

# shrinking the lab down

to size

Much of the technology is still in development, but some labs-on-a-chip are already on the market.

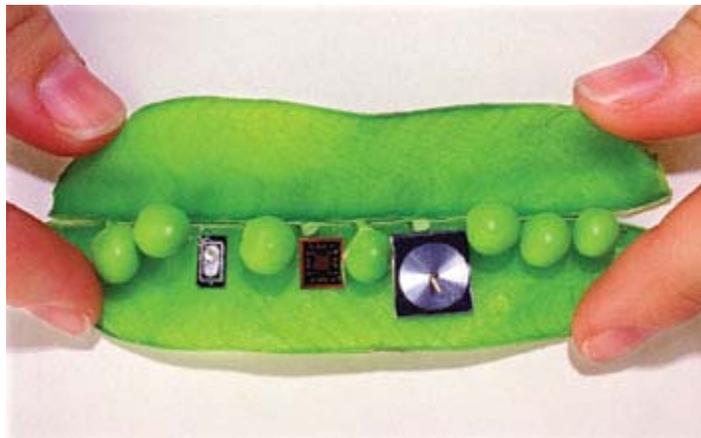
by Gayle  
Ehrenman,  
Associate Editor

**W**hat's smaller than a postage stamp and capable of finding one bad cell out of thousands? A lab-on-a-chip, the catchall term used to describe chemical analysis devices that operate on a nanoscale.

A chip can perform sensitive, selective chemical analysis in one small package, rather than on multiple pieces of equipment spread across a laboratory bench. In essence, they're shrinking bench-scale biochemical and cell-based assays down to a nano size. Since the chips are working with such small volumes of fluids—a matter of picoliters, in many cases—they are able to provide complex analyses quicker and more economically than possible using standard lab technology.

"In essence, you're taking all the beakers, pipettes, and processes from the lab bench down to just a single chip," said Chang-Jin Kim, a professor of mechanical engineering at UCLA and head of its micromanufacturing laboratory. "You're recreating all the functions people perform in a lab, in less time and for less money."

Art Pontau, manager of the microfluidics and microseparation program at Sandia National Laboratories in Livermore, Calif., pointed out that a lab-on-a-chip performs in a fraction of a minute an analysis that would take hours using traditional methods. "The technology opens up new possibilities for detection of biological and chemical agents," he said.



*Three principal components of Sandia National Laboratories' Micro ChemLab devices are small enough to fit inside a snow-pea pod.*

Saving money is another appealing aspect of the lab-on-a-chip technology. According to Seth Cohen, director of application sciences for Caliper Life Sciences of Hopkinton, Mass., "The reagents used for protein and DNA testing are very expensive. With a traditional microplate assay, you might need 100 milligrams of an enzyme, while with a lab-on-a-chip assay, you only need 1 milligram to perform the same series of tests."

The lab-on-a-chip testing also generates higher-quality data, since there's less human intervention, and the testing is done in a sealed environment that's less subject to contamination, according to Cohen.

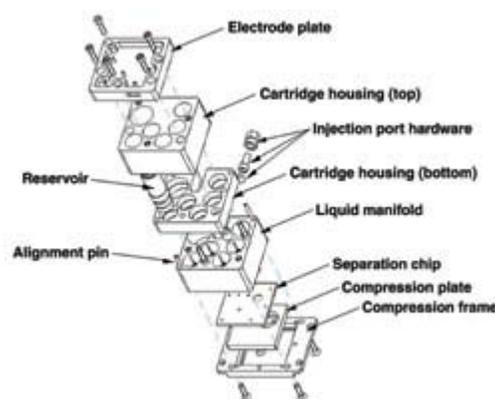
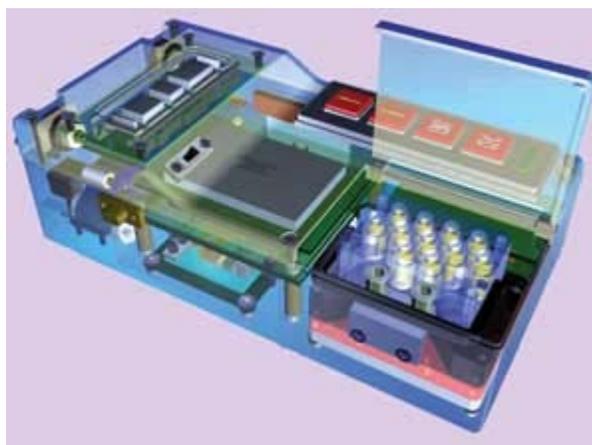
Lab-on-a-chip technology is being touted for everything from the detection of airborne bioterrorism agents to DNA testing to drug discovery. Much of the technology is still in development, but some commercial applications are already on the market.

