Microfluidics

Chapter · September 2013

DOI: 10.1016/b978-0-12-409547-2.05351-8

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Microfluidics

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Introduction

The field of microfluidics involves the use of microstructured devices, featuring dimensions typically on the order of tens to hundreds of micrometers, that allow the precise handling of low volumes (usually nanoliters or less) of fluids within them (Figure 1).[1]

The original driving force behind miniaturization was the enhanced performance that could be gained by down-scaling analytical systems, and the possibility of integrating multiple components within a single device. While the first microfluidic device was developed in the 1970s,[2] it was not until the early 1990s that microfluidics came to the fore.[3] These 'lab-on-a-chip' devices originally focused on aspects of analytical chemistry, but microfluidics has since expanded into many areas, particularly in chemistry and biology. The principle and development of microfluidics can be traced via a series of reviews published since 2002,[4] and through numerous other review articles[5] and books.[6]

Flow within microfluidic devices is almost always laminar (Figure 1(b)), as opposed to turbulent, meaning that mixing generally occurs by molecular diffusion. While mixing based on diffusion could take days in conventional flask-based systems, the small distances within microfluidic channels enable complete mixing within seconds or minutes.[7] A further advantage of such small dimensions is that volumes of samples and reagents are significantly reduced, saving costs on reagents and producing less waste. Integration of multiple components and processes can be achieved on a single device, yielding a platform with a small footprint. It is this potential for integration that drives the 'micro Total Analysis System' (microTAS, μTAS) concept,[3b] in which all aspects of an analysis process, from sampling to detection, can be performed on one device, enabling 'sample in-answer out' capabilities with short analysis times. As such, microfluidic devices are very well-suited to point-of-care (POC) diagnostics.[8]

Microfabrication

Microfluidic devices can be fabricated from a range of materials using different methods.[9] Fabrication typically follows the process of forming channels on the surface of a solid substrate, before drilling or punching access holes into the substrate, and finally bonding it to another plate to seal the channels. Tubing or reservoirs can then be connected to the access holes, allowing solutions to be introduced. Early devices were fabricated from silicon and glass via photolithography and wet etching methods, and glass in particular remains a popular material.[10] Polymer chips have become common due to their amenability to mass fabrication.[11] However, the most common chip material employed in the research lab nowadays is the flexible elastomer, poly(dimethylsiloxane) (PDMS),[12] which is well-suited to rapid prototyping. It is sometimes required that microchannel surfaces be modified to exhibit certain properties or functional groups, which can be achieved by several techniques[13] such as the deposition of organosilanes.[14] Paper microfluidic devices are now also being developed.[15]

Pumping, Valving and Mixing

Several methods are available for pumping solutions through microfluidic channels,[16] but the two most common are hydrodynamic and electroosmotic flow (EOF)-based pumping (Figure 2). Hydrodynamic pumping involves the application of pressure, for

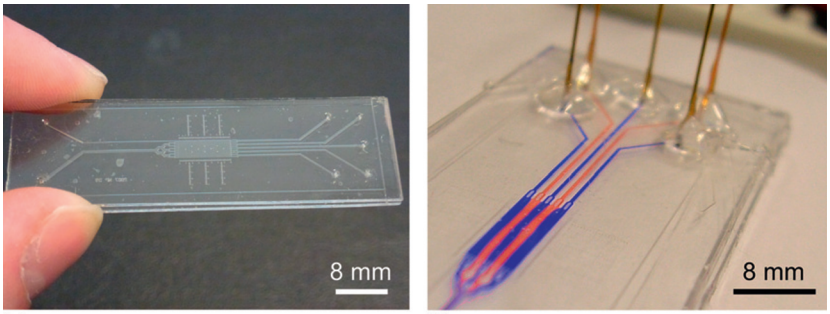

Figure 1 (a) A glass microfluidic device, featuring a network of microchannels in which fluids can be manipulated. (b) Laminar flow of red and blue inks within a microfluidic device. Courtesy of Sally A. Peyman.

