers plan to build an array of three-lens confocal microscopes, each measuring one cubic millimeter, according to Lee. Each microscope will be able to capture three-dimensional images. The Micro Confocal Imaging Array will be "cheap, small [and] mass producible," he said.

The array could be integrated with microfluidic systems to form labs-on-a-chip that channel biological fluids like blood into position under the microscopes, according to Lee. The array could also be built on the tips of endoscopes, which are probes that can be inserted into the body, in order to capture images of cells at work.

So far, the researchers have built scanners consisting of two lenses and the microelectromechanical actuators that move them. The lenses are formed by placing a drop of liquid plastic in a ring about half a millimeter in diameter and hardening the plastic with ultraviolet light. The actuators that move the lenses are microelectromechanical systems (MEMS), which are made using computer chip manufacturing processes.

The lenses work with visible light, and the researchers plan to expand their range to ultraviolet and near infrared, said Lee. The researchers' next step is integrating the lenses and actuators with microlasers and detectors, said Lee. The Micro Confocal Imaging Array could be in use in two to five years, he said.

The researchers' work "is a first step towards a chip-scale confocal microscope," said Ming C. Wu, a professor of electrical engineering at the University of California at Los Angeles. "Miniaturization is important to integrate [microscopes] with lab-on-a-chip type devices," he said.

The Berkeley device compares favorably to other miniature confocal microscopes, said Wu. "Theirs uses scanning lenses, and is a transmission device, which is more compact than reflection devices," he said.

Lee's research colleagues was Sunghoon Kwon. They presented the research at the IEEE International MEMS 2002 Conference in Las Vegas in January. The research was funded by the Defense Advanced Research Projects Agency (DARPA).

Timeline: 2-5 years
Funding: Government
TRN Categories: Biotechnology; Data Acquisition; Microelectromechanical Systems (MEMS)
Story Type: News
Related Elements: Technical paper, "Stacked Two Dimensional Micro-Lens Scanner for Micro Confocal Imaging Array," IEEE International MEMS 2002 Conference, Las Vegas, January 20-24, 2002

TRN

Microfluidic Channels
Nanoscale Rubber Hoses Debut

April 9/16, 2003

Researchers from Cornell University have found a way to fabricate flexible tubes whose diameters are 100 nanometers, which is 50 times smaller than the diameter of a red blood cell. The tubes are ten times narrower than those used in today's microfluidic systems, according to the researchers.

The tubes could be used to make stacked, interconnected fluidic networks designed to shunt fluids around biochips that sense and analyze chemicals.

The researchers hit on the method when they noticed that depositing a certain type of polymer into tiny silicon grooves caused the the polymer at the tops of the grooves to close across the gaps, forming tubes. They realized the process could be used to make tiny networks of tubes for use in microfluidics.

The method is also compatible with conventional chipmaking processes, and so can also be used to integrate the networks with electronic chip components.

The process could be ready for practical use in less than two years, according to the researchers. The work appeared in the November, 2002 issue of the *Journal Vacuum Science and Technology B*.

TRN

Integrated Biochips Debut

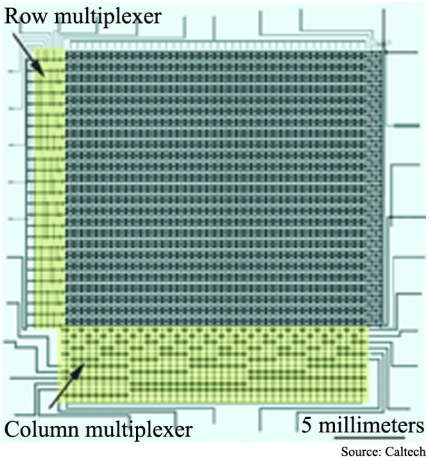
By Eric Smalley, Technology Research News
October 2/9, 2002

When the computer chip was invented forty-four years ago, it set the stage for computers to shrink from room-size behemoths filled with light-bulb-size vacuum tubes to handheld devices powered by microscopic transistors.

Researchers from the California Institute of Technology are mirroring that effort with a chip that stores tiny drops of fluid rather than magnetic or electronic bits of information.

The researchers are aiming to replace roomfuls of chemistry equipment with devices based on a fluidic storage chip that can store 1,000 different substances in an area slightly larger than a postage stamp.

The technology could eventually allow experiments that involve hundreds or thousands of liquid samples to run on desktop or even handheld devices, potentially reducing the cost and complexity of medical testing, genetics research and drug development, said Stephen Quake, an associate professor of physics and applied physics at Caltech. "Small volumes mean lower cost for expensive reagents, and mean that samples can be tested for a broader range" of diseases, he said.



Source: Caltech

The grid in the center of this rubber chip contains 1,000 tiny chambers, which can each hold about one 80th of a drop of water. A pair of multiplexers control the flow of fluid through the chip, allowing each chamber to be accessed individually.

The fluidic storage chip has 1,000 chambers arranged in a 25 by 40 grid with 3,574 microvalves. "It's small plumbing—pipes, valves, pumps, et cetera—all integrated on a small rubber chip," said Quake.

Each chamber holds 250 picoliters, or about one 80th of a drop of water. The connecting channels are 100 microns wide and nine microns high, which is about twice as high as red blood cells are wide.

Like the bits that store 1s and 0s in computer memory, the chambers that store fluids at the intersections of the rows and columns of the researchers' chip can be accessed individually. The key is a pair of multiplexors that address each chamber by row and column. Computer memory chips use similar electronic multiplexors to access individual bits of digital information.

In the fluidic storage chip, the row multiplexor pushes fluids along one or more rows to fill or purge the chambers in those rows, and the column multiplexor applies pressure to close the input and output valves of the chambers along one or more of the columns.

The fluidics multiplexors allow the researchers to control the 1,000 chambers using only 22 connections to the chip, said Quake. "We can control exponentially many fluid lines," as outside connections, he said. Thirty connections could theoretically control 32,000 fluid lines and 40 connections could theoretically control one million fluid lines. "This greatly simplifies the input/output and connections required from the real world to the chip," he said.

To make the fluidic chip, the researchers etched patterns into plastic molds using the same photolithography process used to make computer chips, then used the molds to shape thin layers of rubber.

The top layer contains fluid channels and chambers, and the bottom layer holds multiplexors and control lines. In between is a thin sheet of rubber. The intersection of a fluid channel and a control line forms a valve; hydraulic pressure in the control line deflects the thin membrane between the top and bottom layers and pinches off the fluid channel. The multiplexors determine where the pressure is applied in order to control the flow.

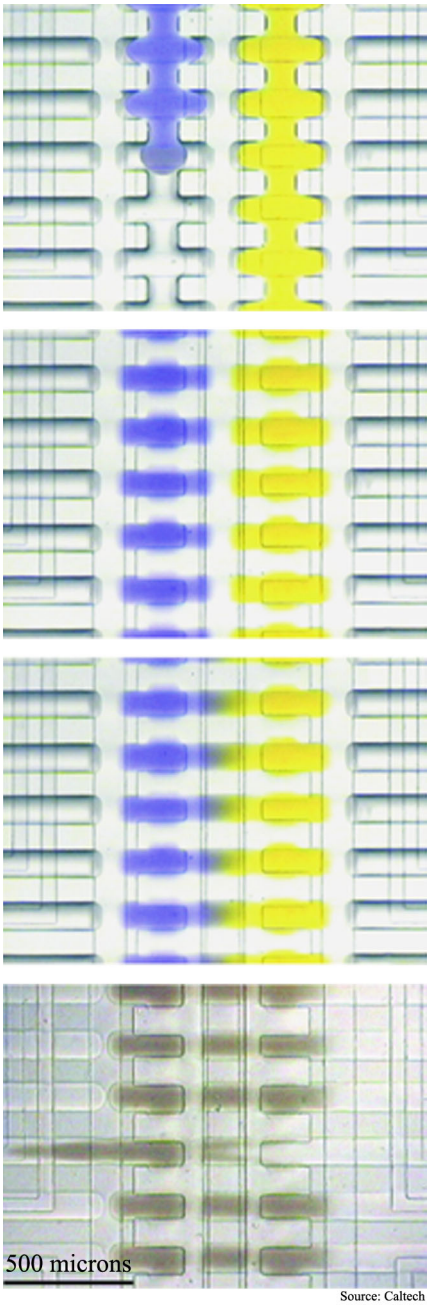
The chip is made completely of flexible silicone rubber, rather than the hard silicon used in computer chips. Fluids enter the chip through steel pins connected through holes punched into the rubber, which forms a tight seal around the pins.

The researchers also made a chip-size comparator, which measures samples against a scale or standard to determine properties like the pH concentration of a fluid.

The researchers' comparator has an array of 256 chambers arranged in four columns of 64, and is about twice the size of the storage chip. It contains 2,056 microvalves and performs more complicated manipulations than the storage chip, according to Quake. Two fluids can be mixed

in any number of the chambers and the results from any chamber in each column can be removed for further examination, he said.

The researchers took the comparator through its paces by loading individual bacteria into some of the chambers and adding a fluid that becomes fluorescent in the presence of a particular enzyme. This allowed the researchers to determine which bacteria produced the enzyme.



Source: Caltech

These close-ups of a second rubber chip show two fluids filling chambers in separate columns, the filled chambers, the fluids mixing, and the mix being purged from the chip.

There are limitations to the rubber chips, according to Quake. Some liquids, like certain organic solvents, can break down the chip's rubber material, and there is a danger of contamination from molecules diffusing through the walls of the chambers and channels. There is also a possibility that some molecules will stick to the walls after the chip's contents have been emptied.

In addition, the chip designs are limited by the need to avoid cross-contamination as samples are shunted about. For example, the contents of only one of the 64 chambers in each column of the comparator can be removed without being contaminated because any residue from the first sample would contaminate subsequent samples passing through the channel, according to Quake.

The researchers' work is an impressive and significant advance, said Kenny Breuer, an associate professor of engineering at Brown University. "There have been many attempts at building such microfluidic elements, but this is by far the most complex that I have seen, and the approach... offers the most flexibility for building a wide variety of microfluidic systems," he said.

The system does have limitations, Breuer added. "There is... significant hidden machinery that is required to operate the device—supplies of compressed air, banks of solenoidal valves and, most importantly, very large volumes of fluid that need to be flushed through the system as each cell is loaded and purged," he said. The volume of this supporting infrastructure could limit the size and complexity of fluidic systems made with this technology, he said.

It is also true, however, that the first electronic computer chips used large amounts of power and were not able to do much, but "still enabled a revolution in electronics and engineering," said Breuer. The ability to create large-scale integrated microfluidics systems with such complexity is very exciting, even if this particular design may eventually be supplanted by other approaches, he said.

The researchers next plan to use the devices in biological research, said Quake. "One area will be in environmental microbiology."

The technology could be used in practical applications in one to two years, said Quake. There are some manufacturing issues that need to be addressed, but "it is already working in some practical applications," he said. Quake is a director of Fluidigm Corporation, which is commercializing the technology.

Quake's research colleagues were Todd Thorsen and Sebastian Maerkl. They published the research in the September 26, 2002 online issue of the journal Science. The research was funded by the Defense Advanced Research Projects Agency (DARPA) and the Army Research Office (ARO).

Timeline: 1-2 years
Funding: Government
TRN Categories: Microfluidics and BioMEMS; Biotechnology; Engineering
Story Type: News
Related Elements: Technical paper, "Microfluidic Large-Scale Integration," *Sciencexpress*, September 26, 2002

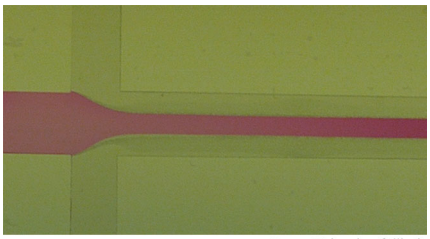
TRN

Surfaces Channel Liquids

By Kimberly Patch, Technology Research News
March 14, 2001

The best way to make water run downhill is to make sure it starts at the top of a rise.

Researchers from the Universities of Illinois and Wisconsin have found a way to direct the flow of liquid inside microchannel networks of hydrogel that have no sides by making sure the path they want the water to flow through is attractive to the water.



Source: University of Illinois

The red liquid flowing through this microchannel is guided by the hydrophilic nature of the top and bottom surfaces of the channel.The width of the liquid stream is about 1 millimeter, the height is about 200 microns. The non-red regions of the channel contain air.

Hydrogels are soft organic materials that can be fashioned into very small systems.

The researchers made the devices using a coating of hydrophobic, or water-repelling material. They bombarded the coating with ultraviolet light through a mask. Where the light hit the coating, the surface became hydrophilic, or water attracting.

A sandwich of two pieces of this material made a channel with no sides. The material naturally sticks together. When the researchers injected water into the system, it parted the material, but only in the hydrophilic pathways. "The water you flow in only flows where it is wanted. It is sort of like the parting of the Red Sea. Because of the strong influence of surfaces one can actually achieve such a parting at the microscale," said David Beebe, an assistant professor of biomedical engineering at the University of Wisconsin-Madison.

The channels were one or more millimeters across and 180 microns deep. There are 1,000 microns in a millimeter. The researchers also used the device as a pressure sensitive switch. Under this setup, the central region of a channel was hydrophilic, but the two sides and several perpendicular channels were modified to be less hydrophilic, requiring more pressure to pump water through those areas.

The method may eventually prove useful for mixing tiny amounts of liquids or liquids and gases in hydrogel devices and on microchips, said Beebe. "The directed flow methods make it easy to create large liquid/gas interfaces inside microchannels that could be the base of reactions or separations," he said.

Ultimately, the method gives researchers using hydrogels another tool to make the tiny systems capable of more complicated control, Beebe said.