Making a miniature lab isn't just a case of shrinking conventional equipment down to size. Working with just a picoliter of fluid—about 34 trillionths of a U.S. fluid ounce—introduces its own set of considerations.

For one, there's the sheer size issue to deal with. Fluids in such small volumes don't undergo the same turbulence they do in larger volumes, and it's the turbulent flow that standard processes use for mixing and propelling fluids through a channel.

Then, there's the issue of pressure. Channels as small as a

hair's width require thousands of times more pressure than millimeter-size channels to maintain similar flow, according to Kim.



*The two handheld devices (shown in the cutaway and the diagram above), the Bio Detector and the Chem Detector, are intended for use by first responders who aren't necessarily trained in chemical analysis.*

Microfluidics, the branch of nanotechnology that deals with the complexities of manipulating minute quantities of liquids, has made some impressive progress in dealing with these issues. There are several different approaches to moving the tiny streams (or, in some cases, droplets) across a chip, and of controlling the flow.

For the most part, the chips themselves are fabricated like those used in computers. Photolithography is used to etch channels into silicon or glass wafers. Tiny streams of fluids travel through these channels. The etched wafers can be stacked to create more complex pathways.

The microfluidic chips typically connect to a power source, to reservoirs that hold and dispense the fluids, to lasers to excite the fluids, and to assorted data processing

systems. Software is used to run the whole system.

The systems can be either handheld, as is the case with Sandia's MicroChemLab Bio Detector, or laboratory-based, as with Caliper Life Sciences' LabChip 3000 drug discovery system.

### **In the Field**

Sandia National Laboratories is seeking commercial partners for two handheld biological chemical analysis and detection systems using its microfluidic technology.

The two devices, MicroChemLab Bio Detector and MicroChemLab Chem Detector, are intended for use in the field by first responders who are not necessarily trained in chemical analysis.

MicroChemLab Bio Detector is a liquid-phase system that discriminates among proteins to detect and identify biotoxins, viruses, and bacterial agents. The first generation of the system successfully detected seven different forms of the biotoxin ricin and could distinguish between two staphylococcal enterotoxin variants.

MicroChemLab Chem Detector is a gas-phase system that can be used for the detection of chemical warfare agents and toxic industrial chemicals, explosives, and organic solvents. The system has been tested with nerve and blister agents.

With MicroChemLab Bio Detector, the analysis takes place in a 10 cm long sealed separation channel that is chemically etched in a 2-square-centimeter fused silica microchip. The chip design allows protein samples tagged with a fluorescent dye to be pressure injected by the user directly onto the chip, according to Ron Renzi, lead engineer for the MicroChemLab project. Electric fields are used to manipulate nanoliter volumes of fluids in the microchannels. Components of the sample are separated for identification as they move through the channel.

The microfluidic module includes the chip and a cartridge, which holds reservoirs for reagent fluids. The microfluidic chip is compressed against a manifold and the reservoir. This module is attached to the optical system, which includes a miniature violet laser diode that excites dye-labeled proteins, inducing fluorescence. A

photomultiplier tube detects the fluorescence emission, and on-board data processing identifies target proteins in near real time. The system is controlled with an embedded microprocessor. Fluids or ions are manipulated using high-voltage power supplies, while the entire system runs on batteries.



*Caliper Life Sciences, one of the few companies marketing lab-on-a-chip systems, offers systems for DNA and protein analysis, and drug discovery.*

A big challenge in creating a handheld lab-on-a-chip system was figuring out how to bring fluids from the world to a channel thinner than a human hair, according to Renzi. To solve that problem, Renzi's team at Sandia developed its own manifolds, fittings, and cartridges to hold the buffer solutions and reagents, laser-induced fluorescent system, and high-voltage power supplies. It's seeking to license all that technology to commercial partners.

