

**analytical  
chemistry**  
feature

## Microfluidics: On the Slope of Enlightenment

Rajendrani Mukhopadhyay

Now that the hype has blown over, will microfluidics live up to its promise of providing marketable applications?

*“One could argue that miniaturized chemical analysis systems are just a fashionable craze. However, it is difficult to foresee the impact a new technological concept will have, when it is in its early stages of development.”*—Andreas Manz and colleagues (*Chimia* 1991, 45, 103–105).

Pessimism and optimism walk hand in hand in the field of microfluidics. Some experts feel that the research endeavor is in danger of falling into a rut. Andreas Manz, currently at the University of Freiburg (Germany), feels a twinge of disappointment with the current state of affairs. He had bought into the hope carried by the first wave of patents, scientific publications, and start-up companies that occurred before 2000. But now he thinks, “It’s very well possible that microfluidics will end up in a never-ending cycle where it eventually reaches a steady state, just running through all kinds of [academic] applications or all sorts of technical innovations with no major outlet.”

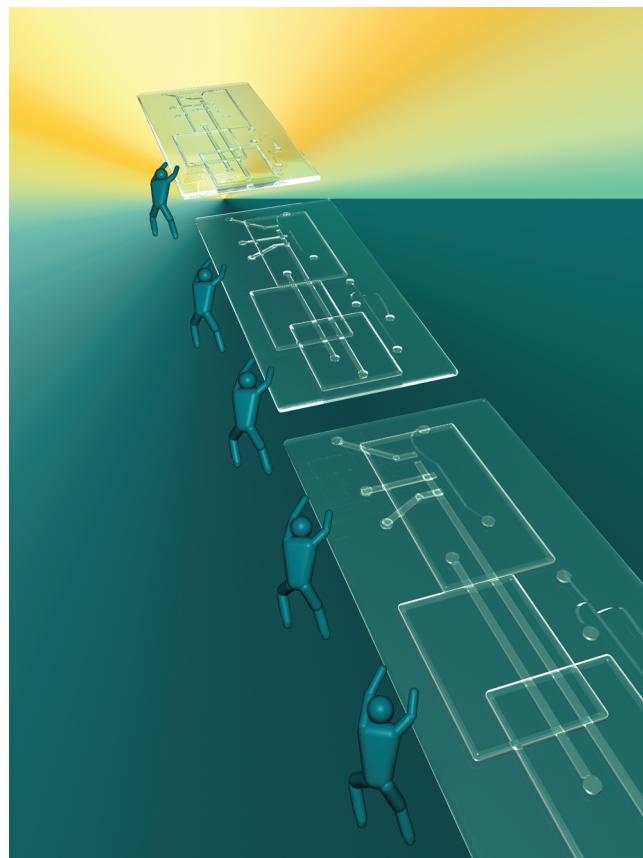
Others take a different attitude. Microfluidics, in and of itself, won’t sell. What will sell are the solutions it can provide to certain analytical problems. “When you go to the commercial landscape, technology doesn’t make money,” states the University of Washington’s Daniel Chiu, who helped found the company Celectricon. “Applications make money.”

The wildly varying views of the field are dizzying. But Holger Becker at the microfluidic Chip Shop (Germany) explains that this rift is perfectly normal. He says that microfluidics is tracking the Gartner Hype Cycle (*Med. Device Technol.* 2008, 19, 21–24).