"Our ultimate goal is low-cost, easy-to-make autonomous microfluidic systems... that require no external power supply but are still capable of complex functionality," he said. "The directed flow methods... are just one piece of the puzzle towards that final picture. Our previous work on responsive hydrogels in microchannels is another piece. Other researchers are also adding pieces to the puzzle."

The gel channels could easily be manufactured en mass, said Jeffrey Moore, a professor of chemistry at the University of Illinois at Urbana-Champaign.

The surface directed liquid flow method could be used in practical applications in close to two years, according to Beebe.

Beebe's and Moore's research colleague was Bin Zhao of the University of Illinois at Urbana-Champaign. They published the research in the February 9, 2001 issue of Science. The research was funded by the Defense Advanced Research Projects Agency.

Timeline: > 2 years
Funding: Government
TRN Categories: MicroElectroMechanical Systems (MEMS)
Story Type: News
Related Elements: Technical paper, "Surface-Directed Liquid Flow Inside Microchannels," Science, February 9, 2001.

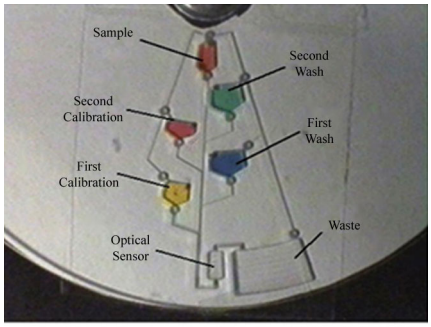
TRN

Lab-on-a-CD Corrects Itself

By Eric Smalley, Technology Research News
October 4, 2000

Adding to an ongoing effort to turn the lowly CD player into a medical laboratory, researchers have developed a method of calibrating the optical sensor on a diagnostic compact disc.

The calibration method is a major step forward in an effort that already includes techniques for carving channels and reservoirs in compact discs with the aim of allowing a computer and CD drive to replace laboratory equipment for analyzing blood, saliva and urine samples. The channels will allow fluids from different reservoirs to be combined as the CD spins. The CD player's laser will power an optical sensor that will analyze the prepared sample.



Source: Ohio State University

This medical diagnostic CD works like a centrifuge. The fluids crossthe optical sensor at the edge of the disk from the outermost reservoir inward. The size of the channels and the speed at which the disk spins determine how fast the fluids move.

The researchers built a two-point calibration system on the compact disc by carefully positioning four reservoirs — two for washes and two for calibrating fluids— between the sample reservoir and the optical sensor, and then programming the CD player to spin the disk at different rpm's in order to move the fluids across the sensor at the appropriate times. (See photo)

Calibrating sensors is a basic analytical function, said Marc Madou, professor of chemistry and material science and engineering at Ohio State University, and director of the NSF Center for Industrial Sensors and Measurements. "If you do a pH measurement, the first thing you would do is calibrate the sensor," he said.

Being able to calibrate a CD's optical sensors is critical because the sensors' sensitivity changes as they age and they would otherwise have no shelf life, he added.

Two-point calibration is important because if you plot the sensitivity of the sensor as a curve, you have to plot at least two points on that curve to accurately measure—and therefore correct—changes, Madou said. Two-point calibration is common for laboratory equipment.

"I think [CD-based medical testing] is a very good idea, because… you can have sample preparation and also read out just in a CD drive," said Chih-Ming Ho, professor of mechanical and aerospace engineering and head of UCLA's Micro Systems Laboratories.

CDs are a good platform for medical diagnostics for several reasons, Madou said.

Most important, a CD is a good platform for sample preparation, he said. "Let's say you want to do a DNA analysis. You could put the sample of cells in there and… set up fluidic structures that can break [down] the cell, extract the DNA and even do [the] DNA analysis."

The CD is also inexpensive. "We use established CD stamping methodology [and] player technology for the manufacture of the instrument and [CD]," he said. And the CD can include software and data, including instructions on how to run the tests and interpret the results, he said.

Madou is continuing to develop the CD platform by looking for more uses for the CD's laser. "We're looking at how we can energize reactions, perhaps by light," he said. If the laser is powerful enough, it might even be possible for the system to perform polymerase chain reaction (PCR), the technique laboratories use to amplify DNA samples, he said.

The CD technology could be used for a test to determine blood type within a year, Madou said. The research is funded by NASA and the National Science Foundation.

Timeline: <1 year
Funding: Government
TRN Categories: MicroElectroMechanical Systems (MEMS)
Story Type: News
Related Elements: Photo

TRN

Sandia Speeds Microtube Chip Making

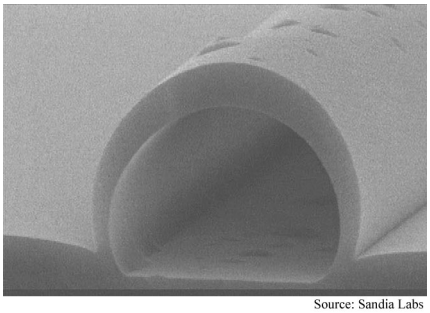
By Eric Smalley, Technology Research News
June 21, 2000

Researchers at Sandia National Laboratories have developed a process for more quickly and cheaply putting networks of tiny tubes on microchips.

Sandia's room temperature, single-wafer fabrication process dramatically increases yields for making chem-labs-on-a-chip and other biological and chemical MicroElectroMechanical Systems (MEMS).

BioMEMS, which are comparable in size and appearance to integrated circuits, use tiny channels to control the flow of small amounts of gases and liquids. These microfluidic devices power the emerging class of portable laboratories that includes chemical warfare sensors, pollution detectors and DNA analyzers.

Current processes for fabricating BioMEMS involve etching matching trenches on two wafers, lining up the wafers precisely and fusing them using heat or glue. The breakthrough that enabled the single-wafer process was the invention of room temperature silicon oxynitride film deposition, according to Carolyn M. Matzke, a postdoctoral appointee at Sandia's Compound Semiconductor Research Laboratory in Albuquerque.



Source: Sandia Labs

An electron microscope image of an eight micron silicon channel.

"This is a key process that allows us to dissolve the sacrificial polymer out from the inside of the channel in the final processing step," she said.

In standard integrated circuit fabrication, which uses single wafers, circuits are created in thin layers of silicon, which are then sandwiched between layers of an insulator. But these films of silicon are applied to the wafer at high temperatures that would destroy the polymer ridges that are critical to the Sandia process, Matzke said. The low temperatures of the process also mean that other materials that would be damaged or destroyed at high temperatures can be integrated into the devices.

The current two-wafer BioMEMS processes tend to be difficult and time-consuming, and produce yields of around 10 to 15 percent. "The materials must be thermo-mechanically matched so that under high temperatures, which chemically bond the two pieces together, one doesn't break or warp.

The surfaces [must be] pristine… and the wafers must be globally flat so that they make contact," Matzke said.

The single-wafer BioMEMS process developed by Matzke, Carol I. H. Ashby, Monica Bridges, Leonardo Griego and Channy Wong avoids these problems. It produces yields of around 90 to 95 percent and takes about one-third the time of the two-wafer processes, Matzke said. It is also compatible with standard integrated circuit fabrication.

The researchers have made channels as small as eight microns in diameter on silicon wafers.

The process has a lot of potential for making even smaller channels, said Marc Madou, director of the Center for Industrial Sensors and Measurements, a National Science Foundation center at Ohio State University in Columbus. "Here you might have an opportunity to make very small things, perhaps even submicron," he said.

Madou pointed out, however, that the two-wafer technology "is not sitting still, either. Better bonding processes, including room temperature bonding processes, are being found there, as well," Madou said. In addition, "The whole field is moving toward plastic, and it's hard to beat plastic in terms of cost."

In the Sandia process, the researchers apply a thin layer of photoresistant polymer—a material the changes properties when exposed to light—to a wafer of silicon, quartz or glass. They lay a mask over the polymer and expose it to light, then use chemicals to wash away the exposed areas, leaving the unexposed areas as ridges on the surface of the wafer.

Next, the researchers heat the wafer to 100°C for 20 seconds in order to round off the edges of the ridges. They then apply a 2-micron thick film of silicon over the wafer. Last, they soak the wafer in chemicals that dissolve the remaining polymer, leaving the desired channels.

The researchers are currently integrating microvalves, pumps and a micro hot plate with the channels to build a micro protein processing plant, Matzke said. Another potential application for microfluidic channels is on-chip cooling systems for integrated circuits.

Given its compatibility with existing integrated circuit fabrication technology, the Sandia process could be used commercially within two years, according to Matzke. The research was funded by the U.S. Department of Energy. Sandia Labs was granted a patent for the process in May.

Timeline: <2 years
Funding: Government
TRN Categories: MEMS; Semiconductors and Materials
Story Type: News
Related Elements: Photo of eight micron diameter microfluidic channel

TRN

Artificial Cells Make Mini Lab

By Eric Smalley, Technology Research News
February 21, 2001

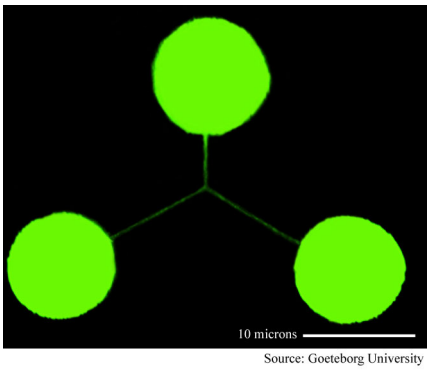
If a brilliant but mentally unstable bacterium wanted to conduct fiendish experiments, it could use as its chemistry lab a network of microscopic containers and tubes created by a Swedish research team.

The researchers used lipids derived from egg yolks or soybeans to make liposomes, which are tiny, artificial sacks that resemble cell membranes. Liposomes have been used as miniature containers in biochemical experiments for years.

The researchers fashioned the liposomes into networks by flattening them under microscope coverslips to hold them in place and then slicing them with a tiny carbon fiber. Like a soap bubble, a bisected liposome forms two daughter liposomes. But unlike daughter soap bubbles, the two daughter liposomes have a narrow tube connecting them.

"The technique... enables us to freely vary the size of the containers, the length of the tube... and the angle between different nanotube extensions emanating from a common container," said Owe Orwar, a biophysical chemistry professor at Chalmers University of Technology in Sweden.

The networks of tubes and containers can be used to guide and mix tiny amounts of substances, allowing the networks to serve as chemical sensors, chemical neural network-type computers and models for studying biochemical reactions in biological cells, said Orwar. They could also be used as templates for microelectronic devices, he said.



Source: Goeteborg University

Three artificial cells, each twice the size of a red blood cell, are linked via nanotubes.

The liposomes, at 5 to 100 microns across, can be as small as red blood cells. The tubes connecting the liposomes range from .05 to .3 microns in diameter and 5 to 50 microns long, Orwar said. The tubes are as many as 1,500 times narrower than a human hair.

The research builds on the 1996 discovery that nanotubes can be formed by drawing material from the surface of a liposome, said Orwar. The carbon fiber technique makes it possible to build more complicated networks, he said. The researchers have made networks with as many as 11 interconnected liposomes.

The Swedish team's work "takes us to a next step in the sense that the structures are getting a little more complicated than [those] we put together," said Evan Evans, one of the

researchers and who created the first liposome nanotubes. Evans is a professor of physics and pathology at the University of British Columbia and a professor of engineering at Boston College.

The networks created by slicing liposomes can be combined to make even larger networks by fusing liposomes using an electric field, said Orwar's research colleague Roger Karlsson, a graduate student at Goeteborg University. To do this, the researchers apply a short pulse of electricity to the point of contact between adjacent liposomes, which breaks down the liposomes' membranes.

Substances like enzymes, dyes and genetic material can be inserted into individual liposomes and transported between liposomes through the tubes. The researchers have moved a particle from one liposome to another through a tube.

Evans said he is skeptical about the liposome networks being used directly in practical applications. "The key thing... is going to be coming up with a way to make a durable structure," he said. "To do that, you're going to have to... use these [networks] as templates for other structures."

The Swedish researchers are exploring methods for creating three-dimensional liposome networks, said Orwar. Using the liposome networks for biochemical experiments should be possible in two to five years, said Karlsson.

Orwar and Karlsson's research colleagues were Anders Karlsson, Mattias Karlsson, Ann-Sofie Cans, Annette Strömberg and Frida Ryttsén of Göteborg University. They published the research in the January 11, 2001 issue of Nature.

The research was funded by the Royal Swedish Academy of Sciences, the Swedish Natural Science Research Council, the Swedish Research Council for Engineering Sciences in the Swedish Foundation for Strategic Research.

Timeline: 2-5 years
Funding: Government
TRN Categories: Semiconductors and Materials
Story Type: News
Related Elements: Technical paper, "Networks of Nanotubes and Containers," Nature, January 11, 2001

TRN

Microfluidic Control

Biochip Moves Liquids with Heat

April 9/16, 2003

Researchers from Princeton University have made a microscopic device that uses heat to move, mix and split droplets of liquid. The device could be used in small, battery-operated chemical sensors and hand-held medical testers.

The device consists of an interconnected network of hydrophilic stripes on an otherwise hydrophobic, or water-repelling surface. The droplets are confined to the hydrophilic stripes much like a train is confined to a train track.

When the droplets are warmed up by embedded heating elements, the surface tension of the liquid changes, and the droplets move in the direction of cooler surface temperatures. Temperature changes can happen as quickly as two tenths of a second. The right surface tension changes at the right times allow the researchers to control the direction, timing and flow rate of the droplets.

The Princeton droplet manipulator could also be used to test new materials and chemical compounds.

The device could be used in practical applications in two to five years, according to the researchers. The work appeared in the January 27, 2003 issue of Applied Physics Letters.

