

nano

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Nano for smarter planes
and cars, better healthcare
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PLUS: LAB-ON-A-CHIP: REALISING ITS LONG-AWAITED POTENTIAL

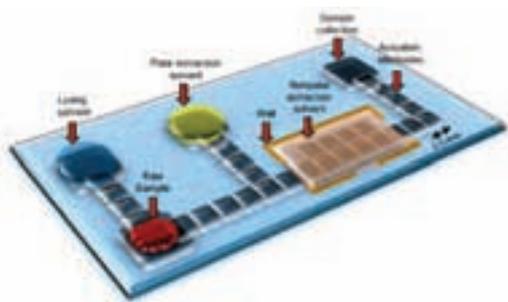


Figure 1: The digital microfluidic device used by Aaron Wheeler's group to extract oestrogen from small tissue samples. Reproduced with permission from the authors of *Sci. Transl. Med.*, 2009, 1, 1ra2, 'Droplet Scale Estrogen Assays in Breast Tissue Blood and Serum'



CHEMISTRY IN THE FUTURE

Katherine Elvira discusses how digital microfluidics technology is enabling the long awaited potential for lab-on-a-chip to be realised.

Why the breakthrough, now?

One of the current hobby horses of scientists is the development of a lab-on-a-chip. The ideology behind it is simple. If one can program computers to do mathematics, can chips be designed to perform traditional laboratory tasks?

From sample preparation to product analysis on a device the size of postage stamp, the advantages are endless. How to monitor the in vivo effects of novel medical treatments in real-time is an enduring challenge for researchers. This poses an even greater conundrum in cases which require intrusive sample-gathering procedures or time-consuming lab work before an answer can be reached.

At the Aaron Wheeler Lab at the University of Toronto, scientists have developed an innovative solution to this problem, by designing a chip capable of testing oestrogen levels. Although oestrogen plays

a key role in the development of breast cancer, can affect fertility and is widely used as a contraceptive, there are no existing methods for continuous monitoring of tissue concentrations. The existing processes for determining oestrogen levels in breast tissue can require the extraction of significant amounts of tissue under local anaesthesia, an unpleasant prospect for the patient, and one that effectively prevents regular examination.

Comparatively, the sample size needed for on-chip processing is three orders of magnitude smaller, and can be gathered by thin needle aspiration (*figure 2*). In addition, the time required for sample processing decreases dramatically, from 5-6 hours of lab work by specialised personnel, to 10-20 minutes on a fully automated device. The device shown in *figure 1* was used by the Wheeler group to purify and extract oestrogen from tissue and blood samples. In the simplest of forms, this technology

could lead to a device where patients can self-monitor hormone concentrations by finger pricks, and would be applicable to many widespread diseases.

How lab-on-a-chip works

It was the escalation of microfluidic technologies in the 1990s that greatly advanced research into the lab-on-a-chip. Conventional microfluidic devices are analogous to the miniaturisation of a complete industrial chemical plant! Micro- or nanometre-scale channels are patterned in glass or PDMS (a flexible, see-through polymer) and used for continuous or segmented flow. Segmented flow, or droplet microfluidics, is perhaps more interesting from the chemistry point of view. Two separate liquid streams, one oil, the other aqueous, are forced into the channels. The shear force at the point where they meet creates discrete aqueous droplets that are encased in the oil. Droplets are created at a rate of hundreds per second, and each one can be considered as



Figure 2: Slightly gruesome comparison of the sample size necessary for conventional breast tissue (top) to the droplet required for analysis by digital microfluidics.

Reproduced with permission from the authors of *Sci. Transl. Med.*, 2009, 1, 1ra2, 'Droplet Scale Estrogen Assays in Breast Tissue Blood and Serum'

an individual, self-contained reaction chamber, akin to the reaction vessels used in standard laboratories, but orders of magnitude smaller.

The advantages of miniaturisation are many. Working in the sub-millilitre regime on these devices, it is straightforward to create high-throughput systems where the speed of heat transfer and reagent mixing promote rapid reactions, matched by the concomitant decrease in analysis time. What's more, since sample sizes range from pico- to microlitre volumes, reagent consumption using lab-on-a-chip techniques is greatly reduced, as is cost per reaction. The applicability of these devices range from chemistry to biology, engineering to healthcare; it is fair to say that channel microfluidics has irrevocably changed the landscape for high-throughput sample processing.

Getting results!

However, there are also shortcomings with these systems, as it is extremely hard to control the fate of an individual droplet in a stream of them. Hundreds of droplets can be processed per second, and each droplet can have different concentrations of reagents, to find the best reaction conditions. But when an interesting droplet is found, it is complicated to manipulate it individually.

