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Methods for pumping fluids on biomedical lab-on-a-chip

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TABLE OF CONTENTS

1. ABSTRACT

Lab-on-a-chip is an enabling technology that has influenced areas from biology, drug research to the development of point-of-care devices. The essential of Lab-on-a-chip technology is the "mobile liquid" in channels with dimensions of tens to hundreds of micrometres, for which a liquid pumping system generally is indispensable. We review the methods for pumping fluids on biomedical lab-on-a-chip developed over the last decade with the emphasis on their basic principles and typical applications. Electroosmosis and pressure are the two methods most widely employed. Pressure can be generated by various means, including positive displacement, reciprocating displacement, gravity, surface tension, centrifuging, *etc*. In the discussions of these techniques, we provide a number of important biomedical applications in an effort to show the potential of microfluidics for those outside this field who can potentially benefit from this technology.

2. INTRODUCTION

Lab-on-a-chip, sometimes called microfluidics, is the science and technology of systems that process or manipulate small (10^{-9} to 10^{-18} litres) amounts of fluids, using channels with dimensions of tens to hundreds of micrometres (1). These microchannels, being comparable to human hairs, guarantee very small sample consumption for a microfluidics-based assay. For example, on a microdevice with dimensions comparable to a coin, a single researcher was able to set up 144 protein crystallization experiments (2). Each experiment uses only 10nl of protein sample, as compared to 1microlitre for conventional microbatch or hanging-drop vapor diffusion technique (one microlitre represents the volume contained in a cube 1mm on a side, equaling to 1000 nanolitre). The consumption of protein sample can be further reduced to 4nl by using another microfluidic design (3, 4). For structural biology, the reduction of sample consumption is especially

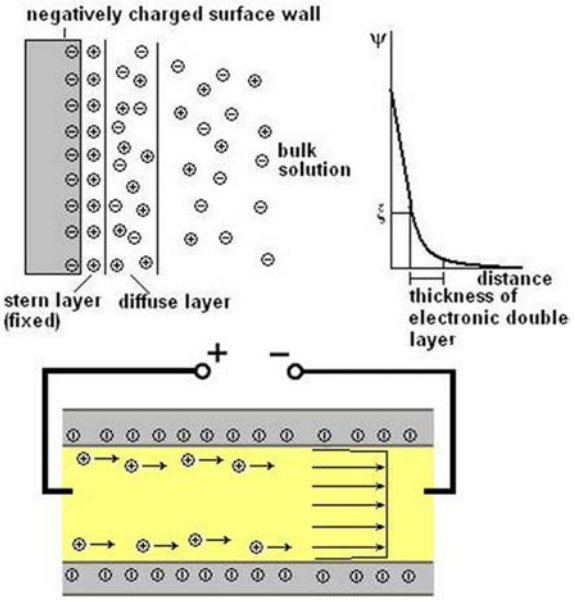

Figure 1. Illustration of the principle of electroosmotic flow.

important, considerably reducing the cost and time for producing and purifying a large volume of concentrated biomacromolecular samples (5). Miniaturization has had a profound impact on the design and fabrication of biomedical engineering systems of next generation (6).

Fluid transportation in the microchannel has many unique characteristics (7-9). Each of them can be exploited and offer advantages to microfluidics-based assay. Most typically, the motion of fluids in the microchannels features very small Reynold number (typically less than 100), a parameter used for identification of the profile of a flow. Two fluid streams thus flow in prarallel when they come together in a microchannel. Ismagilov *et al.* used this specialized phenomenon to regulate the embryonic development spatially and temporally (10), which is otherwise impossible with conventional macroscopic techniques. This approach also can be used to understand and control biological systems (11) and chemical reaction networks (12, 13).

On a substrate made of silicon, glass, or plastics, with dimensions of ~1cm^2, microchannels can form high density networks that are similar to integrated circuits (IC) in microelectronic industry. The power of these networks lies in its ability to integrate various sample handling operations within a single microdevice, which would exert revolutionary impact on science (1). Landers *et al.* developed a microfluidic genetic analysis system capable of accepting whole blood as a crude biological sample with the endpoint generation of a genetic profile (14). Upon loading the sample, the glass microfluidic genetic analysis system device carries out on-chip DNA purification and PCR-based amplification, followed by separation and detection in a manner that allows for microliter samples to be screened for infectious pathogens in <30 min. Quake *et al.* constructed a microfluidic chemostation enabling long-term monitoring of unnatural behavior programmed by the synthetic circuit, which included sustained oscillations in cell density and associated morphological changes, over hundreds of hours (15). High level integration results in sample-in-answer-out sample processing, associated with simplified instrumentation, reduced sample consumption, short time for sample handling, high sensitivity and resolution, and low cost (16).

