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Microfluidics streamlines laboratory operations

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Reducing the cost will trigger a boom in lab-on-a-chip technology -- reusable or disposable paper chips may hold the key.

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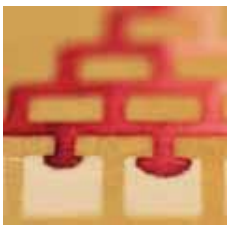

Lab-on-a-chip technology -- more properly referred to as microfluidics -- has been making headlines since the 1990s when the U.S. Defense Advanced Research Projects Agency (DARPA) funded the technology in the hope of developing handheld sensors for hazardous materials and/or healthcare monitoring. In the intervening years, the technology has become both more and less than anyone expected. Massively parallel arrays with stupefyingly large numbers of reaction sites are now commercially available and yet no killer app has emerged to bring the economies of scale required for widespread adoption. Let's take a closer look at why and review some of the more recent advances in the area.

Microfluidic chips consist of substrates patterned with channels, valves, mixers, chambers, and so on, typically on the order of tens of microns in scale. Forget about the 384-sample DNA well plates of the past. Today's researcher can purchase a microfluidic chip for single-cell analysis that features 30,000 valves, over 100,000 channel segments, and 20,000 chambers, says Gajus Worthington, co-founder, president and CEO of Fluidigm Corp. (South San Francisco, CA). He views this as a logical extension of the development process. "We had to get to the point where we could make many thousands of things happen on the chip -- not just simple things but complex things -- before we had something that was really different."

The biggest benefits of microfluidics arise from the size of the structures. The small volumes involved in microfluidic chips provide significant savings on reagents compared to conventional techniques. The scale also means that reactions take place at a much faster timescale, which can be critical for complex, highly iterative applications like DNA sequencing. The fact that each chip integrates multiple laboratory functions also speeds the process. Meanwhile, automated analysis helps minimize human error, improving both accuracy and reliability.

Two important advances have helped move the field forward. One was the development of rapid prototyping systems using poly(dimethylsiloxane) (PDMS). The polymer can be easily patterned using lithographic techniques to form a microfluidic chip transparent at wavelengths longer than 230 nm. "You can make very complicated structures with very little effort," says George Whitesides of Harvard University (Cambridge, MA), one of the key developers of the technology and chairman of the editorial board for the journal *Lab On A Chip*. PDMS chips can be used as is or as masters to replicate additional devices.

The second important advance was the development of a microfluidic valve by Stephen Quake, professor of bioengineering at Stanford University (Stanford, CA). The basic concept involves a pair of crossed channels separated by an elastic membrane that can selectively close one channel or the other. That cleared the way for more complex systems that included mixers and stirrers, or streams of reagents running into common chambers. The combination of these two technologies ushered in the modern era of microfluidics.

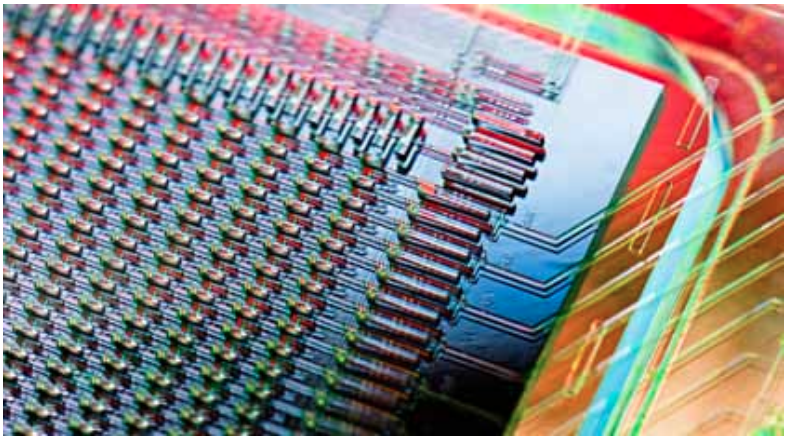

Figure 1. Poly(dimethylsiloxane) (PDMS) microfluidic chip can be reused as many as five times. Current models feature 2304 reaction sites, with a 4608-data-point chip slated for 2011 release, providing an avenue to pricing of as little as a

penny per reaction. (Photo: Fluidigm)

Cheap Chips

Applications for microfluidic technology include nearly any task that requires fluid handling and processing, such as genomics and proteomics, drug discovery, and medical diagnostics. The market for micromachined silicon and glass microfluidic chips in diagnostics and drug discovery alone should reach $109 million by 2014, buoyed by a CAGR of 15%, according to market research firm iSuppli Corp. (El Segundo, CA). Meanwhile, Yole Developpement (Lyon, France) expects the total microfluidics market to reach $3 billion by the same time. The technology is poised for growth and yet it is nowhere near the behemoth it could be. A number of barriers must be surmounted before it can reach its potential. The first is cost.

