The Digital Revolution: A New Paradigm for Microfluidics

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The digital revolution has come to microfluidics. In digital microfluidics (DMF), discrete droplets are manipulated by applying electrical fields to an array of electrodes. In contrast to microchannels, in DMF each sample and reagent is individually addressable, which facilitates exquisite control over chemical reactions. Here, we review the state-of-the-art in DMF, with a discussion of device formats, actuation physics, and biological and non-biological applications. Along the way, we identify the key players in the field, and speculate on the advances and challenges that lie ahead. As with other fronts in the digital revolution, there have been and will be unexpected developments as DMF matures, but we posit that the future is bright for this promising technology.

1. Introduction

Digital microfluidics (DMF) is a relatively new microscale liquid-handling technique, in which picoliter–microliter-sized droplets are manipulated on arrays of electrodes.[1–3] Like the more established technique of microchannel-based fluidics, DMF is being used to miniaturize a wide range of applications, with the advantages of reduced sample size, fast heat transfer and reaction rates, and integration capacity (i.e., the lab-on-chip concept). Although microchannels have been also used to manipulate droplets,[4] DMF is a distinct paradigm; the principal difference is that in DMF, samples are addressed individually, while in channels, they are controlled in series. For example, as depicted in Figure 1a and b, in DMF, a droplet containing samples or reagents can be dispensed from reservoirs, moved, merged, and split into smaller droplets, each independently from the others. A second difference is reagent isolation – droplets serve as discrete microvessels, in which reactions can be carried out without cross-talk between samples or reagents; this stands in contrast to microchannels, which are prone to undesirable hydrostatic and capillary flows.[6] A third difference is the geometry – as DMF is inherently an array-based technique, it is a good match for array-based biochemical applications. Finally, since droplets are manipulated on relatively generic platforms (e.g., an $M \times N$ array), DMF devices are straightforward to use, and are reconfigurable for any desired combination of droplet operations.

In the following, we present a summary of the state-of-the-art in DMF, describing device formats and fabrication, the physics of droplet actuation, and a sampling of the myriad applications to which the technology is being applied, which we broadly classify as biological and nonbiological applications.

2. Device Format and Fabrication

DMF is typically implemented in one of two different configurations (Fig. 1c) – the closed format (also known as the two-plate format), in which droplets are sandwiched between two substrates patterned with electrodes (the substrates house driving and ground electrodes, respectively), and the open format (also known as the single-plate format), in which droplets are placed on top of a single substrate, housing both actuation and ground electrodes. In both configurations, an insulating layer of a dielectric material is deposited on top of the actuation electrodes, to limit current and prevent electrolysis. Typically, the insulating layer is covered by an additional hydrophobic coating, which reduces droplet-sticking to the surface.

The closed and open DMF configurations have complementary advantages. Closed DMF devices are best suited for a wide range of droplet operations – dispensing, moving, splitting, and merging are all feasible.[7] In contrast, open DMF devices are typically not capable of splitting and dispensing (only feasible in unique conditions[8]); however, the open format facilitates fast sample and reagent mixing,[9] the capacity to move large droplets, and better access to samples for external detectors. Additionally, evaporation rates are higher in open-format devices, which may be advantageous or inconvenient, depending on the application.

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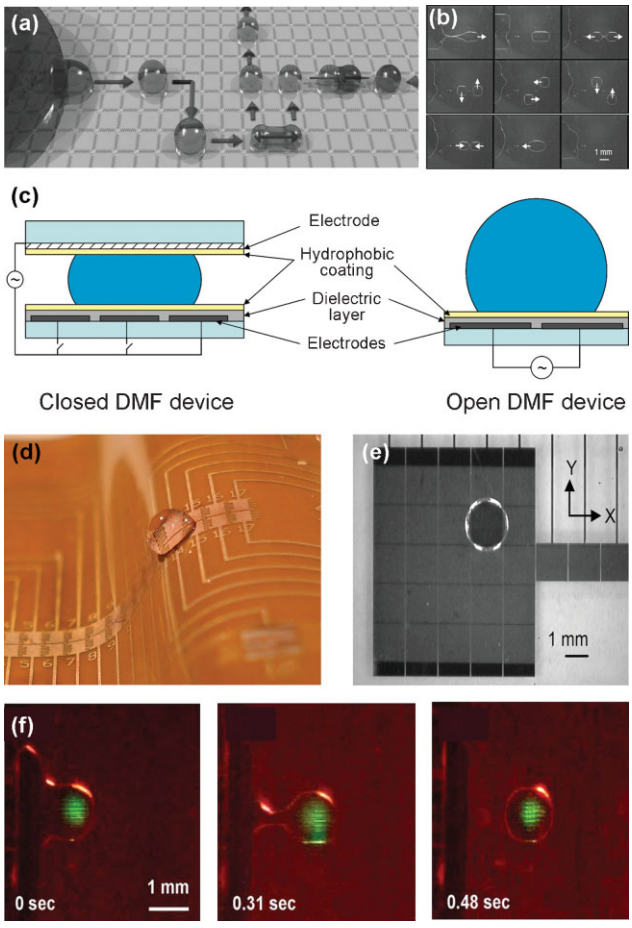