With remarkable advantages mentioned above, microfluidics has exerted strong influence on various research areas, including molecular and cellular biology (6), drug discovery (17, 18), diagnostics (19), chemical synthesis (20), optics (21), single molecule detection (22), *etc*. About ~120 companies, including IBM, Agilent, Motorola, PE, and Beckman, have put an effort to seeking the commercialization of this technology. Mathies has launched a project that sends a microfluidic organic analyzer into outer space and explore the biomolecular signatures of life on Mars (http://www.cchem.berkeley.edu/ramgrp/alpha/). Whitesides developed *et al.* an integrated approach to a portable and low-cost immunoassay for use in resource-poor countries (23). Microfluidics has been expanding its influence into nearly all fields involving fluid handling.

For all applications of microfluidics, manipulating fluids in microchannel networks is the essential. Although how to manipulate fluids is essentially application-specific, the methods for transporting liquids are available in a limited number. We review these techniques, discussing their basic principles, advantages and disadvantages. In the discussions, we provided a number of applications for showing biologists what microfluidics can do in the biomedical research.

3. ELECTROOSMOSIS

Electroosmosis (EOF) is a kind of surface phenomenon associated with external electric field. For a system with high surface area to volume ratio, such as microchannel networks, this phenomenon can be prominent and used for pumping liquid (24). Most solid surfaces are negative charged due to the ionisation of the surface (typically, fused silica) or the adsorption of ionic species (typically, plastic). When the solid surface comes in contact with liquids, the cations of the liquid phase will gather together near the solid surface to maintain the charge balance, resulting in a double layer of ions near the interface and potential difference. This is known as zeta potential.

When the voltage is applied parallel to the microchannel surface, the cations forming the electric double layer are guided to the cathode. They therefore move through the microchannel, and as they are solvated, drag the bulk solution moving towards with a uniform velocity profile (25). (Figure 1). The bulk velocity v can be calculated using the following equation:

$$v=Zeta\cdot Epsilon\cdot E/4\cdot Pi\cdot Eta$$

where v is the average velocity of the fluid in the channel, Zeta is the zeta potential at the channel wall, Epsilon is the dielectric constant of the fluid, E is the

electric field strength, and Eta is the viscosity of the fluid. Generally, the maximum volumetric flow rate of electroosmosis pumping is less than 1microlitre/min.

Electroosmosis has the following adavantages for pumping microflows: (1) Eletroosmosis can be linearly adjusted through external electric field (equation 1); (2) Microelectrodes as part of channel design permits local generation and control of the electric field, and thus of induced EOF; (3) Electroosmosis can be actuated in microchannels made of a range of materials including quatz, glass, and polymers; (4) Electroosmosis shows blunt flow profile with which it can minimize the broadening of bands of sample in the microchannel that occurs with many pressure-driven systems like liquid chromatography. Electroosmosis thus has been intensively used for electrophoretic separation with offering high resolution separations of ionic species such as DNA (26, 27), protein (28), small molecules (29), chiral drugs (30), *etc*. Electroosmosis also was used in the field of mixing (31), electrochromatography (32), isotachphoresis (33), sample preconcentration (34), genotyping (35), microfluidic array (36), biocomplementary interaction (37, 38), immunoassays (39), *etc*.

For microfluidic applications based on electroosmosis, a stable electroosmotic flow is generally required. However, this is often challenged by adsorption of biomolecules onto the channel wall, which tends to alter the surface charge condition and thus electroosmosis. This occasion is especially obvious in microdeives made of PDMS. Surface modification of PDMS has already been an important branch of lab-on-a-chip technologies. PDMS material possesses very low free surface energy (~20 erg/cm^2), thus it can irreversibly adsorb most biopolymers from aqueous solution. The development of routine, simple, and well-defined surface modification protocols for PDMS is essential to the development of microfluidic technology in PDMS-based substrates. Oxygen plasma (40) and ultraviolet light (41) are used mostly to convert PDMS surfaces from hydrophobic and inert into hydrophilic and reactive, although the hydrophobicity recovers quickly. Hydrophilic polymers like polyacrylamide have been linked to PDMS surfaces by UV (42, 43) and cerium ion (44) inducing grafting, or atom transfer radical polymerization (45), which improved the separation of peptides. Phospholipid bilayer adsorption (46), three layer biotin-neutravidin sandwich adsorption (47), and chemical vapor deposition (CVD) (48) incorporated functional groups on PDMS surfaces, which could be used for further biochemical derivatization. Our group also developed several methods to avoid protein adsorption on channel walls (49, 50).

