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Dielectrophoretic Chip: Potential for Biomedical Applications

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Abstract: The dielectrophoretic (DEP) chip is used for the separation, focussing, manipulation, and sorting of cells. This review included solutions to cell separation problems like heat generation, single-cell analysis, cell sorting against fluid flow, etc. Cell trapping efficiency increases using optical pressure, DEP, and electroporation at low ionic strength, large multi-layered electrode structure, batch & continuous separation, gel-based sieving method, electrodeless dielectrophoresis (EDEP), DEP impedance measurement (DEPIM), electrodes in a trapezoidal manner. These DEP chips have many applications in biotechnology, biomedicine, cell analysis, etc.

Keywords: dielectrophoretic chip; lab-on-a-chip; cell trapping; electrophoresis; biomedical application.

1. Introduction

Dielectrophoresis (DEP) was initially discovered by Pohl in 1958. Electrophoresis-based DEP chip helped to separate the non-polarized particle under DEP force, allowing particles to move under a non-uniform electric field and used for quantitative analysis of particles.

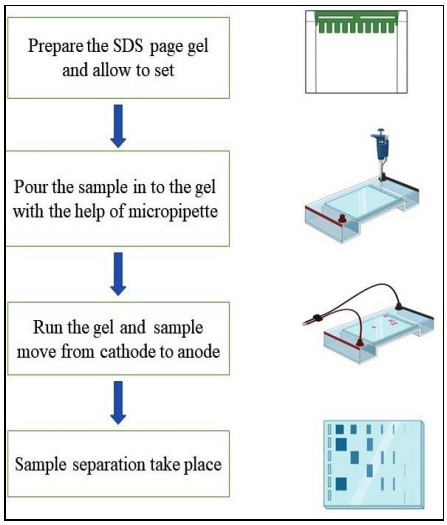

Figure 1. Principle of electrophoresis

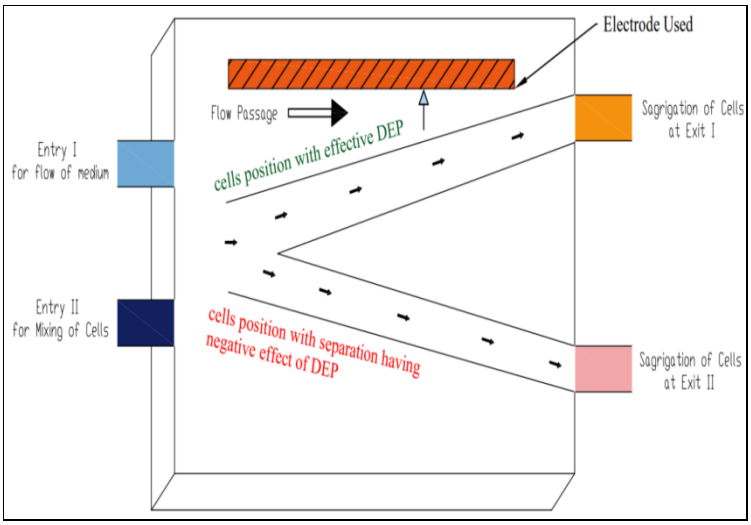

Figure 2. Hydrodynamic di-electrophoresis (DEP) process flow

DEP force magnitude and direction are based on the degree of electrical field and conductivity of the medium used for the particle suspension. Two types of DEP force, negative

DEP force (nDEP) & positive DEP chips (pDEP), have been used to separate cells. Negative DEP force (n DEP) propelled the cells away from electrodes. Positive DEP chips (pDEP) pull the cells toward the electrode [1].