Figure 1. The DMF paradigm. a) Schematic and b) pictures from a movie depicting the four principle DMF processes: dispensing, moving, splitting, and merging. Reproduced with permission from [5,7]. Copyright 2006, 2007 IEEE, respectively. c) Schematics of closed and open DMF devices. d) Picture of an ATDA device, capable of manipulating droplets on flexible substrates. Reproduced with permission from [11]. Copyright 2008 The Royal Society of Chemistry. e) Picture of a DMF device powered by a cross-reference electrode array. Reproduced with permission from [17]. Copyright 2003 IEEE. f) Series of pictures from a video (left-to-right) depicting droplet dispensing on an optically driven DMF device. Reproduced with permission from [20]. Copyright 2008 IEEE.

DMF devices are typically fabricated in a clean-room facility using conventional techniques, such as photolithography and etching; electrodes are formed from substrates common to such facilities (e.g., chromium, gold, indium-tin oxide (ITO), and doped polysilicon). The insulating dielectric layer can be formed using a variety of techniques, including vapor deposition (parylene, amorphous fluoropolymers, and silicon nitride), thermal growth (silicon oxide), or spin-coating (PDMS or SU-8). The hydrophobic coating is usually formed by spin-coating a thin layer of Teflon-AF. While many DMF devices are used to actuate droplets in air, another common technique uses droplets suspended in oil,[2,10] which prevents evaporation and reduces the voltages required for droplet actuation. Oil-immersed systems have drawbacks, however, including the requirement of gaskets or other structures to contain the oil bath, the potential for liquid–liquid extraction of analytes into the surrounding oil,[11] the incompatibility with oil-miscible liquids (e.g., organic solvents), and the incompatibility with assays requiring drying droplets onto the device surface.[12]

Recently, we[11] and others[13] demonstrated that DMF devices can be formed from flexible substrates (Fig. 1d), which facilitates droplet actuation on nonplanar surfaces, permitting the integration of multiple physicochemical environments on the same device. Our work in this area grew out of efforts to fabricate DMF devices using inexpensive, accessible methods, including microcontact printing,[14] laser printing,[15] and rapid marker masking.[16] These techniques make DMF accessible to any interested party, which we hope will expand the innovations in and applications of the technology.

All of the conventional and unconventional fabrication methods described above are limited in electrode density. In such systems, to address electrodes in the center of an array, electrical contacts must be positioned between driving electrodes – such space is inherently limited. Several solutions to this problem have been developed; one creative solution is droplet manipulation by cross-referencing.[17] In this method, linear driving electrodes are patterned on both the bottom and top plates of a closed DMF device, and the plates are aligned, such that the electrodes are normal to each other. In this format, droplets are actuated by energizing combinations of electrodes normal to the direction of motion (Fig. 1e). A more conventional solution to limits on electrode density is the use of multilayer printed circuit board (PCB) fabrication, which allows for isolation of contact wires from driving electrodes by means of vertical interconnects between multiple conducting layers.[18,19] A third solution to the limitation on density is to replace hard-wired electrical contacts with optically actuated "virtual electrodes."[20] Using this technique, any desired pattern of electrodes can be actuated (and changed) by projecting different patterns of light onto a photoconductive substrate (Fig. 1f).[20] Although fabrication of such devices is more complex than traditional DMF techniques, this method has the capacity to implement droplet manipulation on an unlimited number and variety of electrode patterns.

