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Continuous Flow Pressure Driven Microfluidic Techniques for Point of Care Testing

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Abstract: The recent advent of the miniaturization technology witnessed over the last decades has led to development and creation of several conventional microfluidic techniques. A microfluidic platform can be broken down into a set of fluidic unit operations which are miniaturized versions of orthodox large scale (bio-chemical) laboratory operations. These miniaturized operations are designed for easy integration and automation within a well-defined fabrication technology; which permits simple, easy, fast, and cost-efficient implementation of different application-specific bio-chemical processes for point care diagnostics. Processes that can be automated at this scale include nucleic acid extraction, amplification and detection. The improvement in technology within the previous decades has led to significant developments of techniques used in implementing several microfluidic processes. The auspicious developments that have greatly impacted areas in medical research, therapeutics and POCT applications are brought into focus by this research on a continuous flow configuration. Through these visualization platforms such as pressure driven flow, magneto-hydrodynamics dielectrophoresis, large-scale integration are analyzed under continuous flow characteristics. Finally this review also provides adequate examples whilst investigating the strengths and limitations of every technique. *Copyright © 2014 IFSA Publishing, S. L.*

Keywords: Continuous flow, Pressure driven, Microfluidics, Point of care testing, Lab-on-a-chip.

1. Microfluidics Technology

In the latter period of the 20th Century, the interest in the innovative use of microfluidic technology for expedient clinical application especially in the case of "point-of-care" diagnosis of diseases grew propitiously [1, 2]. This growing trend brought about the inception of the device known as "lab-on-a-chip" i.e. the miniaturization of laboratory processes within a microfluidic device. This technology is a multidisciplinary field intersecting engineering, physics, chemistry, micro-technology and biotechnology, with practical applications to the design of systems in which small volumes of fluids are required. The systems developed by microfluidic technology can be used to automate biological experiments by manipulating geometrically constrained small quantities of fluid, typically within the sub-millimetre scale. This conventional technology depends on the behaviour of continuous liquid flow through micro fabricated channels. However, actuation of flow is implemented with external assistance of micro-pumps and micro-valves which are complex and cumbersome. The physical

properties of fluids at the micro-scale differ from the generic behaviour of macro-scale quantity in factors such as surface tension, energy dissipation and fluidic resistance. Microfluidics analyze how these properties can change, and how they can be exploited for specific design requirements.

The microfluidic lab-on-chip device is a subset of micro-electromechanical systems (MEMS) for biological application which is collectively known as (BioMEMS). MEMS technology involves integration of electrical and mechanical components which is inclusive of micro sensors, micro pumps and micro actuators in the same platform using standard fabrication techniques of the semiconductor industry with similar equipment and materials [3]. The advent of this technological breakthrough has led to the development of micro-total-analysis-systems (μ-TAS) which is similar to lab-on-a-chip platforms (LOC). LOC technology involves the scaling of single or multiple lab processes down to chip-format, whereas "μTAS" is dedicated to the integration of the total sequence of lab processes to perform chemical analysis and can also be used in diverse application for other analysis including chromatography (Vilker et al., 2002). Rapid development of miniaturized laboratory diagnostic devices could provide a great impact on modern society's health by allowing rapid and low cost diagnosis of diseases. In recent years there has been tremendous interest in harnessing the full potential of this approach and, consequently the development of countless microfluidic devices and fabrication methods. Materials such as poly-dimethyl siloxane (PDMS) and Poly-methyl methacrylate (PMMA) have emerged recently as excellent alternatives to the silicon and glass used in early devices fabricated by MEMS processes [4-6]. Increase in popularity of their use in the manufacturing of microfluidic devices stems from low cost, excellent optical transparency, attractive mechanical/chemical properties and simple fabrication procedures.

The revolutionary idea of fitting an entire laboratory on a chip was motivated by the electronic industry fitting an entire computer on a microelectronic circuit chip. In a typical diagnostic scenario, the sample is collected from the site and sent to centralized laboratories for analysis, which is a cost intensive and time consuming process. Miniaturized laboratory analysis techniques offer many advantages over standard bench-top procedures: small volume requirement which means only small quantities of reagents are needed reducing costs and waste, contamination is reduced by removing pipetting stages and lab on a chip is conducive to automation, analysis times are also effectively shortened since efficiencies are usually higher when working on a smaller scale with operational simplicity. Benefits include fast analysis time, portability, cost reduction, disposability, reduced consumption of reagents and efficiency, all of which are revolutionizing clinical diagnostics and many biochemical laboratory procedures by these means making the lab-on-a-chip technology ideal for near-patient and point-of-care testing. Simplified device fabrication and the possibility of incorporating densely integrated microvalves into designs [6] have helped microfluidics to explode as ubiquitous technology that has found applications in many diverse fields, however complete 'sample-in to answer-out' solutions have delayed LOC devices reaching the market. Whilst amplification [7] and detection methods have been well developed for individual systems with low limits of detection; sample preparation has had little development and is impeding development of true POC devices which are simple, rapid, sensitive, specific and affordable [7-9].

2. Point of Care Diagnostics (POCT)

POCT is peripheral laboratory testing or Near Patient Testing (NPT) that involves any analytical test performed for or by a patient outside the conventional medical laboratory setting [10, 11]. The principal concept behind POCT is to provide quick identification of diseases at the time the test is carried out [9]. This innovation improves the likelihood that the patient, physician, and care team will receive the results faster thus making room for instantaneous clinical management decisions to be made. Examples of POCT include blood glucose testing, blood gas and electrolytes analysis, infectious disease testing, urine strip testing and pregnancy testing. Commercialization of this medical diagnostic innovation involves the combination of the POCT concept with microfluidic technology. This combination has led to production of handheld and portable diagnostic kits that come either in multiple parts or a compact integrated piece (all in one kit). Fig. 1-2 provides an illustration of the multiple parts diagnostic kit that includes the sample collection platform (LOAC) and an electronic identification component. On the other hand the integrated diagnostic kit has both the sample and detection platforms in a compact piece, leading to possible trade-offs in reusability over compatibility. The use of one device to test multiple predisposed disease symptoms has led to POCT industries investigating reusable devices. This approach encourages sound economic advantages in cost reduction and material wastage. Top amongst various design initiatives are the disposable LOC platforms that can provide these POCT production companies a convenient means to achieve this economic and versatility advantages. Furthermore the user friendliness approach of diagnostic testing kits operation adds another dimension to the overall system, such that a semi-skilled operator or patient self-test can be carried out conveniently to achieve reliable results. With these qualities public acceptance and adoption becomes easier which improves marketability. Besides the diverse fields of applications that are associated with a number of POCT devices, there some important

requirements of the different market segments that include [12]:

- Portability: miniaturized, hand-held device with low energy consumption;
- Output: number of samples/assays per day;
- Cost of instrument: investment costs of the instrument (reading device);
- Cost of disposables: defining the costs per assay (together with reagent consumption);
- Number of parameters per sample: number of different parameters to be analyzed per sample;
- Low reagent consumption: amount of sample and/or reagents required per assay;
- Diversity of unit operations: the variety/comprehensiveness of laboratory operations that can be adopted;
- Precision: the volume and time resolution that is applicable;
- Programmability: the flexibility to adapt liquid manipulating protocols without fabricating a new chip.

Fig. 1. Disposable chip and automation control device.

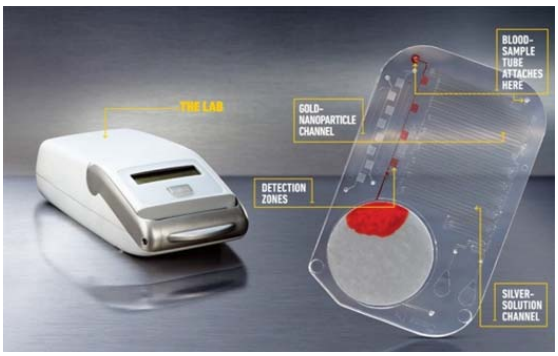


Fig. 2. Lab-on-a-chip with external automation [115].

