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REVIEW PAPER

Particle Manipulation by Miniaturised Dielectrophoretic Devices

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ABSTRACT

This paper presents a review of dielectrophoresis (DEP) devices which provide an effective way to manipulate and separate micro- or nano-bioparticles automatically and quickly by polarisation effects in a non-uniform electric field. A detailed review for designs and operation principles of various microfabricated DEP devicesis given and some advantages and disadvantages of current devices are noted to the final system to attain the unprecedented levels of performance.

Keywords: Microelectromechanical systems, bio-MEMS, dielectrophoresis, cell manipulation, dielectrophoretic devices, DEP

1. INTRODUCTION

In recent years, the development of lab-on-a-chip technology has attracted more and more interest in the biological and medical fields. Lab-on-a-chip means that the sensors, heaters, pumps, fluid handling, separators, and detectors are integrated into one chip, size of a fingernail[1]. The objective of this chip is to deal with sample preparation, its transportation and analysis automatically and quickly in a single chip. One of the most favourable areas of this device is the development of automatic sample preparation systems to manipulate micro- or nano-bioparticles such as cells, viruses, DNA, and bacteria. There are many methods available for manipulation of particles in a fluid, such as flow cytometry, optical tweezers, and dielectrophoresis (DEP). Of these techniques, DEP has attracted most attention due to its great advantages, for instance lower sample consumption, fast separation speed, selectivity, miniaturisation, integration, and non-contact manipulation of particles. This device provides a great potential in biological and medical applications such as point-of-care diagnostics, surface-based biosensors, rapid cell, DNA analysis, etc.

The term dielectrophoresis was first coined by Pohl[2]. DEP is a motion of dielectric particles caused by polarisation effects in a non-uniform electric field. A particle suspended in a medium of different dielectric characteristics becomes electrically polarized in an electric field. Due to the difference in electric field strength on the two sides of the particle, a net dielectrophoretic force pulls it towards the higher electric field gradient region (positive DEP) or pushes it towards the lower electric field gradient region (negative DEP), (Fig. 1).

Early dielectrophoretic devices were made from thin electrical wires or other machined metal electrodes[3-5]. For many years, their applications were limited to the micro-scale particles, due to the size of the electrodes, which is not small enough to generate high electric field gradient. After 1990, with the development of microfabrication technologies, a large number of micro- or nano-scale complex electrode arrays designed for particle manipulation can be precisely fabricated and integrated to form miniaturised dielectrophoresis chips. This paper gives a detailed review for various microfabricated DEP devices.

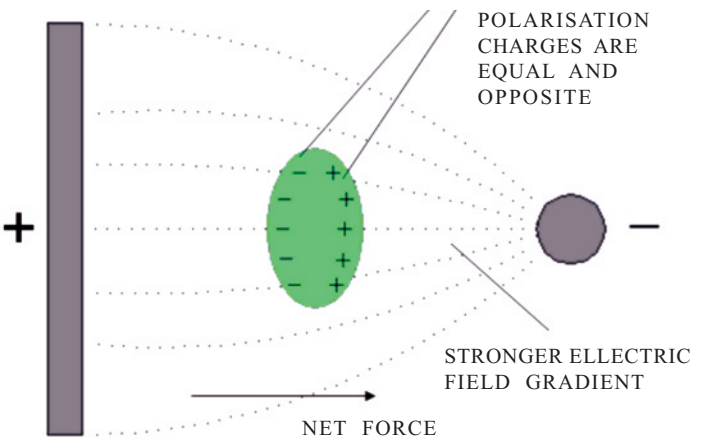

Figure 1. Principle of dielectrophoresis.

2. ANALYTICAL CONSIDERATION

The time-average dielectrophoretic force for the general field is defined[6] as

$$\left\langle \overline{F}(t) \right\rangle = 2\pi\varepsilon_1 R^3 \left\{ \begin{matrix} \mathrm{Re}[K]\nabla E_0^2 + 2\,\mathrm{Im} \\ [K](E_{x0}^2\nabla\varphi_x + E_{y0}^2\nabla\varphi_y + E_{z0}^2\nabla\varphi_z \end{matrix} \right\} \quad (1)$$

where, E_{i0} and $\varphi_i (i = x; y; z)$ are the magnitude and phase, respectively, of the field components in the principal axis

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directions. This expression contains two terms contributed to the DEP motion.