3. Physics of Droplet Actuation

DMF was popularized in the early 2000s by Fair and coworkers[2] and Kim and coworkers,[3] at Duke and UCLA, respectively. The technique was explained as being a phenomenon driven by surface tension, and was called "electrowetting" or "electrowetting-on-dielectric" (EWOD). This idea followed from the observation that for aqueous droplets, the contact angle between a droplet and the device surface is dramatically reduced (i.e., wetted) when electrical potentials are applied. In this scheme, droplet movement was understood as being a consequence of capillary pressure arising from non-symmetrical contact angles on either side of a droplet. However, the electrowetting description does not explain droplet motion for dielectric liquids[21] or for low-surface-tension liquids that have no apparent changes in contact angle;[22] nor can it explain related phenomena, such as contact-angle saturation (i.e., the observed limit on contact-angle change above a threshold in applied potential).

A better understanding of the physics of droplet actuation is derived from electrodynamics analysis,[23–25] which explains the phenomenon in terms of electrical forces generated on free

charges in the droplet meniscus (in case of conductive liquids) or on dipoles inside of the droplet (in case of dielectric liquids). These forces can be calculated by integrating the Maxwell–Stress tensor, T_{ij} (Eq. 1), over any arbitrary surface surrounding the droplet:

$$T_{ij} = \varepsilon\left(E_i E_j - \frac{1}{2}\delta_{ij}E^2\right) \quad (1)$$

where i and j refer to pairs of x, y, and z axes, δ_{ij} is the Kronecker delta, and E is the electric field surrounding the droplet. Unlike electrowetting, this formulation explains the motion of dielectric liquids and liquids that do not experience a change in contact angle. In addition, it provides a rationale for the phenomenon of contact-angle saturation, as an equilibrium between electrical and surface-tension forces.[24,25]

4. Biological Applications of Digital Microfluidics

DMF is an attractive platform for biological applications, which often require the use of expensive or precious reagents. However, a nontrivial challenge in the implementation of DMF for such applications is nonspecific adsorption (or fouling) by biological molecules. This phenomenon can lead to sample loss and cross-contamination, and even more troubling, it can promote droplet sticking, which renders devices useless. In an important step toward overcoming this problem, in 2004, Srinivasan et al.[10] demonstrated that fouling could be minimized by suspending droplets in an immiscible oil; this technique facilitated manipulation of a variety of fluids containing high concentrations of potential surface-fouling molecules, including blood, serum, plasma, urine, saliva, sweat, and tear (Fig. 2a). We recently demonstrated an alternative strategy, not requiring oil, in which samples and reagents are mixed with low concentrations of amphiphilic polymer additives – this technique also facilitates the actuation of serum and other concentrated solutions.[26] Thus, it would seem that DMF is poised to make contributions in biology and related fields. We describe several examples below.

4.1. DNA Extraction, Repair, and Amplification

Handling, purifying, detecting, and characterizing samples of DNA have become critical steps for a wide range of basic and applied fields of science. Thus, it is not surprising that such processes have been an attractive match for DMF. For example, in recent work, we demonstrated the first of these processes, DNA handling and purification, using DMF to implement liquid–liquid extraction of a heterogenous mixture of DNA and proteins.[11] In this work, all-terrain droplet actuation (ATDA, Fig. 1d) was used to drive aqueous droplets containing a mixture of DNA and proteins into and out of a pool of phenolic oil, which had the effect of removing proteins from the droplet and purifying the nucleic acid. A second application, repair of oxidized lesions in oligonucleotides, was recently implemented in DMF format by Jary et al.[27] In this work, droplets containing the DNA repair enzyme Fpg (fapy glycosylase) and damaged DNA were merged by DMF, incubated, and then the repaired DNA was