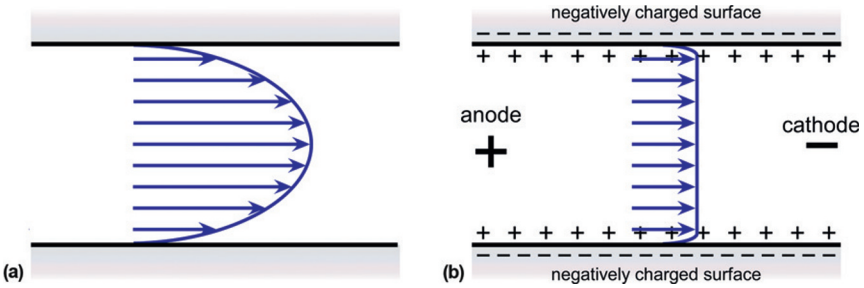

Figure 2 (a) Parabolic flow profile of a fluid as it is passed through a microchannel via hydrodynamic pumping. (b) Flat profile generated by electroosmotic flow (EOF) through a microchannel.

example via a syringe pump, or hydrostatic and centrifugal[17] forces, and is characterized by a parabolic flow profile. EOF-based pumping occurs when a voltage difference is applied across a microchannel that features charged surfaces. An electrical-double layer is formed at the channel surface, and the application of the voltage drives the bulk solution through the channel, with the flow profile being almost completely flat.

Integrated valves have become an important part of many microfluidic systems.[16,18] The most common type is the 'Quake' valve, which relies on the flexibility of PDMS (Figure 3).[19] Here, a fluidic channel fabricated in PDMS can be closed by applying air pressure to a control channel present in a layer above (or below); releasing the pressure allows the valve to reopen. Such pneumatic valves enable complex, highly parallel processing, in what is known as 'microfluidic Large-Scale Integration' (mLSI).[20]

A number of methods exist for enhancing the mixing of reagents within a microfluidic channel in order to perform even faster reaction and binding events.[21] These methods range from intelligent channel design to the application of force fields that induce turbulence within the flow.

Separations

Microfluidics began with the miniaturization of analytical chemistry methods for the separation and analysis of sample mixtures, and this remains a strong focus. Capillary electrophoresis was one of the first success stories of lab-on-a-chip due to the ease with which it could be miniaturized and the increase in performance achievable,[3c] and has since become a mainstay in many microfluidic technologies.[22] Of particular importance is the cross-injection method for reproducibly injecting a sample into a separation channel (Figure 4).[23] On-chip chromatography can be achieved by a number of methods,[24] including the use of packed particle beds, functionalized monoliths, and the fabrication of pillars within a channel.

The separation of particles and cells has also become significant. Surface-functionalized particles can bind target analytes in a sample, allowing separation of the target from the matrix. Cell sorting and counting is an important process for biological studies, while the separation of cells from a sample, such as in the separation of blood cells from plasma,[25] is a crucial step for analysis. Particles or cells can be manipulated (Figure 5(a)) via barriers, or forces such as magnetism,[26] acoustophoresis,[27] surface acoustic waves (SAW),[28] optical tweezers,[29] dielectrophoresis,[30] inertial forces[31] that can also utilize cell/particle shape and deformability,[32] optoelectrofluidic forces,[33] optoacoustic tweezers,[34] thermophoresis,[35] and diffusiophoresis.[36] These techniques can be applied to