In addition to external applied voltage, electroosmosis also can be adjusted by varying the zeta potential. By integrating an electrically-insulating layer of silicon dioxide into a silicon substrate, field-effect control of electroosmotic flow was achieved on a microfluidic system (51). Varying the magnitude and the polarity of the resulting radial electric potential gradient across the silicon dioxide layer gave direct control of the zeta potential and the resulting electroosmotic flow. Electroosmosis also can provoke hydraulic pumping that can be used to differentiate ion transport on a microfluidic chip (52). The microdevice contains a tee-junction with one inlet held at high voltage and one outlet at ground. The ungrounded outlet experiences pressure-induced flow when electroosmosis in the ground channel is reduced by a viscous polymer coating. Anions can be switched between outlets by changing the flow resistance in the field-free channel relative to the ground channel. In another electroosmotically-pumped device gaseous electrolysis products were removed though a permeable polymeric membrane (53). The electroosmotic flow rates were dependent on applied voltage, however independent of the field strength and length of the electroosmotic pumping.

Many reviews or books have discussed electroosmosis-related phenomenon. Probstein explored the principle of electroosmosis in detail (54). Bruin presented a review about electrokinetically-driven microfluidic separation devices, in which microchip layouts, functional elements, use of alternative materials to glass, and multiple detection methods were discussed (55). There is a good review about surface modification of PDMS microchannel by Makamba *et al.* in 2003 (56). Bousse reviewed applications of electrokinetically-driven microdevices in the field of DNA separations, enzyme assays immunoassays, and polymerase chain reaction (PCR) amplification integrated with microfluidic assays (57). Yao and Santiago presented a detail description of history and development of electroosmosis pumps (58).

4. PRESSURE

Pressure is another major means for transporting liquids on microdevices in addition to electroosmosis. As compared to electroosmosis, pressure has the following advantages: (1) there is a number of mechanisms for generating hydraulic pressure with offering a wide spectrum of flow rate; (2) the pressure flow is independent of solution composition, without causing preferential transportation of solutes; (3) the pressure flow rate is also independent of the channel material and charge condition of channel wall; (4) the amount of pumped liquid can be readily controlled in a known manner, and the fluid frontier can be easily and precisely located. The complication of pressure lies in the fact that pressure-driven flow in a channel exhibits a non-uniform velocity profile, which is pseudo-parabolic, depending on the cross section of the microchannel. The flow rate decreases from the maximum value in the center of the channel is maximum to zero velocity immediately proximal to the channel walls. Although the theoretical basis of the fluid dynamics has been well-established, known as the Navier–Stokes equations with proper boundary conditions (59, 60), the implications of this behavior for microfluidic assays remain an active area of research (61, 62).

4.1. Positive displacement

On a microfluidic chip, hydraulic pressure can be easily generated by positive displacement, typically through a syringe pump, via a chip-to-world interface consisting of tubing, sample reservoir, and epoxy glue (or screw) for sealing. This configuration was popular in

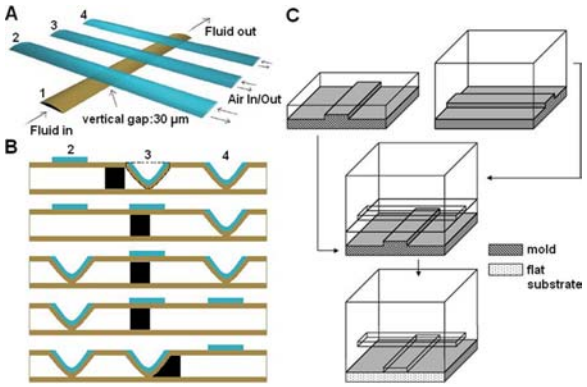

Figure 2. (A) Diagram of an on-chip reciprocating displacement pump; (B) Working principle of the pump; (C) The fabrication process of pneumatically actuated in-line microvalve using PDMS rapid prototyping. [From ref 78 (M. A. Unger, H. P. Chou, T. Thorsen, A. Scherer and S. R. Quake: Monolithic microfabricated valves and pumps by multilayer soft lithography. Reprinted with permission from (78).