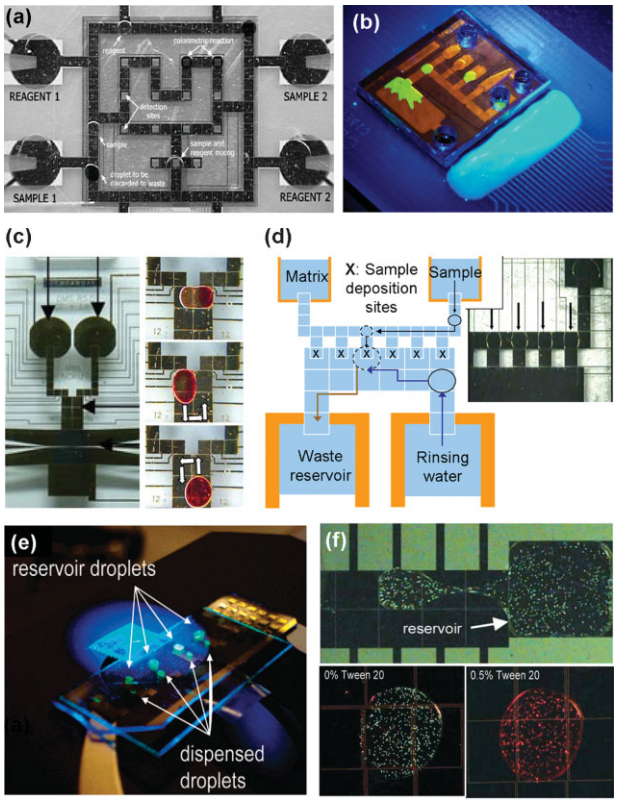

Figure 2. Biological applications of DMF. a) Picture of DMF device used to perform glucose assays. Reproduced with permission from [10]. Copyright 2004 The Royal Society of Chemistry. b) Picture of DMF device used to implement DNA repair reactions. Reproduced with permission from [27]. Copyright 2006 NanoScience and Technology Institute. c) Picture of DMF device used to perform PCR; the pictures on the right are frames from a video depicting the mixing of target DNA and reagents/primers, by moving a merged droplet in circles. Reproduced with permission from [29]. Copyright 2006 Springer Netherlands. d) Schematic and frame from a movie of a DMF device used to perform multiplexed proteomic sample preparation. Reproduced with permission from [12]. Copyright 2006 The Royal Society of Chemistry. e) Picture of a multiplexed DMF device used to study enzyme kinetics. Reproduced with permission from [34]. Copyright 2008 The American Chemical Society. f) Pictures of DMF device used for cell-based toxicity assays. The main panel depicts the dispensing of a droplet carrying Jurkat-T cells labeled with calcein AM (which fluoresces green). The two frames below depict droplets containing cells challenged with 0% (left) and 0.5% (right) Tween 20. Cells exposed to high concentrations of Tween 20 die and fluoresce red when labeled with ethidium homodimer-1. Reproduced with permission from [35]. Copyright 2008 The Royal Society of Chemistry.

detected by fluorescence microscopy (Fig. 2b). Liu et al.[28] demonstrated a similar application, in which a DMF device was developed to facilitate DNA ligation, by merging droplets containing vector DNA and the enzyme, DNA ligase.

The most complete DNA application using DMF was reported by Chang et al.,[29] who implemented the polymerase chain reaction (PCR). In this work, a digital microfluidic device with an embedded microheater was developed to facilitate thermal cycling. As shown in Figure 2c, droplets containing an oligonucleotide to be amplified, and PCR reagents were merged, mixed, and then delivered to the integrated heater. The

fluorescent signals from DNA amplified on-chip were comparable to those generated using a bench-scale PCR machine, with 50 and 70% reductions in total time and sample consumption, respectively.

4.2. Proteomics and Enzyme Assays

The field of proteomics is technology poor – experiments typically require tedious, multistep sample processing prior to analysis by mass spectrometry or other detectors. For example, in the widely used technique of shotgun proteome profiling,[30] samples are subjected to a multi-day procedure, including acidification, denaturing, reduction, alkylation, enzymatic digestion (twice), purification, and dilution. The capacity of DMF for individual addressing of many reagents simultaneously renders it a good fit for such processes. While a completely integrated proteomic workup by DMF has not yet been implemented, the field is moving in this direction. For example, Garrell and coworkers and Kim and coworkers at UCLA[31,32] developed DMF-based methods to purify peptides and proteins from heterogeneous mixtures. The methods comprised a series of steps, including drying the sample droplets, rinsing the dried spot with DI water droplets to remove impurities, and finally delivering a droplet of matrix-assisted laser desportion/ionization (MALDI) matrix to the purified proteins, for analysis on-chip by mass spectrometry. The same team then improved upon this process by implementing simultaneous purification of six samples (Fig. 2d).[12] In related work, we have demonstrated on-chip enzymatic digestion, which represents another important step toward integrated proteomic sample processing.[26]

Enzyme assays are another common goal in proteomics, and have been a popular target for DMF. In one of the first reports of the use of DMF in biological applications, Taniguchi et al.[33] demonstrated a bioluminescence assay for luciferase (in the presence of ATP). More recently, the Fair group at Duke University demonstrated a fully automated glucose assay in a range of physiological fluids (serum, saliva, plasma, and urine) on a DMF device (Fig. 2a).[10] Droplets of glucose oxidase were merged with sample droplets spiked with glucose, then mixed, and the glucose concentration was measured using an integrated LED/photodiode detector. Finally, we applied DMF to the study of enzyme kinetics, by mixing and merging droplets of alkaline phosphatase with fluorescein diphosphate on a multiplexed DMF device (Fig. 2e).[34] Enzyme reaction coefficients, K_m and k_{cat}, generated by DMF, agreed with literature values, and the assays used much smaller volumes, and had higher sensitivity than conventional methods.

