NATIONAL CANCER INSTITUTE
NCI Alliance for Nanotechnology in Cancer

Chips Ahoy - The Lab-on-a-Chip Revolution Is Near

Taking a cue from the microprocessor industry, nanotechnologists are shrinking entire lab benches to fit on a chip the size of a dime. In this first of a two-part series, Nano.Cancer.Gov News covers the basics of lab-on-a-chip technologies.

Next month's feature will delve into some of the more promising systems being developed and the exciting results those systems are generating.

Chips are ubiquitous in our society. Chips permit us to send email from our personal computers. Chips make our appliances "smart." Chips "sense" when our cars require a quart of oil. Modern science and medicine are possible, too: think microprocessor enabled-MRI scanners and gene arrays, for example.

Chips, some the size of a dime, some closer to that of a compact disk, some made of silicon, others of glass or polymer, are now on the verge of unleashing a new wave of tools that will help revolutionize cancer research. Sitting at the heart of miniaturized laboratories, these chips are being outfitted with nanoscale valves, channels, pumps, heaters, chromatography columns, laser detectors, and even chemical reactors that can perform complex separations and analyses fast, inexpensively, in parallel, and with very little sample.

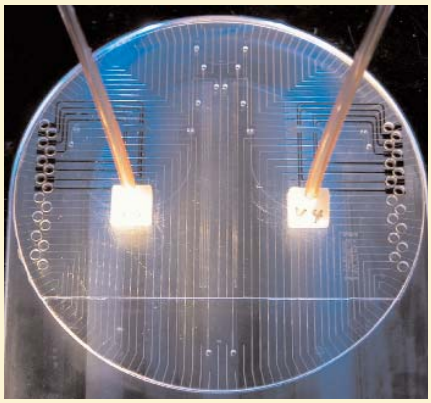
Imagine one day, in the not too distant future, when the various cell types in a tumor can be separated in a matter of minutes and then studied to determine how each cell responds to a particular growth or apoptosis signal. Imagine being able to run 100,000 PCR reactions a week or sequence a genome in a matter of weeks. Imagine a time when huge libraries of compounds can be screened in just a few hours for their ability to bind to a receptor or other drug target. When those visions come true, thank the many lab-on-a-chip technologies now being developed.

"Integrate an entire PCR lab or a gene sequencer, for example, on a chip," says Richard Mathies, Ph.D., professor of chemistry at the University of California, Berkeley, "and you will totally change the economics of doing research and the time it takes to get results." Indeed, say many involved in this field, without this kind of technological advance, cancer researchers will continue to struggle to understand the complex signaling networks and interacting pathways that are involved in cancer.

Within five years, predicts Marc Madou, Ph.D., professor of mechanical and aerospace engineering at the University of California, Irvine, lab-on-a-chip devices will be capable of performing complex separations, enzyme-linked immunoassays (ELISA), and even PCR. More importantly, he adds, these devices will be available in commercial systems. "It's really just a matter of funding at this point, but these types of applications should be in routine use in the research laboratory by then," he says.

Eventually, should current engineering efforts in miniaturization pan out, nearly any laboratory-based analytical technique will be a candidate for inclusion on a chip. "What we're seeing now is an acceleration of the trend toward miniaturizing what we do in the laboratory that started when we moved from test tubes and beakers to micropipettes and microtitre plates," explains Dr. Mathies. Whether this trend persists depends on engineers continuing to develop methods for etching pumps, columns, valves, and other fluid-moving equipment more commonly associated with gigantic refineries than microscopic laboratories. But should progress continue as it has over the past five years, the payoff should be in the development of devices capable of affecting biomedical research at a level perhaps unmatched since the advent of PCR.

Courtesy of Richard Mathies, Ph.D.



Integrated Sequencing Microchip

Chemical engineering at the nanoscale

A microfluidic device, or lab-on-a-chip, comprises one or more channels with at least one dimension less than 1 mm and a means of

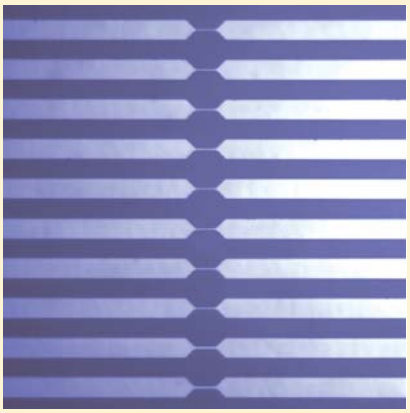
getting fluid - whole blood, serum, tissue extracts, even cell culture medium with cells in it - to flow through those channels. Nanofluidics merely refers to devices with channels that are 100-1000 times smaller - there is no firm boundary between microfluidics and nanofluidics. The channels themselves can be modified in numerous ways to accomplish various bioanalytical tasks. Columns can be coated, for example, with materials that turn them into nanoscale chromatography columns. They can be connected to nanoliter-sized reservoirs containing reagents or outfitted with heater elements to speed chemical reactions or lasers for optical detection of molecules passing through a given channel. Most importantly, once a micro- or nanofluidics device has been created, it can be duplicated across the surface of the chip, providing highly parallel, multiplexed capabilities.

There are many advantages to translating macroscale laboratory techniques to the micro- and nanoscale. Because the volume of fluids within microfluidic channels is very small, usually several nanoliters or less, the amount of reagents and analytes used is quite small. This fact is especially significant for expensive reagents, such as those used in PCR analysis, or when analytes, such as tumor tissue, are precious or scarce.