Although initial work focused on chips machined in silicon, glass, and quartz substrates, both materials and fabrication technologies can be expensive. One avenue to lowering price at the chip level is reusable silica or quartz microfluidic devices. Such systems involve flushing the channels using techniques similar to those for cleaning high-pressure liquid-chromatography columns. Even a chip with a high initial cost becomes reasonable when amortized over 1000 uses.

Switching to disposable polymer microfluidic chips replicated from a master provides a different type of cost-control measure. Especially for the larger substrates required for massively parallel arrays, polymer is significantly more economical than glass from a materials perspective. Add reusability, and the cost for a polymer chip can drop as low as a penny per reaction. "Lab on a chip is a big market today, growing but eventually transitioning mostly to plastic for volume," says Richard Dixon, senior analyst for MEMS and sensors at iSuppli. "We believe the vast majority of the high volume microfluidic markets -- for example, point-of-care diagnostics -- will be with disposable polymer microfluidic chips."

Such an approach might be useful for point-of-care testing. In the medical industry, for example, the real money lies not in expensive instrumentation like blood gas analyzers and MRI machines but in cheap, disposable items such as gauze. The hope would be that lab-on-a-chip devices would fit this model. At present, it's still a work in progress. "We haven't achieved the razor and razor blade advantages yet, but that's the long view on it," says Stephane Mouradian, senior director business development at Caliper Life Sciences (Hopkinton, MA), which produces conventional microfluidic chips and readers, and collaborates with partners to fabricate polymer devices. "Right now, people make more money on the instruments than on the devices."

In a bid to lower chip costs even further, not to mention simplify, the Whitesides group has developed what they call paper chips, paper patterned with lines of hydrophobic material such as wax to form microfluidic channels (see figures 2a-2c). So far, the team has used the paper chips for immunoassays and metabolic assays. "Instead of printing words on paper, we print fluid-handling capabilities on paper," Whitesides says. "It's very robust, very simple, and very, very cheap." The paper chips can be produced with an inkjet printer set up to print solid wax rather than liquid ink. "My theory is that if you make it very simple and cheap, people will begin to find uses for it and then patch together more complex systems," he adds.

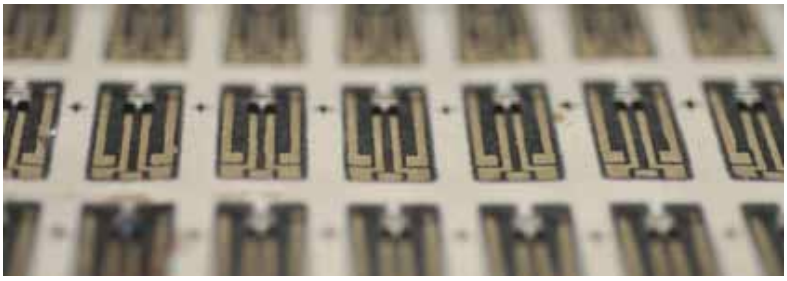

Figure 2a. Microfluidic chips formed of wax patterns on paper provide a simple, economical option two other materials. (Photos above and below: Jabulani Barber, Harvard Univ.)

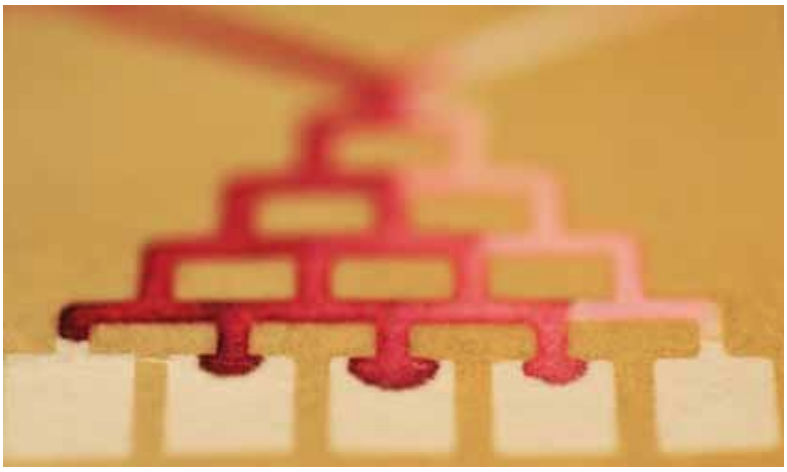

Figure 2b. Wax channels printed on paper can confine and direct fluids, allowing the formation of simple, cheap microfluidic chips.