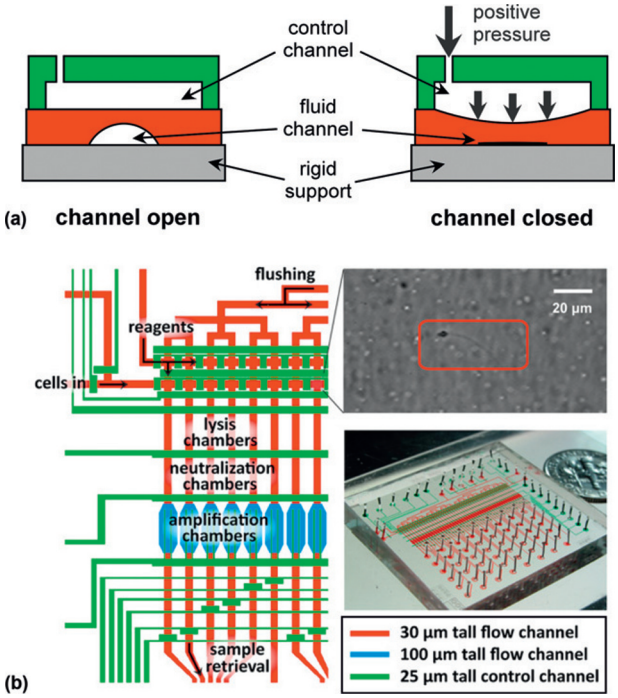

Figure 3 (a) Operation of a microfabricated 'Quake' valve: air pressure is applied via a control channel, forcing the PDMS fluidic channel to close (redrawn from Studer, V.; Hang, G.; Pandolfi, A.; Ortiz, M.; Anderson, W. F.; Quake, S. R. *J. Appl. Phys.* 2004, *95* (1), 393–398). (b) A microfluidic device incorporating numerous Quake valves (green lines = valve control channels) for whole genome amplification from single sperm cells. Reprinted from Wang, J.; Fan, H. C.; Behr, B.; Quake, Stephen R. *Cell* **2012**, *150* (2), 402–412, with permission. Copyright 2012 Elsevier, Inc.

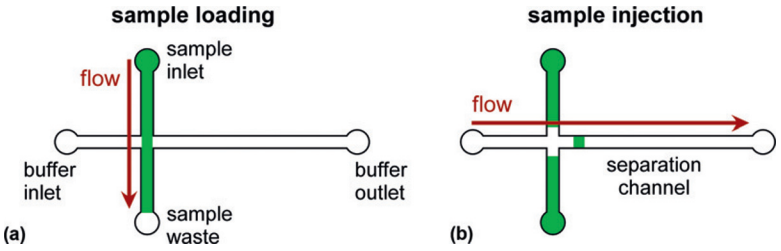

Figure 4 Cross-injection method of sample introduction. (a) Sample is pumped through the cross in the channel such that a small plug of sample is present in the main channel. (b)The flow is switched to inject the plug into the separation channel.

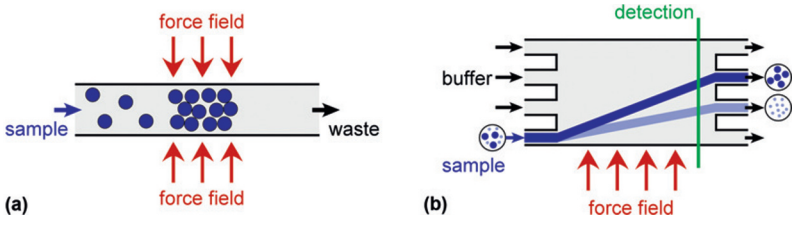

Figure 5 Particle and cell processing in microfluidic devices. (a) Trapping of particles, allowing separation or reactions. (b) Continuous deflection of particles, enabling separations or even reactions if the particles are deflected through laminar streams containing reagents [redrawn from Pamme, N. *Lab Chip* **2007**, *7*, 1644–1659]. In both cases, physical barriers can also be employed rather than applied forces.

the trapping of particles/cells within the channel for separations, exposure to reagents, and observation.[37] Continuous flow separations involve pumping a sample through a microchamber and deflecting the particles laterally, again via barriers or forces, until they are separated from the sample stream (Figure 5(b)).[38] These continuous flow mechanisms can also be applied to on-chip focusing, a crucial component of cytometric methods.[39]

Reactions

On-chip reactions include organic synthesis[40] and immunoassays.[41] The most basic process is to introduce two or more reagent streams at a junction and to let them mix by diffusion.[42] Reactions can also be performed on microchannel walls if reagents are bound to them, or on functionalized particles that are trapped or being passed through a reagent stream.[43] The use of microvalves allows very controlled introduction, mixing, and pumping of reagents, enabling parallelization and automation of highly complex procedures. Reactions may also be carried out within droplets via the use of droplet or digital microfluidic systems, as described below.

The amplification of DNA is an important procedure for clinical diagnostics and forensic science, and is achieved using the polymerase chain reaction (PCR).[44] Both thermocycled PCR and isothermal amplification[45] can be performed on-chip.

Detection

A wide range of detection methods have been developed for microfluidic devices. Off-chip detection with conventional methods is feasible if a suitable volume of sample can be collected. However, on-chip detection is normally desired in order to realize a fully integrated device or to observe effects *in situ* and in real-time. Optical detection methods are often employed,[46] in particular fluorescence[47] but also absorbance or chemiluminescence, and these may be aided by optical fibers, microlenses, and waveguides. Electrochemical detection can be achieved via the integration of electrodes during microfabrication of a chip.[48] Significant development has also gone into the combination of microdevices with mass spectrometry,[49] usually via electrospray ionization (ESI). Many other detection techniques have also been applied on-chip,[50] including surface plasmon resonance (SPR), Raman and infrared (IR) spectroscopy, and nuclear magnetic resonance (NMR).