(a) The first term relates to the real component of the induced dipole moment in the particle and to spatial non-uniformity of the field magnitude. This force directs the particle towards higher or lower electric field regions, depending on whether the Re*K* is positive or negative. This is the conventional DEP term. The classical DEP force can be given by

$$F_{DEP} = 2\pi R^3 \varepsilon_1 \mathrm{Re}[K] \nabla E_0^2 \quad (2)$$

(b) The second term relates to the imaginary component of the induced dipole moment and to spatial non-uniformity of the field phase. This force directs the particle against or along the direction of travel of the electric field depending on whether the phases of the field components are larger (*ImK*>0) or smaller (*ImK*<0). This is called travelling wave dielectrophoresis (TWD). The expression can be given[6] by

$$F_{TWD} = \frac{4\pi^2 \varepsilon_m r^3 \mathrm{Im}[K(\omega)] E^2}{\lambda} \quad (3)$$

(c) When *ReK*=0 or *ImK*=0, the particle experiences no positive or negative DEP force. The frequency where the particle shows no DEP force is called crossover frequency. The crossover frequency depends on dielectric properties of particle and medium.

Here, *K* is the well-known complex Clausius-Mossotti factor, and is defined as

$$K = \frac{\varepsilon_2^* - \varepsilon_1^*}{\varepsilon_2^* + 2\varepsilon_1^*}, \varepsilon^* = \varepsilon - j\frac{\sigma}{\omega} \quad (4)$$

where, ε_2^* and ε_1^* are the complex permittivity of the particle and medium respectively.

The complex permittivity for a dielectric material can be described by its permittivity ε, conductivity σ, and angular frequency ω of the applied electrical field E_0. Taking the example of conventional DEP item, the DEP force acting on a spherical particle is a function of Clausius–Mossotti factor *ReK*, which determines the direction of the DEP force. The Clausius-Mossotti factor is a function of electric field frequency, as shown in Fig. 2. At a range of frequencies, the particle experiences positive DEP while it shows negative DEP at another range of frequencies. The frequency where the particle shows no positive and negative DEP is called crossover frequency. The change of the permittivity and conductivity of the particles and the medium will cause the shift of the crossover frequency. Thus at a selected frequency range, one population of particles experience positive DEP while the other population exhibits negative DEP. This provides a possible basis to separate the mixture of different particles.

A particle suspended in a solution, is not only subjected to DEP force, but also many other forces such as hydrodynamic force, gravitational force, and electro-hydrodynamic force. For sub-microparticles, Brownian force must be considered. It is still a big challenge to overcome the Brownian force for manipulation of the sub-microparticles. A detailed calculation of various forces was described by Castellanos[7], *et al*. The movement of the particle in a fluid is determined by the resultant force of many factors. Considering the influence of all kinds of forces, different separation mechanism can be performed based on different microfabricated DEP devices.

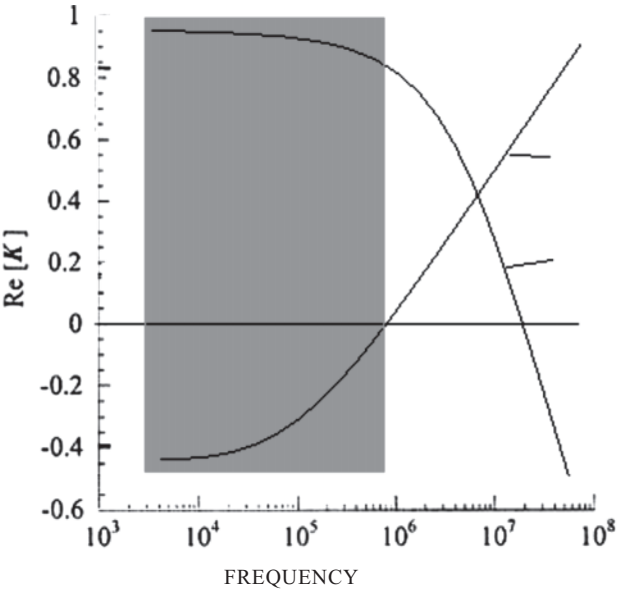

Figure 2. Clausius-Mossotti factor *Re*(*K*) versus frequency.

3. DIELECTROPHORETIC DEVICES FOR PARTICLE MANIPULATION

Based on microfabrication and MEMS technologies, a lot of DEP devices have been developed for a broad range of particle manipulation and separation. According to the solution for generation of electric field gradients, the devices can be classified in to:

(a) Change of phase of the applied electric field (travelling wave DEP),
(b) Change of dielectric media (insulating DEP),
(c) Change of electrode shapes (conventional DEP),
(d) Change of electric field gradient by optical image (image DEP), and
(e) Others.