Fig. 3 illustrates a block diagram of a LOAC diagnostic chip. A POCT diagnostic device has three fundamental functionalities: sample preparation, amplification (only for DNA) and sample analysis or detection. However, an additional step might be needed for pre-processing of the sample to increase the concentration of the target molecules such as filtering and pre-mixing (i.e. urine sample).

3. Microhydrodynamics

Since most microfluidic systems operate at low Reynolds numbers the physical properties of fluids at the micro-scale can differ from the generic behaviour of macro-scale quantities in factors such as surface tension, energy dissipation and fluidic resistance. The field of micro-hydrodynamics analyses how these properties can change, and how they can be worked around, or exploited for specific design requirements. In microfluidic systems, liquid movement can be categorized under two means of fluid transportation; which are continuous flow and discrete flow.

Continuous flow is defined by incessant and seamless flow of fluid/fluids (miscible or immiscible) which are composed of molecules that collide with one another within a confined boundary (microfabricated channels). Moreover, these molecules are assumed to obey the continuum assumption [13], which considers fluid being made up of molecules in a continuous phase rather than in a discrete phase. As a result, physical properties such as pressure, density, temperature, and velocity of infinitesimally small fluid particles are assumed to vary continuously with reference to one another [14]. Most pressure driven flow POCT devices operate under these means of fluid transportation. Some examples of pressure driven flow which makes use of micropumps, plungers or mechanical blisters utilize this means of fluid transportation. Furthermore non-mechanical techniques such as sound waves or a combination of capillary forces with electrokinetic mechanisms (e.g. electro-osmotic flow) [15, 16] also utilize this means.

On the other hand, discrete microfluidics commonly known as droplet microfluidics, utilizes minute or discrete volume of fluid in the form of droplets contained within an immiscible continuous phase as means of transportation (Zengerle & Ducrée, 2004; Liu, Deng, Qin, et al., 2011). The small volumes of fluid are isolated from each other in continuous motion offer the opportunity of novel solutions to today's biomedical engineering challenges for innovative POCT protocols and therapeutics. For instance, droplets allow significant reduction in sample volumes to be analyzed, leading to corresponding reduction in cost. Furthermore, compartmentalization in droplets improves assay sensitivity by increasing the effective concentration of rare species and reducing the time needed to reach the detection threshold [17, 18]. In addition, the platform dimensional scaling advantage encourages controlled and rapid mixing of fluids in the droplet reactors, resulting in significantly reduced reaction time, accurate generation and repeatability of droplet operations. Droplet microfluidics incorporates two distinct methods which are digital microfluidics and segmented flow microfluidics [19, 20].

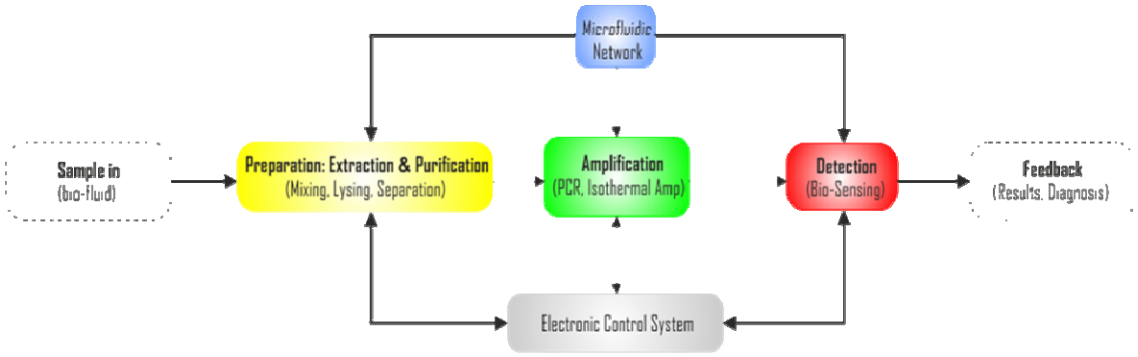


Fig. 3. A block diagram of a LOAC diagnostic chip.

One of the significant properties shared by both types of fluid flow is viscosity (μ); which can be described as the ratio of shear stress to velocity gradient. Viscosity describes the resistance of a fluid to any deformation caused by either external body immersed in fluid or between different layers inside the fluid [21]. In addition, the higher surface to volume ratio, higher mass-heat transfer ratio and low Reynolds number are other characteristic properties of fluids in micro-systems.

Another major characteristic endemic at the micro-scale is the flow disposition which is practically defined as laminar flow. Laminar flow or steady flow occurs when fluids move in parallel layers, exhibiting no disorder between their repetitive layers [22, 23]. In fluid dynamics, the velocity of flow varies from zero at the walls to a maximum along the centreline with the flow regime characterized by high momentum diffusion and low momentum convection since there are no cross currents perpendicular to the direction of flow, nor eddies [24, 25]. At low velocities the particles of these fluids are very organized, enabling them to move in straight lines parallel to the pipe walls which in turn inhibit lateral mixing as a result of the adjacent layers sliding past each other effortlessly. When taking into consideration scientific and empirical observations of fluid flows in microchannels of a microfluidic device, Reynolds number of much less than 1 is observed [23, 24, 25, 26]. This type of flow is also known as creeping motion or Stokes flow and it is an extreme case of laminar flow where viscous (friction) effects are much greater than inertial forces [27-29]. This relationship is defined as Reynolds number as a dimensionless parameter and is given by the ratio of inertial force ($\rho V^2 L^2$) to viscous force (μVL) as follows:

$$Re = \frac{inertial\ force}{viscous\ force} = \frac{\rho V^2 L^2}{\mu VL} = \frac{VL}{v}, \quad V = \frac{\mu}{p}\left(\frac{m^Z}{s}\right) \tag{1}$$

where V is the characteristic velocity of fluid, L is characteristic length of the geometry, ρ is the fluid density, μ is the dynamic fluid viscosity and v is the kinematic viscosity of the fluid.

In microfluidics it is usually assumed no gravity, incompressibility and dominant viscous forces. The flow of a fluid through a microfluidic channel can be characterized by the Reynolds number, similar to equation 1:

$$Re = \frac{LV_{avg}\rho}{\mu}, \tag{2}$$

where V_{avg} is the average velocity of the flow, L is the most relevant length scale, ρ is the fluid density and μ is the dynamic fluid viscosity.

Fluid flow through a control volume can be described by the complete Navier-Stokes (N-S) equations. These equations can be derived from the principles of conservation of mass, momentum and energy. Navier-stokes equations are a non-linear set of differential equations which explain the motion of fluid in general. This equation is defined by applying Newton's second law to fluid motion by assumption of continuum fluid and small fluid velocity compared to the speed of light. The general form of these equations has no solution and is used in computational fluid dynamics. Also the equations do not dictate position but rather velocity. A solution of the Navier–Stokes (N-S) equations is called a velocity field or flow field, which is a description of the velocity of the fluid at a given point in space and time. Once the velocity field is solved for, other quantities of interest (such as flow rate or drag force) may be found. The complete equation is shown below [30]:

$$\rho\left[\frac{\partial y}{\partial t} + v \cdot \nabla v\right] = -\nabla p + \nabla \mathbb{T} + f, \tag{3}$$

where v is the flow velocity, ρ is the fluid density, p is the pressure, T is the (deviatoric) stress tensor, and f represents body forces (per unit volume) acting on the fluid and ∇ is the Del operator.