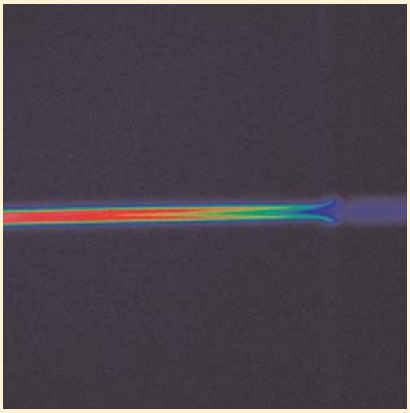
Small volumes also translate into very few molecules flowing past detectors, which means that microfluidics devices can be constructed to make measurements on individual biomolecules, such as a single enzyme binding to its substrate or a single piece of DNA. "In the past, our analytical methods have given us the average behavior of millions of molecules, but now we can actually make measurements on individual molecules," says Harold Craighead, Ph.D., professor of applied and engineering physics at Cornell University. "Since much of biology results from the actions of individual molecules, we expect that this new capability will allow us to ask and answer whole new kinds of questions, particularly those concerning the rare biochemical and genetic events that are now so difficult to study."

As mentioned above, individual microfluidic devices can be multiplexed, or combined in parallel, enabling hundreds or even thousands of analyses to be performed simultaneously. At microfluidics company BioTrove, for example, most weeks see the company routinely running 300,000 PCR reactions, a stunning number. And a research team in Norway, headed by Anja Gulliksen, Ph.D., of NorChip in Oslo, recently demonstrated that they could conduct 1400 simultaneous analyses for human papilloma virus (HPV) using nucleic acid sequence-based amplification. Such a system could reduce the time needed to diagnose HPV infection, the major cause of cervical cancer, from weeks to as little as 2.5 hours.

Courtesy of Harold Craighead, Ph.D.



Optical micrograph of a parallel array of submicrometer fluidic channels.



False color optical micrograph of diffusion in a microfluidic laminar flow mixer.

All promise aside, though, the engineering challenges in turning macroscopic pumps, tubing, reaction vessels, mixers, heaters, and detectors into nanoscale features on a chip are not trivial. The science of designing, manufacturing, and formulating devices and processes that deal with volumes of fluid on the order of nanoliters (nl) or picoliters (pl) is known as microfluidics. Microfluidic devices require design and construction methods that differ from macroscale devices. Indeed, it is usually not possible to take conventional device designs, reduce them in size, and then expect them to work in microfluidics applications.

"When the dimensions of a device or system reach a certain size as the scale becomes smaller, system behavior alters dramatically," explained Dr. Madou. This change in behavior is reminiscent of the way that materials behave differently when shrunk from the macroscale to the nanoscale. "From a fundamental view," continued Dr. Madou, "we still don't understand much at all about fluid flows at this scale. In fact, there are plenty of contradictions and controversy in this field, and we need a lot more fundamental studies in fluidics at the micro- and nanoscale before we move from the realm of engineering science to just plain engineering."

In the macro world, for example, moving a fluid through a column is done either using gravity or a pump. Need to move more fluid? Pick a bigger pump. But at the micro- and nanoscale, fluid pushes back with such force that it will overwhelm a nanoscale pump. To overcome this fundamental obstacle, researchers are learning to master capillary action and centrifugal force, among other concepts, to get fluid from here to there in a reliable and consistent manner.

Forging ahead

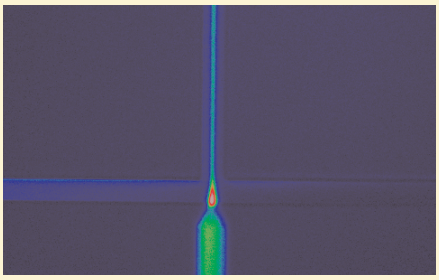
Though the theoretical underpinnings of fluid flow at the nanoscale are not yet well developed, engineers have not stopped forging ahead - successfully - with their design and validation efforts. Already, various groups have developed prototype systems for conducting mutational analysis, for separating cells and monitoring their reaction to chemical stimuli, and for isolating individual DNA molecules, among other tasks. PCR analysis and gene sequencing are major areas of focus, as is the development of systems for conducting ultra-high throughput screening of drug candidates. Caliper Life Sciences, for example, has developed a capillary electrophoresis chip that can simultaneously assay the activity of 500 different kinases,

enzymes known to play a role in many human diseases, including cancer. This chip, which can analyze 12 chemicals every minute or so, is useful for finding drug candidates that bind to a specific kinase while avoiding all others.

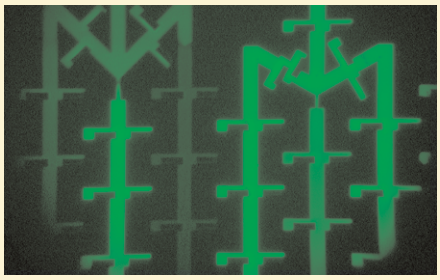
The Caliper chip, and others like it, are just the start of the microfluidics revolution. Next month's feature will examine how engineers have been solving miniaturization challenges and the kinds of devices they are creating to advance the ongoing revolution in biomedical research.

— Joe Alper

Courtesy of Harold Craighead, Ph.D.



False color optical micrograph of diffusion in a microfluidic laminar flow mixer.



Optical micrograph of fluorescence in a microfluidic laminar flow mixer created using a sacrificial layer fabrication process.

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