Professor Wheeler from Toronto University found an answer to this. He started his research career working on traditional microfluidic devices, and is now a world-leader in the field of Digital Microfluidics (DM) or ElectroWetting-On-Dielectric (EWOD) devices. When asked to explain why he chose to work in this field, he says he had become frustrated with the ever-increasing-complexity of microchannel devices, designed to implement simple processes. Digital microfluidics seemed like a much less complicated way to tackle these types of problems.

"I think digital microfluidics is really well suited for sample preparation. Sample prep. is the ugly step-sister of chemical analysis - it's boring, routine, and tedious, compared to the relative sexiness of detection and separation, but it's important, nonetheless. I think the special attributes of digital

microfluidics - easy to work with large samples containing solids, etc. - makes it very well suited for sample prep."

Digital microfluidic devices enable droplet movement on flat surfaces. The path followed by each droplet is reconfigurable and the devices are reusable. This allows potentially unlimited permutations of droplet movement, splitting and merging. The geometrical design of these devices makes them well suited to assay-based and step-wise syntheses.

Digital Microfluidics and the generation and control of droplet formation

Fabrication of the chip is relatively simple. Initially, individually addressable electrodes are patterned onto a flat glass surface; this is the lower 'plate' of the device (see figure 3). The electrodes are then covered by a dielectric layer (such as Parylene, silicon oxide or PDMS), which acts as an insulator, preventing droplet electrolysis and allowing for the build-up of charge required for droplet actuation. This layer also provides a level surface onto which a hydrophobic coating (generally Teflon) is deposited, the aim of which is to force the droplets to sit in the device in a non-wetting state. The top plate of the device consists of an unpatterned ground electrode, covered simply with a hydrophobic coating. Droplets are effectively sandwiched between the two plates, which are kept apart by a spacer. To get an idea of the scale of these devices, electrodes are usually 1 mm squares, and the distance between the plates is on the order of 100 μm . Droplet volume is controlled by the electrode size and the spacing between the plates, and further miniaturisation to take droplet volume into the nanoscale is only limited by electrode patterning capabilities.

Droplet movement is initiated by applying a voltage across the droplet, between the ground plate and individual electrodes on the patterned plate that are in contact with the droplet. Consecutively applied voltages to successive electrodes cause droplet movement. Droplets can be dispensed from larger 'reservoir' droplets, merged and split. Dispensing with the need for channels, since droplets are moved over flat surfaces, the possible permutations for droplet motion are unlimited. More interestingly, these devices can be fully controlled by a computer program, and individual droplets can be precisely manipulated. In essence, a chip can be programmed to do chemistry!

When asked about the advantages and disadvantages of DM devices, Aaron explains that whilst the advantages are many because the devices are easy to

fabricate and use, good for a wide range of volumes (up to milliliters!), compatible with manipulation of solids, liquids, gases, no moving parts, independent addressability of all samples and reagents, the disadvantages, although also including fabrication problems such as the fact that they are extremely sensitive to surface heterogeneities, centre on the lack of research power devoted to this field: "less people/time/resources = less innovation".

And it is true that a lot of the work in this field has, up until now, focused on developing the technology to build these devices rapidly and easily. More recent developments have focused on the use of these devices as tools for proteomic sample processing, PCR and enzyme assays, but perhaps the most meaningful development in this area came from the Wheeler group itself, and their oestrogen analysis work.

The history of science, and chemistry in particular, includes alchemists devoting their lives to discovering how to convert

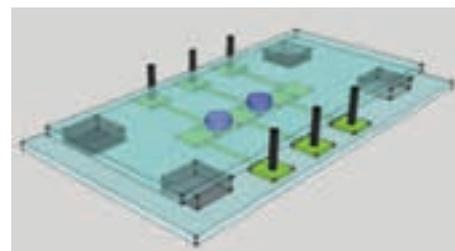


Figure 3: Sketch of a typical digital microfluidic device. Droplets are sandwiched between two plates held apart by spacers (black). At the centre of the device, in green, are the electrodes used for droplet movement. Their size is typically 1mm x 1mm. Contact pads at the edge provide a connection to the voltage source required for droplet movement. Created by R. Evans

metals into gold. However, many of the features of modern day laboratories were probably familiar to them; they messed about with chemicals in beakers, creating strange coloured liquids and horrible smells. Modern day scientists will spend a lot of their time trying to find out what they have made through the use of NMR and IR spectroscopy. But will the day come when they spend less time in the lab and more time programming a computer to do the work for them? What will the future look like? Digital microfluidics, the newest revolution in the area of lab-on-a-chip devices, is poised to cause a paradigm shift in the way that scientists perform research.



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