### THE HYPE CYCLE

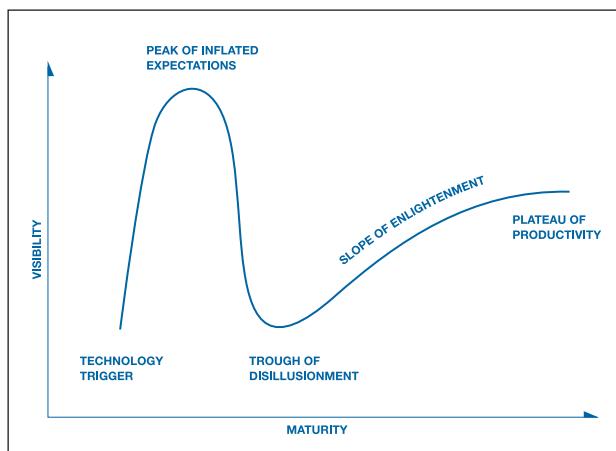
Gartner, an information technology research and advisory company, introduced their Hype Cycle Model in 1995. The model has five stages: a technology trigger, a peak of inflated expectations, a trough of disillusionment, a slope of enlightenment, and finally, a plateau of productivity. Over the years, Gartner has applied the model to many arenas, including the automotive industry, Web 2.0, and higher-education institutions.

The microfluidics “technology trigger” happened in the early 1990s when the early publications by Manz and his colleagues kicked off the field. Everyone agrees that the field’s “peak of



inflated expectations” crested later that decade when the hype about what microfluidics could achieve was at its zenith. According to Gartner, during such a peak “the early publicity produces a number of success stories, often accompanied by scores of failures.” In the case of microfluidics, the poster child of a successful application was the Agilent Technologies–Caliper Life Sciences Bioanalyzer.

Microfluidics experts think that the field’s “trough of disillusionment” probably happened in the early 2000s, when the technology failed to meet inflated expectations. “Because of the bad rap microfluidics got at the end of the 1990s, with the promises and the lack of delivery, it was a very challenging funding environment for microfluidics entrepreneurs in the wake of that,”



The Gartner Hype Cycle Model explains five key phases of a technology's life cycle. The first step is the technology trigger that occurs when a breakthrough takes place. Stories in the media set off publicity, but the commercial viability of the technology is unproven. During the peak of inflated expectations, the early publicity produces some success stories but lots of failures. Some companies may jump on the bandwagon, but many don't. The trough of disillusionment creeps in as the technology fails to be implemented. During the slope of enlightenment, people better understand how the technology can benefit the scientific enterprise and society. At the plateau of productivity, the technology becomes mainstream and the criteria for assessing its viability become clearly defined. (Copyright 2009 Gartner, Inc.)

says Gajus Worthington of Fluidigm. "There was a loss of credibility, and investors shied away from the space for a while."

In addition, some analytical instrument vendors had doubts about how to make money off the technology. "In the early days, an instrument manufacturer told me, 'Why on earth would I do electrophoresis on a chip 100 $\times$  faster with the same quality of analytical information?'" recalls Manz. "It would destroy their market! They said, 'What we want is to be 1 $\frac{1}{2}$  $\times$  faster, not 100 $\times$  faster.' The need has to grow, and the technology has to fulfill that growing need. You will destroy the market by throwing in a technology that does everything in no time and costs very little!"

But now, Holger Becker argues, microfluidics is starting to climb the "slope of enlightenment" because people are finally realizing that the technology can solve certain problems that conventional technologies can't. "Everybody expected, 10–15 years ago, [that] the killer application or the single device would make \$100–300 million in annual turnover," he says. "But what we are seeing—and I think it is actually closer to its character—is microfluidics emerge as an enabling technology. Microfluidics is creeping up in a huge variety of products where it is part of a system and actually defines or determines a lot of the functionality. In the sense of an enabling technology, we see these applications covering a huge range of fields, from environmental analysis, to clinical diagnostics, biotechnologies, drug discoveries, [the] pharmaceutical industry, and the food industry."

In 5–10 years' time, he and others predict, the technology will become matter-of-fact, and the field will reach its "plateau of productivity". According to Gartner, in this stage, "mainstream adoption starts to take off. Criteria for assessing provider viability are more clearly defined." The final height of the plateau will

depend on whether the technology is broadly applicable or works only in a niche market.

