Big Lab on a Tiny Chip

Squeezing a chemistry lab down to fingernail size could provide instant medical tests at home and on the battlefield

By Charles Q. Choi

KEY CONCEPTS

- Researchers are devising tiny, portable chips that could rapidly detect pathogens or biological weapons in a sample of a person's blood.
- Microfluidics—using air pressure or electricity to move droplets through tiny chemical reactions—is the key to making labs-on-chips practical.
- The University of Michigan at Ann Arbor has devised a chip that could test for influenza, but it still requires an external air supply. The Massachusetts Institute of Technology has crafted an electric conveyor that could efficiently drive microdroplets.
- Ultimately, consumers could have labs-on-chips in their home for fast diagnosis of common illnesses. —*The Editors*

Imagine shrinking the beakers, eyedroppers, chemicals and heaters of a chemistry lab onto a little microchip that could dangle from a key chain. A growing number of companies and universities are claiming to have devised such marvels, ready to perform vital analyses from detecting biological warfare agents in a soldier's bloodstream to identifying toxins in a tainted package of hamburger meat. Almost all the new devices are surprisingly far from portable, however. The sensor that examines a drop of blood or speck of beef might indeed fit in one's hand, but the equipment required to actually move a fluidized sample through the chip's tiny tubes often occupies a desktop or more.

Two research teams are overcoming that hurdle with creative microfluidics—the precise manipulation of microscopic droplets. By moving liquid molecules with air or electricity, the groups are integrating the equipment needed to sample, analyze and report, all on a fob the size of a USB flash drive. And although the current chips are being crafted by hand, the designs could ultimately be mass-produced. That prospect would finally bring labs-on-chips to the places they are most desirable—the developing world, the battlefield and the home—where they could quickly detect HIV, anthrax or *Escherichia coli*. A chip could even be implanted into a diabetic's body to help monitor the person's glucose and insulin levels.

Pushed by Air

As a tool, labs-on-chips have become increasingly popular among researchers because they can conduct hundreds of experiments simultaneously at a mere fraction of the time, space and cost of long-standing benchtop processors. Tiny channels and valves inside the chips can heat, cool or mix small samples and reagents, as well as enable more exotic tests such as electrical stimulation. The surrounding apparatus required to perform the internal heating, cooling and mixing is often comparatively bulky, however, because of the unique behavior of fluids. When trapped inside incredibly narrow tubes, even watery compounds behave like syrup: they are difficult to push around. And ironically, when they do flow, they are remarkably free of turbulence, making it hard to mix them with reagents for chemical reactions. Forcing liquids through the chips with compressed air requires bulky plumbing. Electrically driving the liquids requires high-voltage power supplies.

The tests these desktop labs-on-chips can handle have gotten progressively more sophisticated. In 1998 chemical engineer Mark Burns and geneticist David Burke of the University of Michigan at Ann Arbor demonstrated the first chip that could identify a particular gene or variation of it. Since then, the researchers have

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ACTUAL SIZE: **The University of Michigan's influenza chip measures 1.5 by 1.6 centimeters.**

steadily miniaturized and integrated the surrounding equipment. "The vision," Burns says, "is to get genetic analysis equipment to whoever wants it, including people at home." For example, a concerned parent could quickly determine if a child who becomes ill at 2 A.M. might have influenza, instead of hauling her to an emergency room and having to wait for results from a lab.

Analyzing the genes in a droplet begins with amplification: heat and the addition of particular enzymes facilitate the creation of millions of copies of the genetic material. Those clones are then mixed with digestive enzymes that locate and snip out specific DNA sequences. Fluorescent dye molecules attach to the DNA snippets. Electric fields then move the snippets through a gel, a process known as electrophoresis. The speed at which the snippets move, which depends on their size and electric charge and is observed with light, reveals details about the DNA, such as whether it matches segments from deadly germs or harmless ones.

Burns's work had actually begun in 1993, and by 1998 his group had devised ways to propel droplets down channels using small puffs of air, "much like one would blow liquid through a straw," Burns explains. Further design enabled temperature sensing, amplification, electrophoresis and fluorescence detection to all take place on a wafer roughly half a centimeter wide and three centimeters long—about the size of a half-stick of chewing gum.