various microfluidic applications, including mixing (63), T filter (64), electrochemical sensor (65), biomolecular recognition (66), temperature gradient assays (67), immunoassays (68), pharmacological profiling (69), *etc*. because its implementation is very simple, and can be realized in nearly all laboratories. For example, Chen *et al.* used it to sequentially load neutral FITC-estrogen sample for electrophoresis, which can eliminate the notorious injection bias occurred with electrokinetic sample loading (70). Furthermore, it enabled a waste-removing function due to incorporation of an enlarged sample waste reservoir and several subreservoirs into the injector. Ye *et al.* used it to load cell and drug into a microdevice investigating process of cell apoptosis (71). This apoptosis analyzer can be easily multiplexed and used for drug screening at the cell level. Zhong *et al* (72) used it to construct on-chip solid phase extraction column, on which purification DNA from crude samples was performed. This device is readily subject to integration with other components to realize sample-in-answer-out DNA analysis.

Although extremely widely used, syringe pumps have some disadvantages including mechanical complication, overall package size, and the fact that such pumps are rarely available for lower flow rates. Because all the syringe pumps are actuated by a group of gears, even the most precise commercially available syringe pumps can not provide a non-pulsatile flow suitable for many microfluidic applications. In addition, this type of ultra-precise syringe pump is very expensive. The interface of syringe pump and microdevice also is a problem, which has been discussed in detail by Futterer (73). An ideal interface should be zero dead volume, rigid, and hydrophilic, or spurious flow or strong hysteresis inevitably occurs in the microchannels.

4.2. Reciprocating displacement

Quake's group developed a kind of pneumatically driven reciprocating displacement pumps made by lithographically patterning multiple layers of a soft elastomeric substrate, most typically, a PDMS one (74-78).The basic configuration of such pumps is illustrated in Figure 2 A. Channel 1 is fluid transporting channel, while channel 2, 3 and 4 are valve channels that are pheumatically actuated. When pressurized gas was applied to the valve channels, the elastic PDMS material is deformed and able to obstruct the fluid transporting channel tightly, thus pinch off the flow of fluids inside. The whole pumping process is demonstrated in Figure 2 B. Depending on periodic on/off process of the valve channels, the fluid can be pumped in the fluid transporting channel. The fabricating process of this microfluidic system is illustrated in Figure 2 C, which is straightforward. Typical channels were 100 micro-metre wide and 10 micro-metre high, giving the valve an active area of 100 micrometre × 100 micrometre. The valve was closed with a pneumatic pressure of 60 kPa within several milliseconds, and back to its initial opening position by its own restoring spring force (40 kPa) (78).

The most significant advantage of these pneumatically actuated pumps lies in its ability to pattern fluids on microdevices, associated with involvement of additional pneumatically actuated valves, thus it enables a true laboratory on a chip. Such pumps also can readily handle sample of nanolitre volume with nearly zero waste, thus tremendously reduce the sample consumption for a biomedical assay. Many important biomedical applications have been fulfilled with this superior powerful solution pumping method, such as single cell sorting (76, 79, 80), enzymatic assays (81, 82), large-scale screening of protein crystallization conditions (2), chemical syntheses (83), and polymerase chain reactions (74, 84). Large-scale integration in microfluidic systems analogous to integrated circuits in the microelectronic industry was realized, with which liquid can easily patterned and displayed on a planar substrate (75) (Figure 3). The significance of this kind of large-scale integration was exemplified by the 400 PCR reactions performed on a 20 × 20 microfluidic channel matrix containing 2860 in-line microvalves (74). Each reaction consumed only 2 nl aliquot of polymerase. Furthermore, the large valves or the small valves were selectively actuated because they had different thresholds of hydraulic pressure necessary for actuation. The microfluidic large scale integration provided a general method to perform chemical and biological experiments with precious reagents in a highly automated mode.

