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Digital Microfluidics for Chemical and Biological Applications

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1. Introduction

Droplet-based ("digital") nanofluidics is a new concept for lab-on-a-chip devices [1]. Liquids are transported as droplets between parallel plates, rather than as streams in channels. The droplets are created, moved, joined and divided by applying electrical potentials sequentially between electrodes buried beneath a hydrophobic, dielectric layer. The resulting device is completely reconfigurable, has low power requirements, and can be used as a platform for integrated and parallel chemical processes. The platform is very versatile, enabling manipulation of a wide range of liquids, including water, organic solvents, and solutions containing surfactants or proteins. Droplets can be created, moved, merged and divided, and can be manipulated individually or in parallel. Several droplets can be processed simultaneously in identical or in unique ways, enabling multiple syntheses or assays to be conducted on the single device, sequentially or concurrently. Presented here are examples that illustrate the versatility of droplet-based microfluidics for chemical and biological applications.

2. Device design and operation

Figure 1 illustrates the general architecture of a typical two-plate (top and bottom) digital microfluidics device. The bottom plate is shown with an array of conductive electrodes, dielectric layer and hydrophobic Teflon-AF coating. The top plate has a single ITO electrode and Teflon-AF coating. The droplet is sandwiched between the two plates with spacing between plates, *d*. The medium between the plates is air. This avoids contamination and emulsification problems that can arise when hydrocarbon or silicon oil is used as the ambient medium.

The bottom plate was formed from a borofloat glass wafer. Chromium and gold electrodes were patterned by photolithography followed by wet etching. The electrodes were covered by a dielectric layer of parylene-C (9800 Å, chemical vapor deposition) or silicon dioxide (SiO_2, 1.4 µm, plasma enhanced chemical vapor deposition). On devices covered with silicon dioxide, the electrode contact pads were opened by photolithography followed by etching with buffered hydrofluoric acid; this step was unnecessary for the parylene devices, as parylene could be scratched away from the contact pads before testing. The devices were then primed with hexamethyldisilazane (HMDS, 5 min) vapor and spin-coated (2000 RPM, 60 s) with 1.2 % Teflon-AF. The SiO_2 devices were post-baked on a hotplate (160 ˚C, 10 min) and in a furnace (330 ˚C, 30 min) to form a uniform ~500 Å layer of Teflon-AF. The parylene devices were post-baked on a hotplate at 110 ˚C for 5 min followed by 180 ˚C for 15 min.

The top plate was formed from indium tin oxide (ITO)-coated glass pieces. A ~500 Å layer of Teflon-AF was spin-coated onto the ITO coated glass as described above. The two plates were joined with one, two, or three pieces of 3M double-sided tape, which formed spacers of ~100, 200, or 300 mm. For ~50 µm spacers, single-sided polyimide tape (Kapton tape, Bertech, Torrance, CA) was used.

Droplets (0.2–2.0 mL) were sandwiched between the two plates, and moved by applying 90 V_{rms} AC potentials at 10 Hz–8 kHz between the electrode in the top plate and successive electrodes in the bottom plate.

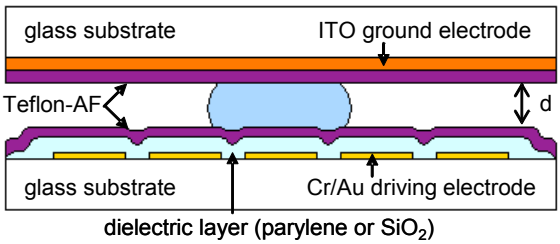

Fig. 1 Two-plate device for digital microfluidics.

3. Chemical manipulations

A variety of chemical applications of digital microfluidic devices can be envisioned, notably in the areas of sensing (e.g., biosensors, water analysis, and medical diagnostics), screening (e.g., drug discovery) and combinatorial synthesis. The basic functions required for these applications are the ability to move droplets to prescribed locations at specific times, to merge and mix droplets, and to deposit and dissolve solids.[2] More sophisticated functions include solid phase extraction, in which the droplet dissolves only one of several components from a spot of solid material, and liquid-liquid extraction, through which one or more substances can be transferred between immiscible phases. We have demonstrated all of these functions, and will present illustrative examples that make possible the types of applications noted above.

We have significantly extended the versatility of the platform by demonstrating the feasibility of transporting many different types of liquids in air.[3] The liquids include insulating fluids such as toluene, conductive liquids such as aqueous salt solutions, and many liquids that are neither pure insulators or pure conductors. A general electromechanical model for droplet actuation is now being developed. It shows that two mechanisms contribute to droplet movement: electrowetting and dielectrophoresis.

4. Biological applications

We have recently demonstrated the utility of digital microfluidics for processing samples for array-based techniques such as matrix-assisted laser desorption mass spectrometry (MALDI-MS).[4] Droplets of sample can be transported, desalted, treated to cleave chemical bonds, deposited, merged with matrix material, and crystallized. The entire device is then placed directly into the mass spectrometer, where the sample is desorbed, ionized and analyzed, without the need to transfer the sample to a conventional MALDI-MS target.

For example, Fig. 2 shows the MALDI mass spectrum of a droplet of insulin that had been subjected to a sequence of biochemical manipulations: (1) reaction with TCEP, which cleaves the disulfide bonds, breaking it into two fragment peptides, A and B; (2) proteolytic digestion by the enzyme trypsin, which breaks insulin A and B into much smaller peptide fragments; The droplet containing the fragments was then merged with a droplet of matrix material, which crystallized with the droplet components and prevented photothermal damage to the substances when they were desorbed and ionized by the laser for the mass spectral analysis. The spectrum shows a small amount of unreacted insulin, along with the products of each of the two reactions. The tryptic peptide fragments essentially represent a fingerprint that can be analyzed to reveal the amino acid sequence of the original protein.

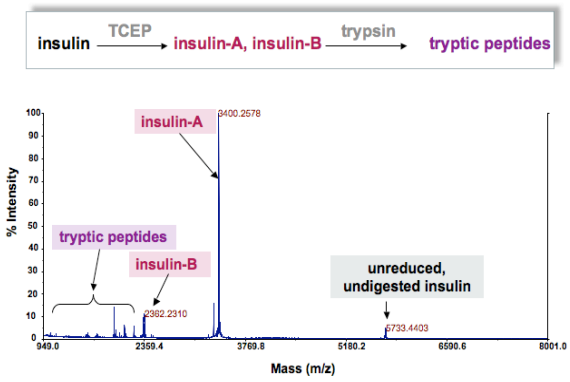

Fig. 2 MALDI-mass spectrum of insulin processed by digital microfluidics.

Another potential application of digital microfluidics is cell-based assays. It will be shown that live organisms such as yeast and zebra fish embryos can be transported and positioned without harm to the organisms.

In summary, digital microfluidics is a very promising new platform for chemical and biological applications on the micro- to nano-scale. We have discovered that droplets of a wide range of liquids can be manipulated, including aqueous and nonaqueous solvents and solutions. The actuation mechanism is electrowetting or dielectrophoresis, or a combination of the two. On-chip separations can be achieved by solid phase extraction or liquid-liquid phase transfer, opening the possibility of using droplet-based nanofluidics for synthesis, purification and analysis on the nanoliter scale. We have also used this platform to automate sample preparation for proteomics and direct analysis by MALDI-MS. Transport, crystallization, disulfide reduction, alkylation and proteolytic digestion can all be done on-chip, and the device placed directly in the mass spectrometer for analysis. Related applications include biosensing and drug discovery.

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