Droplet and Digital Microfluidics

Droplet microfluidics has become a particularly valuable tool for chemical and biological processes.[51] It involves the generation of discrete volumes of a 'dispersed phase' solution in an immiscible 'continuous phase' liquid, usually by devices that feature either a T-junction or a flow focusing layout (Figure 6). By modifying the surface properties of the microchannel and the flow rates of the immiscible solutions, it is possible to generate water-in-oil droplets or oil-in-water droplets, as well as droplets-within-droplets. Microbubbles of gas can also be generated via similar processes.[52] These droplets can be produced at a rate of hundreds or even thousands per second in a highly reproducible manner, and can therefore act as identical reaction or analysis vessels. Multiple reagents can be introduced into the droplet and mixed within milliseconds. Applications include particle synthesis, protein crystallization, polymerase chain reaction (PCR), and enzyme kinetics.

Digital microfluidics also utilizes droplets but in a different manner. Here, the device consists of an array of electrodes coated with a hydrophobic insulator, onto which droplets can be placed and then manipulated by the application of electric fields (Figure 7).[53] The droplet movement can be controlled such that they can be dispensed, merged, mixed, and separated, allowing chemical reactions, extractions, and cell studies to be performed.

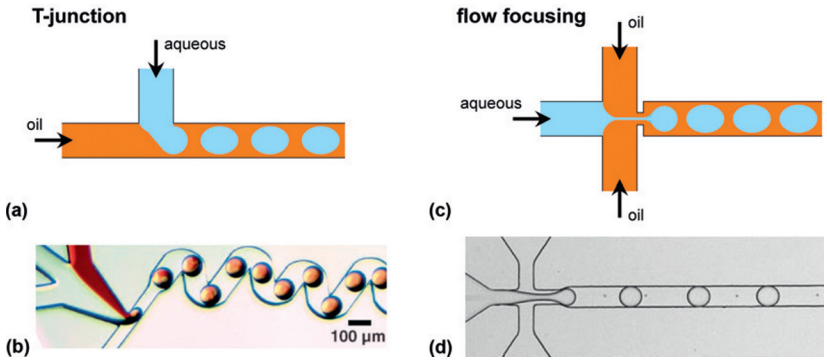

Figure 6 Common chip designs for droplet generation: (a) T-junction generation, with (b) a photograph showing formation of the droplets in a fabricated device (reprinted from Song, H.; Bringer, M. R.; Tice, J. D.; Gerdts, C. J.; Ismagilov, R. F. *Appl. Phys. Lett.* **2003**, *83* (22), 4664–4666, with permission. Copyright 2003 American Institute of Physics). (c) Flow focusing generation, with (d) a photograph of droplet production. Adapted from Bauer, W.-A. C.; Fischlechner, M.; Abell, C.; Huck, W. T. S. *Lab Chip* **2010**, *10* (14), 1814–1819, with permission. Copyright 2010 Royal Society of Chemistry.

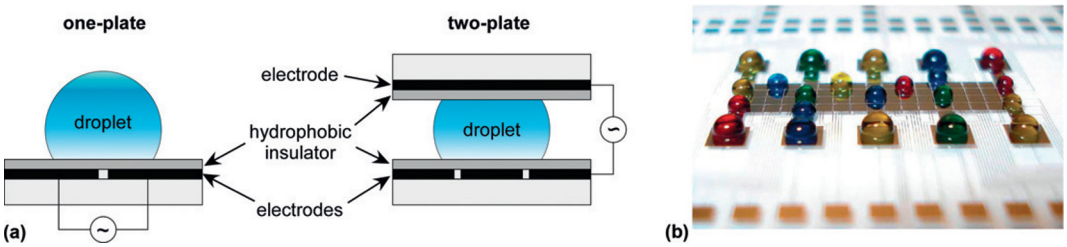

Figure 7 (a) One-plate and two-plate electrode arrays for digital microfluidics (redrawn from Jebrail, M. J.; Wheeler, A. R. *Curr. Opin. Chem. Biol.* **2010**, *14* (5), 574–581). (b) Photograph of an electrode array with multicolored droplets. Reprinted from Jebrail, M. J.; Wheeler, A. R. *Curr. Opin. Chem. Biol.* **2010**, *14* (5), 574–581, with permission. Copyright 2010 Elsevier, Inc.