## BUT WHAT DOES "MICROFLUIDICS" MEAN?

Before going any further, "microfluidics" has to be defined. The word is like a giant beach umbrella. Even at its simplest definition, an analytical system that's small and based on flow, it covers a lot of ground.

Norm Dovichi at the University of Washington says that some very old technologies, though not typically thought of as microfluidic by analytical chemists, are enjoying the umbrella's shade. "The most wildly successful form of microfluidics is 30–40 years old," he says, pointing to on-strip tests such as home pregnancy or glucose test kits. "Home pregnancy test kits wholesale for ~\$1. One dollar per analysis!" he exclaims. "And it can be done by extraordinarily untrained people at home. It's an astonishingly successful technology."

The ink-jet printer is another example of a successful microfluidic application. "But most people don't recognize it as such because it's so embedded in a product designed for an application not normally associated with microfluidics," says Steve Becker of Raindiance Technologies.

Dovichi places nucleic acid hybridization assays, such as the Affymetrix chip and products made by Illumina and Biacore Life Sciences, under the umbrella as well. But he doesn't consider them as successful because the devices cannot be used outside the laboratory, require technical training, and lack the volume of sales that the on-strip tests has enjoyed.

But "none of these technologies comes to mind when analytical chemists think of the word 'microfluidics,'" states Dovichi. "When they think 'microfluidics', analytical chemists are almost always thinking about a planar-format system manufactured using microfabrication technology and primarily employed for separation based on electrophoresis or perhaps chromatography." In this category, Dovichi believes, these systems have so far failed to have an impact on the market.

However, that perception may be flawed because many companies do not want to explicitly label their products as microfluidic. Raindiance, well-known for developing nucleic acid assays within picoliter droplets, considers itself a microdroplet, not a microfluidic, company. Fluidigm calls itself an integrated fluidic circuit company, not a microfluidics company. Caliper has branched out in so many directions that a newcomer to the field may fail to recognize the company's roots in microfluidics. And then there are a host of companies that make devices that would fall under the umbrella of microfluidics if they would use that label: Biosite Diagnostics, which makes the Triage system to check for cardiac arrest; Celectricon, which manufactures the Dynaflow instrument for screening drugs against ion channels; and all the next-generation DNA sequencing instrument manufacturers, who are turning to smaller flows and sample sizes to make genomic sequencing cost-effective (*Anal. Chem.* 2009, 81, 1736–1740).

For the purposes of this article, the term microfluidics will cover all systems based on micro-, nano-, and picoscale fluid volumes in a microfabricated system.

## WHO CARES IF IT'S MICROFLUIDIC?

Experts agree that slapping every benchtop analytical procedure onto a chip format isn't the way to go forward. "If you have a

hammer, the whole world looks like a nail," says Nate Cosper of Caliper. "If you have microfluidics technology, you can't go around asking, 'Where can I put microfluidics?' That's the wrong way to go about it."

Instead, the right application has to first be found; whether microfluidics plays a role in that is a different consideration. David Weitz at Harvard University speaks from the experience he gained from watching four companies, one of which is Raindance, spin out from his laboratory. "I see their struggles as not always finding the right niche," he says. Microfluidics "is an enabling technology, but it's the niche, what you do with it, is what really counts."

Now that microfluidics has fallen off the peak of inflated expectations, it is no longer the selling point for instruments, and a mind shift has occurred in the commercial sector. "Nobody buys a system because it contains microfluidics," says Holger Becker. "But people will buy a system because it helps them solve their analytical problem or their analytical need."

The Bioanalyzer illustrates how Agilent took advantage of the mind shift. The instrument is a microfluidics platform that can carry out RNA quality control and DNA as well as protein sizing and quantitation. The system launched in September 1999. "At that point in time there was a lot of hype about microfluidics in general, so the acceptance [of the instrument] was very good," says Knut Wintergerst at Agilent. "From what I heard internally, this was one of the most successful product launches we ever had at Agilent."