The equipment that drove those operations still surrounded the wafer, however. Burns and Burke spent the next seven years miniaturizing it. Along the way, the duo replaced the original DNA amplification method (strand displacement amplification, or SDA) with the increasingly popular technique known as polymerase chain reaction (PCR). PCR required only one enzyme instead of two, greatly simplifying the onboard chemistry. But PCR also required extraordinarily intricate changes in temperature. For SDA, the chip needed to heat the sample to 50 degrees Celsius and keep it there. PCR demanded a cycle of heating and cooling, from 90 degrees C down to 50 and back up to 70, which had to be repeated 35 times. The researchers had to hit more than 100 unique temperature points, which had never been attempted with anything nearly as portable as the device Burns and Burke envisioned.

Furthermore, the spot where each step took place had to be thermally isolated, a huge feat when all the processes are crammed onto a microchip. Burns and Burke spent months experimenting with different materials, along with gate patterns and valves—shaping channel junctions and testing coatings so they could move and mix molecules and siphon away excess fluids caused by certain reactions.

By 2005 the team had integrated the electronics, sensing, heating and electrophoresis components onto a silicon wafer about the size of a quarter. A glass substrate housed the liquid channels. Instead of requiring many pressurized air connections to supply the pneumatic force needed to open and close each valve and push fluid around, the chip required just two conduits, significantly reducing its bulk. A single air supply became feasible after Burns and Burke found they could make the many valves with wax. Electronics on the chip would heat each valve individually at the right time during analysis, making the wax mobile enough for air pressure to push the values open or closed.

The team named their genetic analysis chip "VIPER" (*v*alved, *i*ntegrated *P*CR *e*lectrophoresis *r*estriction digest), and its function is to distinguish variants of influenza virus genes [*see illustration on next page*]. The chip can perform genetic analysis in as little as 15 minutes, 10 times faster than PCR takes in a standard lab. As Burns points out, "Other diseases could be detected by merely changing the liquid reagents, or 'wetware,' just like many programs can be run on a computer by changing the software.... The size suggests that mass production could be relatively cheap, under $1 per chip."

The primary remaining hurdle is the source of air pressure, which is still external to the chip. The system could use a low-pressure carbon dioxide cartridge about the size of a finger, as well as off-chip electronics, to distribute the air power to various valves. The other off-chip compo-

MARK BURNS University of Michigan (chip)

CHIPS IN DEVELOPMENT

HIV TEST
Harvard-M.I.T. Health Sciences
Disposable wafer the size of a business card would test for HIV and read out immediately; intended for poor countries.

MRSA TEST
Cepheid
Chip for hospitals would sense methicillin-resistant staph bacteria to reduce the spread of hospital-acquired infections.

CANCER SCREEN
University of Alberta
Wafer would perform "fluorescent in situ hybridization"—a screening test that can detect the chromosome mutations of various cancers.

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The tiny size "suggests that mass production could be relatively cheap, under a dollar per chip."
—Mark Burns

nent is a blue LED that illuminates the genetic material during electrophoresis. Burns says these pieces could be shrunk onto a second chip, with both chips fitting onto the equivalent of a USB flash drive. "Getting to the USB drive size gives me claustrophobia," Burns says, "but it is possible. It would be easier to make an iPod-size device, giving room to put a small compressed air cylinder inside, as well as multiple chips."

Private money may be needed to realize either configuration; Burns and Burke do not have the funding to develop them. Yet biomedical engineer David Beebe of the University of Wisconsin–Madison thinks that Burns and Burke "have made the most convincing argument that a portable lab-on-a-chip might actually be possible in a commercial way." Perhaps the investment will come.

Propelled by Electricity

As Burns's story illustrates, the greatest challenge in devising labs-on-chips may be moving the liquids onboard with as little power as possible. By tweaking the design of a tiny pump, researchers affiliated with the Massachusetts Institute of Technology's Institute for Soldier Nanotechnologies have taken a major step toward solving that problem.

Martin Bazant, an applied mathematician, leads the M.I.T. work, and he has chosen electricity as his propellant, not pressurized air. "There are no moving parts, making things simpler," he says. The pump his team is developing requires only a few volts, which a watch battery could provide.