4.3. Cell Assays

Cell-based assays have been a popular target for miniaturization, as the reagents and other materials are often prohibitively expensive. Despite this obvious match, cell-based assays have been ignored by the DMF community, until very recently. This changed in the past year, with the publication of three different studies describing cell manipulation by DMF.[35–37] In our cell-based work,[35] we implemented a toxicity assay by DMF, in which droplets carrying Jurkat-T cells were merged with droplets containing different concentrations of the surfactant Tween 20 (lethal to cells). The droplets containing cells were then merged again with droplets carrying viability dyes (Fig. 2f), and were analyzed using a fluorescence plate reader. The DMF assay was more sensitive than an identical one performed in a 384-well plate, such that the DMF-generated results gave a better approximation of the empirical value of the 100% lethal concentration, and also had a 30× reduction in reagent consumption. Additionally, actuation by DMF was found to have no significant effects on cell vitality. This agrees with the second DMF cell study, in which Zhou et al.[36] reported no increase in number of dead osteoblasts after droplet actuation. In the third study, Fan et al.[37] used dielectrophoresis to separate neuroblastoma cells to different regions of droplets that were manipulated by DMF. The original droplets were then split into daughter droplets containing different cell densities, a technique which may be useful for on-chip cell concentration for a wide range of applications.

4.4. Immunoassays

Immunoassays are routinely used to detect analytes in biological samples with high selectivity. This application has recently been targeted by the DMF community; for example, Sista[38] reported the use of DMF to detect insulin and Interleukin-6 using droplets carrying magnetic beads modified with immobilized antibodies. In this work, droplets containing the beads were merged with those containing known concentrations of analyte, and a magnetic field was then used to separate the beads from the supernatant. The beads were afterwards resuspended in a new buffer droplet, and the immobilized analyte was detected by chemiluminescence. The assay had low detection limits (0.24 pg μL^{-1}), and standard errors of less than 3%.

5. Non-biological Applications of DMF

While the most popular applications of DMF have been in the area of biological assays, there are a growing number of nonbiological applications that are attracting attention. Here, we enumerate a few of our favorites, including cooling of microelectronics, droplet-based chemical synthesis, and some creative examples that defy classification.

5.1. Electronics Cooling

Microchannels have been applied to electronics cooling, and have been shown to be capable of achieving cooling rates as high as 100 W cm^{-2};[39] however, such capacity is not sufficient to cool local hot spots on integrated circuits (300 W cm^{-2}). DMF seems well suited for this application, as droplets can be moved directly to hot spots, by-passing the regions not requiring cooling. Paik et al.[19] demonstrated this scheme, using thin-film microheaters as surrogate hot spots, and shuttled water droplets back and forth over the spots at different frequencies (Fig. 3a). Temperatures were monitored using an infrared camera, and the results showed a 23 °C decrease in the temperature of hot spots after eight droplet passes at 32 Hz. Time-averaged measurements showed that the