3.1 Change of Phase of the Applied Electric Field

As previously described, the change of phase of the applied electric field can generate the electric field gradient, causing linear motion of the particle. For example, when the electric field phase shift in a sequence of 0°, 90°, 180°, 270° along a parallel electrode in a line like a travelling wave as shown in Fig. 3, the interaction between the electric field and the induced dipole generates a force parallel to the electrode, causing the particle to move along the electrode. This phenomenon is called travelling-wave dielectrophoresis (TWD). The common structures for this method are spiral[1, 8], parallel[9, 10] as suggested by many groups. These structures can be easily fabricated by depositing a thin film multi-metal electrode such as *Cr/Au*, or *Ti/Pt* on a substrate through classical photolithography technology.

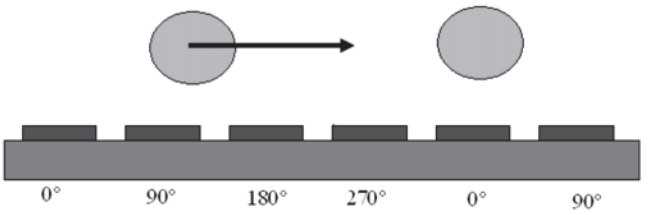

Figure 3. A schematic of travelling wave dielectrophoresis.

Travelling-wave dielectrophoresis was first reported by Masuda[11], *et al.* to manipulate blood cells by applying poly-phase voltage to a parallel electrode array and coined as travelling-wave dielectrophoresis (TWD) by Hagedorn[9], *et al.* Huang[10], *et al.* demonstrated that cell's linear motion induced by a travelling field acting on a cell is directly related to the imaginary component of the induced dipole moment. The direction of the TWD depends on the dielectric properties of the particle and medium. This provides a strong basis to separate the mixture of the particles. At a selective frequency, one population of particles experience positive DEP and move to the end of the array while the other population of particles experiencing negative DEP travel to the opposite direction of the array, and these collected respectively as shown in Fig. 4(a). Another separation method using TWD is based on the fact that the moving rate of the particles is related to the dielectric properties of the particles. Particles with different dielectric properties move at different speeds and are separated from each other after a long travelling as shown in Fig. 4(b). This method has been used to separate colloidal particles[10], viable and non-viable yeast cells[12], different sized latex beads[13], T cells and monocytes[14], viable and nonviable lymphoma/ myeloma cell lines[15].

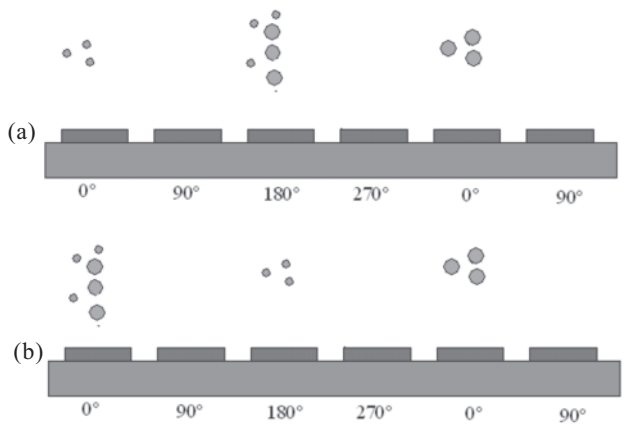

Figure 4. Separation using travelling-wave dielectrophoresis.

3.2 Change of Dielectric Media (Insulating DEP)

The non-uniform electric field can be produced by patterning geometrical constrictions in an insulating substrate such as quartz, glass, plastics, and polymer, instead of metallic microelectrodes[16]. For these devices, an inhomogeneous electric field is generated by spatially non-uniform insulating structures between electrodes (Insulating DEP). This method was first reported to perform cell fusion at the field constriction by Masuda[17], *et al*. Such structures have also been successfully used to manipulate cells, virus, DNA, and polystyrene particles by many researchers[16,18-24]. Recently, Iliescu[25], *et al*. proposed a novel 3-D dielectrophoretic chip where two planar electrodes were made from a stainless steel mesh, and bonded on both sides of a glass frame which is filled with round silica beads, as shown in Fig. 5. For this device, an ac electric field applied to the mesh-electrodes generates an electric field gradient inside the chamber due to the non-uniformity of the media between the electrodes caused due to the presence of silica beads.