2. Technology

A single cell can be confined at the center of a microscope by optical pressure and oriented toward the electric field produced by DEP force. This approach is applicable to DNA and single-cell control.DEP force plays a crucial role in the separation of submicron bioparticles[3] and controls the adhesion of microbeads coated with biochemical probes [4-6]. When beads get trapped, the force is turned off, and a microfluidic platform aids in the detection of analyte molecules in samples of body fluids. These combined systems allowed low-cost, quick, careful, selective, label-free detection and analysis of bioparticles. A cell can be manipulated, collected, aligned, moving stepwise, and localized using these forces and high-gradient electric fields. A single square voltage pulse applied to buried electrodes increases [7]. Bidirectional fieldflow in a DEP chip with 3D electrodes and a hydrodynamic DEP process is used for continuous cell separation[8-9].

The liquid channel interface causes a remarkable increase in separation responsible force [10]. The conventional DEP impedance measurement (DEPIM) method detects bacteria based on the electrical conductance of all cells' arrest onto the microelectrode under di-electrophoresis. The electro-permeabilization phenomenon helps increase the conductance of bacteria trapped in a high AC electric field, which helps release intracellular ions of trapped bacteria. DEPIM and electro-permeabilization integrated methods help detect biological cells and bacteria. Electro-permeabilization-assisted DEPIM (EPA-DEPIM) used positive DEP force to detain live bacteria from suspension. This phenomenon has applications in Bio-MEMS devices[11-12]. Travelling-wave-DEP (twDEP) forces are used to employ microparticles and yeast cells on a microchip fabricated by micromachining techniques[13]. Tweezers are also employed to manipulate the object under DEP stress, but a high-spatial end effector is required [14]. This tweezer and localized 3D movable electric field configuration also operate cells and beads[15]. Blood cells have magnetic and dielectric properties that can be predicted using a continuous lateral magneto-DEP (MAP–DEP) microseparator to enrich circulating nucleated cells effectively [16]. This force is generated by a ferromagnetic wire array present on the bottom glass substrate &planar interdigitated electrode array of a top glass substrate, uniformly distributed on the whole surface. The tobacco mosaic virus is handled and spatially sorted by a microelectrode array in batch and continuous modes. A batch microsystem has an application in the DEP sorting of microparticles based on size or dielectric properties. This device is operated with conductive cell culture media, which results in less electric loading. Ohmic heating can cause field distortion, which reduces the force.

The field-flow-fractionation method can also be used for human leukocyte differential analysis by DEP. No fluid is required for sorting in this design, but separation occurs according to dielectric properties[17]. Field-Flow-Fractionation DEP cell-separation technique worked on time-varying DEP force, which depends upon the difference in the density, membrane, and dielectric properties of cells. This technique is used for the sorting of maximum human leukocyte subpopulations. The thin chamber had a range of microfabricated integrated electrodes on the bottom surface. It does not require cell-labeling or cell-modification steps which is a new advancement in hematological analysis.

A 3–D fabricated IC technology with RF electric field has applications in suspended microscopic dielectric particle sorting and aggregation[18]. A new AC field cage can efficiently trap the cells against the stream. The low frequencies DEP trapping is feasible with the metallic structures in the cage[19]. Electrodeless dielectrophoresis (EDEP) is working for the congregation and patterning of both single-strand and double-strand DNA. DEP force increases with an increase in the length of DNA for a given trapping voltage. EDEP force can be controlled by altering the shape and cross-section of constriction. The DNA concentration can enhance the sensitivity of the detection component & gene hybridization. Microfluidic devices cellomics work on mechanical and electrical principles in cell sorting, trapping, and sampling[20-21]. It is a commercial cell sorter and flow cytometer and is suitable for cellular studies like cell lysis and cell fusion. It helps define the cellular environment and composition of a single cell LAB – IN- CELL (LIC).

