Microfluidics: Neat and Tidy Solutions

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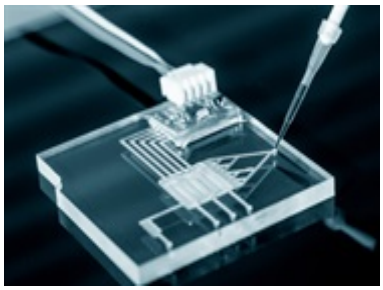

What's not to love about a technology that performs all the functions found on a lab bench, but in an automated and integrated fashion, with less reagent and sample usage, with greater speed—and performs more accurately and with greater sensitivity, to boot? Thus were the promises, or at least the dreams, of incorporating microfluidics into miniaturized devices when microfluidics came on the scene over two decades ago. And many of these promises have been fulfilled—some in the form of single, handheld instruments that are inexpensive enough to be tossed away without a second thought (picture an in-home pregnancy or glucose test).

Yet with few exceptions, most notably genetic analysis, microfluidics is still more the province of engineers than of biology researchers and health-care professionals [1].This is in part because of the lack of a "must-have application"—something for which microfluidics is either the only solution or is enough of an improvement that it can overcome the inertia of established solutions. It is also partly because of the (at least perceived) expertise needed to set up and operate all but the simplest devices. It may also be related to the Catch-22 of few commercially available devices for the bio research community.

What is microfluidics?

A microfluidic device, literally, is one in which fluids are manipulated on the micron scale "rather than having pipes with millimeter or centimeter dimensions," says Anubhav Tripathi, professor of

There are two closely related concepts: Lab-on-a-chip (LOC) is a platform in which lab functionalities are miniaturized to fit in an enclosed plastic or glass chip. Because these functionalities are so small, many can be integrated into a single chip, and thus the result is often called a miniaturized total analysis system (μTAS). Microfluidics can be integrated into a LOC to perform one or more of the functions, acting as microreactors or microseparators, for example.

Alternatively, microfluidic technology can function in a stand-alone unit or be "powered" by pumps and valves and magnets and electrodes, for example. Or a microfluidics component can act as a "drop-in" element for an otherwise macro-scale device. Usually calling something "microfluidics" implies more than just simple one-directional fluid flow—"when you're talking about microfluidics, you're basically having reactions and separations, incorporating different samples at different times" and performing other related processes, Tripathi explains.

Why microfluidics?

Microfluidic solutions are sometimes the result of transferring an existing technology to a chip, making the detection faster and less expensive—"the assay is equivalent, but it's better (if possible) and lower cost," explains XiuJun Li, professor of chemistry and biomedical engineering at the University of Texas at El Paso. Many solutions have been proposed, designed and in some cases tested for point-of-care diagnostics in resource-constrained settings including, for example, rapid on-chip nucleic acid testing of HIV load, monitored by colorimetric readout [2].

And sometimes the microscale offers solutions that conventional or large-scale cannot achieve, adds Li. For example, Li and his colleagues used the high surface-to-volume ratio found in microdroplets to develop aptamer-functionalized graphene oxide nanosensors for the single-step detection of estradiol and other extremely low-solubility molecules, in the process "improving the reaction kinetics and sensitivity by several orders of magnitude [3]."

> Other attributes of microscale fluidics include the relatively small effects of gravity compared to those of surface tension and capillary forces.

The latter can be used for passively pumping fluids, local mixing and forming droplets—which can be made to move, merge, split and dispense from reservoirs by use of electrical, magnetic, thermal or acoustic forces, for example, in a technique termed digital microfluidics (DMF) [4].

The tiny size of microfluidic channels naturally lends itself to use of diminutive sample sizes (which may be very precious), allowing for a commensurate time savings for mixing, incubating, moving, heating, detecting and

solutions for analyzing macromolecules. “You require much less sample” for PerkinElmer’s LabChip GX Touch systems than for traditional electrophoresis systems, says PerkinElmer applications scientist James White. For example, with the HT DNA X-Mark LabChip and the new NGS 3K reagent kit and the new NGS 3K reagent kit for quantifying DNA, “DNA “we obtain a linear concentration range of 5 – 500 pg/µl for smears, and we need only a few microliters to sip from.” The system can process 96 samples in 2-1/2 hour.

Another area of active interest is the use of microfluidics to capture and quantify cell-free DNA, for example from a single droplet of blood.

Live cells

Cell culture can also benefit from the microscale. MilliporeSigma’s CellASIC®Onix is an environmentally controlled, stage-top, automated live-cell imaging system featuring microchambers built into what looks generally like a 96-well plate. These are fed by microfluidic channels, allowing for continuous control of the media (including drugs and inhibitors) in which the cells are bathed. “One key application is in imaging nonadherent cells, which are typically hard to keep in a single focal plane and track over time, and at the same time keep them healthy,” says Philip Lee, head of cell culture systems marketing at MilliporeSigma. “But with our microchambers, the cells are well contained, and you can follow the same set of cells over hours or days.”

“Organs-on-a-chip” have been created (several are in various stages of commercialization) in microfluidic devices, growing kidney or gut cells, for example, with different channels allowing the controlled addition of media or drug treatment and the disposal of waste. Some of these have been designed as systems in which the media from different cell types—but not the cells themselves—are allowed to interact either bi- or uni-directionally. Researchers have taken that concept to an extreme, creating what are termed “humans-on-a-chip” or “bodies-on-a-chip” consisting of, for example, sequential layers of various cell types grown on membranes separated by perforated plastic discs, to better mimic the absorption, distribution, metabolism and excretion (ADME) testing process in pre-clinical drug discovery [5].

Single cells

Microfluidic devices designed to capture and in some cases analyze rare cells, such as cancer stem cells (circulating tumor cells) and fetal cells in maternal blood, have also garnered a great deal of scientific interest. There are two main ways to detect circulating tumor cells (CTCs): with affinity techniques (used by CELLSEARCH®, the only FDA-approved test) or with “microfluidics of one form or another, many of which are very sophisticated, bleeding-edge filtration techniques,” chief technology officer of ANGLE Plc, maker of the Parsortix cell-separation

stairs and the roof—we've actually been able to compress between one-quarter and one-half meter of separating capacity on that microscope-slide-sized cartridge." Booth adds that 10 ml of blood will result in small handful of viable target cells in a few thousand white blood cells.

DEPArray™ from Silicon Biosystems images fluorescently labeled cells trapped in one of 300,000 dielectrophoretic "electronic cages." Cells can then be individually electronically sorted based on their fluorescent profile. Samples containing rare targets must be significantly enriched before being loaded on the DEPArray—something Booth says Parsortix is sometimes used for.

Whether manipulating droplets, identifying macromolecules, sorting cells or performing complex series of reactions from sample preparation through detection, microfluidics—on its own or within integrated systems—offers opportunities to do things better, faster, cheaper and with less sample, and sometimes even to do things that can't otherwise be done. Microfluidics may just be the solution your research needs. There are commercial solutions that are currently available. A growing option for many researchers interested in employing microfluidics into their workflow may lie in collaborations with tool-providers that will lead to more widespread adoption as well as further improvements to the technology.

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