The general form of N-S equations can be simplified by assumption of incompressible flow which is common in microfluidics [31]. This

assumption simplifies the form of N-S equations and can be written as the following:

$$\rho\left[\frac{\partial y}{\partial t}+v\cdot\nabla v\right]=f_{pressure}+f_{friction}+f_{volume}, \quad (4)$$

where $\partial v/\partial t$ is the unsteady acceleration, $v\cdot\nabla v$ is the convective acceleration, ρ is the density, $f_{pressure}$ (∇p) is the pressure gradient, $f_{friction}$ $\left(\mu\nabla^2 v\right)$ is the viscosity of fluid, f_{volume} $(-\rho g)$ is the body force of fluid.

In microfluidics, the fluid flow is mostly described by Poisson equation. This equation can be derived from N-S equations by applying boundary conditions in micro-channels. When a fluid is bounded by solid walls, the fluid velocity is assumed zero at liquid-solid interface. This is because of molecular interactions between two phases which forces the fluid molecules to seek the momentum and energy equilibrium of solid surface. This phenomenon is called no-slip condition and will be used as boundary condition at interface between fluid and solid surfaces. Therefore the simplification of N-S applies the following conditions for two dimensional flows [31, 32]:

- No slip at the wall;
- Infinitesimal gravity, $\rho g = 0$;
- Convection effect is negligible, $v\cdot\nabla = 0$;
- Laminar flow (steady flow), $\partial v/\partial t = 0$;

Therefore Poisson equation for a pressure driven flow is given as:

$-f_{pressure}$ $(-\nabla p)$ is the pressure gradient

$= f_{friction}$ $\left(\mu\nabla^2 v\right)$ is the viscosity of fluid

$$\nabla p=\mu\nabla^2 v, \quad (5)$$

Equation 5 can be further expressed in two dimensional Cartesian co-ordinates as [30-31].

$$\frac{dp}{dx}=\mu\frac{\partial^2 u}{\partial y^2}, \quad (6)$$

3.1. Viscosity Effect

In general, viscosity is the quantity that describes a fluid's resistance to flow. Fluids resist the relative motion of immersed objects through or besides them as well as the motion of layers with differing velocities within them in any flow [33-35]. These layers move at different velocities and the fluid's viscosity arises from the shear stress between the layers that ultimately oppose any applied force. Viscosity is important because it acts as an opposing force in mixing of two liquids [34]. Viscosity of a fluid might change by changing the temperature or pressure but if the viscosity of a fluid is constant at all shear rates at constant temperature and pressure; the fluid is known as Newtonian. The relationship between the shear stress and viscosity and velocity in Newtonian fluid can be described as follows [36]:

$$\tau=\mu\frac{\partial u}{\partial y}, \quad (7)$$

where τ is the shear stress, μ is the fluid dynamic viscosity coefficient (du/dy) is velocity gradient.

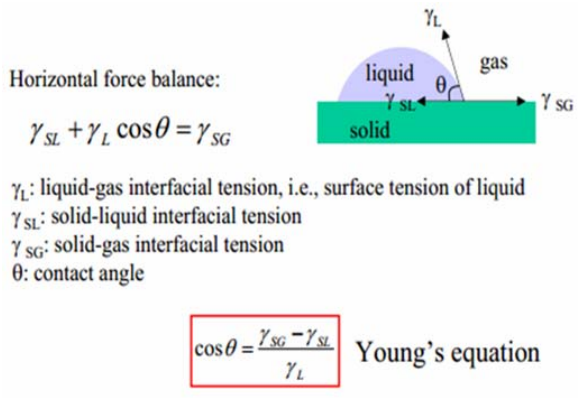
Basically, the viscosities of most liquids (Newtonian) decrease with increasing temperature, and vice versa [36]. As the temperature increases, the average velocity of the molecules in a liquid increases and the amount of time they expend "in contact" with their nearest neighbours decreases. Thus, as temperature increases, the average intermolecular forces decrease [34, 37]. Another factor is pressure, viscosity is normally independent of pressure, but liquids under extreme pressure often experience an increase in viscosity. Since liquids are normally incompressible, an increase in pressure doesn't actually result in bringing the molecules significantly closer together i.e. increase in pressure doesn't register a significant change in viscosity of an incompressible fluid [21, 31].

In the case of non-Newtonian fluids the viscosity is a function of mechanical variables such as shear stress or time. These fluids are also directly affected by temperature and are classified as shear-thinning and shear-thickening [36]. Materials that thicken when worked on or agitated are called shear-thickening fluids. While materials that experience decrease in viscosity under shear stress are described as shear-thinning fluids. Blood falls under this category and is also known as a Bingham plastic [36] because it requires a threshold shear stress for it to make a transition from a high viscosity to a low viscosity fluid. The blood fluid must reach a shear rate of about 100 (1/sec) to be assumed Newtonian and after this shear rate is reached the viscosity is about five times as great as the viscosity of water [38]. Urine at room temperature can be categorized as a Newtonian fluid due to the fact that it contains about 95 % of water [38].

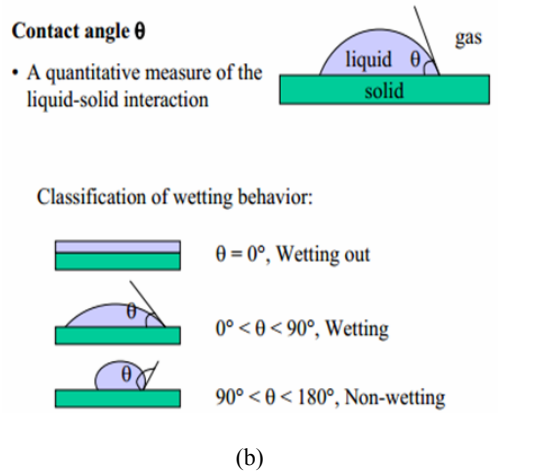
3.2. Surface Tension Effect and Capillarity Phenomenon

The cohesive forces between the liquid molecules are responsible for this phenomenon of surface tension which allows the surface of a liquid to resist an external force as a result of imbalance molecular attractive forces at the interface [30, 39]. In a bulk solution, each molecule is pulled equally in every direction by neighbouring liquid molecules, resulting in a net force of zero. The molecules at the surface do not have other molecules on all sides of them and therefore are pulled inwards. This creates some internal pressure and forces liquid surfaces to contract to the minimal area [40]. The surface tension

depicted in Fig. 4 is the excess energy per unit area of the fluid surface when it is in contact with another material) or phase (solid or fluid) [41].



(a)



(b)

Fig. 4. Young equation depiction of solid-liquid interaction in ambience air, this schematic shows the surface tension forces at the contact line. (a) Liquid drops placed on a flat surface try to adopt spherical cap shape in other to minimize the surface energy. (b) describes the surface wettability in relationship to liquid-surface angle [39].

This largely determines the spherical shape of the fluid droplet placed on a solid surface. Young's equation shows a liquid droplet in contact with a solid surface and ambient air Fig. 4.1(a), the equilibrium forces due to the surface tensions at the liquid-gas (γ), solid-liquid (γ_{SL}) and solid-gas (γ_{SG}) interface dictate the contact angle, $\theta_Y = (\gamma_{SG} - \gamma_{SL})/\gamma$ of the liquid on the solid [39]. On the other hand Fig. 4.1(b) describes the wettability of the internal surface which is a major criterion in micro-hydrodynamics for controlling in flow. This is solely based on the contact angle of water on the solid surface, the surface can either be classified as hydrophilic (water loving, $\theta_Y < 90°$) or hydrophobic (water hating, $\theta_Y > 90°$) [42]. One of the major side effects of high surface tension in fluid flowing through a conduit is that is friction resistance between the solid-fluid interfaces. Due to this surface tension, a stream of fluid splits to form several small droplets in order to minimize the total surface energy [39]. This is known as "Rayleigh-Plateau instability" as a result of the surface tension going to zero. In general, increasing the temperature of a liquid will decrease its surface tension. Likewise Surfactants can also be used to lower the surface tension of a liquid [35, 43]. Besides, this procedure can also be applied to interfacial tension between two liquids or that between a liquid and a gas.