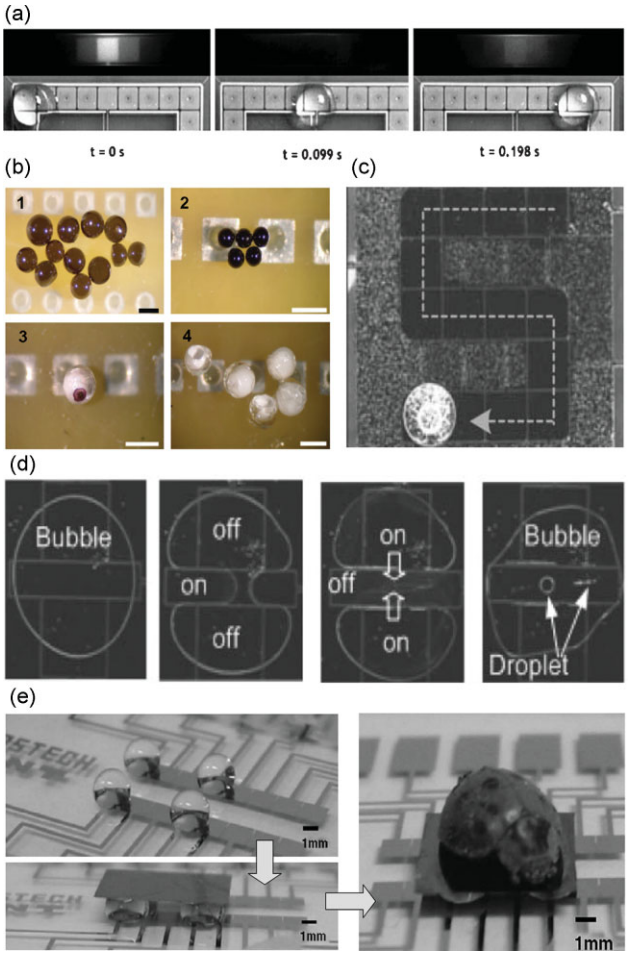

Figure 3. Nonbiological applications of DMF. a) Pictures depicting the use of DMF to cool an artificial hot spot (an imbedded microheater). The top half of each frame shows an infrared image of the hot spot (white = hot); the temperature drops significantly during and after the droplet passes over it. Reproduced with permission from [19]. Copyright 2008 IEEE. b) Pictures depicting particles being synthesized using DMF. The products include conductive gold/SU-8 particles (1), semiconducting polypyrrole particles (2), "eyeball" microbeads (3), and "cups", formed by drying water droplets that were originally encapsulated in latex (4). Scale bars: 1 mm. Reprinted with permission from [40]. Copyright 2005 Nature Publishing Group. c) Figure depicting a droplet sampling particles on the surface of a DMF device. Reproduced with permission from [42]. Copyright 2006 The Royal Society of Chemistry. d) Frames from a movie depicting bubble splitting and merging on a DMF device. Reproduced with permission from [44]. Copyright 2007 The Royal Society of Chemistry. e) Pictures of a microbelt conveyer system based on DMF; the picture on the right shows a lady bug carried on a silicon wafer supported by four droplets. Reproduced with permission from [45]. Copyright 2006 Elsevier B.V.

hot-spot cooling can be achieved without significant increases in droplet temperature.

5.2. Chemical Synthesis

The format of DMF, in which droplets form isolated microreactors, seems well suited for synthetic applications, an assertion greatly strengthened when Chatterjee et al.[22] demonstrated the capacity to actuate organic solvents (required for most syntheses). In an early demonstration of chemical applications in DMF format, Millman et al.[40] synthesized microparticles with a range of characteristics, including polymer capsules, semiconducting microbeads, and anisotropic striped and "eyeball" particles (Fig. 3b). The devices used in this study were slightly different from conventional formats, in that droplets were manipulated while floating in a layer of oil, without direct contact with the electrode array. In this format, droplets containing suspensions of micro-/nanoparticles, polymer solutions, and polymer precursors were merged, mixed, and dried, to yield the different types of particles. In the most unique design, the "eyeball" beads, darker microparticles (forming the "iris") were driven to the droplet surface by internal convection currents, induced by evaporation.

In another example of synthesis applications in DMF devices, Dubois et al.[41] performed Grieco's reaction using ionic-liquid droplets as microreactors. Ionic liquids are advantageous because of their low vapor pressure – reactions can be implemented in relatively small droplets (<1 μL) on single-plate devices, with no worry about evaporation. In addition to low vapor pressure, the use of ionic liquids as DMF microreactors has other advantages, such as intrinsic conductivity, thermal stability, and capacity to serve as solvents for a wide range of organic, inorganic, and organometallic compounds.[8]

5.3. Miscellaneous Applications

The unique characteristics of DMF have rendered the technology attractive for a diverse set of applications that do not fit into any of the categories described above. For example, Zhao and Cho[42] demonstrated the use of droplets controlled by DMF to collect particles from surfaces of microfilter membranes; the collection efficiency was as high as 95% (Fig. 3c). This technology may be useful for sampling bioaerosols (e.g., airborne pollen, fungal spores, and bacterial cells) for environmental applications. In another creative application, air bubbles, instead of droplets, were manipulated on DMF devices (Fig. 3d), and were used to effect a chemical reaction between gaseous reagents.[43,44] Finally, Moon et al.[45] used DMF to form a conveyer system, by placing a piece of thin silicon wafer on top of four water droplets, which were moved on a track of electrodes (Fig. 3e).

6. Conclusion and Outlook for the Future

As described herein, the digital revolution in microfluidics has resulted in a technology distinctly different from microchannel-based fluidics. Like many new technologies, DMF began as a curiosity for aficionados, but in the past few years the technology has matured, and is making unique contributions in areas ranging from cell-based assays to microelectronics cooling. Of the applications discussed, we propose that proteomics is the most attractive target for DMF, given the current limitations of that field; however, the trajectory of creativity in the DMF community suggests to us that the ultimate "killer application" may not yet be known.