Electro-osmosis helps in channel circulation and long-range interaction. It can combine with DEP for the handling of particles in a fluid. A pair of electrodes (EO-electrodes) can induce a circulated electro-osmotic flow in the channel when particles come close to the second electrode and get captured due to voltage. Microfluidic channels having metallic electrodes based on electro-osmosis (EO) dielectrophoresis (DEP) (EODEP) can control micro- or nanoparticles[22]. Microfluidic pumps with AC electro-osmotic flow systems have the advantage over conventional electro-osmosis as they require a regular battery supply. So, it is suitable for portable lab-on-a-chip systems[23]. Drift-diffusion dynamics is employed to analyze particles at electrodes[24]. DEP device efficiency decreases with increases in the centration of biological material around the electrode.The 3D numerical computational model has applications in the simulation, focusing & separation of bioparticles[25-26]. This model solves equations for particle movement and joule heating with applications in separating the biological cell system. The optoelectrostatic micromanipulation (OEMM) method is used to measure biological cell and DNA molecules.

3. Design

DEP chip is used as a sandwich form of the glass/silicon/glass DEP chip[27-30]. The top glass layer contains two inlets and two outlets for the inlet/outlet of particle suspension and buffer solution. It has an ITO top electrode, flow chamber, middle electrode on the SU-8 surface, and bottom electrode under the SU-8 micro-cavity. Cells are trapped and released under a DEP force generated by AC voltage at the top and middle electrodes[31]. The microfluidic device 3D electrodes generate a uniform DEP force and help achieve a velocity gradient. The channels can be large or without an orifice according to particle size. Chip with multiple arrays also has applications in a single cell's hold and programmable liberation. It has many applications for the effective attraction of biological cells[32]. The cells are focused on an inlet of funnel-shaped insulating structures. Entered cells are attracted toward the center due to the negative DEP forces. So, a hike in the electric field improved the performance of microdevices. Microfluidic biochip integrated actuation electrodes improve cell focusing. The impedance detection method with sensing electrodes helps to detect trapping[33].

A multi-layered electrode structure with a large area has been fabricated with electrode arrays powered by an AC power supply [34]. This electrode generates a traveling electric field, which induces a traveling wave DEP to separate particles. These DEP chips have applications in techniques like microscopy and spectroscopy. 3-D microelectrode structures integrated with micropumps have lab-on-a-chip applications. Quadrupole electrode structures are used in

multipolar theory[35]. A micro-manipulation system with fluid containment & microelectrode has been developed by using different materials[36]. A planar microelectrode array microfabricated device can sort thousands of mammalian cells[37]. The parallel–plate flow chamber contains thousands of trapping electrodes on the bottom, and each electrode can confine only one cell. In this device, the cell can be trapped at a low voltage, which is harmless for the cell. An integrated stacked micro laboratory has been used for automated electric-field-driven immunoassays and DNA hybridization[38]. It contains four cylindrical microfabricated gold posts in a quadrupolar fashion, which is interconnected by the stunt in a trapezoidal manner[39]. This trapping system is batch fabricated, switched electrically, and easily arrayable. Lithographically fabricated gold electrodes onto microscope coverslips and DNA/protein are manipulated using DEP generated in the gap between the electrodes[40]. This model works for trapping DNA but is not suitable for the charge double layer. Nanosensor technology uses porous membranes as a template[41]. This nanostructure has been manipulated for individual assembly and characterization using DEP force.