In micro-scaling, surface tension at the interface between the liquid surface and the micro-channel surface is significant to the design because with dimensions in the order of microns, the lengths liquids will travel easily using the capillary force [42]. At a microscopic scale, with gravitational effects minimal, the surface-to-volume ratio increases due to the exceedingly small volumes employed. This characteristic improves the surface tension effect which shares a direct relationship with capillarity [41, 42].

The phenomenon known as capillary action, or capillarity, is the ability of a liquid to flow against gravity, inertia or basically flow spontaneously without the aid of an external force through a narrow space such as a thin tube, microchannels, porous materials such as paper or non-porous materials such as liquefied carbon fibre [36, 42] and it occurs because of inter-molecular attractive forces between the liquid and solid surrounding surfaces. Subsequently at microscale the gravity effect is infinitesimal, so the diameter of the tube or cross section of a channel has to suffice for the process to be sustainable.

So since the energy stored in surface tension is equivalent to the multiplication of the surface tension and surface area; therefore reduction in conduit surface area of any microfluidic system will naturally minimize surface energy which significantly eases fluid flow [41].

Putting this phenomenon in perspective with regards to microfluidics that deal with very narrow channels with liquids under infinitesimal gravitation and high viscous forces with amplified fluid-solid surface tension; capillarity consequently behaves as a medium through which fluid flow can be alleviated. Similarly fluid flow velocity can also be controlled by altering the capillary surface energy. Capillarity therefore plays a major role in aiding fluid flow within the LOAC platform by requiring less external pressure or energy input needed to actuate the flow [31, 35].

4. Microfluidic Large Scale Integration

Microfluidic large scale integration shares semblance to an electronic circuit that has diverse patterns of wiring circuitry responsible for taking current from one point to another [44-46]. However, this is a microfluidic tool that entails microfluidic

channel networks integrated with thousands of micromechanical valves and hundreds of individually accessible reservoirs [47] organized systematically to carry out complex POCT, medical or bio-chemical applications. These plumbing networks have microvalves that open or close with respect to the pneumatic pressure applied due to elastic membranes that is situated between a liquid-guiding layer and pneumatic control-channels [48]. The overall configuration involves combining several microvalves more multifaceted units like micropumps, mixers, multiplexers, etc. having hundreds of units on one single chip [20].

4.1. Microfluidic Multiplexer

The fluidic multiplexer is a key component of microfluidic large scale integration networks because it contains a blended arrangement of binary valve in patterns that significantly allow specific addressing of large number of independent chambers, increase the processing power of fluidic network exponentially and enabling complex fluid manipulations with a minimal number of controlled inputs [47, 49-51].

4.2. Micromixer

Micromixing in microfluidic devices is generally achieved due to the significant small length which is an endemic factor in miniaturization. This length advantage drastically increases the effect of diffusion and advection necessary for diffusion to occur [52]. Correspondingly the channel geometries of micromixers are also designed to decrease the mixing path and increase the contact surface area [49, 53]. Induced mixing at the microscale is generally classified as being passive or active. Passive mixers depend solely on pumping energy, while active mixers make use of an external energy source to achieve mixing.

4.2.1. Diffusion and Advection

Diffusion and advection are both relevant in the study of transport phenomena in fluid flows. The term advection with reference to microfluidics refers to the transport of substance (biological species) from one region to another [49, 53]. While diffusion is the process by which a concentrated group of particles in a volume will by Brownian motion spread out over time so that the average concentration of particles throughout the volume is constant [52]. In this distribution, the given entity moves from regions of higher chemical potential towards lower chemical potentials as shown in Fig. 5. In physics, diffusion can be realized as heat diffusion and molecular diffusion or Brownian motion.

Advection and diffusion in micromixers are also generally characterized accordingly to three nondimensional fluid parameters: Reynolds number Re, Peclét number Pe, and Strouhal number St. Peclét number is defined as:

$$Pe = \mu \frac{uL}{D}, \tag{7}$$

This is a measure of the relative importance of advection and diffusion in providing the mass transport associated with the mixing. Advection is dominant at high Pe [23].

The Strouhal number is defined as:

$$St = \frac{fD_h}{u}, \tag{8}$$

where f is the frequency of the disturbance action, is generally associated with active micromixers, and represents the ratio between the residence time of a species and the time period of disturbance [54-56].

Brownian motion acts in the presence of non-uniform distribution of molecules or particles inside a fluid. Diffusion can be described mathematically in one dimension by the equation below:

$$d^2 = sDT, \tag{9}$$

where d is the distance a particle moves in a time t, and D is the diffusion coefficient of the particle. Because distance varies to the square power, diffusion becomes very important on the microscale [57].

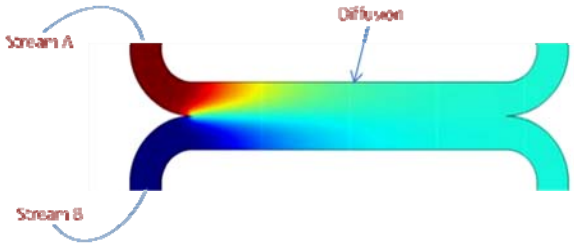


Fig. 5. Illustration of stoke flow diffusion occurrence between two different streams at relatively equal velocity.

4.2.2. Active Mixing

Active mixing uses external excitation to initiate time-dependent perturbations that stir and agitate the streamlines within the fluid for the sole purpose of accelerating the mixing process [58]. They are categorized with respect to the type of external perturbation energy such as acoustic (ultrasonic)-driven [59], thermal-induced [60], pressure field-driven [61], magneto-hydrodynamic [62], electrokinetic [63], dielectrophoretic [64, 65] or electro-wetting [66]. The prominent advantage age of

active micromixers is better mixer efficiency in comparison to passive mixers [67]. However, they suffer from the inconvenience cumbersome integration encumbrance from their peripheral devices e.g. actuators, which in the end lead to complex and expensive fabrication process [49]. Furthermore, the use of ultrasonic waves, high temperature gradients lead to extensive damage biological fluids or matrices. A number of groups have used silica particles impregnated with Fe_3O_4 to actively mix fluids in a microchamber using a magnetic field from either a permanent rotating magnet or an electromagnet [68]. Figure below shows the use of 5 mm neodymium-iron-boron magnetic particles (MQP-15-7, Magnequench International, Inc, Singapore) for optimum active mixing performance at an optional upper frequency limit of 100 Hz [69]. This time-dependent microfluidic operations utilizes flow mixing patterns of two dye streams (black and white) in the presence of ciliated structures as depicted Fig. 6. In general, active mixers are not a popular choice when applying microfluidics to chemical and biological applications [54]. Overall, implementation of such devices in practical applications is limited.

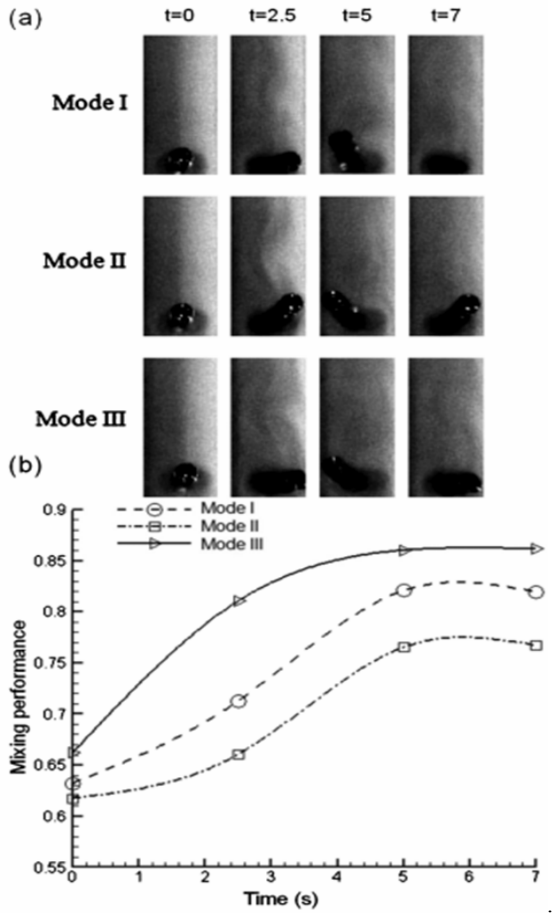


Fig. 6. Time-dependent flow mixing behaviour in three different beating modes (a) and the 2D graphical corresponding mixing performance (b) [69].