Figure 2c. The paper-chip approach can be used to make simple, economical liver function tests in volume. (Photo credit: Frédérique Deiss, Harvard Univ.)

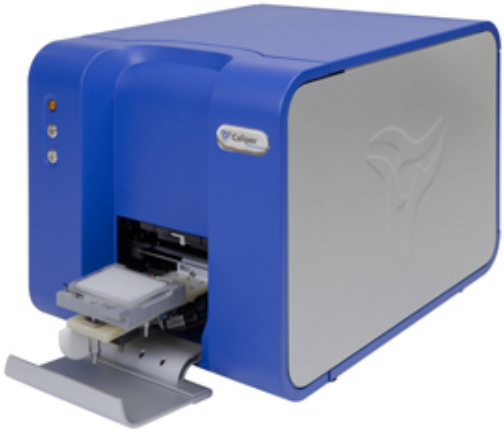

Figure 3. Today's microfluidic devices typically require prep instrumentation and readers. (Photo: Caliper Life Sciences)

Chip In A Lab

Although controlling chip cost is a key aspect, it's far from the only issue. The devices themselves may be small, but they're often surrounded by instrumentation (see figure 3). "Few platforms are able to deliver on the 'lab on a chip' feature and are generally 'chip in a lab,'" says Abraham Lee, professor at University of California, Irvine.

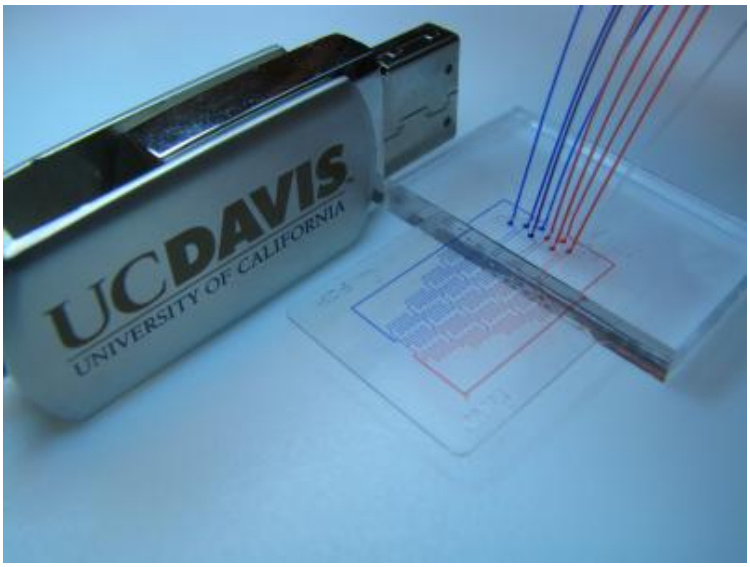

Figure 4. Connector (clear block) provides macro-to-micro interface with microfluidic chip (clear card). The USB flash drive provides scale. (Photo: Tingrui Pan, UC Davis)

A major challenge for microfluidics has been finding an effective way to interface the micro and macro worlds. After all, you can't analyze a sample until you get it onto the chip. Fluidigm, for example, embeds their chip in a DNA well plate, using its micropipette system for the interface. In an intriguing new development, researchers at the University of California, Davis, led by biomedical engineering professor Tingrui Pan, have announced what they're calling a microfluidic analog to a USB connector (see figure 4). Dubbed fit-to-flow, the adhesive-free device provides self-aligned, hermetically sealed connections between the macro world and a microfluidic chip. It provides self-guided positioning accuracy to better than 10 μm and seals to 336 kPa.

Of course, getting the sample on the chip is just the start. Once there, it must be routed through the appropriate channels to undergo processes like separation, mixing, and chemical reactions. Techniques such as syringe pumps or electro-osmosis may be effective, but the space and power they require increases the overall size of the system. "Everyone shows a tiny chip device but nobody actually shows you the huge pump sitting beneath the table," says Leslie Yeo, research fellow and associate professor at Monash University (Clayton, Australia) and editor of *Biomicrofluidics*. "You can't have true miniaturizability if you don't make all the different components that make up the chip small enough."

Yeo's group focuses on acoustical transport methods. They top a microfluidic substrate with a piezoelectric material, then pattern interdigitated electrodes on top of that. When current flows, the piezoelectric material generates a localized surface acoustic wave that pushes the fluid down the channel. "The acceleration achieved by the acoustic waves is around 10 million g's, which can propel fluid to move rather quickly, close to what people are getting with syringe pumps," he says. "The only thing is that the back pressures are not that high so there's still some way to go in trying to overcome pressure challenges." The device operates at high frequency, which minimizes cavitation. The low current levels required also reduce power demands.