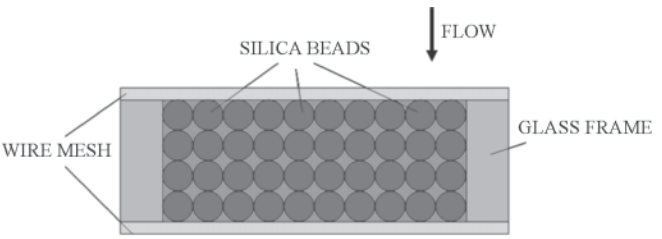

Figure 5. A schematic of 3-D DEP filter using silica beads.

Furthermore, a dc electric field can be applied in this device to achieve a high cell trapping efficiency when a high voltage is applied. Later, Iliescu[26], *et al*. demonstrated a field-flow separation method based on the non-uniformities of the electric field and fluid flow around the silica beads using viable and non-viable yeast cells. Recently, Demierre[27], *et al.* reported a novel focusing and continuous separation of cells based on the opposition of two DEP force fields, generated by a geometrical arrangement of lateral metal electrodes and a patterned insulator. Two inhomogeneous DEP force fields at different frequencies determine the different positions of equilibria for particles with different dielectric properties.

3.3 Change of Electrode Shapes (Conventional DEP)

In general, the non-uniformity of the electric field can be achieved by changing the magnitude of the applied electric field, by changing the electrode shapes. Microfabrication technologies confer the advantage of complex microelectrode arrays for particle manipulation and separation to form different miniaturised dielectrophoresis chips.

3.3.1 DEP Devices with Planar Electrodes (2-D DEP)

Although applications to manipulate and separate all kinds of particles have been developed in a wide range of biological and medical fields, most of the devices for DEP are simple and similar. To date, most of the DEP devices are made of planar electrodes using a thin film metal layer deposited on the glass surface[28] or silicon substrate[29] to form the electrodes, as shown in Fig. 6. The thin metal electrodes are generally made of *Cr/Au*[30], *Ti/Au*[31], *Ti/Pt*[32-34] (thickness < 1-2 μm). The presence of *Cr* or *Ti* is to improve the adhesiveness between glass and *Au* or *Pt*. Then the glass/silicon wafer is bonded to glass[35], plastic gasket[36,37], polycarbonate[38], PDMS[39], or SU-8[40] to form the microchambers and mircochannels.

Such devices have been successfully applied to trap cells[41], bacteria[42,43], viruses[44-46], proteins[47], DNA[48-51] and even nanostructures such as carbon nanotubes[52-54], and nanowires[55,56]. Based on the 2-D DEP devices, two separation methods have been developed: (a) flow separation, and (b) DEP field-flow fractionation (FFF).

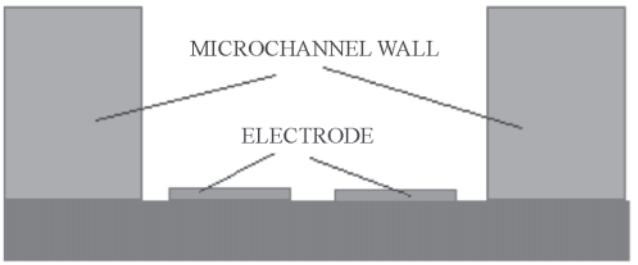

Figure 6. DEP devices with planar electrodes.

3.3.1.1 Flow Separation

Flow separation is a simple and practical method to separate binary particles as shown in Fig. 7. Two population of particles suspended in the fluid are pushed into the chamber. At certain selective frequency, one population of particles experience positive DEP and are trapped onto the edges of the bottom electrodes while the other population of particles experience negative DEP and are repelled into the centre of the chamber. Then, the particles which experience negative DEP are flushed away to the outlet and collected. After that, the DEP force is removed and the particles which experience positive DEP are flushed away to the outlet and collected. A stumbling block for this method is that as the distance of particles from the electrode surface increases, the DEP force decreases quickly, resulting in a force not large enough to trap the particles distant from the electrode surface. Consequently, the separation efficiency of the particles will be much lower.

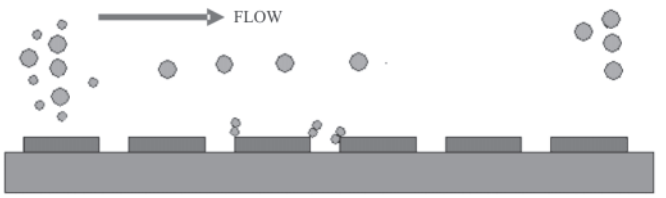

Figure 7. Flow separation by planar electrodes.