TRN

Chip Juggles Droplets

By Kimberly Patch, Technology Research News
September 4/11, 2002

We've become accustomed to using electric pulses to represent the binary bits of digital information, and manipulating these bits by moving them through the logic circuits of computers. Although drops of liquid are very different from digital bits, researchers have found a way to transport water that makes working with minute amounts of fluids a lot like computing.

Researchers from Duke University and Nanolytics are using electricity to push around, carve up and mix tiny droplets of liquid on a chip.

The process could lead to reconfigurable biology and chemistry labs-on-a-chip that perform many different tasks that involve controlling minute amounts of matter.

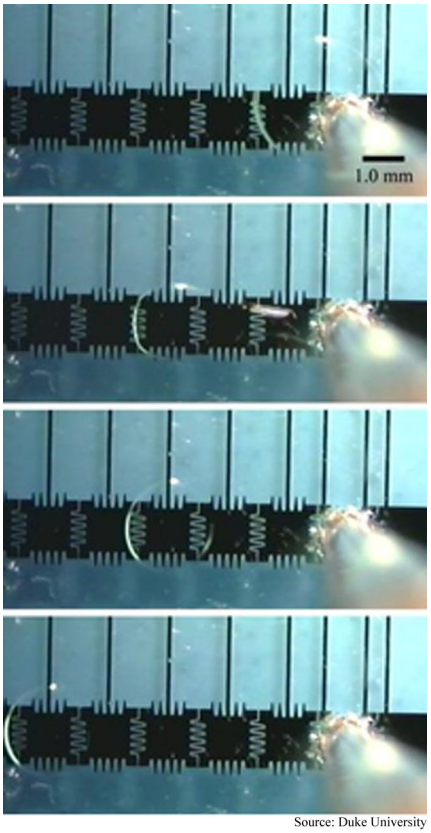
The electronic transport process, which also automatically mixes the liquid within droplets, replaces the network of channels usually required to contain and direct liquids on chips with a smooth surface dotted with electrodes. The idea is that many of the advantages of the digital approach in microelectronics might apply to a microfluidics system as well, said Michael Pollack, a researcher at Duke University.

Sliding drops around in the absence of channels makes for a physically simple but flexible chip, said Pollack. "Because we actuate the droplets directly, there is no need for pumps or valves in the system," he said. The lack of channels, in turn, makes the entire operation of the chip potentially reconfigurable, he said.

Most other microfluidics devices are continuous-flow systems where liquids are driven through a network of channels permanently etched in glass, plastic or silicon, said Pollack. Those systems work well for specific applications, but "are relatively inflexible and difficult to integrate" to form more complicated systems, he said.

Because each droplet in the Duke/Nanolytics system can be controlled independently, "complicated systems or operations can be built up from discrete parts that operate and interact in well-understood ways," said Pollack. This modular approach is similar to the way software programs are made, and makes complicated systems much simpler to design and control, he said.

Ultimately, the technique could be used for a general-purpose biochemistry workstation, he said. "A researcher or clinician could load sample and reagent droplets into the chip and then select or write a program for carrying out any protocol using these initial droplets as sources for forming hundreds of thousands of smaller droplets," said Pollack.



Source: Duke University

These four frames show a drop's progress as electric fields pull it across a surface.

The key to using electricity to transport water across a surface is surface tension. The researchers sandwiched droplets between glass plates, and used electric fields generated by electrodes lining the bottom plate to change the droplets' surface tension, which, in turn, changed their shapes.

This happens because the combination of a droplet, the insulating surface of a plate, and an electrode makes a kind of capacitor that can store electrostatic energy. As the droplet gains energy, the chemical tension between the droplet and surface is reduced, causing the droplet to spread out.

By applying different electric fields to different parts of a droplet, the researchers were able to move, join and split droplets on the surface.

Using a series of electric field changes, the researchers caused droplets to travel as quickly as 20 centimeters per second. "By activating the patterned control electrodes on the bottom plate we can create a surface tension well, and if the droplet is overlapping a portion of one of these wells, it will move," said Pollack.

To produce continuous motion, the researchers repeated the process many times. "As long as the droplet maintains an overlap with the adjacent electrodes, we can transport it through successive alignments to the next... electrode," Pollack said.

A key attribute of the process is that the size of the droplet does not affect its speed, said Pollack.

Because smaller droplets can cover the same distance in the same time as much larger droplets, as the system is scaled down to smaller sizes, the speed of the droplets relative to the size of the system will increase. "For example, at 15 centimeters per second, a 1.5 millimeter diameter droplet can be moved 100 times its length in a second, but a 0.15 millimeter diameter droplet can be moved 1,000 times its length" per second, he said.

This is 100 times faster than previously demonstrated methods of moving droplets using electricity, 40 times faster than electrochemical actuation, and more than 2,000 times faster than light-driven actuation, according to Pollack.

In addition, the researchers' method includes a built-in mixing function because it causes droplets to roll, rather than slide across a surface. "This is very important because it means that there is a circulation of liquid within the droplet as it moves," which quickly and efficiently mixes its contents, said Pollack.

Getting the contents of a very small amount of liquid to mix is an issue. In a channel as small as the width of a human hair, for instance, water doesn't slosh like it does in an eight-ounce glass, but moves more like honey.

The work is an important step forward, said Glenn Walker, a researcher at the University of Wisconsin at Madison. The technique sidesteps a common problem in microfluidics, which is how to move, mix and dispense fluid without harming the sample, said Walker. "The technique... is one answer to this problem," he said.

The work is "beautiful," said Menno Prins, a scientist at Phillips Research in the Netherlands. "The control of formation, splitting and joining of droplets by electrowetting has not been demonstrated before to such [an] extent," he said.

The method should find use in future lab-on-a-chip devices, said Prins. The method "will become very powerful when the researchers are able to extend the technology to wider classes of fluids," he said.

It will be exciting to see the researchers' technique adapted to biological experiments and assays, said Walker. Assays are tests that screen samples for particular microbes or chemicals. The challenge will be avoiding sample contamination and surface fouling, which are common problems in working with biological substances, he added.

The researchers' next step is to demonstrate that the technique is useful for biological assays, said Pollack. "We have shown that all of the individual parts work— droplet forming, transport, mixing, splitting—and that we can transport droplets containing biological solutions, so now we are interested in putting these parts together to demonstrate

that a range of biological assays can be carried out on the chip," he said.

There are potential applications for the technology "wherever there is a need to do biology or chemistry in a highly automated or high-throughput way," said Pollack. "For example, in clinical diagnostics, environmental monitoring... drug discovery or genotyping applications," he said.

The droplet technology could be ready for practical application in two to four years, Pollack added.

Pollack's research colleagues were Alexander D. Shenderov of Nanolytics in Raleigh, North Carolina and Richard B. Fair of Duke University. They published the research in the second quarter, 2002 issue of the journal *Lab on a Chip*. The research was funded by the Defense Advanced Research Projects Agency (DARPA).

Timeline: 2-4 years
Funding: Government
TRN Categories: Microfluidics and BioMEMS
Story Type: News
Related Elements: Technical paper, "Electrowetting-Based Actuation of Droplets for Integrated Microfluidics," Lab on a Chip, second quarter, 2002; Related technical paper, "How to Make Water Run Uphill", Manoj Chaudhury and George Whitesides, Science, June 12, 1992.

TRN

Biochips Get Pumped

By Kimberly Patch, Technology Research News
August 21/28, 2002

An important aspect of making microscopic machines is producing minuscule versions of basic mechanical parts like pumps that can shunt around tiny amounts of matter.

Scientists from the Colorado School of Mines have constructed two types of valves and two types of pumps that are not much bigger than a red blood cell. "We have the ability to locally control minute volumes of fluid as well as individual particles or cells in microsystems," said John Oakey, a Colorado School of Mines researcher.

The devices, which are an order of magnitude smaller than existing micro pumps, are a step toward making microscopic biological and chemical labs-on-a-chip, including sensors or drug delivery vehicles that could be implanted within human bodies.

The pumps are twice the size of red blood cells and push forward one millionth of a liter, or about one 20th of the volume of a drop of water, per hour.

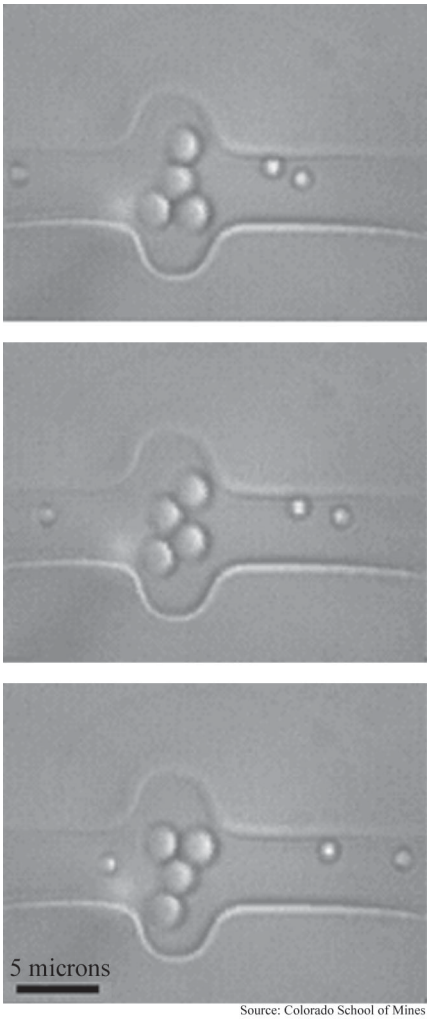
The key to the microscopic mechanics is positioning groups of spherical particles within tiny channels and using them to coax liquid to flow in a particular direction, said Oakey. The insight that led to the devices was realizing that colloidal spheres could be used as the active parts, he said.

A colloid is a liquid mixture that contains particles finer than those generally suspended in a solution.

These colloidal building blocks measure three microns across, and the mechanical devices just under 10 microns, or one hundredth of a millimeter. A red blood cell is about five microns in diameter.

To make the parts, the researchers corralled the colloids they needed from the solution and positioned them using laser tweezers. Laser tweezers are computer-controlled laser beams that bombard the minute particles with photons in order to manipulate them in a way similar to the way a strong wind can move solid objects. The pumps "operate by controlling the motion of a few individual colloidal particles that comprise the pieces of the pump," said Oakey.

To make a valve the researchers used laser tweezers to line up a group of colloids as they floated within the tiny channel, then polymerized, or cemented the particles together to form the flap of the valve. "In a focused laser beam, multiple particles will align... with the beam," said Oakey. "The interaction of the trapped particles and the surrounding hydrogel [solution] results in the polymerization," he said.



Source: Colorado School of Mines

These sequential frames demonstrate the pumping effect of a device made up of four tiny particles. Tinier tracer particles in the flow show that the fluid is being pumped from left to right.

The researchers two pump designs—gear and sine-wave — operate on the same principles as their macroscopic cousins, said Oakey.

Gear pumps are generally made of a pair of gears that trap fluid against the walls of a chamber. The trapped fluid causes a drop in pressure across the gears and the meshing of the gears in the center prevents fluid from falling back through the gears.

Although the round particles and straight-walled channels don't fit as precisely as precision-machined gears, the basic effect is the same, said Oakey. "The particles in our pump are always in contact in the center... like meshing gears, [and] around the outer perimeter the particles are almost contacting the walls. These gaps around the perimeter trap fluid and [push] it forward incrementally."

A screw, or sine-wave pump works in a similar way. As the screw mechanism turms, a plug of fluid is trapped, propelled along with the threads, and spit out the other side. The sine-wave version works the same way, "except in two dimensions and with much smaller plugs of fluid," said Oakey.

The researchers have also constructed two types of valves: a passive check valve, which allows fluid to flow in only one direction, and a similar valve that is moved around and opened and closed using laser tweezers. "These valves... are simply a string of particles polymerized together in situ, connected to a larger particle which serves as a tether," said Oakey. The tether particle can either be attached to the wall of a channel or held in place using laser tweezers.

The researchers thought of using colloidal particles to construct tiny mechanical parts while using a particular set of laser tweezers they had constructed as a tool to study the behavior of individual colloidal particles. "We constructed an optical trap capable of rapidly manipulating individual particles," Oakey said. Doing so "led us to recognize the potential utility of incorporating individual colloidal particles within microchannels," he said.

The researchers' prototype pumps are already about an order of magnitude smaller than existing devices, said Oakey. And in theory, colloidal pumps could be made considerably smaller, said Oakey. "They could potentially be scaled down by at least an order of magnitude," he said.

Aside from the colloidal pumps, "the smallest pumps I know of [move an elastic] membrane using pneumatic actuation," said Oakey. These have reached a size limit due to the dimensions of the membrane, he said. At a certain point the membrane itself "prevents deflection into channels which are too narrow—the aspect ratios just get prohibitive."

What may eventually prove a size limitation for colloidal pumps is the wavelength of light used by the optical tweezers, said Oakey. The colloidal pumps "can theoretically be made... down to the diffraction limit of the optical trap, and perhaps smaller," he said.

The researchers intend next to combine several of their microscopic devices into a working array, said Oakey. Operating many pumps in parallel would increase the amount of liquid the device could pump per hour, said Oakey. The main goal of making a very small pump, however, is to accurately control a very small amount of liquid, he said.

Many tiny pumps could eventually be included in more complicated systems like quickly-acting biological assays or chemical sensors that could be used within living bodies, said Oakey. "We are interested in [combining] device arrays with sensing and feedback operations," he said. "Colloid-based pumps and valves... could be incorporated within implantable devices in vivo and used as monitoring or targeted drug delivery vehicles," he said.