Of course no analysis is complete without readout and processing. Currently, most microfluidic systems use optical interrogation, for example fiber-coupled fluorescence microscopy. It's a powerful technology but one that is difficult to miniaturize. Instead, the microfluidic chip must be processed and interrogated with multiple desktop instruments, some the size of a mini refrigerator. Quake doesn't consider that a huge drawback. "There's an awful lot that microfluidics can provide for people without being handheld, where it's a component in a larger system that sits on a bench," he says.

A number of companies are already leveraging this approach, offering chips that can perform PCR, single-cell analysis, and even certain diagnostic tests. Even with robust, reliable, manufacturable technologies that offer benefits of speed and reduced reagent use, though, carving out market share is still an uphill battle. "Typically these technologies come in and displace existing workflow," says Mouradian. "Users don't really pay much attention to whether there is a nice sophisticated microchannel inside their system or device, they just want it to work and expect to pay about the same price as what they were before."

On the opposite side of the complexity divide sits Whitesides. Among various projects, his group demonstrated a readout circuit based on an indium gallium aluminum phosphide diode laser operating at 654 nm coupled with an optical integrated circuit that combined a photodiode, amplifier, voltage regulator, based on commercial-off-the-shelf

components costing a total of about $45. To achieve the ultimate goal of a handheld device, researchers need to develop these types of light, compact, economical optical systems.

"The semiconductor folks need to figure out how to make CCD detectors that are extremely high density, really inexpensively, but the other challenge is the optics," says Worthington. "How do you collect enough photons without big, high-numerical-aperture lenses?" Possible technologies might include waveguides or integrated optics. The ideal solution would be economical enough that it wouldn't significantly swing the price point of the chip. "Right now, the [read] platforms cost about $200,000 apiece," he notes. "People would love to see a $100 system but that's still a ways off."

Building a Market

What does it take to get to that point? As industries as disparate as consumer electronics and automotive have shown, volume provides the ultimate downward price pressure. The question is, what would generate the volume? "I think there's a chicken and egg problem," says Whitesides. "Cell biologists say we just don't have the time or interest to make chips ourselves but we'll buy them. [Manufacturers] say we would be happy to make them but there has to be a demand. Figuring out the application and putting it together in sufficient volume that the user just rips open a baggie with a pre-sterilized chip, that's the stage we have to get to and we haven't yet."

"There is an economic scale necessary to make this happen and there needs to be a killer application to make it realistic and wide-spread," agrees Lee. "Once chips can be batch fabricated with select surface coatings and inlets, outlets, and sealed-in reagents, then the field has a chance to take off in a wide variety of applications. This type of infrastructure cannot come easily from a single organization, be it academia or industry. The plastic packaging and manufacturing organizations would need to develop the processes and the equipment to make it work."

As to what the killer app might be, opinions differ. Certainly, point-of-care therapeutics or diagnostics -- care to do your own physical at home? -- offer great appeal. It's equally likely that the application will be one that no one is even thinking about right now. "Commonsense says that it will change the way we do things today either by producing something in large quantities that we need or making something new available that becomes a necessity for the masses," says Lee. One thing that seems clear, is that it is just a matter of time.

The original promise of microfluidics was of highly specific, accurate, and portable devices. While the technology has not quite reached that level, it has made enormous strides since its inception. The bulk of the technology challenges have been tackled and the discipline is headed toward maturity. The next decade should hold exciting advances. For now, the sector is ticking along just fine, thank you very much. "It's made the transition from a technology in search of an application to technology people are actually doing science with," says Quake, "and that's really exciting to see."

Thanks go to John Bergin of BCC Research for useful insights.

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Putting it to work

Microfluidics plays important roles in research areas like genomics and proteomics. Although a killer application has yet to emerge, several possibilities are already in development. One area currently attracting a lot of attention is single-cell analysis-performing gene expression on individual cells. Although cell populations appear to be homogeneous, they often are not. Microfluidic technology allows researchers to analyze bacteria populations to find the superbugs, for example, or sift through tumor cells to find the ones capable of runaway growth.

Interest is growing in the use of microfluidic for bio-agricultural applications-genotyping livestock, plants, fish, etc. Such data could be enormously beneficial but seeds, for example, often contain only trace amounts of DNA. With microfluidic chips, researchers can run polymerase chain reaction (PCR) on the DNA to amplify it for further study.

Of course, microfluidic chips don't have to perform any analysis of all to be useful. They can act as micro-reactors to produce industrial chemicals that are unstable or toxic. A wall-sized rack mount of massively parallel micro-arrays can rapidly synthesize large quantities of chemicals like phosphine or hydrogen cyanide. Manufacturers can have the volumes they need without ever having to store large amounts of the material.

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