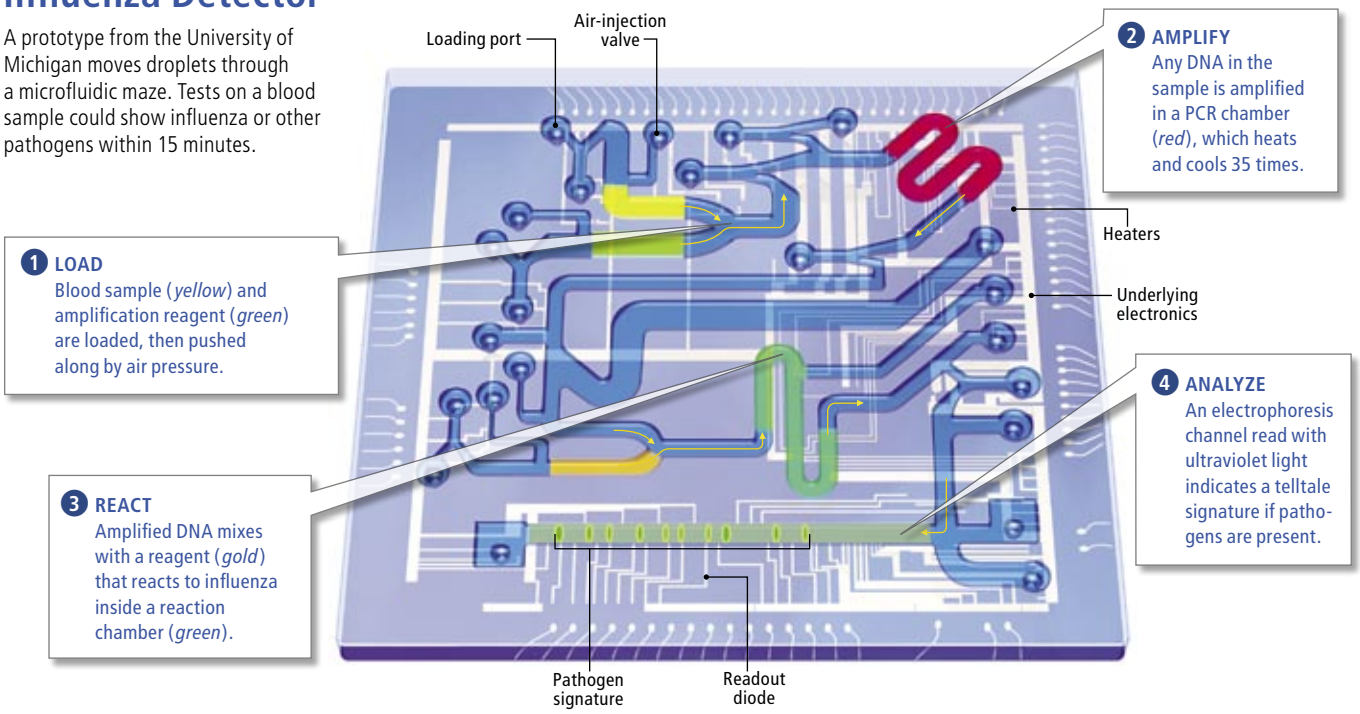
Bazant studies electroosmotic flows, wherein electric fields drive charged molecules in solution. For years electroosmotic pumps operated on direct current (DC) of 100 volts or more, untenable for a portable lab-on-a-chip. In 1999 scientists began reporting alternating current (AC) electroosmosis; AC systems require far lower voltages because they can use multiple electrodes spaced throughout a channel, whereas DC systems rely on one big electrode placed at each end of a channel.

An AC design can be visualized as a length of railroad track. The low, flat railroad ties are electrodes, and fluid covers them between the rails. If electrodes alternate between positive and negative charges, liquids flow in one direction. At first glance this seems impossible; a fluid molecule should simply oscillate back and forth between two given electrodes, resulting in no net movement. But introducing irregularities in electrode shape, spacing or coatings causes fluids to prefer one direction.

The problem for labs-on-chips, however, was that the AC pumps moved fluids too slowly. In 2003 Bazant and his colleagues theorized that electrodes shaped like a set of two stairsteps (if viewed on end) would lead to complex three-di-

Influenza Detector

A prototype from the University of Michigan moves droplets through a microfluidic maze. Tests on a blood sample could show influenza or other pathogens within 15 minutes.



GEORGE RETSECK; SOURCE: UNIVERSITY OF MICHIGAN AT ANN ARBOR

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mensional flows that might generate quicker net movement. This, too, seemed counterintuitive; wouldn't a stairstep interfere with flow?

Perhaps so. But Bazant realized he could use the interference to his advantage. AC designs were slow because the alternating current made fluid molecules slip backward between the flat electrodes and oppose the overall progress. The stairstep, however, should cause back-slipping molecules between adjacent electrodes to circulate in a loop, creating a local eddy. A series of eddies between a string of electrodes could behave like the rollers under a conveyer belt, helping the fluid above them move along [*see box at right*].

In 2006 Bazant's team presented an AC electroosmotic conveyor that flowed more than 10 times faster than prior designs at the same voltage. The flow rates "approach the flows seen in [air] pressure-driven systems," Bazant says. Furthermore, when his group tested a prototype conveyor, the researchers found that molecules in the eddies stayed trapped there only briefly, with most diffusing out in milliseconds. In a chip, that circulation would ensure that all the molecules in a sample would advance downstream and undergo reactions, dispelling concerns that certain target molecules could be missed if they stayed stuck in the eddies.

One limitation is that ions could crowd one another near an electrode surface, hindering flow. But Bazant thinks he could overcome this problem by diluting samples, adding molecules that break up crowding, or giving the electrodes special water-repellant coatings. His team is just beginning the laborious task of adding microfluidic-analysis components to its conveyor for a complete lab-on-a-chip. "Our goal," he says, "is to deliver to the [U.S.] Army a device the size of a wristwatch that can look for specific signals in the saliva or blood, such as messenger RNA sequences, that mark the body's response to exposure to a wide variety of biowarfare agents."

Worth the Bother?

Although truly portable labs-on-chips seem inevitable, some critics wonder if anyone will want them. In the U.S., physicians deliver patient samples to off-site testing labs that are cost-effective and efficient. Hospitals have labs on-site. "And for most tests, you don't need answers right away," Beebe admits.

Nevertheless, large markets loom. Labs-on-chips could fulfill many uses at home. They could also improve medical diagnostics throughout the developing world, where conventional labs are rare and where doctors often see patients once and then never again, "so you better give them an answer while they're there," Bazant says.

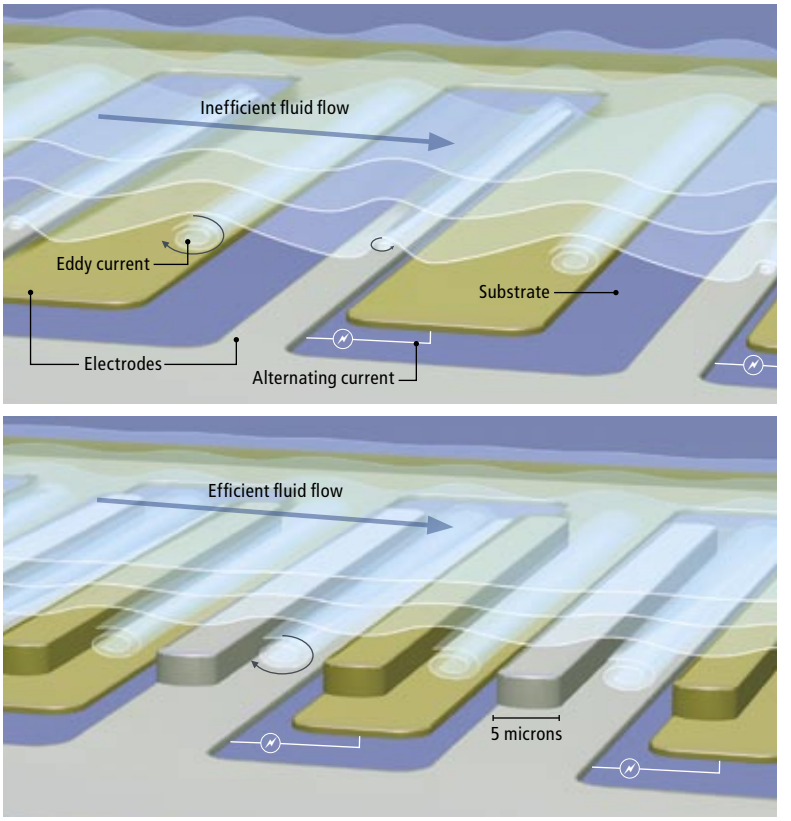
Medics on battlefields cannot just send a sample to a lab either. And even in suburbia, Bazant notes, "you can imagine paramedics and other first responders getting answers on patients right away," which could improve survival rates at the scene or during treatment in an ambulance. If made small enough, labs-on-chips might even be implantable; attached to a tumor, a chip could track whether it is growing or how drugs are affecting it. So the designers push ahead. "We want to show what's possible," Burns says. "We want to show how intelligent and powerful these devices can become." ■

Charles Q. Choi, a frequent contributor, wrote about the International Polar Year in the March issue; he has traveled to seven continents.

[NEW DESIGN]

Microconveyor

Alternating current along a string of electrodes can pump liquids along a microfluidic channel. But turbulence between electrodes (*top*) makes the net progress slow. A novel pump design from M.I.T. (*bottom*) speeds flow by a factor of 10; shaping each electrode like a step creates eddies that act like rollers in a fluid conveyor belt.



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MORE TO EXPLORE

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