4.2.3. Passive Mixing

Passive mixing devices depend exclusively on the energy from fluid pumping and judicious use unique channel designs to constrain the flow configuration therefore increase mixing velocity by reducing the diffusion length and optimizing the contact surface area between the different fluids [26, 49]. A good example is the use of a serpentine microchannel structure to coerce the fluid in mixing; as depicted in Fig. 7. Molecular diffusion and chaotic advection are the main reason this mass transport phenomena is possible. Moreover, the design modifications carried out to aid the influence of the laminar flow inside and mixing time reduction is generally achieved by splitting the fluid stream using serial or parallel lamination [70, 71], hydrodynamically focusing mixing streams [72], injecting bubbles of gas (slug) or liquid (droplet) into the flow [73, 74] or improving chaotic advection using ribs and grooves fabricated on the channel walls [75, 76].

Unlike active mixers, passive mixers are generally less costly and involve simpler fabrication methods; they are far better to integrate into more complex LOC platforms [49].

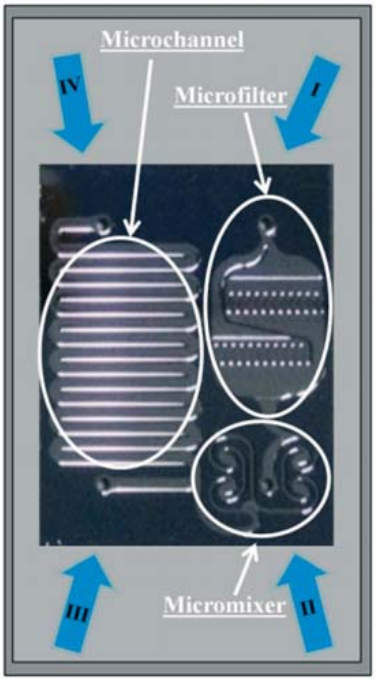


Fig. 7. A picture of a microfluidic chip consisting of microfilter, micromixer and microchannel. (I–III) Inlets for additional samples, lysis buffer, washing and elution buffer. (IV) Outlet for gathering of the extracted DNA [116].

4.3. Micropumps

Since the Reynolds number is typically low in microsystems, several different means of achieving fluid flow control in microfluidics have been

developed. The selection of a pump is mostly biased to mostly moderate performance and low-cost applications, provided that other requirements, like reproducibility and operational stability, can be satisfied.

The majority of these miniaturized pumps come under the classification of electric/electronic (Fig. 8), magnetic, external pressure generators, manual and passive pump systems [77]. Examples of electric/electronic pumps are the piezo actuator, electro-osmotic and peristaltic pumps, while the case of magnetic systems is represented in the form of magneto-hydrodynamic pumps and ferrofluidic pump. Piezo-electric, electro-osmotic and peristaltic pumps can be used for complex microfluidic operations and can be fabricated cheaply. The case of piezo-electric pumps which are the most compact pumps can be used for intermediate flow rates (μL) while electro-osmotic pumps due to their simplicity can be easily integrated into a microsystem. These integrated pumps are mostly the preferred choice for contemporary applications which requires multiple and complex fluidic operations, although the pressure produced for fluid motion cannot be necessarily considered independent of scale (miniaturization).

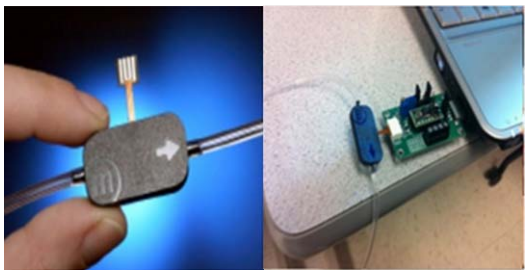


Fig. 8. Disposable microfluidic pump (Bartels Mikrotechnik mp6 Micropump) capable of pumping both air maximum flow: 18 ml/min (300 Hz) and water maximum flow: 7 ml/min (100 Hz).

Commonly used manual pumps are syringes and blisters, while passive pumps makes use of surface tension or capillary effect to drive fluid flow. The main benefit of these low cost syringe pumps and blisters is their ability of initiating flow rate across microchannels irrespective of the fluidic resistance. This is due to the fact that the fluid traffic is largely dependent on the force displacement of the plunger or finger (blister) which in this case is sufficient (mechanical advantage). On the other hand, the main drawback of manual pumps is the development of pulsatile flows at low flow rates and lack of adequate flow control required for complicated fluid flow sequence.

Finally, the external pressure generators are mostly mechanical computer controlled mechanical devices that can excite pressure when connected to the microfluidic chip. They can also exist as hydrostatic generators which depend on gravity to cause pressure difference for fluid flow. Most of these devices are expensive and are not easy to integrate into standalone microfluidic platforms. However, these simple and low cost pumps generate the required pressure difference needed for fluid flow by varying the altitude of the liquid to air (atmosphere) interface within different reservoirs. This technique makes it impossible for applications in closed fluid flow systems. In all cases, whether the pump is external or integrated, pressure differences within the system are generally inferior to those produced by external sources.

It is made up of a heat and chemical resistant plastic covering ($30 \times 15 \times 3.8$ mm^3), weigh 2grams, 2 piezo actuators, 0 - 70 °C operating temperature and an estimated 5000 hours live time [117].

4.3. Microvalves

The capacity to manipulate fluid flow using valves is indispensable in many microfluidic applications [78]. There are two types of valves: passive valves that require no energy and active valves that use energy for operation. The type of valve used in a device depends on the amount and type of control needed for the application [77, 79].

Active valves often use external macroscale devices that control the actuation and provide energy. Some recent designs include an electromagnetically actuated microvalve [80] and an air-driven pressure valve [81]. Other active valve designs use energy from the driving fluid, eliminating the need for external power or energy from direct chemical to mechanical conversions.

Passive valves can be used to limit flow to one direction, to remove air, or to provide a temporary flow stop. Passive are one way that control flow through the resistance of the fluid flow along the channel (Fig. 9). By changing the fluid resistance (i.e., the geometry) the passive pressure theory applies [82]. The passive valve theory is a fundamental building block of the structurally programmable microfluidic system (sPROMs) system and much research effort has been directed toward the development of efficient passive valves [83]. The passive valve as described in this work is a device that utilizes the surface properties of a hydrophobic substrate and a geometrical feature control to regulate fluid flow [84].

If the fluid is flowing at a very low velocity, such that the surface tension effects are dominant in controlling the flow characteristics, this abrupt change in width results in a significant increase in the pressure required to move the liquid further as shown in Fig. 10. The required pressure, to push the liquid into the narrow channel, for this geometry can be derived from the principle of virtual work (Hosokawa et al., 1999). Since the fluid entering the narrow channel would experience a higher surface-area-to-volume ratio, there would be an increase in the surface energy of the system. This can be used to

derive the expression for pressure needed to overcome the passive valve as [83, 85, 86]:

$$\Delta P = 2\sigma cos(\theta_C)\left[\left(\frac{1}{w_1}+\frac{1}{h_1}\right)-\left(\frac{1}{w_Z}+\frac{1}{h_Z}\right)\right], \quad (10)$$

where W_1 is the width of inlet channel, h_1 is the channel depth, h_1 is the channel depth, σ is the surface tension, θ_c is the fluid contact angle.