Several challenges and unanswered questions about DMF remain. A key test for the field will be for the DMF community to reach consensus on the physics of droplet motion. We propose that numerical simulations of the electrodynamics of droplet

motion in DMF will provide better understanding of the effect of electrode shape on actuation forces, optimum actuation voltage/frequency, effect of liquid properties (e.g., conductivity, permittivity, and surface tension) on droplet actuation, and effect of contact angle on actuation forces. A key practical challenge is the limitation of current fabrication techniques in terms of electrode-array density. While PCB fabrication offers some relief from this problem, the spatial resolution of that method is suboptimal (i.e., 75 μm gaps between electrodes compared to 5 μm gaps for clean-room fabrication). Optically actuated virtual electrodes may be an ideal solution to avoid wiring problems altogether. In addition, by developing algorithms to modulate projected-light patterns in real time, different electrode shapes may be used to suit particular processes. For example, larger electrodes may be projected to create reservoirs, and droplet splitting may be facilitated by projecting wider electrodes. However, as only a few studies have been reported describing this actuation scheme, more work is required for better understanding of its advantages and limitations.

In the final analysis, we are optimistic about this technology – there is an undeniable attraction to the capacity to exercise absolute control over samples and reagents in parallel. In 2004, a company, Advanced Liquid Logic (ALL; www.liquid-logic.com), was established to translate this advantage to end users. In the next decade, we speculate that the ever-expanding community of DMF researchers (including academics, ALL, and others) will solve some of the mechanistic and practical problems that remain, such that DMF will become a widely practiced technique. We liken the current state of the digital revolution in microfluidics to that of microchannels in the mid-nineties – poised to have a significant impact on the way science is done.