A planar MEMS silicon structure has application in recording ion channel currents in biological cells[42]. Recently, a glass micropipette was used to perform an electrophysiological experiment. The micropipette tip generates heat because of the conical structure and is responsible for pipette resistance. So, a silicon biochip is used for the characterization of the resistance and capacitance of the planar pipette. These models represent a new way of determining chip resistance and conductance with physical parameters. A tip with a single multi-walled carbon nanotube (MWNT) affected the shape of the apex in the atomic force microscope (AFM)[43]. A novel microfabricated DEP chip has been designed to sort long single-cell arrays [27, 44]. This strong DEP force can hold particles firmly against the practical flow. This model has been used to understand the effect of trapping and cell size on efficiency. It also provides a unique method of cell trapping, which has applications in biology experiments. This type of chip is easy to fabricate and pack and helpful for a wide range of cell sizes. There are three methods to generate an electric field. The first is by electrodes of different shapes, the second is by the traveling wave chip, which changes the stage of an applied electric field, and the third is by a nonhomogenous dielectric medium between electrodes. The asymmetry of electrodes generates the electric field gradient for particle sorting. The thin electrodes, which have a stronger electric field, generate positive DEP. When generating negative DEP, particles drift away from the electrode. The generation of an electric field gradient by changing electrode shape is a unique characteristic of this chip. This structure has a DEP force two times stronger than the planar structure. Glass's good isolation properties make it perfect for various frequencies[28]. "Lab-on-a-Chip" system with DEP gives better accuracy, shorter analysis time, high resolution, and precision in comparison to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) of reference protein molecular weight estimation[45]. DEP enhances through the various geometry of the electrodes. It has four categories of DEP devices based on design: parabolic electrode, castellated electrode, electrode array, electrodeless device.

All devices have distinct advantages. For example, castellated electrodes have pDEP and nDEP originating well for cell sorting. The electrodeless devices have been less with metallic electrodes, which are helpful in metal-delicate biosamples. The parallel track electrode array is a popular choice because of its construction simplicity. It has electrodes of a rectangular shape of identical width. The efficiency of the chip can be enhanced by replacing rectangular electrodes with triangular ones, which can create a band of distinct electric field strengths[46].

A collagen-coated planar interdigitated ring electrode (PIRE) array generates p-DEP that works on three types of DEP, positive, negative, and both. This unique electrode array has the following characteristics: A ring-shaped electrode gives maximum length along the edges, the electrode has sufficient width for accelerating the cell patterning, and the gap region is critical for quality cell patterning. The inner area of PIRE is smaller than the outer, PIRE has many applications because of its wide diameter and spacing; it also requires less wiring to connect the electrodes.

4. Problems

The electrochemical adhesion and stimulation phenomena have various problems, such as a medium's flow and heat production[14]. So, microelectrode chambers have solved heat production at low ionic strength in DEP and electrorotation measurements [47]. ACC cage can reduce heat production by adjusting electrodes on the same potential [48]. Another advantage is that no particle displacement suffers at a higher voltage. So, a higher trapping force has been induced at less liquid streaming. DNA molecules for optical trapping can be manipulated in an aqueous solution [49]. Submicron bioparticles are separated because of the difference in the DEP chip's amplitude and regulation[50]. It affects the bioparticles' different populations and generates a non-uniform electric field for single-cell analysis. It is used to trap cells more strongly. Field gradient is also used to manipulate a single cell in biotechnology. Quadrupolar fashion-designed DEP chip has been used to trap firmly against flow [39]. Microfluidic free-flow electrophoresis (μFFE) separation technique works on liquid support medium and mild separation conditions, but applications are restricted due to bubble production restrictions [51].

5. Application

The microfabricated device with a planner microelectrode array can manipulate the cells in a controlled manner with applications in detecting/sensing components and biosensors. Cell health has not been harmed due to device voltage shown in cell proliferation and viability. An integrated, stacked micro laboratory has applications in detecting bacteria and biowarfare agents [39].

Nanosensors also have many applications like signal processing, communication circuitry & post–IC assembly. DEP microdevice based on insulators has many ineffective applications focusing on biological cells, the biomedical field that is easy to operate & integrate [32]. DEP microcage with a high-resolution optical detection system has many applications in life sciences[48]. It can be used in blood component fractionation and medical purposes like sorting single objects or aggregates of cells, viruses, organelles, and ribosomes. Lab- on- Chip technology and transient ITP coupled to free zone electrophoresis (t-ITP-MFZE) mode, which helps in the separation and detection of proteins[45, 52].