The most common channel geometry, have equal depth along the microchannel. Hence, setting $h_1=h_2$ simplifies equation 10 to:

$$\Delta P = 2\sigma cos(\theta_C)\left[\left(\frac{1}{w_1}-\frac{1}{w_Z}\right)\right], \quad (11)$$

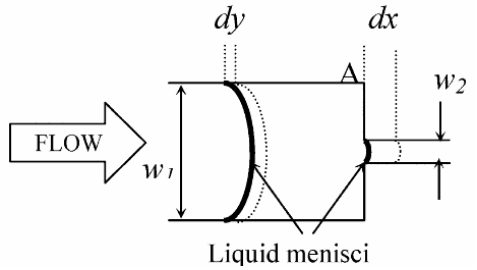


Fig. 10. A schematic of fluid flow through an abrupt junction passive microvalve.

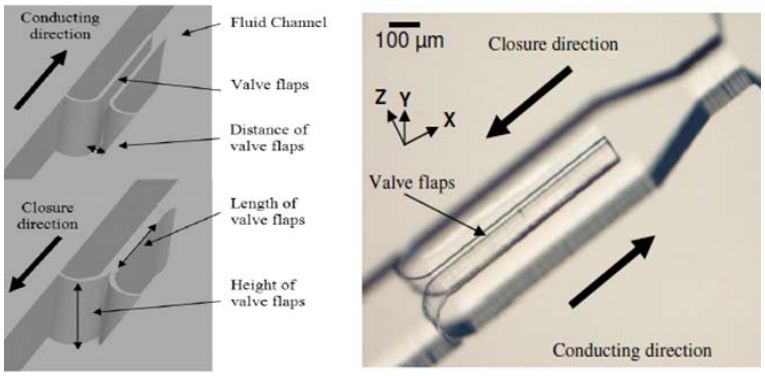


Fig. 9. The passive design is based on two extruded symmetric flexible PDMS-based cantilever bars which act as valve flaps). The distance of the valve flaps is 20 µm, the height of the valve flaps is 70 µm and the length of the valve flaps is 300, 550, 700, and 1000 µm, respectively [118].

5. Pressure Driven Flow

This phenomenon is also known as Poiseuille flow and it exhibits a parabolic flow profile which is basically characterized by liquid movement as a result of pressure gradient between two or multiple points within the system. The liquid control is mostly constrained to a one-dimensional liquid flow in a straight, curved or circular microchannel (Fig. 11) [31, 36, 37]. The nature of process entails the flow of fluid from a region of high pressure to a region of low pressure.

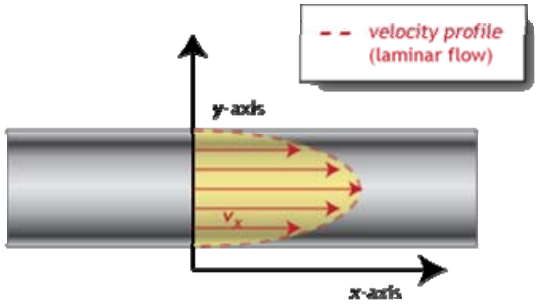


Fig. 11. Schematic representation of the parabolic path way of liquid in a cylindrical conduit [119].

Fluid operations carried out on this platform are either capillary driven or linearly actuated. Capillary driven flow involves the high dependence on capillary forces which in turn rely on the channel geometry design (i.e. width, length and height) and surface properties (hydrophobic or hydrophilic) [42]. On the other hand linear actuated devices propel flow by mechanical displacement of liquid through application of force. For instance fluid stored in a reagent reservoir can be propelled by the aid of a plunger into a micro-conduit of negative pressure (Fig. 12).

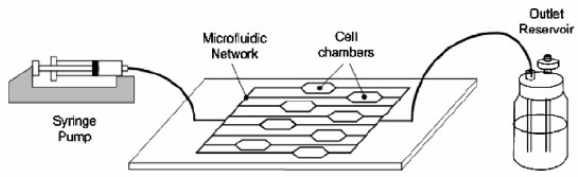


Fig. 12. Schematic representation of external syringe pump used to supply typical pressure-driven microfluidic platform for living cell analysis [120].

The common denominator that makes all these methods of fluid actuation significant is the presence

of the generated pressure gradient. Furthermore novel methods such as electro-osmotic force can also be used to induce pressure driven flow through insertion of in-channel electrodes of relatively small electric potentials [87, 88].

Simplified Navier Stokes equations for pressure driven micro-flows characterized by the significantly reduced Reynolds number (Re<<1)

$$0 = -\nabla p + \eta \nabla^2 \vec{u}\,, \tag{12}$$

where p is the pressure, u is the fluid velocity and η is the dynamic viscosity of the liquid.

The relation between pressure and flow rate is described by the Hagen-Poiseuille equation, In the case of cylindrical microchannels experiencing a parabolic flow is given below [89]:

$$\Delta P = \frac{8\eta L Q}{\pi r^4}, \tag{13}$$

where ΔP is the pressure drop between the two ends of the cylindrical conduit, L is the total length of channel, r is the radius, Q is the volumetric flow rate of the channel and v is the average flow velocity across the section.

In the case of planar channels with a height, h, which is much less than the width w (h<<w,) the solution of the Poiseuille flow gives [90, 91]:

$$\Delta P = \frac{12\eta L Q}{w h^3 \left(1 - \frac{h}{w}\left(\frac{19Z}{\pi^5}\sum_{n=1,3,5}^{\infty}\frac{1}{n^5}tanh\left(\frac{n\pi w}{zh}\right)\right)\right)} \tag{14}$$

5.1. Electric Circuit Analogy Concept of Fluidic Resistance

The concept of Hagen-Poiseuille equation rewritten as Ohm's law clearly depicts the average flow rate of a liquid within a microfluidic channel as proportional to the pressure gradient imposed on both ends of the channel (Fig. 13) [92, 93].

$$\Delta P = R_H Q\,, \tag{15}$$

The fluidic resistance R_H will depend on the geometry of the cross section (e.g. cylindrical and planar). For instance equation 5.11 and equation 5.12 are the cylindrical and planar Hagen-Poiseuille circuit analogy representation of equation 5.14 and 5.15.

$$P_H = \frac{8\eta L}{\pi r^4}, \tag{16}$$

$$P_H = \frac{12\eta L Q}{w h^3 \left(1 - \frac{h}{w}\left(\frac{19Z}{\pi^5}\sum_{n=1,3,5}^{\infty}\frac{1}{n^5}tanh\left(\frac{n\pi w}{zh}\right)\right)\right)} \tag{17}$$

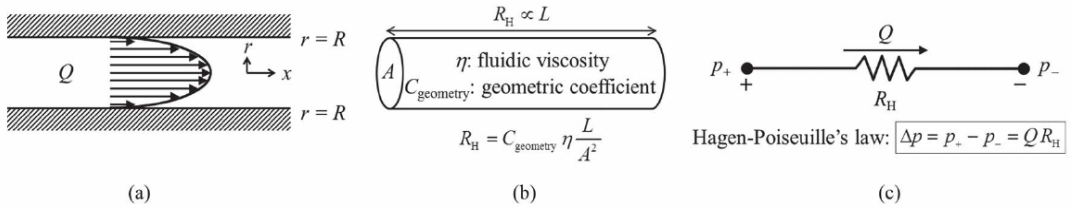


Fig. 13. The physical similarities between the flow of a fluid and the flow of electricity: (a) Poiseuille flow in a circular channel, (b) the hydraulic resistance of the circular channel (Cgeometry¼ 8p for the circular channel), (c) equivalent circuit symbol of a fluidic resistor for the hydraulic resistance and Hagen–Poiseuille's law analogous to a resistor for the electric resistance and Ohm's law [93].

