Lab on a Chip

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HIGHLIGHT

Research highlights

Šeila Selimović,[ab] Omar Z. Fisher[c] and Ali Khademhosseini*[abde]

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Point-of-care ELISA

Point-of-care medical devices offer ways to bring life-saving diagnostic tests directly to critical or hard-to-reach patient populations. For widespread use these devices must be affordable, durable, and simple to use. With these criteria in mind, Sia and colleagues developed an ELISA-based point-of-care microfluidic chip that offers reliable and simultaneous diagnosis of syphilis and HIV infection.

In their recent paper, Chin *et al.*[1] detail the capabilities of this microfluidic platform. The device was injection molded from low cost, transparent polystyrene and cyclic olefin copolymer, with feature fidelity down to 1 μm. It contained a detection zone coated with HIV and syphilis antigens, as well as antibodies to goat IgG. A small volume of analyte—less than 1 μl of whole blood—could be introduced into the device *via* a hand-held plastic syringe. Human antibodies that remained in the detection zone after washing were then exposed to gold-labeled goat antibodies that recognize human IgG. Finally, the reduction of the silver particles on the gold-labeled antibodies led to a visibly detectable color change within 5 min.

Diagnostic tests were conducted on blood samples from HIV and syphilis infected individuals, both on-site in Rwanda and in the laboratory at Columbia University. The field application of the device included less well controlled elements than the laboratory tests. However, the reagents proved stable for at least 6 months, despite fluctuations in ambient temperature and humidity. Both sets of experiments (171 HIV tests and 67 simultaneous HIV and syphilis tests) yielded similar results, with close to 100% sensitivity and specificity factors above 90%. These rapid tests of less than 15 min were thus shown to be comparable to standard laboratory diagnostic tests.

There are multiple benefits in this microfluidic platform. In addition to high sensitivity and accuracy, this device is simple and affordable. The cost of materials per chip is $0.10 or less and more than one chip can be fabricated per minute. Furthermore, since the chip has no active elements, sample and reagent loading is easy and can be done with little training in the field. Devices with these capabilities have great potential to revolutionize the point-of-care medical support to individuals as well as the public health system as a whole in developing areas.

Leaky chips

The utility of lab-on-a-chip technologies is not restricted to the study of liquid or colloidal systems. They can also be used to control multiphase gas–liquid–solid reactions. One such platform has been developed by Yuen and DeRosa.[2] In their recent paper, they applied a solvent/non-solvent mixture to polystyrene to swell the

Fig. 1 Fabrication process of porous and flexible polystyrene devices. Panels (a): mask-protected polystyrene film, (c): swollen film after exposure to the solvent mixture, (e): swollen film without the protective mask, and (h): fully assembled device, show stages in the fabrication of a device with a porous bottom surface. Panels (b), (d), and (i) show the same stages of a device containing porous walls. Panel (k) depicts the flexible nature of the device. Figure reprinted with permission from the Royal Society of Chemistry from Yuen and DeRosa.[2]

[a]*Center for Biomedical Engineering, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Cambridge, Massachusetts 02139, U. S. A. E-mail: alik@rics.bwh.harvard.edu*
[b]*Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, U. S. A.*
[c]*David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, U. S. A.*
[d]*Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, Massachusetts 02115, U. S. A.*
[e]*World Premier International - Advanced Institute for Materials Research (WPI-AIMR), Tohoku University, Sendai 980-8577, Japan*

material and render it porous. The 3 mm thick bendable polystyrene film was first protected with a pre-cut vinyl mask on the side to be treated and with adhesive tape on the back side. It was then briefly dipped into the solvent mixture (Fig. 1). During this time the exposed regions of the polystyrene film swelled by ~50 μm. SEM images showed that these raised features consisted of interconnected pores that ranged from below 1 μm to ~40 μm. Feature height could also be controlled by solvent exposure time without affecting pore size. Holes were punched into the film for sample delivery. The device fabrication was completed by removing the vinyl mask and sealing the polystyrene film with adhesive tape.

The porosity of the film was demonstrated in gas and liquid perfusion experiments. In the first case, CO_2 gas was introduced into a porous device and allowed to permeate through the walls into a channel filled with water. The higher the quantity of CO_2 that permeated through the walls and dissolved in water, the more acidic the water became. This was measured with a pH indicator solution, which gradually changed from a blue color to yellow with increasing acidity.