The essential element of this pneumatic pump is elastic PDMS diaphragm, thus it suffers from the drawback of this material. For example, PDMS swells in most organic solvents (85). The swelling of PDMS-based devices makes it impossible for assays involving organic solvents. Mathies and coworkers developed another sort of pneumatically driven reciprocating displacement pump (86), which can partially solve this problem. This pump still is comprised of three valves but only the displacement chamber is involved with PDMS material. When the vacuum applied in the displacement chamber drags the PDMS membrane down, two discrete microchannels are connected. In this case, this valve is turned on. Once the

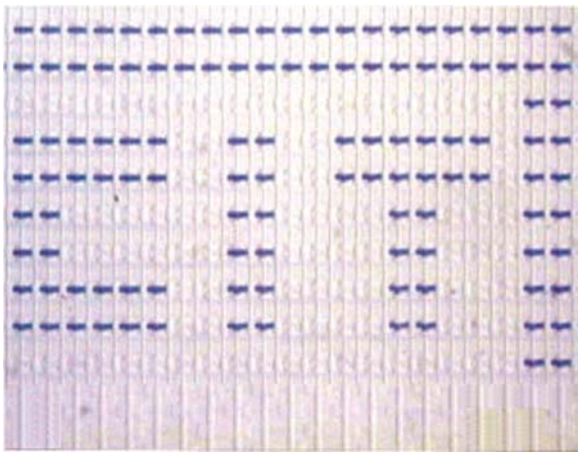

Figure 3. Demonstration of microfluidic patterning: Individual chambers are selectively filled with blue dye to spell out "C I T". [From ref 75 (T. Thorsen, S. J. Maerkl and S. R. Quake: Microfluidic large-scale integration. Reprinted with permission from (75).

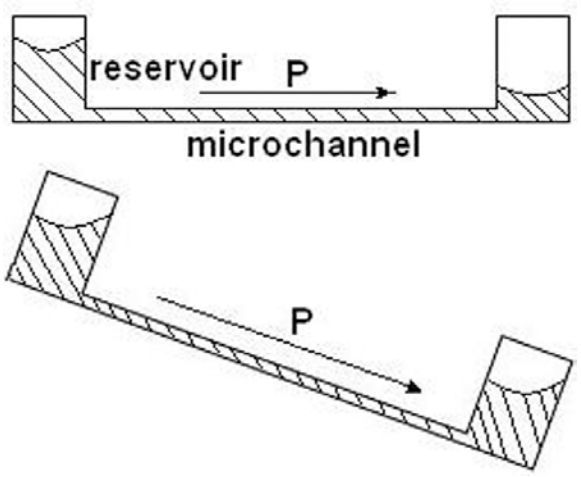

Figure 4. Illustration of the two means to induce on-chip hydrostatic pressure.

vacuum is released, the valve is turned off. Relying on this periodic on/off process, the fluid is pumped in the microdevice. A representative micropump with a 3.0 mm diameter PDMS diaphragm was reported to pump water with maximum volumetric flow rate of 2.8 microlitre min−1 and maximum pressure of 30 kPa (86).This pumping approach minimizes the contact of fluid and PDMS, and has found application in the electrophoresis separation (87) and DNA sequencing in a high level integration manner (16). Rolland and coworkers found a new kind of elastomer named perfluoropolyethers (PFPEs) (88), which can serve as the alternative to PDMS. This material is photocurable and highly chemical-resistant like Teflon. Through similar rapid prototyping method, an in-line microvalve based on photocurable PFPEs was formed.

4.3. Gravity

Gravity is another means to generate pressure in the microchannel. Depending on tilting the microdevice or differentiating liquid level between reservoirs, hydraulic pressure can be generated in the microchannel (Figure 4). Gravity-induced flow, known as hydrostatic pressure flow, is non-pulsatile and free of world-to-chip interface. Although hydrostatic pressure flow is not stable, being subject to a continuous decreasing, it has been widely used in cell handling (89), generating sheath flow (90), immunoassay (91), single molecule detection (92, 93), and electrophoresis injection (94) with offering the advantage of local generation, and thus simplification of microfluidic instrumentation. Yager *et al.* also used gravity as driving force for the famous "T-sensor".