This fluidic resistance is also known as hydraulic resistance and can be used to analyze the flow or pressure relationship within complex microfluidic networks. The validity of this concept relies on some basic assumptions. First of all the flow is considered viscous, incompressible and homogeneous with no presence of convective mixing. Secondly, the steady-state and laminar flow nature of the flow exhibits a parabolic shape profile. Finally, the flow is considered to have a uniform pressure gradient across the microchannel length. By this means estimation of the laminar flow within circular or non-circular channels that are either infinite or finite in length can be with simple mathematical calculation. For instance channels connected in series will be resolved by using "R_H=R_{H1}+R_{H1}+R_{H2}+...R_{Hn}" which will provide the estimated total fluidic resistance of the network. Whereas parallel channels network will have a total resistance of "$1/R_H$=$1/R_{H1}$+$1/R_{H1}$+ $1/R_{H2}$+...$1/R_{Hn}$" [93].

There is an extensive range of diverse applications of these pressure driven systems in the microfluidic platforms. These include the use of plungers, syringes, micropumps (peristaltic and piezo-electric), gas expansion principles, pneumatic displacement of membranes, blisters etc. The advantage they share is the simplicity in design and fabrication processes. They are also economical and affordable but suffer the disadvantages of reproducibility and limited ability to support very complicated microfluidic processes [94].

6. Magneto-hydrodynamics

Magneto-hydrodynamics (MHD) involves the interaction between the flow of an electrically conducting fluid and magnetic fields. This interaction between the electric currents and magnetic fields results in an indigenous pressure known as Lorentz body forces on conductive fluids (Fig. 14) (ferrofluid, buffer solution or cell media) [95-97]. This generated force can then be used to propel, stir and manipulate the fluids; since most applications use buffers and solutions that are often electrically conductive i.e. capable of transmitting electric currents through the solutions [95].

$$F = JxB, \tag{6.10}$$

The MHD force is represented by F, while J and B are depicted as the electric current density and magnetic field.

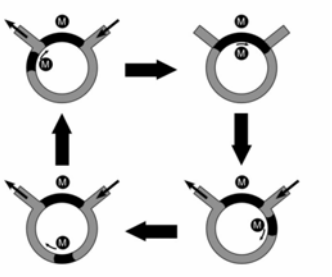


Fig. 14. The principle operation of a circular ferrofluid pump used to manipulate fluids with ferrofluid plugs in circular microchannels [98].

In the domain of microfluidics miniature devices are needed to carry out a large number of operations, MHD offers a sophisticated means to manipulate fluid flow in micro-devices without a need for mechanical components. For example many MHD pumps can be integrated on a lab-on-chip device to enable complex fluidic operations that can be done automatically on a single platform as shown in Fig. 14 [96, 98]. MHD micropumps [99] can be used to pump several conducting liquids especially high-conductivity fluids. These fluids are sometimes present in the aqueous solutions used in medical/biological applications; hence MHD pumps are suitable for POCT. Lab-on-chip applications typically require the use of pumps and valves which are usually cumbersome to implement. In a MHD setting most of the network's channels are equipped with individual electrodes which can be intelligently controlled in the presence of a magnetic field to direct fluid flow along any desired path without a need for mechanical valves [100]. This operation can be used to generate higher flow rates at relatively small electrode potentials, typically below 1 V [100]. This gives it an advantage over electroosmosis as liquid flow does not depend on the chemical nature of the capillary surface [101]. One of the major main disadvantages of this technique is that of the generated Lorentz body forces which scales unfavourably as the conduit's dimensions are reduced. Thus, constraining MHD most applications to channel sizes with characteristic dimensions on the order of 100 μm or larger [100]. Besides, ionization effect causes the bubbles generation which greatly inhibits the flow rate. The effect of Bubble generation is minimized by reversing the direction of the applied voltage which can be done by using an alternating current driving mechanism to improve their performance [99].

7. Dielectrophoresis

Dielectrophoresis (DEP) technique can be used to manipulate, transport, separate and sort diverse categories of bio-particles in microfluidics although DEP is mostly used as a particle separation technique[102-104]. DEP is a tool that can be effectively used for nucleic acid hybridisation, purification and characterization in POCT devices [105]. Whilst other areas such as manipulation and transportation still require extensive research. As a good separation technique it makes use of a polarization effect that occurs when a non-conductive/dielectric liquid is place in the presence of a non-uniform electric field [9, 15, 89, 106, 107]. If the polarization effect of the particle supersede that of the suspending medium, the particle movement will tend towards the region of higher field strength (positive DEP); while, the reverse case will cause the particle to move towards the low potential area (negative DEP). The particles in question maintain an overall net charge of zero regardless of their original randomly oriented state or polarized state. A time-average DEP force applied on a spherical particle can be represented as the equation below [108, 109].

$$(f) = \left[2\pi r^3 \varepsilon_0 \varepsilon_m \, Re\,|\, f_{CM}\,|\right] \nabla E_{rms}^2 + \left[4\pi r^3 \varepsilon_0 \varepsilon_m \, Im\,|\, f_{CM}\,| \sum_{x,y,z} E_{rms}^2 \nabla \varphi\right] \tag{18}$$

$$f_{DEP} = 2\pi r^3 \varepsilon_0 \varepsilon_m \, Re\,|\, f_{CM}\,| \nabla E_{rms}^2, \tag{18a}$$

$$f_{tW-DEP} = 4\pi r^3 \varepsilon_0 \varepsilon_m \, Im\,|\, f_{CM}\,| \sum_{x,y,z} E_{rms}^2 \nabla \varphi, \tag{18b}$$

where r is the radius of the particle, ε_o=8.854×10−12 F/m is the permittivity of the vacuum, ε_m is the dielectric constant of the medium, f_{CM} is a complex variable known as Clausius–Mossotti factor, E_{rms} is the root-mean-square value of the applied electric field, and φ is the phase component of the electric field. The first part (a) of equation (18) can be referred to as 'classical DEP force'. This is the force responsible for pushing the particles towards or away from the regions of strong electric field, i.e. microelectrode tips, with respect to

the polarity of Re[f_{CM}]. For example, If Re[$_{fCM}$] > 0 the particle is pushed towards the regions of strong electric field and such a motion is termed positive DEP response. On the other hand, if Re[fCM]<0 the particle is driven away from the regions of strong electric field and exhibits a negative DEP response Fig. 15a [110].

Subsequently, the second part (b) is called 'travelling wave (TW) DEP force'. In this case the force causes particles to move towards or away from the direction of the wave propagation, according to the polarity of Im (imaginary) [fCM]. For instance if Im[fCM] > 0 the particle travels towards the smaller phase regions and such a motion is designated a co-field TW response. Alternatively, if Im[fCM] < 0 the particle tends to move towards the larger phase regions and such a motion is called an anti-field TW response Fig. 15b.

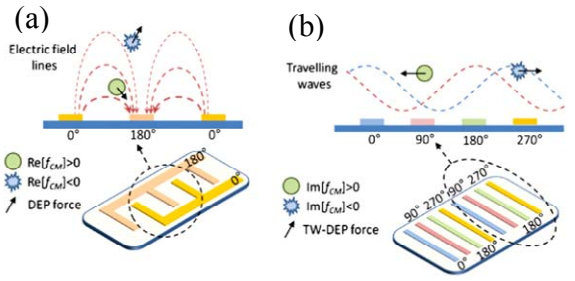


Fig. 15. Non-uniform electric field can be created by metallic microelectrodes patterned on a substrate: (a) the spatial non-uniformity of electric field magnitude induces classical DEP force, while (b) the spatial non-uniformity of the phase component induces TW-DEP force [121].