This method has been used to separate the viable and non-viable yeast cells[57,58], viable and non-viable recombinant myeloma cells[59], live and heat-treated cells of Listeria[60]**.** Separation of different bacteria, such as*, B. cereus*, and *B. megaterium*[61]*, Escherichia coli* and *Micrococcus luteus*[62] has also been reported by some researchers. Morgan[31]*, et al.* reported the separation of different virus TMV and HSV virus in a polynomial electrode in 1999. In addition, Green, and Morgan[63] have demonstrated that particles with the same size but with different dielectric properties can also be separated by flow separation method.

3.3.1.2 DEP Field-flow Fractionation

For thin film planar electrodes, when the negative DEP force and the net gravitational force are equal in magnitudes but opposite in directions thus, exactly balance each other, particle levitates at a given height, as shown in Fig. 8. The expression of F_g is well-known:

$$F_g = \tfrac{4}{3}\pi r^3(\rho_m - \rho_p)g \quad (5)$$

where $\tilde{n}_p$ and $\tilde{n}_m$ are the densities of the particle and medium respectively, and g is the acceleration due to gravity[6]. Thus:

$$F_g + F_{dep} = 0 \Rightarrow \mathrm{Re}[K]\nabla E^2 = \frac{2(\rho_m - \rho_p)g}{3\varepsilon_m} \quad (6)$$

Based on Eqn (6), the levitated height of the particle is determined by dielectric properties of the particle, irrespective of their size. Particles with different dielectric properties levitate at the different heights. As known, the fluid inside the chamber flows at different velocities with a parabolic flow velocity profile along the height of chamber, as shown in Fig. 8. So the particles levitate at different heights will flow at different velocities thus reaching the outlet at different times, and collected respectively.

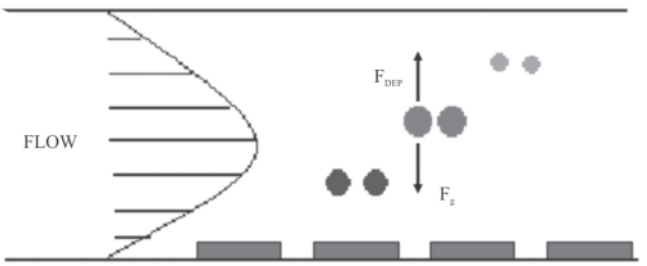

Figure 8. Field flow fractionation caused by flow speed profile of fluid.

Compared to flow separation, this method can separate multi-population simultaneously, not only the mixture of two populations. Huang[64], *et al.* have successfully used this method to separate human leukemia cells from normal human mononuclear cells. DEP-FFF has been also used to separate synthetic polystyrene microbeads of different sizes[65] and to separate monocytes from T- or B-lymphocytes[66]. A detailed review of DEP FFF has been given by Gascoyne and Vykoukal[67].

3.3.2 DEP Devices with Bi-layer Electrodes

Although planar DEP devices have been developed to successfully separate a wide range of bio-particles, a stumbling block has prevented this technique from being used in practical applications in biological and medical fields. This is because DEP force will decrease quickly as the distance from the planar electrodes increase such that only a small number of particles can be trapped, which is not sufficient for practical application. To improve the DEP force, a system consisting of two layers of electrodes array has been developed, as shown in Fig. 9. A technical challenge of these devices is the accurate alignment of the top and bottom electrodes. The misalignment of the

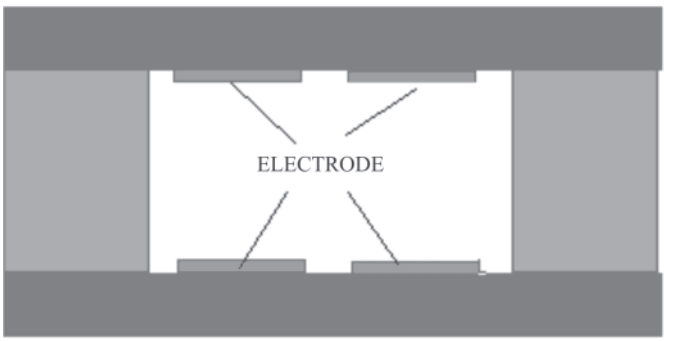

Figure 9. DEP device with two layers of electrode arrays.

electrodes may cause the adverse impact of the holding force[68].