Microfluidic chip electrophoresis (MCE) has applications in DNA analysis, multiple tumor marker (TM) detection, and tumor cell diagnosis from blood based on physical properties [53]. DEP can combine with biosensors to have applications in detecting and separating the element. The electrophoresis titration (ET) model is a portable diagnostic method that helps visualize uric acid in blood and urine[54]. Table 1 gives the technology developed with its advantages and applications used in the field.

Table 1. Technology developed with its basic utility and advantages to the field used.

Sr. no.	Technology/Design	Advantage/ Application	Reference
1.	Opto- Electrostatic micromanipulation (OEMM)	Transport/ Analysis of single cell/ DNA/Cancer detection	[55]
2.	Ultra micro electrode fabricated by electron beam lithography	Reduce heat production and improve heat repellence	[56]
3.	Novel microfabricated device	Trap thousands of single mammalian cells	[36]
4.	Traveling-wave-dielectrophoretic (twdep)	Forces for the manipulation of microparticles and yeast cells	[13]
5.	Hydrodynamic DEP process	Continuous cell separation chip	[9]
6.	EPA-DEPIM	Using a positive dielectrophoretic force to capture bacteria	[12]
7.	(EODEP)	Micro- or nanoparticles suspended in a liquid in microfluidic channels can be manipulated	[21]
8.	Planar MEMS silicon structure	Record ion channel currents in biological cells	[41]
9.	Gold electrodes lithographically fabricated onto microscope cover slips	Position the DNA and proteins at well-defined positions on a chip	[39]
10.	Patterning nanowires	DEP chip with dot matrix electrodes	[57]
11.	Optical tweezers and a microfluidic chip	Dielectrophoretic force measurement of red blood cells	[58]
12.	3D Carbon-Electrodes	Dielectrophoretic Separation of Live and Dead Monocytes	[59]
13.	Optical Sensor and DEP	Label-Free On-Chip Selective Extraction of Cell-Aggregate-Laden Microcapsules from Oil	[60]
14.	Novel insulator-based dielectrophoretic device	Rapid and label-free isolation of small extracellular vesicles from biofluids	[61]
15.	Lab-on-a-chip platform with tilted planar electrodes	Manipulation of microparticles	[62]
16.	Electrode pitch optimization	Dielectrophoretic separation of monocytes from cancer cells	[63]
17.	Dielectrophoretic force-driven biosensor platform	Screening for cerebral amyloid angiopathy based on serological biomarkers analysis	[64]
18.	Dielectrophoretic or Optical Forces	Modeling Brownian Microparticle Trajectories in Lab-on-a-Chip Devices	[65]
19.	DEP-integrated microfluidic device	Microsphere-mediated exosome isolation and ultra-sensitive detection	[66]
20.	Layer-by-layer (lbl) coating on droplets in a wide microchannel	Characterizing and handling colloidal particles	[67]
21.	Sheath-assisted and sheathless DEP separation using tilted electrode	Size-based separation of cells and particles	[68]
22.	Coupled dielectrophoretic detection and impedimetric counting	Drug resistance analysis of leukemia cells	[69]
23.	A microfluidic chip that combines dielectrophoretic motion and electrorotation technology	Single-cell electrical properties characterization	[70]
24.	The electrode is attached to a glass slide and a microchannel	To enrich X-sperm for increasing female offspring in dairy farms	[71]

6. Challenges and Future Aspects

CMOS technology has been used to study the resistance in assembled nanowires [41]. In the future, DEP sensitivity can be tested based on the material or the bead nature [72]. It has applications in stem cell research and lab-on-a-chip systems [6]. The micro laboratory can be improved by decreasing volume and electronic addressing time, which has many applications in biotechnology and the medical field [73]. Electronically controlled circuit assembly can be used for trapping short strands of DNA, nanowires, and nanotubes in the future [40].

Biochips with integrated actuation electrodes have helped control a cell and microbead. It is based on an impedance detection method that can be improved in the future with efficient trapping chambers and feedback control electronics [73]. