Bioscience TECHNOLOGY

The Other Chips: Microfluidic Devices Come of Age

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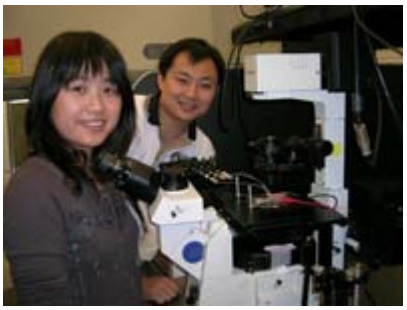


Researchers Hsiang-Yu Wang (left) and Chang Lu operate their simplified microfluidic single-cell electroporation system. Image courtesy Chang Lu.

The clock ticks forward one second. A technician pipets a sample from a crude cellular extract, processes it through a complex preparation protocol with multiple reagents, runs the processed extract on a gel, isolates the desired bands, and characterizes the activities of several novel enzymes. Then the clock ticks again.

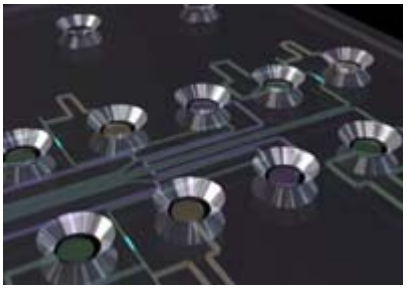
Laboratory directors won't find this turbocharged technician in the job pool just yet, but barring any serious technical hurdles he could be availble for hire within a few years. He won't take much bench space or many coffee breaks, either, because he's etched into a wafer of silicon.

Biologists have been using silicon chip-based assays for several years, in the form of DNA and RNA arrays, but these are passive devices designed for screening thousands or millions of binding events in parallel. Another category of silicon chip, the microfluidic device, does something entirely different: it moves and manipulates minuscule volumes of fluid at mind-bending speeds.

That may sound like just a cute engineering trick, but the technology has enormous potential. Big pharmaceutical companies have already embraced microfluidic drug screening, and a few off-the-shelf systems are finding a niche in large-scale "omics" efforts. As microfluidics trickle down to smaller basic research labs, biologists will need to understand the strengths and limitations of these new tools.

Off-the-shelf

Fans of microfluidics say that many of the most promising devices are in an active development stage, which is another way of saying they're not ready for regular use. However, a few pioneering companies have developed mature, off-the-shelf systems for specific applications.



Artist's rendering of the surface of a channel-based microfluidic device, showing channels for moving reagents and wells for carrying out reactions. Image courtesy Caliper Life Sciences.

The field's 800-pound gorilla is Caliper Life Sciences (Mountain View, CA). The company offers two microfluidic systems, the LabChip 3000 and LabChip 90. "On both our instruments, we use these things called sippers, which are a little straw on the bottom of the chip," explains Michele Boudreau, director of corporate communications for Caliper. The sipper dips into a well on a 96- or 384-well plate and sucks a picoliter-size sample of fluid into the system, where it runs through channels, each 10-50 mm wide, etched into the silicon chip.

The channels can carry the sample into reaction chambers for specific assays, or through gel-filled sections to separate proteins or DNA. Once the sample has been processed completely, the chip moves to the next well of the plate. One disposable chip can generally process one multiwell plate.

The LabChip 3000 is a popular choice for high-throughput drug screening, and Caliper has tailored it for that market. Off-the-shelf chips for this system can perform a variety of enzymatic and cell-based assays, such as checking for the activity of test compounds against panels of G-protein-coupled receptors or kinases. Meanwhile, the LabChip 90 is aimed at the basic research market, with stock systems for proteomics. "It's similar to gel electrophoresis, but in seconds, not minutes or hours," says Boudreau.

A few other companies sell microfluidics to smaller market niches. Fluidigm (South San Francisco, CA) aims squarely at basic researchers, offering microfluidic chips for protein crystallization, real-time PCR, and other techniques now commonly done in multiwell plates. Micralyne (Edmonton, Alberta), an established maker of microelectromechanical systems for industrial applications, also offers a line of simple electrophoresis chips off-the-shelf. Meanwhile, Micronics (Redmond, WA) focuses on a range of practical applications, from environmental sampling to medical diagnostics.

Prices for microfluidic-based research systems vary widely according to the system's complexity and state of development, but stock, mass-produced microfluidic systems are comparable to other major laboratory equipment. A LabChip90 reader from Caliper, for example, sells for around $65,000, plus the ongoing costs of the disposable chips.

Solutions in search of problems

Besides money, researchers moving their multiwell plate experiments to microfluidics must invest some time. "There's definitely a transition," warns Aaron Wheeler, an assistant professor of chemistry at the University of Toronto (Toronto, ON). "For example if your microfluidic device is made of silicone rubber, as many are, you won't be able to use very strong organic solvents," he adds.

Other challenges can include choosing new buffer solutions for a protocol, as many microfluidic devices rely on an electrokinetic pumping system that is sensitive to salt concentrations and pH. "I wouldn't say, however, that it's an unsolvable problem, I think these transitions have been made repeatedly," says Wheeler, who is developing new microfluidic devices for proteomics and high-throughput screening.

In proteomics, the big advantage of microfluidics is their ability to run minuscule samples on electrophoresis gels in a few seconds. While Caliper already sells a system for proteomics, it does not eliminate the bottlenecks in sample preparation and processing. Wheeler and other researchers hope to develop devices that can also handle all of the steps before and after the gel, taking a crude cell extract at one end and yielding a clean sample for mass spectrometry at the other.

That would be an impressive accomplishment, but microfluidics researchers say they are still searching for the "killer app," the term computer scientists coined to describe a breakthrough application that catapults a new technology into widespread use. "There's been a lot of talk about whether we can find a killer app — perhaps one of these days we'll stumble into it," says Wheeler.

The scale of microfluidic devices may give them a special advantage over larger systems in cell biology. For example, single-cell electroporation systems capitalize on the unique ability of microfluidics to channel fluids into cell-sized streams and chambers, where a jolt of high voltage can force DNA or other molecules inside.

In a new twist on this application, researchers at Purdue University (West Lafayette, IN) recently simplified single-cell electroporation to a single-channel microfluidic chip, eliminating several expensive components from the process. The new system consists of a channel with a narrow restriction at one point. The researchers apply a constant current across the channel, then send a stream of fluid-suspended live cells through.

"Just based on simple Ohm's Law, the voltage across a particular section is totally proportional to the resistance across that section, [and] the resistance is determined by the cross-sectional area," explains Chang Lu, assistant professor of agricultural and biological engineering at Purdue and lead investigator on the project. In the wide part of the channel, cells encounter a low voltage; in the restriction, which allows only one cell to pass through at a time, the voltage is much higher, automatically electroporating the cells one at a time as they pass.

"Every cell, as long as it flows through the whole channel, is electroporated," says Lu. While some single-cell transformation systems are already available, the new approach drastically simplifies the design, and replaces expensive electric pulse generators with a common laboratory DC power supply.

Dancing droplets

Current commercial microfluidics — and most experimental models —direct fluid streams through microscopic channels etched into the chip. But a few researchers are now working on an entirely different approach, called digital microfluidics. Instead of pumping samples through channels, digital microfluidics use electricity to move individual droplets across a flat surface.

"From a product standpoint this is very attractive, because I can design one platform for many different applications. For a channel-based system everything is pretty much hard-wired," says Richard Fair, professor of electrical and computer engineering at Duke University (Durham, NC).

In a typical digital microfluidic device, a droplet sits on an array of electrically conductive pads. Changing the charge on a pad alters the droplet's surface tension, and charging adjacent pads differently forces the droplet to migrate from one place to another, anywhere on the two-dimensional surface.

The effect can be eerie to watch. In the videos that often accompany digital microfluidics papers, microliter- and nanoliter-size droplets zip across the screen, merge with each other, split, and run in circles without any visible assistance. Besides making interesting viewing, the technique could have a range of practical applications, and at least one company, Advanced Liquid Logic (Research Triangle Park, NC) is already working to commercialize digital microfluidics.

While channel-based systems are ideal for chromatography and other stream-like protocols, digital microfluidics could be especially useful for multi-step assays that involve mixing a sample with different reagents. Advanced Liquid Logic is working on diagnostic tests that might require only a few microliters of blood and a few seconds of automatic processing. Meanwhile, Fair hopes the technology will be the key to the "thousand-dollar genome," a major goal for biomedical researchers.

In basic research, both channel-based and digital devices are still primarily the toys of engineers and chemists, but biologists should catch on fast once they see what microfluidics can do. "The easy way you can draw two-dimensional cartoons [of the chips] makes everyone feel they can immediately get a feel for how they can use the technology," says Wheeler. The quick uptake will be an important selling point for the next generation of devices. After all, in microfluidics, every milli-second counts.