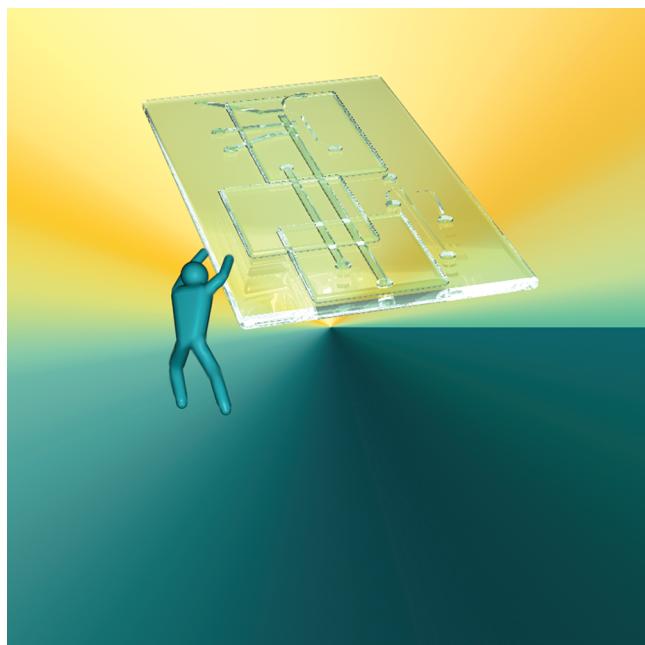
But when the disillusionment started to set in, Agilent changed its game plan. "We figured out that, at the end of the day, when you market it as a type of technology, the target audience we speak to are the techie freaks," says Wintergerst. "They account for probably 5% of the market you want to target. So we switched our marketing messages about 1½ years after the launch to talking about the applications."

Collectron takes a similar approach. One of its products, the Dynaflow, is used for rapidly screening ion channels in live cells with high throughput. The product turns a task that was previously cumbersome, complex, and expensive into something easier and more cost-effective. "But do I see the product as microfluidic in itself? No," says Chiu. He categorizes microfluidics as just another tool in the mechanical toolbox. "If you're going to build a house, you're not going to have one tool. .... You are going to come up with a bunch of tools, and each of them is probably going to be indispensable," he says. Similarly, "microfluidics will be one component, and when it's successful, it will be integrated with other components, and nobody will hear much about it."

Most companies are spending a lot of time and money thinking not about what microfluidics can do but about how it can fit into existing technologies. "While we [at Raindance] could do PCR on a chip, we're actually going to leverage the PCR machines that are already in the marketplace. The output of our product will be millions of reactions that take place in a single tube that are then put on any standard thermocycler," says Steve Becker. "Why not already leverage the customer's capital investment?"

## HUNTING FOR THE POT OF GOLD

Where will the technology have an impact? A hint of weariness hangs over some experts who feel they've seen and heard it all before. Clinical diagnostics has been the buzzword for a while, but Dovichi says, "The trouble with it is if you are doing clinical



diagnostics, you want to do it in a central facility. If you are going to do it in a central facility, what's the advantage of microfluidic-based devices over conventional technologies which are robust and working?"

Others beg to differ. Experts like Antonio Ricco, currently at the NASA Ames Research Center and the Biomedical Diagnostics Institute (Ireland), and James Landers at the University of Virginia say there are clear cases for moving away from centralized testing facilities and into more localized, office-based testing environments. For instance, some medical practitioners want to avoid the time and hassle of shipping assays to centralized laboratories and waiting for results to come back; they would love to have rapid assays with sample-in-answer-out capabilities that operate in settings less formal than a laboratory and prompt better patient compliance with doctor's orders, the assays that microfluidics promises to deliver.