Oakey's research colleagues were Alex Terray and David W. M. Marr. They published the research in the June 7, 2002 issue of the journal *Science*. The research was funded by the National Science Foundation (NSF) and the National Aeronautics and Space Administration (NASA).

Timeline: 2-5 years
Funding: Government
TRN Categories: Microfluidics and BioMEMS
Story Type: News
Related Elements: Technical paper, "Microfluidic Control Using Colloidal Devices," *Science*, June 7, 2002.

TRN

Labs-on-a-Chip Gain Micro Mixer

By Kimberly Patch, Technology Research News
February 6, 2002

Very small things act differently than their larger counterparts. Water flowing in a channel as small as the width of a human hair, for instance, acts more like honey. Even under pressure it travels less than a centimeter per second.

The physics of the very small makes it more difficult for scientists to create devices like microchips that blend tiny amounts of chemicals. These labs-on-a-chip are being designed to do things like sense very small amounts of chemicals, or detect the order of the four bases that make up a segment of DNA. Because mixing solutions is a basic step in many chemical processes, it is important to be able to blend tiny amounts of chemicals on these chips.

A group of researchers from Harvard University, the University of California at Santa Barbara, and the School of Industrial Physics and Chemistry in Paris have developed a method for mixing liquids in small channels. The researchers' device looks more like the bottom of a waxless cross-country ski than a conventional mixer, however.

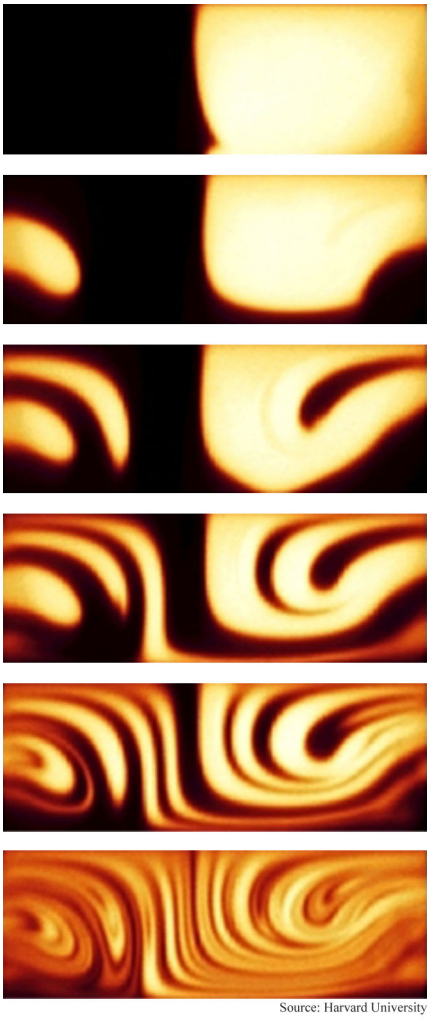
Mixing in microchannels is intrinsically difficult because on such a small scale, turbulence disappears, said Abraham Stroock, a doctoral student and researcher at Harvard University. "In the absence of turbulence, mixing is more like kneading dough then stirring coffee. In order to mix a volume of dough, you must explicitly fold it into itself. To mix the cup of coffee, you can casually stir with a spoon and turbulence will do the rest," he said.

This means it takes a long time for fluids to mix in microchannels. "If streams of two solutions were injected into the same microchannel, the streams would flow side-by-side with only diffusive mixing between them. For typical

proteins, full mixing of the streams would take many minutes even in a channel that's just 100 microns wide," said Stroock.

At the same time, it has not proven practical to shrink the standard, macroscopic mixing devices to a 100-micron scale, said Stroock. "There are no micro-blenders available," he said.

The researchers' device speeds mixing by patterning part of the channel with a series of herringbone-like ridges that encourages the fluids to interact. "We realized that we could create twisting flows with a simple pattern of grooves on one wall of the channel. Once we knew that we could make twisting flows, it was clear that we can design a chaotic mixer," said Stroock.



Source: Harvard University

This series of images shows cross-sections of a flourescent fluid and a non-flourescent fluid mixing in a channel. The process is the equivalent of kneading two types of dough together, then cutting the dough in half to see the resulting pattern.

The twisting motion of the fluid is generated by diagonal grooves. "The grooves act like the helical rifling structure on the inside of a gun barrel. The interaction of the fluid with the grooves transfers some of the [linear] motion of the fluid along the channel into a rotational motion," said Stroock.

This type of mixing is appropriate for microdevices because, unlike turbulence, its effect doesn't become weaker as the channel grows smaller.

By varying the location of the grooves along the channel, the researchers were able to make the liquid fold into itself like kneading bread dough. "The best way to mix, or knead, is to periodically change the orientation of the folding process relative to the volume that is being mixed," said Stroock. "If the folding is done correctly, then the number of folds grows exponentially with the number of steps. A flow that does this is called chaotic," he said.

To confirm the kneading action of the flow, the researchers had to look at cross sections of the fluid. They did this using a type of microscopic imaging system that uses fluorescence. "We achieve the contrast by flowing streams of fluorescent solutions alongside streams of non-fluorescent solutions. As the streams mix we see the bright layers of fluorescent fluid amid darks layers of non-fluorescent fluid," said Stroock.

The mixer could be incorporated into existing lab-on-a-chip devices now, said Stroock. "We already use this mixer in our lab in unrelated microfluidic projects that require mixing," he said.

The researchers have done some nice work, said David Beebe, an assistant professor of biomedical engineering at the University of Wisconsin-Madison. The work "extends chaotic mixing principles across a broader range of flow regimes. And it [expands] the mixing options available to microsystem designers," Beebe said.

Passive mixing schemes have many advantages, but they also have a significant disadvantage, Beebe added. "They require quite a bit of real estate—channel length—which may be a drawback in some applications."

The researchers are currently looking into ways to use the mixer in new types of chemical separations, said Stroock.

Stroock's research colleagues were Stephen K. W. Dertinger, Howard A. Stone and George M. Whitesides of Harvard University, Armand Ajdari of The School of Industrial Physics and Chemistry of the City of Paris, and Igor Mezic of the University of California at Santa Barbara. They published the research in the January 25, 2002 issue of Science. The research was funded by Defense Advanced Research Projects Agency (DARPA), the National Institutes of Health (NIH) and the National Science Foundation (NSF).

Timeline: Now
Funding: Government
TRN Categories: Microfluidics and BioMEMS
Story Type: News
Related Elements: Technical paper, "Chaotic Mixer for Microchannels," Science, January 25, 2002.

TRN

Bioengineers Aim to Harness Bacterial Motion

By Kimberly Patch, Technology Research News
July 18, 2001

What bacteria do all day is sense chemicals. To survive they depend on hardwired chemical sensors, or chemoreceptors, that cause them to swim toward substances they need, and away from substances they don't like.

Researchers from Texas A&M University and the University of California at Los Angeles have modified the

chemoreceptors of an E. coli bacterium to make it swim away from a substance it usually seeks out. At the same time, the researchers have worked out a way to change the bacteria's reaction to a given chemical, so that instead of controlling the direction the bacteria swims, a given chemical could turn on a gene that, for example, causes the bacteria to glow.

Being able to control both what a bacterium reacts to and its reaction will allow the tiny creature to eventually serve as an environmental sensor, said Manson. "You could use it to detect environmental toxins, pesticides, herbicides, heavy metals—all kinds of stuff," he said.

For instance, "you can imagine scattering bacteria over a field which has been seeded with land mines, but nobody knows exactly where they are," said Manson. "Land mines leak TNT. So you would have spots of glowing bacteria where the TNT was leaking and therefore be able to identify where the land mine is."

The researchers have proved experimentally that they can modify bacteria chemoreceptors. There's still a lot of work to be done in order to produce bacteria that can sniff out TNT, however. The researchers are working to develop binding proteins for the chemoreceptors that will enable them to react to chemicals they don't normally recognize. They also have to demonstrate the rewiring changes that will turn on a gene once a bacterium's altered chemoreceptors sense a substance.

"We have to find out what genes we want to hook up to these promoters in order to give us signals that we can monitor. Once we've done that we [can] start engineering the binding sites," he said.

Changing the bacteria's reaction to a chemoreceptor hit will make it easier to see that the bacteria have sensed a substance, said Manson. "[It] will give you something you can measure—either light production, antibiotic resistance or making an enzyme that will turn a chromogenic substrate blue or yellow," Manson said.

Eventually, different types of bacteria could be used to sense a series of substances and give a variety of responses, he said.

The ability to control bacteria's swimming motions is also potentially useful, said Manson. Since bacteria can be coaxed to move toward a certain chemical, they could eventually be used as tiny pack horses in nanofabrication or drug delivery applications, he said. "I can imagine medical uses where the cargo could be things that contain antibiotics or hormones or [chemicals] that would kill tumor cells," he said. The tiny delivery vehicles would move toward their targets by sensing a chemical at that location, which could be, for instance, a substance manufactured by tumor cells, he said.

The researchers are working toward this possibility with a project that will attach florescent beads two tenths of a micron in diameter to the bacteria, Manson said. A micron is one thousandth of a millimeter.

Although the group is working with E. coli bacteria, the work can eventually be transferred to other strains of bacteria that are not harmful to humans, Manson added.

The work is both novel and potentially useful, said Donna Marykwas, an assistant professor biological sciences at California State University at Long Beach. "E. coli has many different sensor kinase proteins that each detect different chemical and/or physical signals in the environment, and E. coli is just one bacterial species.

Other bacteria have sensor kinases too, and so does the baker's/brewer's yeast S. cerevisiae. Therefore, many novel cell-based sensors can likely be made using this approach, and the sensitivity of these sensors is probably much greater than non-cell-based sensors engineered by man," she said.

The technology could eventually be used to detect toxins in the environment, or in an engineered bacterium that could sense and swim towards a noxious chemical compound that it could metabolize into a less noxious substance, said Marykwas.

The researchers are also considering how to control bacteria's swimming motions to control fluid flow in tiny devices, Manson said.

"The way bacteria swim is by having helical spiral flagella which turn at their bases," he said. "If you grab hold of that helical flagellum and don't let it turn, then the cell body turns. So we can tie these guys down by their flagella to a surface and they spin. We have mutants that only spin one-way."

The trouble with fluid flow in tiny spaces is that as the diameter of a tube gets smaller, more pressure is needed to drive liquid through it. It takes less pressure to suck up liquid through a wide straw than a very narrow one, for instance, and the problems get much worse at the microscopic level. A group of spinning bacteria, however, could get things moving through a tube as small as a capillary, according to Manson. "If the bacteria are all turning in one direction they act like little turbines... and they'll cause flow," he said.

The physics works out well in computer simulations and the researchers are planning to make real world measurements with collaborators from the University of Arkansas this summer, Manson said. The ultimate goal of this line of research is to construct flagella-like motors by coaxing proteins to self-assemble into the proper shapes. "We're still trying to define how many proteins are needed to make the minimal motor, what kinds of solid supports we can use to adhere to the... motor and what additional factors... will be needed to get the motor proteins properly inserted, folded and assemble into a membrane," said Manson.

Bacteria could be used as bio detectors and to transport tiny materials in four or five years, said Manson. The flow generation work is likely to take longer, however "five years minimum, maybe close to... 10, maybe never if we are unlucky," he said.

Manson's research colleagues were Scott M. Ward of Texas A&M University and Asuncion Delgado and Robert P.

Gunsalus of the University of California at Los Angeles. The research was funded by the The National Institutes Of Health (NIH) and the Army Research Office.

Timeline:4-5 years, 5-10 years
Funding: Government TRN Categories:Microfluidics and BioMEMS; Nanotechnology
Story Type: News
Related Elements: Technical paper, "Negative Chemotaxis to Nitrate/Nitrate Mediated by a NarX-Tar Chimera: Evidence for the Same Mechanism of Transmembrane Signaling by Bacterial Sensor Kinases and Chemoreceptors."

TRN

Electricity Moves Fluids

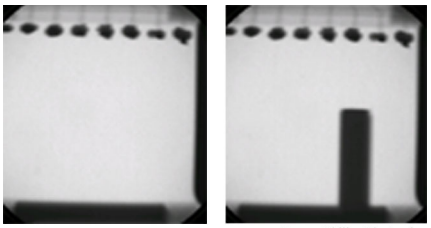
By Kimberly Patch, Technology Research News
March 7, 2001

Researchers from Philips are using electricity to control fluid in networks of very small channels.

The researchers made fluid flow through the 20-millimeter-long channels at a rate of several centimeters per second. The channels are 350 microns wide, or about four times the diameter of a human hair, and there are about 4,000 of them in the researcher's microchannel device.

The inside of each channel is coated with a 20-nanometer layer of aluminum, an 11.5 nanometer insulating layer, and a 10 nanometer hydrophobic coating. This setup, together with liquid in the microchannel, is effectively a capacitor, with the aluminum acting as one electrode and the liquid as a second electrode. A capacitor is a device that stores electric charge.

When the capacitor is charged, the tension between the fluid and wall decreases, which draws the fluid into the channel. In a device with many channels, this pushes the liquid along at a rate that is useful.



Source: Philips Electronics

The picture on the left is a side view of an empty microchannel device. The picture on the right shows the fluid level in one micro-channel rising as the current flowing between the corresponding electrode and fluid decreases the tension between the fluid capillary walls.

"We wanted to achieve fast control of liquids in a device with thousands of micro-scale channels," said Menno Prins, a senior scientist at Philips Research.

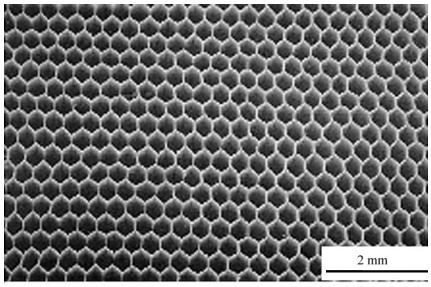
The technique could be used to quickly transport fluids that conduct electricity, like water or saltwater, in microelectromechanical systems (MEMS) without having to use external pumps.

The technique also allows for dynamic control of fluid in MEMS because the researchers can shift the pressure in a channel at will. "In present-day devices the capillary pressures are static and fixed by the channel dimensions," said Prins.

MEMS using this type of flow control could eventually be used to quickly mix fluids in lab-on-a-computer-chip devices. "With [electrocapillary pressure] more accurate, complex and flexible chips become feasible," said Prins.

Finely controlled microchannel devices may also eventually be used in printers to achieve higher resolution printing, according to Prins.

In addition, changing the level of water changes its optical properties: transparency, reflectivity and absorption of light. Devices that allow for fine control of these properties could eventually be used to switch optical signals and to filter x-rays to gain better image quality at lower radiation doses, according to Prins.



Source: Philips Research

The top of this microchannel device contains trodes that control fluid levels in the channels.

The researchers came up with the idea while looking for a nonmechanical way to control fluids in microscale devices, said Prins. They chose electrocapillary pressure "because of its promises in terms of device speed and the direct electric control. Besides speed it has given us several other advantages—high reversibility [and] low-power," he said.

The research is "interesting and solid" and provides another fluid manipulation technique for the emerging field of microfluidics, said David Beebe, an assistant professor of biomedical engineering at the University of Wisconsin. "It gives the designer more methods from which to choose."

The approach overcomes a couple limitations of other electrically driven flow mechanisms because it avoids electrolysis and does not consume very much power, Beebe added. It has its own limitations however: "the use of relatively high voltages and [relatively complicated] electrode/insulator/coating could limit [it's] use, but it clearly will have important niche applications," he said.

Because the devices can be readily interfaced to electronic systems, they will "likely first find use in systems that already have an electronic infrastructure," Beebe said. Practical electrocapillary devices could be made within two years, he said.

Prins' research colleagues were W. J. J. Welters and J. W. Weekamp. They published the research in the January 12, 2001 issue of Science. The research was funded by Philips Research.

Timeline: <2 years

Funding: Corporate
TRN Categories: MicroElectroMechanical Systems (MEMS)
Story Type: News
Related Elements: Technical paper, "Fluid Control in Multichannel Structures by Electric Capillary Pressure," Science, January 12, 2001.

TRN

Gels Make Micro Plumbing

By Kimberly Patch, Technology Research News
January 3, 2001

The obvious difficulties of fabricating very tiny machines are the limitations of human sight and dexterity. Less obvious are the way the laws of physics at very small scales, where surface forces like static electricity loom large, making it difficult to assemble tiny parts even if you can find them.

Researchers from the University of Illinois at Urbana-Champaign are trying to sidestep the assembly problem by fabricating whole machines at once using hydrogels, which are soft polymers that change size by absorbing or expelling water when the pH or temperature around them changes.

"We set about to try using a new set of materials—responsive hydrogels, which are quite well known from a biochemistry and polymer chemist perspective, but studied very little from an engineering perspective," said David Beebe, assistant professor of biomedical engineering at the University of Wisconsin.

The researchers have built a microscopic valve that sorts liquids depending on the liquid's pH and a one-way valve similar to those found in human veins. A pocket botulism detector is also in the works. The machines are on the order of a couple hundred microns, which is about the width of three human hairs.

Key to building these tiny machines is that the microfluidic channels that house them are also made of hydrogel. This makes the process of building the platform and the machine analogous to building a ship in a bottle, said Beebe.

"We start with nothing and build a microfluidic channel. We flow in a polymer cocktail, we then use either laminar flow or lithography to polymerize shapes inside the channel," he said. The polymer cocktail is hydrogel in liquid form. Using the photolithography method, the researchers fashion the shapes they want by shining ultraviolet light through a mask onto the liquid polymer, causing it to polymerize, or solidify, in the shapes defined by the mask. It takes 15 seconds to a minute for the hydrogel to solidify, said Beebe.

Once the shapes are made, the machine is done. "There's no assembly required because we build all components in place," said Beebe.

The gel's ability to react to its environment gives the machines an automatic control mechanism. Hydrogels can change their volume by about 200 percent in response to environmental changes, compared to about 5 percent for metals. The problem is, hydrogels change relatively slowly in the macro world.

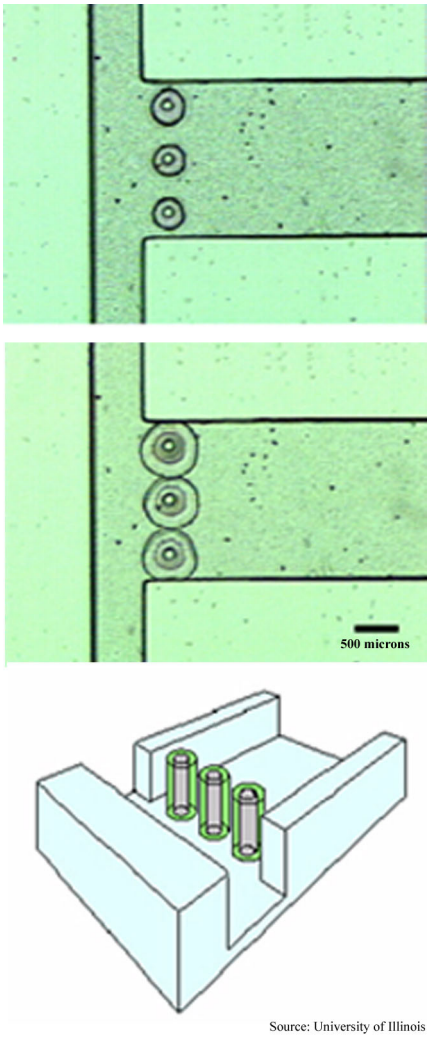
The materials have been around for two dozen years, but "haven't found widespread use... because their response time is typically very slow," said Beebe. Their response time speeds up as they get smaller, however, making the ability much more useful in the microworld. A piece of gel that is one millimeter square will take a day or two to change shape completely, but cut that down to a couple hundred microns and the response time shrinks dramatically to about 10 seconds, said Beebe.

This responsiveness allowed the researchers to close the one-way valve by changing the pH of the liquid flowing through it. The flow sorting valve changes the flow direction depending on pH.

"Working with hydrogen gels that swell and shrink is an important step forward," said Mark Madou, professor of materials science and engineering, and chemistry at Ohio State University. Opening and closing small channels efficiently is difficult, he said.

Hydrogels more closely mimic the soft, environmentally responsive materials living systems use in building cells than the metals and silicon that usually make up machines, Madou added. "In our bodies we don't have any metals, we have ... membranes that are soft with little holes that open and close depending on concentration gradients and [proteins] guiding certain molecules... in and out," he said.

"We're getting closer to that with these hydrogels,"



Source: University of Illinois

The three hydrogel posts in the top image form a valve at the end of a channel. The middle image shows the posts swollen up to close the channel. The posts swell when the pH of the fluid surrounding them changes. The bottom image is a diagram that shows the posts in perspective.

Madou said. "It's not that sophisticated yet but it's definitely in the right direction," he said.

Madou's work includes combining hydrogels with metal plates and using electricity to speed their response times.

The Wisconsin researchers are also working on using the gel's ability to change size to make cheap, tiny sensors, said Beebe. Because hydrogels react directly to their environments, they can be used as tiny sensors without the addition of electronics. "[We] take a hydrogel component in a microfluidic channel, [and] build a cell-like membrane around it," he said. When the membrane is disturbed, the gel expands, showing directly that the material the membrane is made of has been disturbed.

"We're developing a pocket detector for botulism," said Beebe. After that, the sensor could be modified to detect biological and chemical weapons as well as environmental toxins, he said.

The method could be ready to use in commercial applications in one to two years, said Beebe.

Beebe's research colleagues were Jeffrey S. Moore, Qing Yu, Robin H. Liu, Mary L. Kraft, Byung-Ho Jo and Chellnadurai Devadoss. They published the research in the December 5, 2000 issue of the Proceedings of the National Academy of Sciences. The research was funded by Defense Advanced Research Projects Agency (DARPA).

Timeline: 1-2 years
Funding: Government
TRN Categories: Microelectromechanical Systems
Story Type: News
Related Elements: Technical paper, "Microfluidic Tectonics: A Comprehensive Construction Platform for Microfluidic Systems," Proceedings of the National Academy of Sciences, December 5, 2000.

TRN

Structural Manipulators

Tiny Hole Guides Atoms Against Tide

By Kimberly Patch, Technology Research News
January 29/February 5, 2003

One of the most elegant and important processes of life is the ion channel, which underlies the nerve signals that carry communications throughout our bodies.

Nerve cells transmit signals to other nerve cells by allowing positively-charged atoms, or ions, of sodium, potassium and calcium on the outside of a neural membrane to switch places with negatively-charged chloride ions on the inside. This depolarizes the membrane, releasing the energy stored in the original arrangement in order to signal an adjoining neuron.

The trick is getting the ions to flow back so the nerve cell can do it again. Nature uses chemistry to coax the ions to make the return trip against their electrochemical potential through special pores, or channels, within the membrane.

Researchers from the Silesian University of Technology and Jagellonian University in Poland have made a synthetic device that uses an electrical field and an extremely small, conical pore in a thin film of material to coax potassium ions through the artificial membrane against their electrochemical potential.

The device can be used to study and better understand the biological ion pump. It could also eventually be used to power microscopic machines.

It was already known that cone-shaped pores that are as small as molecules produce an asymmetric electrical effect similar to a cell membrane's ion pump. The researchers proved, however, that this effect could be used to pump ions as well. "[We thought] that perhaps our conical pore could work according to the same principle," Zuzanna Siwy, an assistant professor at the Silesian University of Technology in Poland and a guest scientist at the Institute for Heavy Ion Research (GSI) in Germany.

The device works by ratcheting the molecules through the widening, and therefore sloping channel, said Andrzej Fulinski, a professor of physics at Jagellonian University in Poland. The oscillating, or periodic electric field drags the ion to and fro, said Fulinski. The net effect is that ions are pushed through the channels and out the wide side of the pore, concentrating the ions on that side of the device.

A key to making the device pump ions against their natural direction is that once they enter the cone-shaped channel, it is easier to go down the widening sloping of the cone than up the walls of the channel. "It is easier to go uphill along a less steep slope," said Fulinski. This, together with friction, leads to the pumping effect. "This is the principal on which both [the] pump and molecular motors, or ratchets work," he said.

The challenge was making a conical pore small enough for ions. The researchers' pore had an opening that widened from two nanometers to 500 nanometers. A nanometer is one millionth of a millimeter, and two nanometers is the width of 20 hydrogen atoms.

To fabricate such a small opening, the researchers bombarded a tiny bit of polymer, or plastic, film with a high-energy ion beam, then chemically etched the remainder of the tapered hole.

When the researchers put the device in a salt solution, they found that more potassium ions flowed from the narrow toward the wide opening of the cone, increasing the concentration of ions on that side of the plastic membrane. The reaction kept going even when there was a 100-fold concentration difference between the two sides of the membrane, according to Siwy.

The researchers found, however, that as concentration changes, the reaction gets less efficient in terms of the energy

used for the field per ion pumped. The method is 40 percent efficient when the concentration of ions is the same on both sides of the membrane, and drops to 10 percent when the concentration is 7.5 to 1.

The pumping phenomenon is determined by the size of the narrow side of the pore, the surface change of the cone, and the frequency of the alternating electrical field, according to Siwy. When the narrow side of the cone is 15 nanometers or larger, the reaction does not work.

The researchers originally made the device in order to study synthetic models of biological ion channels, said Fulinski. "These enable measurements which are impossible to perform on living material," he said.

While constructing the synthetic pores, however, [Siwy] realized that the electrical characteristic of the pores would allow them to pump ions using an electric field, said Fulinski. "The measurements... confirmed the suggestion, and we were able to show that indeed such a device works," he said.

The pump can be used as a sort of diode that works in a watery environment, said Fulinski. An electrical diode guides current in only one direction. "The pump can be viewed as a rectifier of ionic currents," he said.

The next step in the research is to make the pump work faster and more efficiently, said Siwy. The researchers are looking to decrease the length of the pore, which is currently 1,000 times longer than biological pores. It will take at least two years before the pump can be used in practical devices, Siwy said.

Siwy and Fulinski published the research in the November 4, 2002 issue of *Physical Review Letters*. The research was funded by the Alexander Von Humboldt Foundation in Germany, The Institute for Heavy Ion Research (GSI) and the Foundation for Polish Science.

Timeline: Now
Funding: Government, Institutional
TRN Categories: Biotechnology; Chemistry
Story Type: News
Related Elements: Technical paper, "Fabrication of a Synthetic Nanoporo Ion Pump," *Physical Review Letters*, November 4, 2002

TRN

Magnets Channel Biomatter

By Chhavi Sachdev, Technology Research News
April 3/10, 2002

Fluid is useful for transporting many things, from logs down a river to pollen across a garden.

Microfluidic systems, or labs-on-a-chip, use fluids to transport particles and biological material through tiny channels. The method is often used to count particles in order to determine a chemical's concentration.

One challenge to doing this is counteracting the Poiseuille flow effect, which can cause particles to stick to channel walls where they will not be counted. The same effect is present in large bodies of water. River water, for example, flows more slowly near the shore than in the center of the channel, making particles or biological species near the water's edge move slower than those in the middle. Over time this effect causes particles to spread from the middle of a channel to its sides.

Researchers at Harvard University have come up with a way to work with the Poiseuille effect to guide particles without letting them stick to the sides.

Current microfluidics methods counteract the Poiseuille, using one of three methods, said Gary Zabow, a graduate student of atom-optics at Harvard University.

One method is to make channels non-stick by spraying them with repellent. But coating the side walls will not repel everything, and it won't stop the spreading action.

Another method is to put two fluids in a channel, one inside the other. But eventually, the particles of the inner fluid diffuse into the outer fluids. Having two fluids also requires a bigger channel.

A third method is to use the electric charge of the particles. Most biological entities, including DNA, have a natural electrical charge and so can be moved using an electric current. Particles that do not have a natural charge can be moved along by attaching to them beads which are affected by an electric current.

The Harvard method uses this third method, but also works with the Poiseuille flow effect and another innate property of fluids: the capillary force.

The capillary force determines the curvature of a fluid's surface. Water in a thin test tube, for instance, has a downward curve, with its sides slightly higher than the middle. Mercury, on the other hand, has an upward curve, with the middle higher than the sides. The curvature of these liquids changes with pressure. "If you flow more or less fluid at higher or lower pressure the curvature will change," said Zabow.

By controlling both the curvature and the Poisseuille effect, the researchers were able to guide the flow of particles within a fluid.

To do this they built a doughnut-shaped channel half filled with water and magnetic beads, and used pressure to control the curve of the water. The bottom half of the channel was hydrophilic, or water-attracting, and the top half hydrophobic, or water-repelling. "The surface is pinned at the line where the hydrophilic and hydrophobic regions meet," said Zabow. Making the water height stationery "enables... changing pressure to translate into a changing curvature. Without the [hydrophilic-hydrophobic] division a changing pressure will translate instead into a changing water level, not a changing curvature," he said.

Than they applied a magnetic force to cause the particles to concentrate in the middle of the channel. "If you hold a speaker magnet above the channels, the magnetic particles will cluster to the center," said Zabow. The same is true of passing an electric charge overhead. The direction of the curve determines where the particles concentrate. If the surface of the liquid dips downwards, the particles collect at the sides. If the surface bulges upwards, the particles congregate in the middle of the channel. "The higher the arch, the more they want to go... to the middle," he said.

The researchers' prototype uses a permanent magnet that sits several centimeters away from the chip and does not interfere with its working, said Zabow.

It is important that the method used to generate the electric or magnetic field does not use power, because this would produce heat. "Having no heating is often important because biological things don't like their temperature to change. If your body temperature changes by one degree, you very much know it. So if you're playing with little bio-things down a channel, and the temperature goes up by one degree or two, they could die or change in some way," said Zabow.

The system could be used as an accumulator or as a separator, he said.

For accumulation, the surface would curve upwards to focus the particles in the center of the channel. Imagine that something valuable is dispersed in the fluid, said Zabow. "You could flow a swimming pool through the [system and] concentrate or purify the thing that was in it," because the electrically charged particles would get sucked up to the surface, he said.

This could be used to extract a tiny amount of DNA from a crime scene or sense small amounts of environmental chemicals, Zabow said. "You could stick this into the output of a factory and check out what toxic things they're shoving out in the stream. It may be at a very low concentration that you wouldn't be able to see normally." But with this apparatus, you could concentrate and analyze it, he said.

As a separator, the system would have a downward curve to make particles flow away from the center and spread, diffusing through the fluid, and eventually collecting at the sides. Scraping them from the sides of the tiny channels can be difficult, however, said Zabow.

There is a limit to how large the system can be because the capillary forces are not strong enough if the channels are more than a few millimeters wide. Smaller channels make the system more efficient. The researchers demonstrated that the method worked in channels with diameters as large as 4 millimeters and as small as one tenth of a millimeter, Zabow said.

The work is a clever combination of previously reported concepts, said David Beebe, an associate professor of biomedical engineering at the University of Wisconsin at Madison. "It [is the] first time I've seen [work that] combines surface tension effects dominant at the microscale with electromagnetic forces to migrate particles," he said.

While the concept is potentially useful, it may have limited application because biological molecules, such as proteins, cells, sub-cellular components, and DNA "tend to not like liquid-air interfaces," said Beebe. Proteins, for example, denature, or break down, when they come in contact with air, he said.

Another limitation is the system requires external power, said Beebe. This means "the system won't be small and cheap, which is fine for some applications, but not for truly portable, low cost applications."

The system is ready for practical use, said Zabow. "It's very easy to add to an existing [microfluidics system.]" The researchers plan to further explore different ways of achieving similar results, he said. One possibility is looking at the effect of curvature of the electromagnetic field rather than of the fluid, he said.

Zabow's research colleagues were Fabiano Assi, Robert Jenks, and Mara Prentiss. They published the research in the February 25, 2002 issue of Applied Physics Letters. The research was funded by the National Science Foundation (NSF).

Timeline: Now
Funding: Government
TRN Categories: BioMEMS and Microfluidics
Story Type: News
Related Elements: Technical paper, "Guided Microfluidics by Electromagnetic Capillary Focusing," Applied Physics Letters, February 25, 2002.

TRN

Mechanical Manipulators
Light Spins Resin Rotors

By Kimberly Patch, Technology Research News
January 17, 2001

It is obvious that wind can make windmills rotate, but not so obvious that the energy contained in photons of light can do something similar on the micron scale.

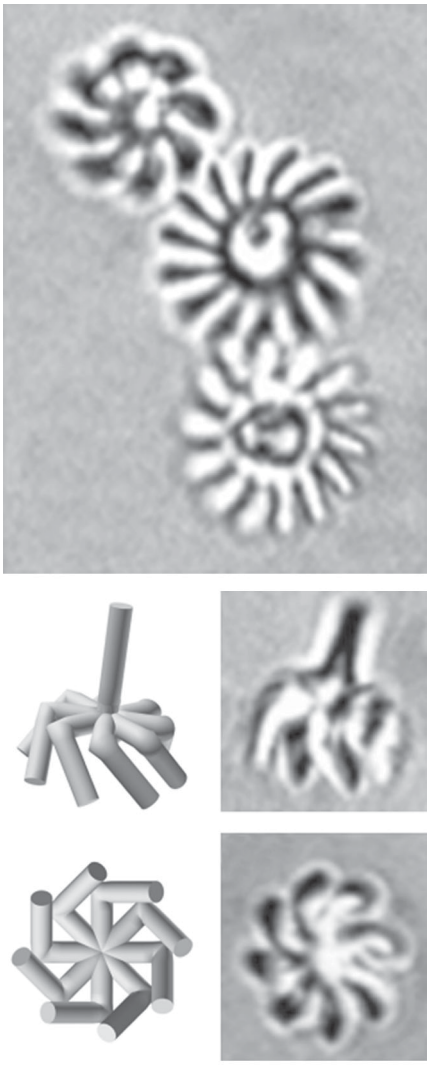
Researchers from the Hungarian Academy of Sciences have shown it is possible to harness the pressure exerted by photons of near-infrared light and use it to spin tiny resin rotors. The researchers also use light to construct the rotors, which can be as small as half a micron.

They got the idea to power tiny objects with light after noticing that microbeads they were trying to manipulate with laser tweezers rotated while trapped in the tweezer's light.

The researchers found literature describing the phenomenon, and adapted the process for making light driven rotors, said Péter Galajda, a Ph.D. student at the Hungarian

Academy of Sciences. "The rotation speed of the rotors is easily controllable by the laser intensity," he said.

To fashion the rotors, the researchers focused green laser light through a microscope onto a sample of viscous resin. By moving the photosensitive resin around in the light the researchers were able to create three-dimensional objects. Once an object was finished, they used acetone to dissolve the remaining liquid resin.



Source: Hungarian Academy of Sciences

These tiny rotors are constructed of photo-sensitive resin and are about five microns in diameter, which is the size of a red blood cell. They rotate via the force light exerts on surfaces, similar to the way wind drives a windmill.

The process allowed the researchers to make parts ranging in size from half a micron to several microns—sizes similar to biological cells like the two-micron-long E. coli bacterium and the five-micron-diameter red blood cell.

Normally, ultraviolet light is used to solidify the photosensitive resin. But the researchers made their parts via two-photon polymerization, using the green light in place of ultraviolet. The resin doesn't normally absorb photons of green light, which carry half the energy of ultraviolet photons, but if the beam is intense, the resin will absorb a pair of green photons at the same time, reacting to them as if they were a single ultraviolet photon.

The two-photon process allowed the researchers to fashion smaller parts, because it solidifies resin at a higher resolution than is possible using ultraviolet light. Using two photons essentially squares the intensity of the beam, which improves the spatial resolution, said Galajda.

The process of making the microscopic objects is cheap and flexible, said Galajda. "The costs are fractions of those of clean labs using silicon techniques, [and] arbitrary shapes can be easily generated," he said.

Designing the shape of the rotors so they would rotate in light was tricky due to an unfortunate detail in the physics involved. "Since the size of these objects is close to the order of the wavelength range for visible light... it's hard to treat the problem analytically," said Galajda.

Because the object size and wavelength size are so close, it is difficult to tell the differences among the diffraction, scattering and reflection of the laser light by the rotors. This makes it impossible to calculate the position of a complex shape like a rotor when it is trapped in the laser light, Galajda said. The trouble is, this calculation is crucial to finding the exact the physics of the rotation, he said.

Lacking this information, the researchers simply made the assumption that it was the reflection of light that made objects rotate, and modeled the rotors after windmills. "We tried to find optimal shapes for the rotors intuitively," said Galajda.

Because the shapes they designed with this in mind rotated successfully in the light, the assumptions were probably correct, he said. "It seems that the rotation is similar to a light-driven windmill. Here the role of the wind is played by light," he said.

It's a useful process, said Stephen Quake, an associate professor of applied physics at The California Institute of Technology. "I think it's a very clever way to make the micromachine device and actuate it," he said. Although other researchers have moved objects using light, this process is potentially more useful, said Quake. "This is a much more general result, because they can actually engineer the things they are moving."

The researchers plan to continue the work by producing more complicated devices. "We demonstrated that it's possible [to] construct a working machine with a specified task. We plan in the near future to make working micromachines," such as microscopic pumps, Galajda said.

Eventually, the rotors could be used in lab-on-a-chip technology, said Galajda. "I think that light-induced rotors can find promising applications as part of complex micromachines. These devices could be used to perform... chemical, biochemical or physical analysis on extremely small amounts of samples in a user-friendly way."

The rotor could also be used to measure and manipulate molecules, he said. "The rotor itself [could] be used for... measuring viscosity of microscopic samples or even twisting attached macromolecules and measuring properties of those molecules," he said.

The researchers are continuing to work on understanding the physics of the light rotation process to explain fully the effects they have seen with the rotors, said Galajda. Although it is obvious that an object's position relative to the laser beam is important, it is not clear exactly how this works, he

said. "We are in the very beginning of studying this problem," he said.

Using the rotors in practical applications also depends on developments in the laser industry, said Galajda. "Cheap high-energy semiconductor lasers with good beam quality would boost the applications," he said. The process could be used in practical applications within the next few years, he added.

Galajda's research colleague was Pál Ormos of the Hungarian Academy of Sciences. They published the research in the January 8, 2001 issue of Applied Physics Letters. The research was funded by the Hungarian Research Fund.

Timeline: 3-5 years
Funding: Government
TRN Categories: MicroElectroMechanical Systems (MEMS)
Story Type: News
Related Elements: Technical paper, "Complex Micromachines Produced and Driven by Light," Applied Physics Letters, January 8, 2000.

TRN

Lasers Drive Tiny Toolset

February 26/March 5, 2003

Researchers from Nagoya University in Japan have used light to drive a pair of resin nano tweezers and a nano needle.

The scientists used photocurable resin and a laser beam to fashion a pair of tweezers and a needle whose tips measured 250 nanometers in diameter. A red blood cell is 5,000 nanometers across.

The researchers closed the tweezers and manipulated the needle while the tiny tools were immersed in liquid. The tiny tools could eventually be used to perform surgery on individual living cells, and manipulate individual molecules.

To work the tweezers, the researchers focused a laser beam on one arm to trap it, then swung the laser beam in an arc; the beam of photons, like wind on a windmill, pushed the tweezer arm, closing it against the other tip. The researchers were able to pivot the needle around a central point as fast as 34 times per minute using a similar method.

The method could be applied practically within five years, according to the researchers. The work appeared in the January 6, 2003 issue of *Applied Physics Letters*.

TRN

Tiny Jaws Snatch Cells

By Kimberly Patch, Technology Research News
October 3, 2001

The human circulatory system is full of what are essentially micro machines—red blood cells that carry oxygen, platelets that stop wounds from leaking, and white blood cells that engulf harmful bacteria.

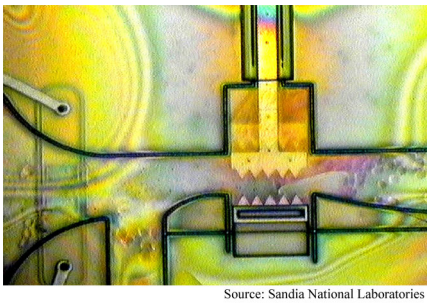
One branch of microelectromechanical systems (MEMS) research is aimed at figuring out ways to make and control inorganic machines as small as some of nature's biological constructions. In that vein, researchers from Sandia National Laboratories have produced a set of tiny, silicon micro jaws that can open and close rapidly to trap and release red blood cells one at a time.

The device demonstrates that it will eventually be possible to puncture and inject substances into single cells, said Jay Jakubczak, a senior manager of MEMS science and technology at Sandia National Laboratories. This will be useful for studying interactions within and among cells, said Jakubczak.

The tiny teeth could eventually be used to isolate, manipulate and gain information about microscopic particles in many different environments, said Jakubczak. "Overall, this technology... may have impact in the areas of drug discovery, drug delivery, prosthetics, vision, and hearing," said Jakubczak.

The jaws are about 20 microns wide, contain five upper and five lower teeth, and are powered by an engine that measures 100 by 100 microns. A red blood cell is about five microns in diameter, and a human hair about 75 microns in diameter.

The lower jaw of the microdevice resides in a tiny channel flowing with red blood cells immersed in liquid. The upper teeth slide back and forth across the channel, trapping and releasing a red blood cell about every tenth of a second.



Source: Sandia National Laboratories

These cell grabbing jaws measure 20 microns wide, and can catch and release a red blood cell every 10th of a second.

The researchers made the device and channel using the same silicon wafers and lithographic processes used to make computer chips. This means many of the tiny machines can be stamped out on a single silicon wafer, making their manufacture relatively inexpensive. To make chips, manufacturers deposit layers of metal, semiconductor and insulator in certain patterns on the silicon wafers, then etch material away to fashion features.

More complicated microfluidics machines can also be constructed this way, according to Jakubczak. "The big impact of a technology such as this is that many functions needed in a fluidic system can be integrated onto a single silicon chip—pumps, valves, actuators, electrodes, channels, mixers—[and] these microfluidics silicon chips can be manufactured

in silicon wafer fabrication facilities like the ones used today to make integrated circuits."

One key to the prototype's success is that the microchannel is made from silicon nitride, which is both transparent and an electrical insulator. This makes it easier to track what is happening in the channel by taking advantage of the transparency to use optics, and the insulation properties to use electrical and magnetic fields to analyze and manipulate the contents of the channel without shorting out the chip.

The next step is to get the microteeth to actually puncture the cells to allow them to absorb substances, said Jakubczak. "Though not demonstrated to date, these microteeth would roughen the cellular membrane of individual cells, making it possible for molecules of interest to be inserted through the cell. These molecules would be present in the channel with the cells or might be inserted through hollow capillaries in the microteeth themselves," he said.

If Sandia is able to use the technique to make a device that successfully injects substances into cells, it would pave the way for doing so on a much larger scale and at much lower cost than is possible today, said Jakubczak. Current techniques for introducing chemicals into cells include using electricity to break down cell walls, which kills many cells, and manually puncturing cells with very fine pipettes, which is a labor-intensive process.

The tiny teeth could also be used to manipulate individual nanoparticles within cells, said Jakubczak. "You might envision an array of micron-sized electrical probes that when activated can cause nanoparticles to separate by their particular electronic charge," he said.

The device could find applications in the research community within the next three to five years and in commercial products within five to ten years, according to Jakubczak.

Jakubczak's research colleagues were Murat Okandan, Paul Galambos and Sita Mani of Sandia National Labs. The research was funded by Sandia.

Timeline: 3-10 years
Funding: Government
TRN Categories: Microfluidics and BioMEMS
Story Type: News
Related Elements: None

TRN

Tiny Robots Flex Their Muscles

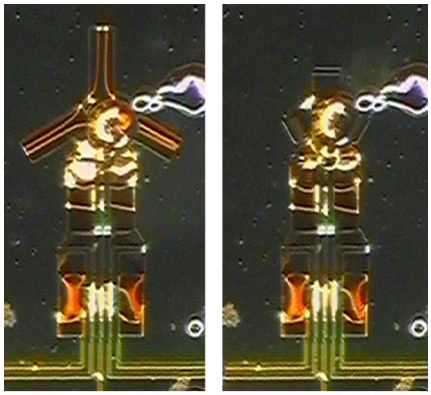
By Eric Smalley, Technology Research News
July 26, 2000

Researchers have produced tiny robot arms that work in salt water, a feat that makes the notion of swarms of microscopic robots performing medical procedures inside your body a little less fanciful.

The arms, developed by a team of researchers at the University of Linköpings in Sweden, are cousins of assembly line robots but with two important differences: they are very small, measuring 640 microns long—or about two-thirds of a millimeter—and they operate in liquids.

"Our principal application [will be] manipulation of biological entities like single cells, bacteria, and multicellular organisms in a lab-on-a-chip," said Edwin W. H. Jager, a graduate student and lead researcher on the project.

The researchers have gotten the microrobots to pick up and move a glass bead 100 microns in diameter. Human egg cells are 100 microns, red blood cells eight microns and the E. Coli bacteria one micron in diameter.



Source: University of Linkopings

These images show a microrobot from below. In the left image, the robot's three fingers are open over a 100-micron bead. In the right image, the robot is grasping the bead.

"It is very exciting work," said Richard Yeh, a graduate student researcher at the Berkeley Sensor and Actuator Center at the University of California, Berkeley. "As far as I know, the microrobot is the first one to manipulate sub-millimeter-sized objects in an aqueous solution."

Given more precise equipment, the researchers' technique could be used to make microrobots one-tenth the size of the current version, Jager said. And in principle they could be made even smaller, he said.

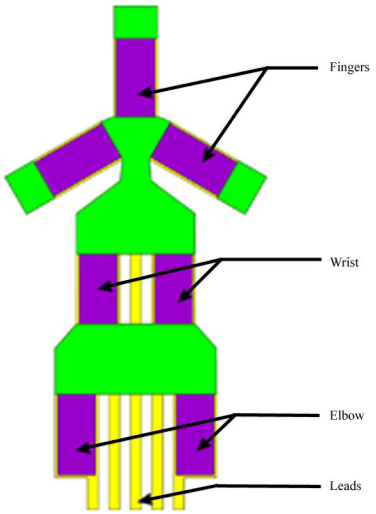
Each microrobot consists of an elbow, wrist and two to four fingers, all made of microactuators. Microactuators are tiny strips of material that bend when a small electric current is applied to them. The microrobots' microactuators consist of a layer of polypyrrole, which is a conductive polymer, and a layer of gold. The polypyrrole shrinks when the current is applied. Because the gold does not shrink, the microactuators bend. The microrobots are designed so this electrochemical reaction occurs when they are immersed in salt water or other electrolytic solution.

The researchers made the robots by first outlining their shapes on a titanium-coated silicon wafer via the photolithography process used to make integrated circuits. Then they layered gold over the titanium. Next, they put a rigid plastic between the actuators. They then deposited a layer of polypyrrole on top of the gold to form the actuators. Last, they dissolved the titanium layer, freeing the microrobot.

The microrobots could be used as minimally invasive surgical tools, said Yeh. They could also be used as miniature

assembly line robots for building other microdevices, Jager said. The microrobots could be ready for commercial use in five to 10 years, he said.

The devices and their construction are described in a paper written by Jager, Olle Inganäs and Ingemar Lundström in the June 30 issue of the journal Science. The research was funded by the Swedish Research Council for Engineering Sciences and the Swedish Foundation for Strategic Research.



Source: University of Linkopings

The purple areas in this diagram are the robot's microactuators, whick serve as both muscles and joints. The green areas are rigid plastic. The yellow lines are electrical leads.

Timeline: >5
Funding: Government
TRN Categories: Robotics; MicroElectroMechanical Systems (MEMS)
Story Type: News
Related Elements: Photo; Diagram; Technical paper "Microrobots for Micrometer-Size Objects in Aqueous Media: Potential Tools for Single-Cell Manipulation" in the June 30 Science.

TRN

Biomotor Powers Propeller

By Kimberly Patch, Technology Research News
December 6, 2000

Ready-made molecular motors have been around for eons in natural systems. The trouble is, these clean, efficient devices are so incredibly small that we haven't been able to use them for anything.

Researchers from Cornell have taken a step toward changing that by combining state-of-the-art abilities in several disciplines to connect a biological motor to a tiny metal propeller.

The device, which may someday lead to molecule-by-molecule drug manufacture, fantastically small sensors, and control of processes inside cells, was made possible by recent advances in several basic sciences, said Carlo Montemagno, associate professor of biological engineering at Cornell University.

The 11-nanometer-square biological motor is anchored on a 200-nanometer nickel post, and sports a 750-nanometer-long nickel propeller. The whole device is several times smaller than a red blood cell, which is 5,000 nanometers across. The tiny bits of metal were produced using microelectromechanical systems (MEMS) processes.

The metal devices could have been machined smaller, but the researchers wanted to make the propeller large enough so its motion would show up on a video. "We could have made a 100-nanometer rod, but this is the smallest I can make it and also be able to see it [working]," Montemagno said. The post, in turn, had to be tall enough to support the outsized propeller.

In order to attach the motor to the post, the researchers had to coat an area of the post as small as the motor with a binding material. They also genetically engineered chemical handles at the bottom of the motor so it would attach in the correct orientation.

"We had to be able to orient and bind the motor at the same size scale as the motor itself," said Montemagno. If a mechanic installing a car engine could position the engine only in increments the size of a football field, it would be "really difficult to build a car. The technology had to be mature enough so we could position that motor with precision," he said.

The motor itself is a biological assembly made by a bacterium. Its three double-ringed molecules change adenosine triphosphate (ATP) into adenosine diphosphate (ADP) in the chemical process that universally fuels life. "It's a chemical engine. It takes ATP and hydrolyzes it, converting the ATP into ADP and an extra phosphate molecule... the energy released from having that phosphate release is what powers the motor," Montemagno said.

One turn of the motor produces about 120 piconewtons per nanometer. One newton is about the force of the weight of an apple and a piconewton is one trillionth of that force. The energy released from the three ATP molecules needed to rotate the motor once is actually 240 piconewtons per nanometer, giving the motor a 50 percent efficiency rate. In theory, this could be improved to as much as 80 percent, said Montemagno.

The width of a human hair, at about 75,000 nanometers, is several orders of magnitude larger than the motor. The force produced by one turn of the motor, however, could move a piece of human hair that is several times as long as it is wide.

"This is really the first construct of a post, [biological] motor and a propeller or a swinging element that I have seen," said Steven Kornguth, assistant director of the Institute for Advanced Technology at the University of Texas. "What's new is essentially you have an anchor point for a motor that's... spectacularly small," he said. The device itself is

only "a fifth of the size of a red blood cell. That's why it's so tremendously useful," he said.

Because they are so small, biomolecular-powered devices like these could someday be incorporated into living cells or traverse the human bloodstream. "There's two kinds of things this allows us to do," said Montemagno. "It allows us to make... a hybrid system in which you would insert something which is not living into a living system. Or we can take something that's not living, and insert some attributes of a living system. It's like getting Legos and all of a sudden having all the pieces be able to fit together."

Practical applications for the devices are a decade away, Montemagno said.

The first applications are likely to be tiny motor systems for manufacturing drugs or inorganic materials, said Kornguth. Nanotubes, which range from 100 microns to less than one micron in diameter, "can deliver exceedingly small amounts of fluids onto a surface. Here you have a way of moving those fluids at that same scale. A lot of manufacturing is essentially assembly of particles on a surface." These tiny biological motors also produce no heat, which is an advantage in manufacturing because heat distorts surfaces, Kornguth added.

Montemagno's group is working on several projects designed to eventually make the tiny devices practical. First, they need better control of the motor. Currently, it runs until the solution it is suspended in runs out of ATP. "[It's] like having a car that's always on full throttle until it runs out of gas. We're working on putting a switch in the motor so that we can chemically turn [it] on and off," Montemagno said.

The group is also working on making a tiny molecular sorter. "Essentially what it will do is grab onto one molecule and then transport it [to] another location," he said.

They are also working on powering the motors with light. In addition to using the motors in cellular environments where ATP is ready-made, the motors could be used outside cells and manufacture their own ATP using an artificial photosynthetic process, said Montemagno.

Montemagno's colleagues in the research were Ricky K. Soong, George D. Bachand, Hercules P. Neves, Anatoli G. Olkhovets and Harold G. Craighead, all of Cornell. They published the research in the November 24, 2000 Issue of Science. It was funded by the Defense Advanced Research Projects Agency (DARPA), the National Science Foundation (NSF), the Department of Energy (DOE), NASA, the Office of Naval Research and a W. H. Keck Fellowship.

Timeline: <10 years
Funding: Government; Private
TRN Categories: Nanotechnology
Story Type: News
Related Elements: Image; Video; Technical paper, "Powering an Inorganic Nanodevice with a Biomolecular Motor, Science, November 24, 2000; Additional videos: falcon.aben.cornell.edu/News2.htm

Optical Manipulators

Lasers Tweeze Every Which Way

March 12/19, 2003

One promising means of powering microscopic machines is light. A stream of photons can affect minuscule objects much like wind turning a windmill.

Researchers from the University of Glasgow in Scotland have found a way to use a pair of laser beams to rotate an object in three dimensions, turning it like a ball rather than a wheel.

The method is a step forward in manipulating microscopic objects because it provides a way to turn an object on any axis—it is not restricted to the axis of the laser beam. The researchers got around this restriction by using a pair of computer-controlled laser beams to hold, or trap different parts of the same object. The researchers were able to rotate a pair of fused spheres by making the traps revolve around each other.

The fused spheres each measured 5 microns in diameter, which is the size of a red blood cell.

The method could be used to drive miniature machines on labs-on-a-chip within five years, according to the researchers. The work appeared in the February 3, 2003 issue of *Applied Physics Letters*.