4.4. Surface tension

In a glass capillary (or microchannel), liquid tends to demonstrate a curved surface due to hydrophilic channel wall. Capillary pressure can be defined as the pressure difference between the inside and outside of the curved surface, which would drive the liquid moving rightward (Figure 5 A). The capillary pressure depends upon the surface tension and the radius of the meniscus and the mathematical formula is,

$$P=2\cdot nu/R$$

where nu is the surface tension at the liquid-air interface (force/distance) and R is the radius of curvature of the meniscus. Obviously, if using capillary pressure to transport liquids in a microchannel, one has to maintain the liquid-air interface in the microchannel. This purpose generally is fulfilled by evaporation. Burn *et al.* (95) developed such an evaporation-capillary pressure system to deliver a microflow with ultra low velocity suitable for investigating stretching of single DNA molecule (Figure 5 B). Delamarche and coworkers successfully used this system in performing surface immunoassay (96). Such system also can be used in on-chip chromatography (97). Zimmermann *et al.* revised the design of evaporation area and reported an evaporation-capillary pressure pumping system based on open microfluidic networks (98). Fang [(99)] integrated normal filter paper into the evaporation area to increase the flow rate by a factor of 10^3.

With respect to transporting microflows, evaporation-capillary pressure system has the following advantages: (1) the microfluidic system is straightforward to fabricate; (2) the pumping system is self-contained and simple to use; (3) the design of the system is flexible; (4) the system is free of dead volumes and easily duplicated to form arrays.

Capillary pressure also can transport liquid droplet in a microchannel. Figure 6 A shows a droplet presented in a glass microchannel; the droplet is static because of the equilibrium between the capillary pressures at both ends of the droplet. Burns and coworkers (100) integrated microheaters into to the microdevice to increases the local temperature of the right meniscus, resulting in a decreased capillary pressure, thus the liquid droplet moved rightwards under the difference of bilateral capillary pressures. By integrating a series of microheaters, this pumping system was used for DNA sample analysis in an

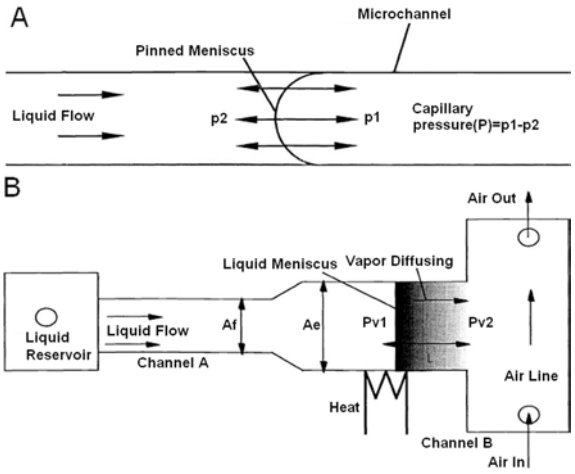

Figure 5. (A) Microflow driven by capillary pressure; (B) Evaporation-capillary pressure pumping device schematic [From ref 95 (V. Namasivayam, K. Handique, D. T. Burke, R. G. Larson and M. A. Burns: A Microfabricated valveless pump for delivering non-pulsatile flow. Reprinted with permission from (95).

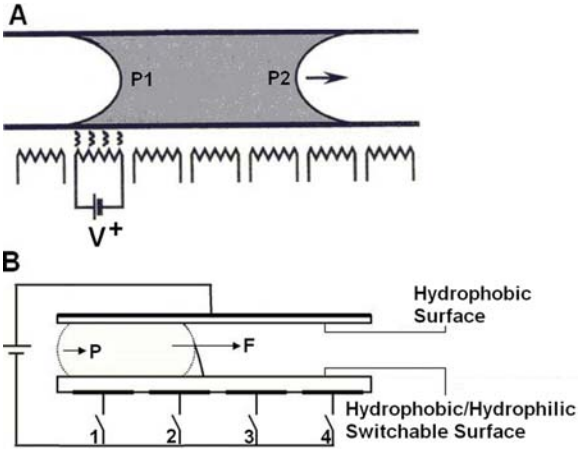

Figure 6. (A) Schematic drawing showing the principle of thermally induced drop motion in a closed channel. [From ref. 100 (M. A. Burns, C. H. Mastrangelo, T. S. Sammarco, F. P. Man, J. R. Webster, B. N. Johnson, B. Foerster, D. Jones, Y. Fields, A. R. Kaiser and D. T. Burke: Microfabricated structures for integrated DNA analysis. Proc. Natl. Acad. Sci. U. S. A., 93(11), 5556-5561 (1996)). Reprinted with permission from PNAS]Reproduced with permission from, ref 100; (B) Schematic diagram showing the principle of electrowetting induced drop motion between two surfaces. Reprinted with permission from (107).