In the second case, changing levels of water acidity were achieved by allowing distilled white vinegar to permeate through the device walls into the water channel. Again, the indicator solution was observed to change color depending on the pH of the water/vinegar mixture.

The authors also showed that the porous polystyrene film could be selectively treated with oxygen plasma. Regions of the film coated with adhesive tape remained hydrophobic, but accessible areas became hydrophilic when exposed to the plasma. This property of the material was retained for a minimum of 90 days, compared to materials such as poly(dimethylsiloxane) (PDMS), which begins to lose its hydrophilicity mere minutes after oxygen plasma treatment.

The described method of microfluidic device fabrication offers several advantages. It can be applied in a regular laboratory setting without any need for expensive equipment. In addition, it generates flexible chips, such that they can be easily joined with other devices. Finally, the devices are portable and contain porous structures, such as walls and membranes, which can be useful for many chemical and biological applications. Possible applications include cell culture with oxygen and media perfusion as well as chemical reactions involving both gas and liquid products.

Biomimetically spun silk

Silk is a naturally occurring and versatile biomaterial with exceptional mechanical properties. Silk is stronger, yet lighter, than steel and is similar in tensile strength to kevlar.[3] Unlike synthetic high strength fibers, silk can be synthesized at ambient temperature and pressure, although the product is mechanically inferior to native silk. The mechanism behind natural silk production is known to rely on precisely controlled fluid flow through the silk gland, which aids in aligning silk proteins for optimum strength. Recently, Wong and coworkers have designed a microfabricated device that incorporates some of the design aspects of spinning glands in order to fabricate synthetic silk with tensile properties closer to the natural fibers.

Kinahan *et al.*[4] developed a PDMS microfluidic device which used two contralateral streams of poly(ethylene oxide) (PEO) solution to hydrodynamically focus a third stream of solubilized silk protein (Fig. 2). The microchannels were tiered to drive the flow of silk protein from all directions and yield rounded fibers, while laminar flow prevented macromolecules from mixing during fiber drawing. Furthermore, the device incorporated a drop in pH levels similar to the acidification that occurs as natural silk leaves the spinning gland.

This technique resulted in fibers with significantly enhanced tensile properties. The fiber thickness depended on the relative flow rates of PEO and the silk protein solution. Thus, drawn fibers could be fabricated as thin as natural silk fibers, yet possessed tensile moduli 7 times greater than thicker, undrawn fibers. Drawn and native fibers also had similar stress *vs.* strain curves, elastic modulus and failure strain values, and outperformed undrawn fibers in all parameters. The mechanical properties of microdrawn fibers could also be tuned by modulating flow conditions through the microdevice.

A major benefit of the depicted microfluidic device is in its optical properties. The transparent PDMS is compatible with various light microscopy methods, *e.g.* polarized light microscopy, which was useful in investigating the structural form of the drawn fibers. PDMS devices are also used *in situ* for direct imaging *via* X-ray or neutron scattering, two detection methods suitable for molecular structure studies.

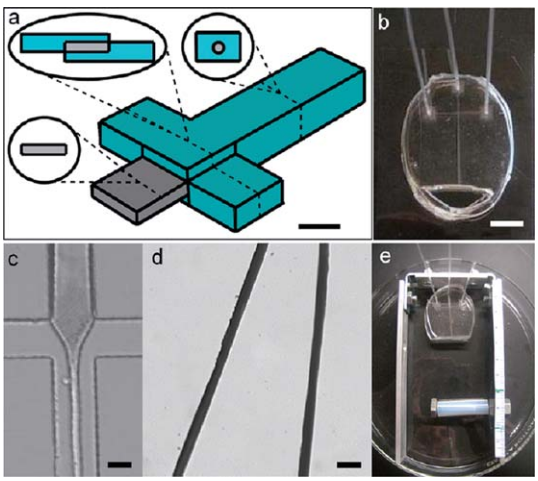

Fig. 2 A microfluidic device to mimic the silkworm silk gland. (a) Schematic tiered microchannel design (scale bar 400 μm). (b) The device had three inlets and one outlet into a reservoir (scale bar 1 cm). (c) Hydrodynamic focusing of the silk solution at the intersection (scale bar 200 μm). (d) Microdrawn silk fibers had smooth surfaces and consistent diameters (scale bar 100 μm). (e) A frame with an adjustable rod was used to aid in fiber collection. Reprinted with permission from Kinahan *et al.*[4] Copyright 2011 American Chemical Society.