TRN

Laser Patterns Particles in 3D

By Kimberly Patch, Technology Research News
May 15/22, 2002

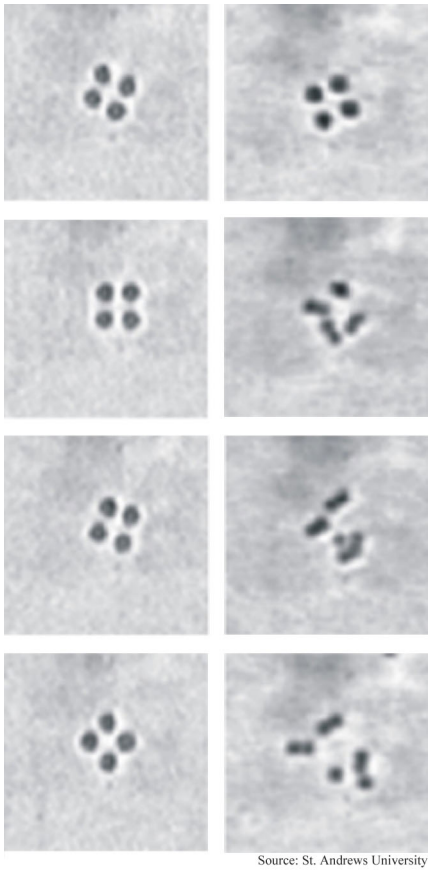
For a couple of decades now, nanotechnology researchers have been able to use beams of light to move microscopic particles. But the optical tweezers method has been limited to moving individual particles or several particles as a group.

Researchers from Scotland and Mexico have improved the tool, making it possible to use photons to arrange microscopic particles into three-dimensional structures, and to rotate these nanostructures. The improved method also opens the door for bioengineering applications that involve observing and affecting the way molecules move in three dimensions.

Optical tweezers are lasers whose photons move tiny objects much like wind energy moves windmills. A glass particle, for example "bends, [or] refracts the light and can act like a lens," said Kishan Dholakia, a lecturer at the University of St. Andrews in Scotland. Changing the direction of the light passing through a particle "causes forces to be exerted on this particle," said Dholakia.

When the particle in question is very small, the force of an intense beam of photons changing direction is enough to pull the particle toward the brightest region of the beam. This bright region of light can be used like tweezers to move small objects around.

The researchers noticed that when a group of particles were drawn toward the light beam at once, they stacked up. "With lots of particles, they all got drawn into the bright region near the focus of the beam and aligned themselves as a long tower in the direction [of] the light beam," said Dholakia. "We realized that if we had many bright sites we [could] replicate this in many places, making an extended three-dimensional structure like [a] cube," he said.



Source: St. Andrews University

The left column of pictures shows a cube of microscopic silica particles held together and rotated into various positions by laser tweezers. The right column shows the cube disintegrating when the laser is switched off.

The researchers used a trick of light—the way two laser beams interfere with each other—to make multiple laser tweezers. "The way we made the many bright spots was to interfere two light beams, analogous to interfering water waves made by throwing two stones into a still lake," said Dholakia.

In contrast to the flat, pancake-like shape of a water wave, however, the wave front of light is helical, like a spiral staircase. "If you take two spirals, each spiraling in opposite directions and add them together you get a series of [bright] spots," said Dholakia. Even though the spots are the results of two spirals, the pattern is stationary and each spot can attract and trap a stack of particles, said Dholakia.

Another key to making the technique work was finding a way to make the pattern of bright spots rotate in addition to making up-and-down and side-to-side motions. Achieving this gave the researchers full three-dimensional control over the particles. "Creating the pattern... and also looking at ways to get the pattern to move and rotate," were necessary to make the plan work, said Dholakia.

To do this the researchers used the angular Doppler effect, which is a more complicated version of the familiar linear Doppler effect heard when a train whistle seemingly changes pitch as it moves away from a listener. "We can make the pattern of spots spin around its axis using the angular Doppler effect" to rotate the three-dimensional nanostructures, Dholakia said.

To use the effect this way, the researchers started with light beams that were circularly polarized, meaning the plane of the electric field surrounding the light rotates. By sending one of the tweezer beams through a waveplate device the researchers were able to speed or slow, and thus control this rotation. When the researchers added the controlled tweezer beam to the second beam "we got our pattern of [spots] to go round," said Dholakia. "This is a neat way to get interference patterns, in general, to move and has wide applicability," he added.

The researchers demonstrated their method by making three-dimensional stacks of silica particles, and transporting and rotating the structures. The method gives nanotechnology researchers a way to assemble and rotate microscopic, three-dimensional structures, said Dholakia.

The method could be used in bioengineering, Dholakia said. "Optical tweezers are very good at grabbing biological materials [like] cells and chromosomes. This can be used to create ordered arrays and help study things such as organ and tissue growth," he said.

Observing the way particles that make up substances like milk, ink, paint or blood collect or aggregate around a uniform structure is a good way to learn about those particles, said Dholakia. "The dynamics of how these... complex systems behave and how the particles within them might organize themselves under a variety of conditions is the subject of intense worldwide investigation and of central importance in industry and basic science," he said.

In order to do this, however, it is necessary to be able to create a uniform microscopic template. "Our cubic and other structures could allow [for] three-dimensional investigations of these effects," Dholakia said. The three-dimensional optical tweezers make it possible to observe microscopic objects in detail, said Dholakia. "We can, with simple video technology, follow the way a particle moves and behaves over time."

Studying how substances behave around ordered arrays may be useful not only for biology and chemistry, but may also give scientists insights into how atoms, electrons and photons interact with materials to create effects like superconductivity, Dholakia said.

The researchers' next steps are to create bigger three-dimensional structures, and to develop a way for inspecting the structures. "We're aiming for a method that will allow us to create extended 3D arrays of particles in a pretty determined order and even look at defects," said Dholakia. Ultimately the researchers are aiming to use the method "to

understand fundamental physics as well as looking at bio-problems such as tissue growth and organization," he said.

Researchers should be able to use the method to make three-dimensional arrays of particles for use in this type of research within five years, said Dholakia.

Dholakia's research colleagues were Michael P. MacDonald, Lynn Paterson and Wilson Sibbett of the University of St. Andrews, Karen Volke-Sepulveda of the Mexican National Institute of Optical and Electronic Astrophysics (INAOE), and Jochen Arlt of the University of Edinburgh in Scotland.

They published the research in the May 10, 2002 issue of Science. The research was funded by the UK Engineering and Physical Sciences Research Council, the UK Medical Research Council, the Royal Society London and the Mexican National Council of Science and Technology (CONACYT).

Timeline: < 5 years
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TRN Categories: Nanotechnology; Optical Computing, Optoelectronics and Photonics
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TRN

Lasers Snatch Free-floating DNA

By Kimberly Patch, Technology Research News
March 20/27, 2002

Working with individual DNA molecules is tricky.

Current technologies involve chemically binding each DNA molecule to a plastic bead, then trapping and moving the bead by hitting it with an intense beam of photons from a laser. A team of researchers from Japan has found a way to drag DNA molecules around without attaching them to a larger object.

The researchers' first approach was to sandwich the DNA between unconnected beads and move the DNA indirectly by bombarding the beads with a laser, said Akira Mizuno, a professor of electrical engineering at the Toyohashi University of Technology and a professor of electronic engineering at the University of Tokyo in Japan.

Although that method worked, it required a high degree of skill to carry out. The researchers went on to find an easier way: they made the beads much smaller and used many more of them. "We used many fine particles... to support a DNA molecule," he said.

Key to the method is the size of the beads. The researchers found that a laser beam would trap, or aggregate a cluster of more than 40 beads that were 200 nanometers in diameter, but would only trap a few beads half that size.

To demonstrate the technique, the researchers put the DNA in a solution that contained 200-nanometer beads. When they focused a laser beam into the solution, a group of beads aggregated at the point of focus. When they focused the beam at the end of a single DNA molecule, a group of beads packed tightly together around that point, and the researchers used the bead cluster to drag the end of the molecule.

The molecule can be released and retrapped by switching the laser off and on, and a single DNA molecule can be manipulated at any point along its length, according to Mizuno. The technique allows researchers to transport, stretch, or keep a DNA molecule in place, he said.

Combined with florescent labeling, which tags a molecule so that it can be seen through an optical florescent microscope, the method allows for real-time handling of DNA molecules, said Mizuno.

"This... can be applied to investigate interactions between a DNA and other protein molecules because we can fix a molecule precisely," which allows for higher-resolution imaging, Mizuno said.

DNA molecules are made up of paired strings of bases held together by phosphate backbones. The order of the four types of bases is a sort of code that allows a cell to make many different proteins. An individual gene is a segment of a DNA molecule that serves as a template to make a specific protein.

The microparticle method is interesting and useful, said Kenichi Yoshikawa, a physics professor at the University of Kyoto in Japan. The microparticle method opens up new possibilities because it makes it possible to manipulate an individual DNA molecule without binding it to a bead, he said.

The method also gives researchers the ability to analyze giant DNA molecules, he said. Present technology can treat a DNA molecule only below the size of 100,000 base pairs, he said. The 46 DNA molecules that make up the 23 human chromosomes are much larger than this—around 10 million base pairs each. "Presently experimentalists are obliged to cut the large DNA molecules to small fragments," to analyze them, he said.

The researchers are working on using the process to develop ways to analyze DNA more rapidly, said Mizuno.

Mizuno's research colleagues were Ken-ichi Hirano and Yoshinobu Baba from the University of Tokushima, and Yukiko Matsuzawa from the Toyohashi University of Technology. They published the research in the January 21, 2002 issue of Applied Physics Letters. The research was funded by the Japanese Ministry of Education, Science and Technology's Japan Science and Technology Corporation and the Japanese Ministry of Economy, Trade and Industry's Joint Center for Atom Technology.

Timeline: < 2 years
Funding: Government
TRN Categories: Biology; Biotechnology; Nanotechnology
Story Type: News
Related Elements: Technical paper, "Manipulation of Single Coiled DNA Molecules by Laser Clustering of Microparticles," Applied Physics Letters, January 21, 2002.

TRN

Lasers Grasp Cell-Size Water Balloons

By Ted Smalley Bowen, Technology Research News
March 13, 2002

Researchers commonly use liposomes to mimic the membranes of living cells. These artificial sacs are made up of phospholipids, which are groups of fatty acids that readily form membranes in water. Phospholipids are also a key part of living cells.

Liposomes smaller than a micron across—which is about the diameter of a bacterium—have several practical uses.

They are regularly used as Lilliputian test tubes to separate or transport minute samples in ultra small-scale labs, and to deliver drugs or other chemicals like enzymes and DNA to specific areas within the human body. The sacs can be injected or swallowed and allow the drug to reach its destination without being broken down.

Liposomes as large as cells, with diameters up to 10 microns, are more difficult to work with, however. They can be likened to large balloons bulging with liquid, and are prone to fusing and deforming when they are manipulated. Because they are similar in size and chemical composition to human cells, they are potentially useful models of their biological cousins.

To date, these giant liposomes have been handled using tapered micropipettes, which can cause damage where they touch.

A pair of Japanese researchers have found a more suitable way to manipulate large liposomes. Moving them using an infrared laser is both less damaging and more precise than using micropipettes, according to Masatoshi Ichikawa, a researcher at Kyoto University.

Although laser beams are regularly used as tweezers to manipulate small objects, it's difficult to create a giant liposome that will withstand the process, according to Ichikawa. Laser tweezers move and trap objects by bombarding them with photons.

The process hasn't worked well for giant liposomes in the past because they're susceptible to warping or splitting, and are likely to slip out of the laser's grasp, according to Ichikawa. The researchers found that things get better, however, depending on what the liposomes contain.

The researchers created a variety of single-layer giant liposomes measuring from 0.1 to 10 microns across with a membrane about 0.005 microns thick. A micron is a thousandth of a millimeter.

They found that they could successfully move liposomes with lasers if they filled them with liquid that had a greater refractivity than the surrounding medium, according to Ichikawa.

Light travels at different speeds through different media. It travels through water, for instance, at about three-quarters the speed it travels through air. Because of this, different types of materials refract, or bend light to different degrees. When a light beam hits the boundary between materials that have different refractivity rates, it bends, which is why an object that is partly in air and partly in water looks distorted.

The researchers tested two kinds of liposomes—one type that contained and was surrounded by purified water and another type filled with glucose and surrounded by saltwater. Glucose is more refractive than saltwater.

To manipulate the liposomes, the researchers bounced an infrared laser beam off a dichroic mirror, then through a microscope toward the liposome they wanted to transport. Dichroic mirrors are coated with thin layers of different metals that transmit and reflect only certain wavelengths.

The change in refractivity at the boundary of the liposome caused the laser light to act on the contents of liposome, rather than just its thin membrane, increasing the tractability of the glucose-filled liposomes in saltwater by about an order of magnitude, according to Ichikawa.

The water-filled liposomes were also more prone to damage because there was more pressure at the point where the photons bombarded them. Changing the refractive index made for less local pressure. "We [produced] attractive and repulsive forces by controlling inner and outer conditions," Ichikawa said.

While other types of lasers can grasp liposomes and other small containers, infrared lasers are best, said Ichikawa. This is because infrared light penetrates deeply into living matter without immediately damaging it or disturbing biochemical reactions, he said.

The work is a sound demonstration of techniques for working with cell-sized liposomes, said Daniel Chiu, an assistant professor of chemistry at the University of Washington. "The method that traps higher refractive index into the vesicle is new. Most large liposomes would have the same refractive index inside and outside," he said.

There has not been a lot of work done in manipulating very large liposomes, Chiu said. Although a few groups have previously used optical tweezers to manipulate these large liposomes, adding the refractive index difference improves the method, he said.

Laser-manipulated liposome test tubes could be put to use in a variety of small-scale experiments, Ichikawa said. "We are considering widespread applications, especially for

biotechnology. For example, enzymatic reactions inside giant liposomes," he said.

The method can also be used to manipulate other types of microscopic containers, said Ichikawa. "Our idea [applies] not only [to] liposomes but also many kinds of vesicles and capsules," he said.

Ichikawa's research colleague was Kenichi Yoshikawa of Kyoto University. They described the work in the December 31, 2001 issue of Applied Physics Letters. The work was funded by Kyoto University and the Japan Science and Technology Corporation.

Timeline: Now
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