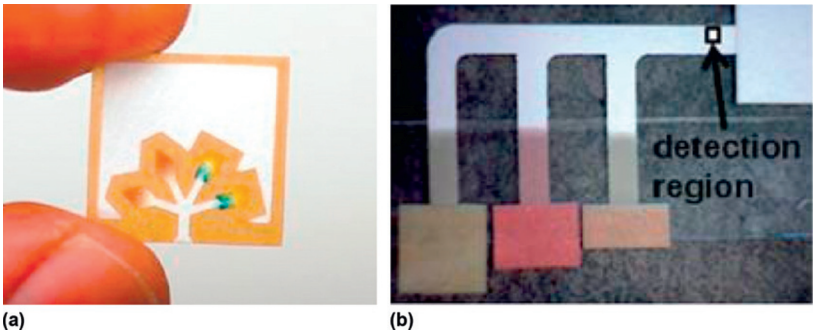

Figure 8 Examples of paper microfluidics for point-of-care (POC) diagnostics. (a) Paper device with hydrophobic channel walls, fabricated by photolithography (reprinted from Martinez, A. W.; Phillips, S. T.; Whitesides, G. M.; Carrilho, E. *Anal. Chem.* **2010**, *82* (1), 3–10, with permission. Copyright 2010 American Chemical Society). (b) Channel structure cut out of paper. Reprinted from Fu, E.; Lutz, B.; Kauffman, P.; Yager, P. *Lab Chip* **2010**, *10* (7), 918–920, with permission. Copyright 2010 Royal Society of Chemistry.

Paper Microfluidics

In recent years, the use of paper as a material for microfluidic devices has become increasingly desirable for low cost point-of-care (POC) diagnostics (Figure 8).[15,54] Hydrophobic channel walls are patterned onto filter paper via printing or photolithography, or alternatively the channel structure can be cut out of paper.[55] When liquid is introduced onto the paper, the natural wicking properties draw the fluid through the channels and into spots of dried reagents, typically yielding a color change that indicates the presence of an analyte. Similar principles have also been employed in which thread is used as the substrate material.[56]

Applications

Lab-on-a-chip technology can be applied to a wide variety of chemical and biological processes. Organic synthesis within microreactors can give high yields of product,[40] with specialized fields also being investigated such as radiopharmaceutical synthesis.[57] Microfluidic devices can be employed for the monitoring of everyday concerns, such as in environmental[58] and food[59] analysis, as well as in forensic science[60] where only small amounts of sample may be available. Microfluidics has become of particular importance for clinical diagnostics, with immunoassays[41,61] and DNA analysis[44] being amenable to miniaturization either in microchannel-based approaches or with microarray technology.[62] Microfluidic technology has been developing more and more towards integrated systems; true μTAS.[4i] With this, a concerted effort is being put into the use of microfluidic devices for point-of-care (POC) diagnostics,[10,53] many of which are available commercially or are on the verge of market release.[63]

While microfluidics began its life as a tool for chemistry, particularly in analysis, it has since grown into its potential for studying many other areas, particularly cell biology.[64] Individual cell studies can be performed by trapping them in flow,[37] or by performing procedures on them whilst still flowing,[38a] as well as in droplet-based systems. The use of Quake valves allows complex, parallel processing of chemical or biological species,[20a,b] even to the extent of performing whole-genome amplification from single cells.[65] Microfluidic platforms can also enable a more accurate portrayal of the conditions within the body compared to traditional, flask-based cell and tissue culture methods. Tissues have been studied on-chip,[66] and even organs-on-a-chip can be produced.[67] From these organ-chips, it can be envisaged that a 'human-on-a-chip' could be formed that acts as a model for the physiology of a human being, allowing a much greater understanding of *in vivo* processes and advancing the fields of drug discovery[68] and personalized medicine.[69]

Future Developments

Microfluidics has now reached the point where individual and multiple integrated processes can be performed for a wide variety of applications. Future developments will be concerned with bringing such technology into commercial devices operated by the non-specialist, and will require standardization of microfluidic components and the improvement of real-world interfacing, allowing intuitive handling and operation by unskilled end-users. Commercialization of systems employing microfluidic devices, whether in POC devices or in a 'chip-in-a-box' format, will become more frequent, with many multi-national companies now investing heavily in microfluidic research and with the many small companies being spun out of university activities. Devices for basic research will also remain highly important, especially on the biological front as researchers strive to produce the 'human-on-a-chip'.

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