And Steve Soper at Louisiana State University points out that the advantage of microfluidics is not just miniaturization; the systems also have closed architectures that reduce the risk of sample contamination and can fully process a sample in an automated format. "The major bottleneck in the utilization of molecular diagnostics is the lack of trained personnel who can run samples using existing equipment," he says.

But Soper also harbors some concerns about the clinical diagnostics market. He worries that the oversight of in vitro and in vivo diagnostics by agencies such as the U.S. Food and Drug Administration, though necessary, will slow progress. "While diagnostics is very appealing in terms of its broad market appeal, it's very difficult to penetrate," he says.

Take, for instance, cancer diagnostics. "This is a problematic area, no matter what you may think, because of the simple fact that many molecular markers for cancers have not been approved by the cognizant agents that need to at least endorse their use, such as the American Society of Clinical Oncology," says Soper.

He goes on to say that the National Cancer Institute and many bodies in the National Institutes of Health love to focus on technology development, such as integrated microfluidic systems for genetic-based molecular diagnostics. "But until the molecular

## The disconnect

Commercial devices based on microfluidics tend to grow out of work conducted in academic settings. But, as with many technologies, a gap separates the worlds of academia and industry. And as academic microfluidics research marches on, some experts worry that the gap is stretching into a chasm. Manz points out that the annual  $\mu$ TAS conference is flooded every year with eager researchers presenting new widgets, “but somehow it doesn’t lead anywhere,” he says. “I believe there is a widening gap between what you need to do under pressure to stay ahead in an academic setting and what industry needs right now.”

Manz cites clinical diagnostics as an example in which the missing connection is obvious. Typical academic research papers are now describing attempts to diagnose various illnesses from bodily fluids, but people in industry are still looking at the fundamentals. “They are asking me questions about electrophoresis on-chip, which had been published in 1993 in *AC*,” says Manz. “They now want this knowledge, but who on earth is still doing electrophoresis on-chip?”

Because the pressure to survive in an academic setting forces people to prove bigger and better things with microfluidics devices, the practical aspects of device design and fabrication fall by the wayside. Complex systems work great in an academic setting when graduate students and postdocs have an abundance of energy and are willing to fiddle around with finicky systems that work only 3 out of 100 times. Industry doesn’t have that luxury. “For industry, it’s much more important to have an assay with robust analytical performance,” states Holger Becker. “For this reason, the systems which are commercially available tend to be fairly simple in the design and layout.”

In addition, “the fabrication methods for these systems and the materials used are totally different,” says Holger Becker. Although many academic devices get churned out on PDMS, “most of the stuff which is a product or becoming a product is actually made in thermoplastic polymers because you would like it to be disposable. Some applications are still carried out on glass, but I would say that’s probably 10–15% of the applications; the rest are on thermoplastic polymer. Unfortunately there is comparatively little academic activity in that field.” (For more on PDMS and its problems making the commercial transition, see *Anal. Chem.* 2007, 79, 3248–3253.)

Soper says that the microfluidics researchers need to be more aware of the needs of the users rather than spewing out complex and clever devices in isolation. “I have collaborators at Sloan-Kettering and [Weill] Cornell Medical College. They are on the front line, doing biomarker discovery and monitoring clinical samples. Many times, I have gone to them and said, ‘We have an idea to do this thing.’ And they say, ‘Ridiculous. Will never translate into the clinic.’” Collaborators outside the microfluidics arena, Soper says, “have helped us come down to earth and keep our development efforts in line with clinical needs.”

He also says that the types of devices being developed need to change. “People have done an extremely good job at developing devices. They have developed a device for electrophoresis, a device for solid-phase extraction of DNA, a device for PCR amplification, as examples. But putting these devices together to build fully automated and autonomous systems? Not much information is out there in the literature,” says Soper. He cites work by Richard Mathies at the University of California Berkeley and by Landers as examples of sample-in-answer-out systems. More of that kind of work is needed, Soper says.