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[1] M. Washizu, *IEEE Trans. Ind. Appl.* **1998**, *34*, 732.
[2] M. G. Pollack, R. B. Fair, A. D. Shenderov, *Appl. Phys. Lett.* **2000**, *77*, 1725.
[3] J. Lee, H. Moon, J. Fowler, T. Schoellhammer, C.-J. Kim, *Sens. Actuators, A* **2002**, *95*, 259.
[4] S.-Y. Teh, R. Lin, L.-H. Hung, A. P. Lee, *Lab Chip* **2008**, *8*, 198.
[5] J. Lienemann, A. Greiner, J. G. Korvink, *IEEE Trans. Comput-Aided Des. Integr. Circuits Syst.* **2006**, *25*, 234.
[6] H. J. Crabtree, E. C. S. Cheong, D. A. Tilroe, C. J. Backhouse, *Anal. Chem.* **2001**, *73*, 4079.
[7] S. K. Cho, H. Moon, C. J. Kim, *J. MEMS* **2003**, *12*, 70.
[8] J. Berthier, *Microdrops and Digital Microfluidics*, William Andrew Pub., Norwich, NY **2008**.
[9] C. Cooney, C.-Y. Chen, M. Emerling, A. Nadim, J. Sterling, *Microfluid. Nanofluid.* **2006**, *2*, 435.
[10] V. Srinivasan, V. K. Pamula, R. B. Fair, *Lab Chip* **2004**, *4*, 310.
[11] M. Abdelgawad, S. L. Freire, H. Yang, A. R. Wheeler, *Lab Chip* **2008**, *8*, 672.
[12] H. Moon, A. R. Wheeler, R. L. Garrell, J. A. Loo, C. J. Kim, *Lab Chip* **2006**, *6*, 1213.
[13] H. Yang, H. Yang, W. Hsu, S. K. Fan, in *Proceedings of The 21st International Conference on Micro Electro Mechanical Systems (MEMS) 2008* (Ed: W. Hsu,), IEEE, Piskataway, NJ **2008**, pp. 607–610.
[14] M. W. L. Watson, M. Abdelgawad, G. Ye, N. Yonson, J. Trottier, A. R. Wheeler, *Anal. Chem.* **2006**, *78*, 7877.
[15] M. Abdelgawad, A. R. Wheeler, *Adv. Mater.* **2007**, *19*, 133.
[16] M. Abdelgawad, A. R. Wheeler, *Microfluid. Nanofluid.* **2008**, *4*, 349.
[17] S. K. Fan, C. Hashi, C. J. Kim, in: *Proceedings of The 16th International Conference on Micro Electro Mechanical Systems (MEMS) 2003*, IEEE, Piskataway, NJ **2003**, pp. 694–697.
[18] J. Gong, C.-J. C. J. Kim, *Lab Chip* **2008**, *8*, 898.
[19] P. Y. Paik, V. K. Pamula, K. Chakrabarty, *IEEE Trans. VLSI Sys.* **2008**, *16*, 432.
[20] P. Y. Chiou, Z. Chang, M. C. Wu, *J. MEMS* **2008**, *17*, 133.
[21] T. H. Hsieh, S. K. Fan, in *Proceedings of IEEE 21st International Conference on Micro Electro Mechanical Systems (MEMS) 2008* (Ed: W. Hsu), IEEE, Piskataway, NJ **2008**, pp. 641–644.
[22] D. Chatterjee, B. Hetayothin, A. R. Wheeler, D. J. King, R. L. Garrell, *Lab Chip* **2006**, *6*, 199.
[23] T. B. Jones, *Langmuir* **2002**, *18*, 4437.
[24] K. H. Kang, *Langmuir* **2002**, *18*, 10318.
[25] E. Baird, P. Young, K. Mohseni, *Microfluid. Nanofluid.* **2007**, *3*, 635.
[26] V. N. Luk, G. C. H. Mo, A. R. Wheeler, *Langmuir* **2008**, *24*, 6382.
[27] D. Jary, A. Chollat-Namy, Y. Fouillet, J. Boutet, C. Chabrol, G. Castellan, D. Gasparutto, C. Peponnet, in: *Proceedings of 2006 NSTI Nanotechnology Conference and Trade Show*, Vol *2*, Nano Science and Technology Institute, Cambridge, MA **2006**, pp. 554–557.
[28] Y.-J. Liu, D.-J. Yao, H.-C. Lin, W.-Y. Chang, H.-Y. Chang, *J. Micromech. Microeng.* **2008**, *18*, 045017.
[29] Y.-H. Chang, G.-B. Lee, F.-C. Huang, Y.-Y. Chen, J.-L. Lin, *Biomed. Microdevices* **2006**, *8*, 215.
[30] M. P. Washburn, D. Wolters, J. R. Yates, III, *Nat. Biotechnol.* **2001**, *19*, 242.
[31] A. R. Wheeler, H. Moon, C. J. Kim, J. A. Loo, R. L. Garrell, *Anal. Chem.* **2004**, *76*, 4833.
[32] A. R. Wheeler, C. A. Bird, J. A. Loo, R. L. Garrell, R. R. O. Loo, C. J. Kim, H. Moon, *Anal. Chem.* **2005**, *77*, 534.
[33] T. Taniguchi, T. Torii, T. Higuchi, *Lab Chip* **2002**, *2*, 19.
[34] E. M. Miller, A. R. Wheeler, *Anal. Chem.* **2008**, *80*, 1614.
[35] I. Barbulovic-Nad, H. Yang, P. S. Park, A. R. Wheeler, *Lab Chip* **2008**, *8*, 519.
[36] J. Zhou, L. Lu, K. Byrapogu, D. M. Wootton, P. I. Lelkes, R. Fair, *Virtual Phys. Prototyping* **2007**, *2*, 217.
[37] S.-K. Fan, P.-W. Huang, T.-T. Wang, Y.-H. Peng, *Lab Chip* **2008**, *8*, 1325.
[38] R. Sista, Ph.D Thesis, Florida State University **2007**.
[39] I. Hassan, P. Phutthavong, M. Abdelgawad, *Microscale Thermophys. Eng.* **2004**, *8*, 183.
[40] J. R. Millman, K. H. Bhatt, B. G. Prevo, O. D. Velev, *Nat. Mater.* **2005**, *4*, 98.
[41] P. Dubois, G. Marchand, Y. Fouillet, J. Berthier, T. Douki, F. Hassine, S. Gmouh, M. Vaultier, *Anal. Chem.* **2006**, *78*, 4909.
[42] Y. J. Zhao, S. K. Cho, *Lab Chip* **2006**, *6*, 137.
[43] T. Ito, T. Torii, T. Higuchi, in *Proceedings of the 16th International Conference on Micro Electro Mechanical Systems (MEMS) 2003*, IEEE, Piscataway, NJ **2003**, pp. 335–338.
[44] Y. Zhao, S. K. Cho, *Lab Chip* **2007**, *7*, 273.
[45] I. Moon, J. Kim, *Sens. Actuators A* **2006**, *130–131*, 537.