Hydraulic resistance and Hagen–Poiseuille's law analogous to a resistor for the electric resistance and Ohm's law [93].

$$f_{CM}\left(\varepsilon_p^*, \varepsilon_m^*, \omega\right) = \frac{\varepsilon_p^*(\omega) - \varepsilon_m^*(\omega)}{\varepsilon_p^*(\omega) + 2\varepsilon_m^*(\omega)}, \qquad (19)$$

where f_{CM} is the dipolar Clausius-Mosotti factor which is the characterizing parameter of a Dielectrophoretic particle [16]. ε_p, ε_m are the complex permittivities of the particle and the medium respectively.

In turn, the complex permittivity is given by:

$$\varepsilon = \varepsilon_r - i\frac{\sigma}{\omega}, \qquad (20)$$

where ε_r is the dielectric constant; σ is the conductivity; ω is the frequency of the applied Electric Field and i is $\sqrt{-1}$.

Furthermore, since they all exhibit substantial amount of di-electrophoretic activity in the presence of non-uniform electric fields, the requirement for pre-charged particles in the system is not a prerequisite condition [110]. The strength of the force exerted by this electric field is directly proportional to the electrical properties of the particles' shape, size and operational frequency of the field. As a result, particles with great sensitivity can be manipulated by a designated electric field. Electric field generation requires fabrication of precise electrodes for the particles attraction; likewise these particles may also require formation of intricate channels for effective separation. It may have certain disadvantages for use with some particles, if their response to the field is not strong enough to be detected. In general dielectrophoresis is a good technique for use in microfluidic devices as the principle of operation is simple and requires less hardware and can also be applied to non-conductive liquids as depicted in Fig. 16 which involves cells in a bio-fluid. Conversely, it covers a wide-span of potential application when compared to standard electrophoresis which requires spatially uniform electric field to pull a charged particle towards the electrode with opposite charge.

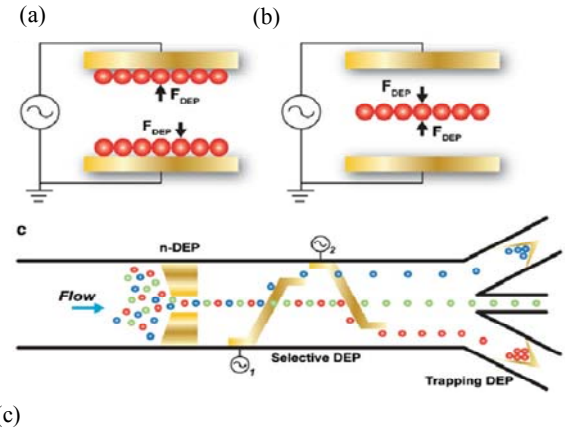


Fig. 16. Dielectrophoretic (DEP) separations can be positive (pDEP) as shown in (a) or (b) negative (nDEP) which affects where cells are positioned within a field. (c): gives a basic depiction of DEP been utilized in a variety of different microfluidic systems [103].

Novel methods like binary separation [111], travelling wave DEP [112] and light induced DEP [113] have been performed. In the case of light induced DEP, light-induced dielectrophoretic forces are used to manipulate aqueous droplets immersed in electrically nonconductive liquid such as oil with a light intensity as low as 400 μW/cm^2 [113]. Of recent researchers have found ways to use dielectrophoresis based continuous-flow technique for gene vaccination production. This innovative technique [104] demonstrates the quick and efficient separation of parental plasmid, miniplasmid, and minicircle DNA as shown in Fig. 17.

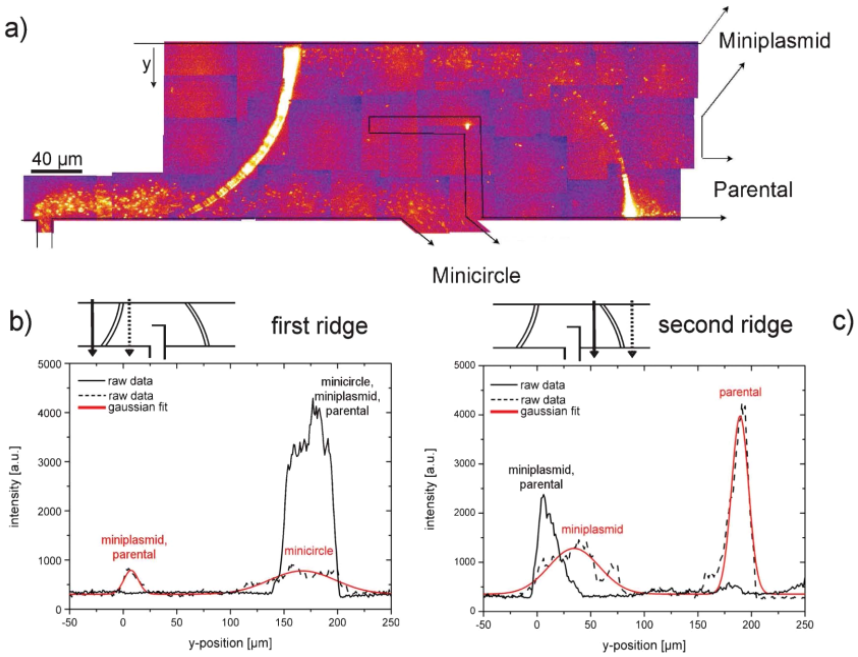


Fig. 17. Separation of the parental plasmid, miniplasmid and minicircle DNA. (a) Combination of the fluorescence microscopy images. A mixture of the parental plasmid, miniplasmid and minicircle DNA is inserted towards the ridges from a side channel (each yellow spot represents one distinct DNA molecule). At the first ridge, the minicircle DNA is separated out of the mixture and directed into a separate channel. The parental plasmid and miniplasmid DNA are deflected and drift towards the second ridge, where only the parental plasmid DNA is deflected. Thus, all three species are retrieved in separate channels. (b) and (c) Fluorescence intensities up- and downstream of the two ridges. The scan paths are portrayed over the graphs. The black lines signify the scans upstream of the ridge; the dashed lines symbolize the scans downstream of the ridge. The red lines are Gaussian fits. (b) At the first ridge the resolution was Res = 1.10. (c) At the second ridge the resolution was Res = 1.25.Consequently, a complete separation of the three species was achieved with very high separation efficiency [104].

8. Conclusion

This paper gives a polarized view of the techniques used in development and design of POCT Microfluidics devices by categorizing them within the broad spectra of continuous flow mechanics. Continuous flow technology is based on the manipulation of continuous liquid flow through microfabricated channels. Researchers in the field are therefore presented with a microfluidic 'toolbox' of techniques and manufacturing methods.

Generally, continuous phase are less complicated and possess simple mode of operation in comparison to discrete. Moreover, they mostly reside in the region of low cost of production or cost-efficient fabrication processes. However, they are more cumbersome; which makes integration of their various techniques more difficult. This is mostly as a result of the dependencies of external sources needed for implementation. For example, the use of plungers, pressure generators and piezo-electric pump in pressure driven flow can be complicated and cumbrous which can significantly affect repeatability.

In summary, selection criteria of each individual technique regardless of the continuous or discrete flow depend heavily on the disadvantage and advantages they present with respect to the intended use, with cost a dominant factor. Within classical microfluidics cost depends on the selected method and fabrication techniques, fluid actuation is required using an external pump or an electric field, thus increasing power requirements; therefore all point of care devices for molecular diagnostics currently require some form of desktop or handheld device to conduct the control of the fluid and read the results. Paper microfluidics is a new field that has the potential to revolutionize diagnostics and significantly reduce the associated manufacturing and material costs. No external actuation of fluid is required which will allow standalone systems to be created that could use consumer electronic products such as a smartphone to act as a sensing device.

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