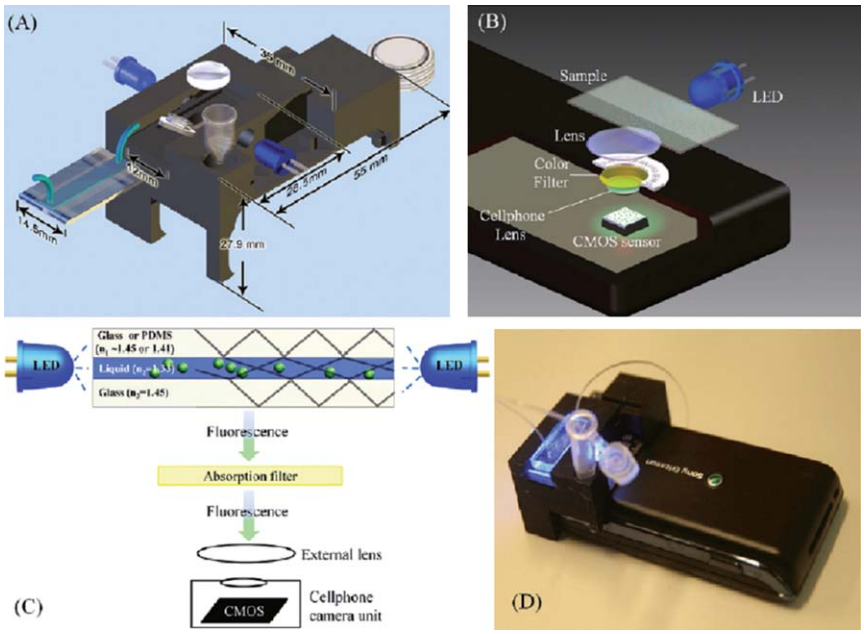

Fig. 3 (a)–(c) Diagrams depicting different structural details of the cell phone cytometry device. (d) A photograph of the cell phone with the optofluidic attachment. Reprinted with permission from Zhu *et al.*[6] Copyright 2011 American Chemical Society.

A new app for your smart phone—optofluidic fluorescent cytometry

Cellular phones have lately become a ubiquitous piece of technology. Close to 70% of all cell phone users reside in developing countries, which has led to a new paradigm for applying cell phones for medical analysis purposes.[5] For example, most cell phones are nowadays fitted with a built-in camera, such that diagnostic test results from autonomous point-of-care chips can be imaged and analyzed on the phone. Alternatively, small external modules for *in situ* testing can be attached to the phones and immediately recorded and evaluated. Ozcan and coworkers have recently developed just such a device for optofluidic imaging, coupled with a cell phone (Fig. 3).

Zhu *et al.*[6] designed a simple, disposable PDMS microfluidic channel attached to a cellular phone *via* a plastic cartridge. Two battery powered LEDs were also attached to the cartridge, such that they shone at the sides of the microfluidic channel. The sample, whole blood containing fluorescently labeled white blood cells, was introduced into the channel *via* a syringe pump, such that the flow was perpendicular to the light sources. As a result, the fluorescent cells were excited by the directly incident diode light as well as by the diode light reflected off the liquid/PDMS, liquid/glass and PDMS or glass/air interfaces. In effect, the device functioned as a planar multi-mode optofluidic waveguide (Fig. 3c). The light emitted from the excited particles in the sample was filtered by an inexpensive absorption filter before passing through a simple external lens, finally being collected by the cell phone camera. The position of the excitation sources merits renewed emphasis: because the LEDs pointed perpendicularly to the filter and the collection lens, a decent darkfield background could be achieved and an inexpensive plastic filter was sufficient to eliminate the scattered excitation photons before they reached the cell phone sensor.

A cell phone camera with an 8 Mpixel color chip was used to record real time videos of the fluorescent moving cells. The video frames were analyzed—and cells were counted—by applying a simple particle tracking algorithm. By choosing an appropriate external lens in front of the CMOS unit, the authors achieved a 7.8× magnification with a spatial resolution of ~2 μm. The hemocytometry results on white blood cells were sufficiently accurate compared to commercial blood analyzers, but the device was more accurate on low (~5000 cells μl^{-1}) cell concentration samples.

The material cost of the optofluidic attachment was roughly $4. In addition to the low cost, it weighed only 18 g. Furthermore, the analysis software was built in OpenCV, which is compatible with standard smart phone operating systems such as iOS and Android. Potential applications of the device include rare cell detection, HIV screening and water quality tests.

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