integrated manner. A problem of this technique is the unneglectable evaporation due to heating, which will alter the concentration and ionic intensity of the solution. This problem is partially circumvented in another capillary-pressure-related liquid transporting technique---electrowetting. As demonstrated in Figure 6 B, the upper surface is hydrophobic, while the bottom surface is hydrophilic/hydrophobic switchable depending on the acuation (or not) of the electric field applied between the both surfaces. Once the switch-2 is turned on, the hydrophobicity of the surface locating the right meniscus is reduced or even converted into a hydrophilic one, causing the decreasing of the capillary pressure generated by the right meniscus. As a result, the droplet moves rightwards. Depending on an array of microelectrodes, droplets in which biomedical molecules of interest are resolved can be created, located, transported, cutted, and merged on microdevices as you want (101). Small droplets can be extracted from larger reservoir droplets transported to specifically designed locations (102) (Figure 7). The small droplets can be merged and mixed to induce chemical reactions (103, 104). The electrowetting-related microfluidics also is called “digital microfluidics”. Kohler (105) and Min (106) give a review of applications of digital microfluidics in the biology. Mugele and coworkers discuss the electrowetting technique from basic principle to applications (107).

4.5 Centrifuging

Centrifugal force, depend on rotating machinery for continuously adding momentum to the fluids, was used for pumping biological samples. It can offer a wide range of flow rate depending on the frequency of rotation. Centrifugal microdevices, generally in a circle shape, are regarded as a suitable way of microfluidics’ approaching the clinical application because bioassays based on centrifugal microdevice is readily accessible to rapidness, reliability, high throughput, low cost, and easy instrumentation. Grumann and coworkers developed a set of point-of-care devices for performing centrifugal microfluidic assay such as whole blood analysis (108), direct hemoglobin measurement (109), multiplexed bead-based fluorescence immunoassays (110), and batch-mode mixing (111). Other assays like protein-ligand binding (112), ELISA (113), nucleic acid hybridation (114), *etc.* also were conducted. Gyros Company has commercialized centrifugal microfluidic technology and produced Gyrolab Bioaffy® CD microlaboratory, which is precise, rapid, and reliable in quantify proteins or disease markers. This company also published a group articles to discuss the potential of this technology in clinical chemistry (115, 116). This technology also found applications in optifluidics (117) and integration of sample preparation and MALDI mass spectrometry (118).

5. CONCLUSIONS

This paper summarizes the popular methods for transporting fluids on biomedical Lab-on-a-chip and provides a number of applications. Electroosmosis introduces a plug-shaped flow in microchannels but the stability of the flow is affected by the charge condition of the channel wall. It is not a generic method to transport the fluids in microchannel. Pressure-driven flow, in principle, is not dependent on the conditions of the channel wall, but suffers from parabolic flow profile. Determination of optimal liquid transporting method relies on particular applications. Pressure can be generated by a number of methods, in which positive displacement is most widely

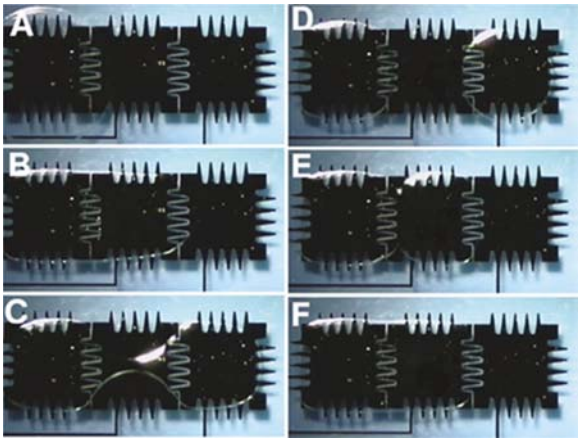

Figure 7. A photograph showing droplet formation using only electrowetting forces [From ref 102 (M. G. Pollack, A. D. Shenderov and R. B. Fair: Electrowetting-based actuation of droplets for integrated microfluidics. Reprinted with permission from (102).

employed; reciprocating displacement pump is suitable for transporting nanolitre-volume sample, enabling large-scale biomedical screening and sample-in-answer-out sample processing on a microdevice. Centrifuging, surface tension, and gravity have brilliant prospect in the development of clinical point-of-care devices.

6. ACKNOWLEDGEMENTS

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Abbreviations: PDMS: Poly-dimethyl siloxane

Key Words: Lab-on-a-chip, Microfluidics, Pumping, Electroosmosis, Pressure, Surface tension, Centrifuging, Gravity, Displacement, Review

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