According to Renzi, the system has just one separation channel per chip, due to technical limitations. "You need really good fluid and electrical isolation on the chip to run multiple channels. Otherwise you get crosstalk between the channels," he said. Sandia is currently working on valves that may allow multiple processes to be run on each chip.

### On the Bench

Caliper Life Sciences is one of the few companies to be marketing lab-on-a-chip systems. Caliper has two

platforms: the LabChip 90 System, for DNA and protein analysis; and the LabChip 3000 System for drug discovery. Both platforms are stand-alone lab-based systems.

Both systems use photo-etched quartz chips with 10- to 50-micrometer channels, according to Caliper's Seth Cohen. The chips use a combination of electrokinesis and pressure to move fluids through the tiny channels.

Electrokinetic flow is generated when electrodes attached to computer-driven power supplies are placed in the reservoirs at each end of a channel and activated to generate electrical current through the channel. Under these conditions, fluids of the appropriate type will move through the microchannels by a combination of forces—electro-osmosis and electrophoresis.

Electrophoresis is the movement of charged molecules or particles in an electric field. It can be used to move molecules in solution and to separate them based on very subtle differences in their charge. Electrophoresis and electro-osmosis generally occur at the same time in channels. Vacuum-driven flow is also used to move solutions through the microchannels, independent of their charge, much like sipping soda through a straw.

Glass capillaries, which Caliper calls sippers, attach to holes on the etched side of the microfluidic chip. These sippers draw fluid up from another microplate onto the chip. The sippers typically sip for less than a second, according to Cohen.

The chip automatically stains the protein or DNA fragments with a fluorescent dye, does an electrophoretic size-based separation, and detects the separated bands using laser-induced fluorescence. Software tracks the changes in fluorescence over time to interpret the data.

According to Cohen, DNA sizing takes just 30 to 60 seconds using the LabChip 90. The drug discovery system, the LabChip3000, uses a four- or 12-sipper configuration for higher throughput, and can generate 20,000 to 30,000 samples per day.

The next step for Caliper is to add more functions to the chips. "We want to add a destaining step, which can't be done with capillary electrophoresis," said Andrea Chow, vice president of research and development for Caliper. "And our next application will be inline PCR."

PCR, or polymerase chain reaction, is a complex, time-consuming technique in which repeated cycles of DNA synthesis are carried out to produce a large quantity of a specific DNA sequence. Part of the difficulty in carrying out this procedure on a microfluidic chip is the need to control rapidly changing temperatures, according to Cohen. A thermocycle can heat a sample to more than 75°C, cool it to 55°C, and return it to 75°C, all in a minute or so. PCR is often used in cancer screening, where many DNA samples may be tested against one disease locus, or one sample against many disease loci, Cohen said.

A lab-on-a-chip PCR test would automate the tedious process and make it easier for researchers to find the one cancer cell in a largely normal sample, Cohen said.

Other techniques for moving minute amounts of fluid along a chip are in development. These techniques include dielectrophoresis and electrostatic actuation.

Tom Jones, a professor of electrical engineering at the University of Rochester in New York, is using liquid dielectrophoresis to move fluids around his lab-on-a-chip.

Dielectrophoresis uses the electrostatic attraction of dipoles to non-uniform electric fields to transport fluids across a surface that has tiny electrodes embedded in it. The electrically neutral liquid is placed in an electrical field that is spatially inhomogeneous. The dipoles are induced in the liquid molecules by the electrical field. However, because the field strength is different on the plus and minus charges of the dipoles, they experience a net force that pulls the liquid toward the high field region.

Jones's scheme uses none of the standard microchannels, ducts, or plenums. Instead, he is using photochemical etching to pattern microelectrodes on a surface. They are coated with a dielectric layer. The electric fields created by these electrodes control the movement of the liquid. When the electric field is turned off, the capillary force takes over, breaking the liquid stream into tiny droplets. The droplets dispensed on the surface of the chip serve as individual samples for chemical analysis. The droplets can be moved, mixed, monitored, and then disposed of when they've served their purpose.