In 1993, Schnelle's group[69, 70] has designed a 3-D microelectrode system, called dielectrical field cage (DFC), consisting of two layers of electrode structures separated by a thick polymer spacer or ceramics forming a flow channel. The dielectrical field cage was formed by eight electrodes symmetrically arranged on the top and bottom glass slides. Subsequently, Suehiro[71], *et al.* proposed a similar structure where the electrode system consisted of two glass plates, on which parallel strip electrodes were fabricated, placed together with a spacer between them so that their electrodes face each other and cross at right angles to form the grid. Such structures have also been reported by many groups[72-78]. Recently, a novel system with thin film vertical electrodes deposited on both sides of the microchannel for DEP trapping has been reported by Wang[79], *et al*. The vertical metal electrodes with different length ratios were fabricated by electroplating on the SU-8 microchannel to generate the non-uniformity of the electric field for particle manipulation.

3.3.3 DEP Devices with Extruded Electrodes

Different from the above idea, Voldman[80], *et al.* proposed an extruded quadrupolar system consisting of cylindrical electrodes fabricated by electroplating gold posts in a trapezoidal arrangement and substrate-interconnect shunts in a SU-8 chamber, as shown in Fig. 10. This device greatly improves the volume where the particles experience strong DEP force and then improves the trapping efficiency of the particles. One disadvantage of this device is that the extruded electrodes still need to be connected to sub-connected planar metal electrodes for electrical contact and a separate SU-8 chamber for channel walls.

Later, Park and Madou[81] replaced the electroplating gold posts and interconnected planar electrodes by carbon structures, which could be more easily fabricated by microfabrication technology. More recently, Iliescu[82], *et al*, Yu[83], *et al*, and Tay[84], *et al* have proposed a novel DEP system with three dimensional (3-D) electrodes[82-84] (Fig. 11), where the electrodes formed by heavily-doped silicon also function as microfluidic channel wall. Compared to other devices, these devices eliminate the need for a separate channel wall material and minimise dead volumes. A unique characteristic of this device is that the electrodes also

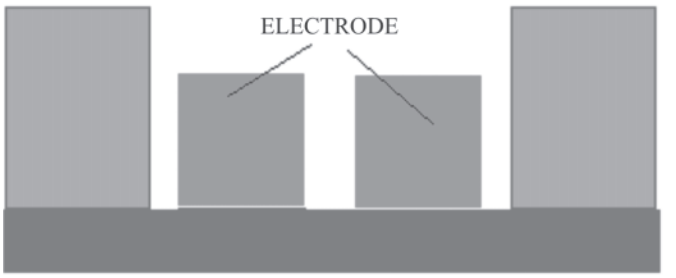

Figure 10. DEP device with extruded electrodes.

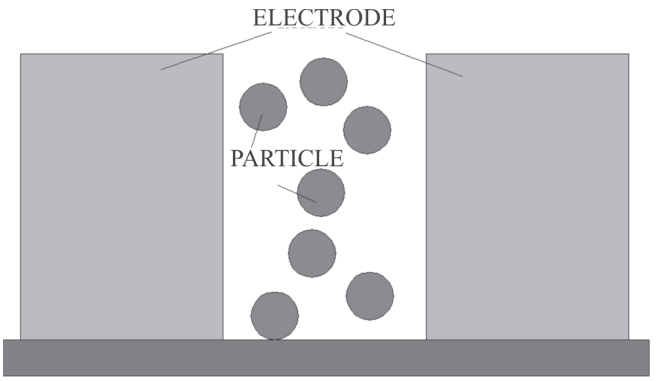

Figure 11. DEP device with 3-D electrodes.

function as the microchannel wall. These electrodes serve double function, to generate positive and negative dielectrophoretic force and in doing so, trap two populations of cells in different locations, and produce a gradient of fluid velocity. Therefore, combined with the DEP and hydrodynamic forces, a new sequential separation field-flow technique[85] has been proposed.

The sequential separation process consists of four steps as presented in Fig.12.

Step(a): Initially the channel was filled with the particle mixture (Fig. 12(a)). At the optimal frequency, one population experiences a negative dielectrophoretic force that drives particles into the dead fluidic zones where these remain trapped. Simultaneously, the other population experiences a positive dielectrophoretic force that focuses these in the region of the channel cross-section where the maximum fluid velocity occurs during flow Fig. (12(b)).

Step(b): After the particles were segregated into the two regions within the channel, fresh buffer solution was pumped through the channel. The population that was focused at the centre of the channel where the velocity was the greatest were swept out by the hydrodynamic force exerted by the flow (Fig. 12(c)).

Step(c): The population trapped in the fluidic dead zones remained trapped under flow or no-flow conditions.

Step(d): The dielectrophoretic force capturing the population in the dead zones was then reversed, and the captured population was swept out (Fig. 12(d)).

Similarly, a continuous field flow separation using a dielectrophoretic chip with 3-D electrodes has been proposed[86].

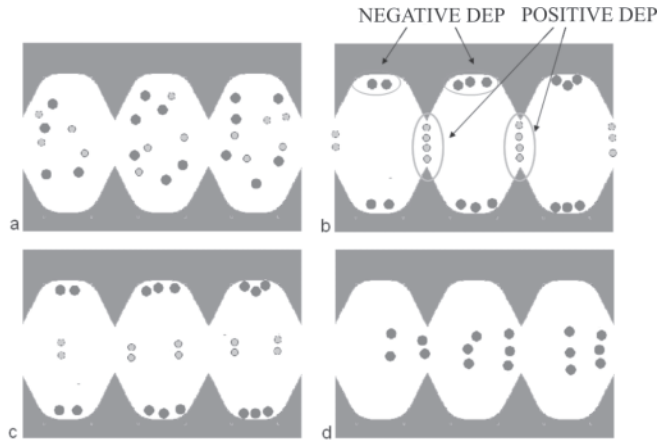

Figure 12. Sequential field flow separation using DEP device with 3-D electrodes.

Moreover, a DEP device with asymmetric electrodes, where one electrode is a thin film while the other one is extruded, functioning as a microchannel wall has also been designed and fabricated by Iliescu[87], *et al*. (Fig. 13). The asymmetry of the electrode in the vertical plane generates an asymmetric electric field that traps the particles for positive DEP-near the thin electrode, where the gradient of the electric field is the strongest. This is a unique characteristic for a DEP device where the gradient of the electric field is generated by changing the electrode's shape. This device can increase the vertical DEP force and decrease the Joule heating effect, which is very useful in many biological and medical fields.

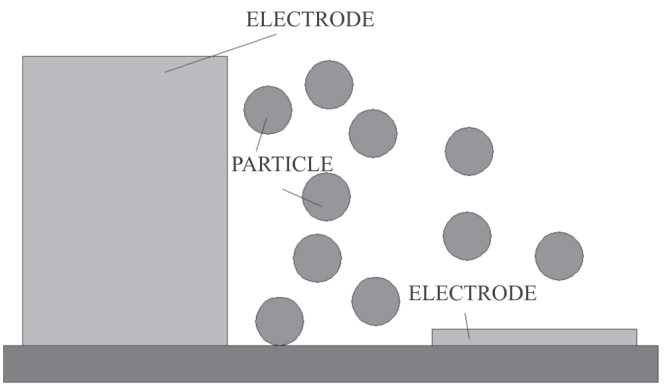

Figure 13. DEP device with asymmetric electrodes.

3.3.4 Change in Electrode Shape (Others)

In 2005, Fatoyinbo's[88], *et al.* proposed a novel 3-D composite DEP devices using drilled laminated structure to form channels bearing electrodes (Fig. 14). The laminate consists of alternating, insulating and conducing layers. Channels are formed through the holes drilled in the laminate and each hole was regarded as a rolled-up 2-D electrode array, which increases the volume where the particle experiencing strong DEP force compared to the planar electrodes. Furthermore, a large number of holes drilled in the laminate can greatly improve the throughout of the devices.

Recently, Abidin[89], *et al*. have reported a novel electrode

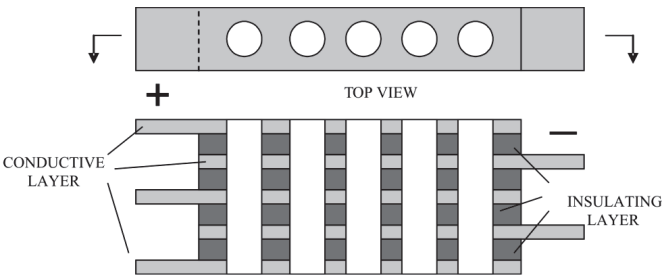

Figure 14. 3-D composite DEP device with alternating conductive and insulating layer.

structure for large-scale particle separation based on weaving technology. A plain weave cloth was made by conductive metal wire and insulating polyester yarns. The metal wires formed the weft and were kept parallel and apart by a warp of flexible polyester yarns. This method has been demonstrated to effectively collect live yeast cells and separate dead and live yeast cells in a chamber consisting of alternating weave cloth and perspex slabs.