Although some experts think the disconnect between industry and academia is more obvious in microfluidics than in other fields, others disagree. “There’s a large gap between proof of concept in academics and industry needs,” Chiu acknowledges. “For every 100 proof-of-concept ideas, maybe one makes it into commercialization. But that is not just microfluidics. That’s true for everything. It’s true for nanotechnology: how many proofs of concept of nanotechnology are there? How many drugs have been proved? If we were rats, we would have been cured of cancer 50 years ago.”

markers get approved, a lot of these tools can’t be used! It’s a catch-22,” he states. “Much of the hardware is there, but the software, the marker panels and assays, needs to be approved.”

Landers points out another catch-22. “It is difficult to penetrate the clinical diagnostics market, primarily because it is dominated by a handful of very large and successful companies,” he says. “However, if you bring forward a paradigm-shifting technology that is more cost-effective, complete, and robust, it would bring significant pressure to bear on select agencies to expedite approval. But until the technology is there, it is difficult to bring on the pressure.”

Microfluidics researchers have also set their sights on point-of-care diagnostics (see, e.g., *Anal. Chem.* 2009, 81, 3216–3221). That, too, Dovichi finds to be a hard pill to swallow. “They have been saying that [about point-of-care diagnostics] for a very long

time now without any success,” he says. “And I again point to the strip assays, the home pregnancy test kits and [the] diabetes test kits. That’s point-of-care, that’s robust technology, and that’s successful. It’s hard to imagine microfluidics displacing that class of technology for those types of assays.”

Ricco agrees with Dovichi that “there has to be a clear performance or cost advantage, preferably both, to justify replacing old technology with new.” But, like Landers, he says that point-of-care diagnostics with microfluidics shouldn’t be dismissed simply because the technology hasn’t yet proven itself. Landers states, “While it may not be possible to displace the home pregnancy or diabetes test kits with the microfluidic counterparts cost-effectively, we can’t discount the possibility that miniaturization will facilitate the commercialization of a plethora of other tests

where, to date, conventional approaches have failed to bring them to market in a cost-effective way."

Ricco sums it up succinctly by saying that the adoption of microfluidic technologies in medical diagnostics has to be "a careful walk rather than a mad dash."

Other applications, such as next-generation DNA sequencers, are being touted as the next big thing. The race to reduce the cost of sequencing the human genome to \$10,000 and then \$1000 has been getting increasingly hot over the past few years. Although many of the manufacturers of the instruments won't label their products as microfluidics products per se, they are harnessing the advantages the technology has to offer. "How can you do DNA sequencing for \$1000, rather than \$10,000?" asks Craig Forest of the Georgia Institute of Technology. "The answer is very fast and very low-volume, whether you're imaging or conducting biochemical reactions or pumping fluids around. You've got to be able to do all of this extremely quickly and in parallel. That's where the push to miniaturization really becomes a compelling case."

Other areas of focus are protein therapeutics, single-cell gene expression, digital PCR, and copy number variation analysis.

### THE CLIMB

Despite some pessimism and disappointment, the companies with microfluidics-based devices are putting their money where their

mouths are. "The future for microfluidics is really bright," says Worthington, but he adds, "You always need to think carefully about applications and figure out if you are in a situation where you can do something that's faster, better, cheaper, and easier to use or if you are doing something that's really unique."

Other experts think that microfluidics won't hold center stage but instead will be masked inside devices and instruments, quietly doing its thing. "Whether the methodology is in DNA sequencing, electrophoresis, or in droplets, it will be integrated or buried in applications that you don't recognize as being enabled by microfluidics," says Steve Becker. "The customers really care about what the technology is going to do for them, not how you got there, but what you can do for them."

The field, it seems, is starting to climb the slope of enlightenment. The technology, most likely, will gain a foothold in some niches; whether those are the niches being touted right now remains to be seen. As the climb begins, it naturally raises the next question: will the slope lead to a high or a low plateau of productivity?

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