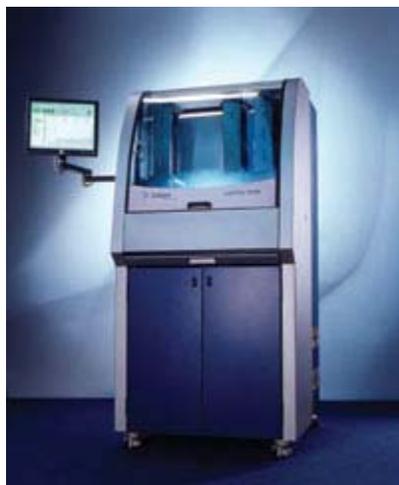
According to Jones, dielectrophoresis allows him to "rapidly dispense a large number of droplets on a substrate with just a simple structure." This system can

form 25 or more droplets of 50 picoliters or less in a linear array. The scheme can be scaled to create two-dimensional arrays of hundreds of droplets, Jones said.

This surface-based plumbing system has some advantages over the traditional closed-channel approaches, according to Jones.

The closed systems, which embed the fluid channels and ductwork within a substrate, require as much as two atmospheres of pressure to move the tiny volume of fluid at a speed to achieve adequate flow. "That's not very high pressure when you're dealing with house-sized plumbing, but it's tremendous for a microscale system," he said. "The risk of leakage in such complex fabrications is very high."

His system, which has been tested with deionized water and sugar solutions, doesn't have problems with pressure or leakage, but has some issues that need resolving.



*Caliper's LabChip 3000 System for drug discovery uses a four- or 12-sipper configuration, and can generate 20,000 to 30,000 samples per day.*

The challenge comes in actuating more-conductive biological solutions, which require higher voltages. So far, the droplets have been irregular in size. Jones has experienced some issues with the wetting properties of the substrate, and variations in the surface of the substrate that cause the droplets to behave differently than expected.

The next step, which should bring the

dielectrophoresis scheme closer to the real world, is to test its performance using analyte solutions containing DNA. It is expected to react differently because of its protein content.

At UCLA, C.J. Kim is also working with droplets, but he's using yet another approach to moving those droplets across a tiny chip.

Where most of the lab-on-a-chip systems rely on

microchannels and nanosize pumps and valves, Kim believes that approach is too expensive to fabricate and has too much potential for leakage around the valve, because of the high pressures. Instead, he's working to create what he calls "a micromachine that's true to scale."

Kim's approach, which he calls a "reconfigurable lab-on-a-chip," uses surface tension to drive droplets around the surface of the chip. "The relative magnitude of surface tension gets greater as the size of things gets smaller," Kim said. "Surface tension is so great at the microscale that droplets make perfect sense. The processes we're automating don't require continuous flow."

Kim's system uses two glass plates. The top plate contains a conduction layer that's similar to the ground plane in an integrated circuit. The bottom plate contains a rectangular array of electrodes covered with a dielectric layer. Kim calls this arrangement electrowetting-on-dielectric. The electrode system is coated with a hydrophobic layer of Teflon, which causes the droplets to form as discrete units that can be moved across the chip by virtue of the signal generated by the electrodes.

The system is more software driven than the typical lab-on-a-chip systems. And the path of the droplets is controlled by software. Changing the software algorithms to create a different path can reconfigure the lab-on-a-chip for a different process.

Kim has begun developing a handheld system using his lab-on-a-chip for healthcare and biodefense applications. He says the system is just 30 percent larger than a Palm Organizer, and can run for 24 hours on four AA batteries. "Usually, lab-on-a-chip applications have problems with high power consumption, but the electrowetting technique has very low power consumption, and is very simple," Kim said. In the current configuration, just a few percent of the complete system's power goes to the fluid system; the electronic circuits that drive the software use most of the power, he said. He believes the circuits can be optimized to use less power and ensure longer battery life.

Lab-on-a-chip systems are still early in their development, but their potential is vast. "Taking a real-world problem, like bioterrorism, and coming up with a bioagent-detection solution is a first big step for us," said Sandia's Pontau. "We're going to see even more uses for this technology in water analysis, home healthcare, and disease detection."

And it all starts with just a nanoliter of fluid and a chip that's no bigger than your fingernail.



[home](#) | [features](#) | [news update](#) | [marketplace](#) | [departments](#) | [about ME](#)  
| [back issues](#) | [ASME](#) | [site search](#)

© 2004 by **The American Society of Mechanical Engineers**