3.4 Change of Electric Field Gradient using Optical Images (Image DEP)

Chiou[90], *et al.* proposed a novel DEP device based on optical image to form the virtual electrodes instead of conventional metal electrodes (image dielectrophoresis). Optical images were created using a light-emitting diode and a digital micromirror, projected onto a photoconductive surface. When projected, light illuminates the photoconductive layer, the optical image turns into the virtual electrodes, generating the non-uniform electric field for particle manipulation. The photoconductive layer consists of multiple featureless layers of ITO-coated glass, an n^+ hydrogenated amorphous silicon layer, an undoped a-*Si*:*H* layer, and a silicon nitride layer, which can be simply fabricated without photolithography. This technique has been successfully applied to trap a single polystyrene bead and separate the live human B cells from the mixture of live and dead cells. However, for sub-micrometer particles, the DEP force generated by virtual electrodes is still not enough to overcome the Brownian motion. Later Huang[91], *et al.* proposed a self-assemble microlens arrays (MLAs) based on DEP energy wells. The electrically polariseable microballs are trapped in energy wells by classical patterned DEP planar electrodes. Then the image dielectrophoresis is applied to redistribute the excessive microballs and to fill up the vacancies in arrays, enabling one microball in one energy well[91]. Similarly, they have applied this method to rearrange NIH 3T3 multicells-to-single cell in one trap[92].

3.5 Other Dielectrophoretic Devices for Cell Manipulation

Recently, a new cell manipulation method using a moving dielectrophoretic force to transport or fractionate cells along a microchannel has been reported by Kua[93], *et al*. In this method cell transportation was achieved by sequentially energising one electrode or one array of electrodes at a

time to form an electric field that moved the cells continuously along the microchannel. The movement of the cells was controlled by interelectrode activation time. The structure and operational principle as shown in Fig.15.

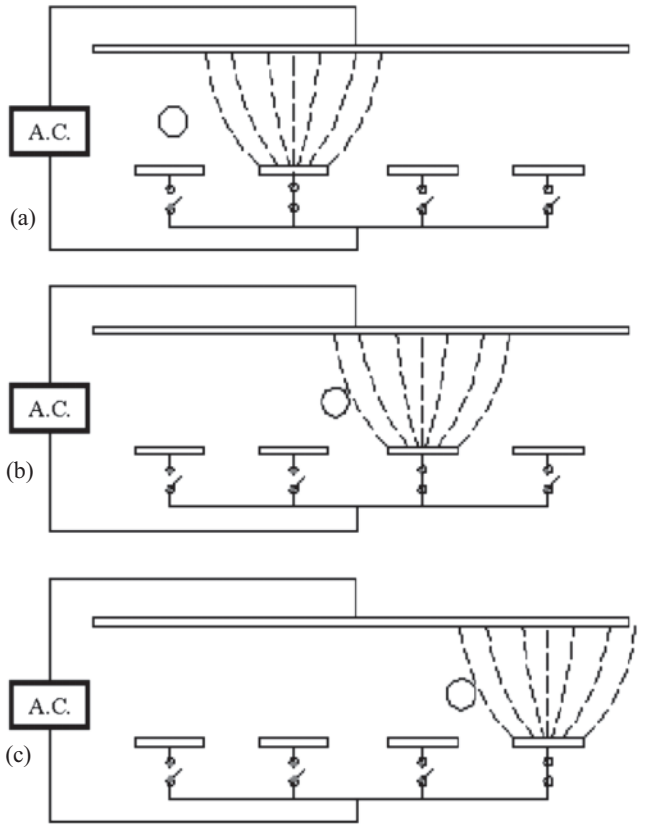

Figure 15. Schematic for moving electrophoresis.

The operation involves the following steps

Step 1: The second electrode from the left is energised, a cell experiencing positive DEP will move towards the highest electric field region, that is the energized electrode edge.

Step 2: Subsequently the third electrode is energised and the cell continues to move to the third electrode under force of attraction.

Step 3: Similarly, the cell moves forward along the microchannel as the electrodes are subsequently energised.

Compared to the conventional DEP, moving dielectrophoresis allows cells to be separated on the basis of the real part of the Clausius-Mossotti factor. Furthermore, this method allows the direct transportation of separated cells without fluid flow as TWD. One distinctive advantage of this device is that cells are transported unidirectionally no matter the cells experience positive or negative DEP.

4. CONCLUSIONS

The DEP is the movement of dielectric particles in a spatially inhomogeneous electric field. In this paper, all kinds of designs and operational principles of the DEP devices have been reviewed. As promising approaches for automatic particle trapping, transportation, and sorting, these devices have been widely applied for manipulation of micro or nano-particles in biological and medical fields. However, there is still a long way to go from research towards commercialisation. More effort is needed to improve the throughput, selectivity, and integration of the DEP devices, and most importantly, to make these cost-effective.

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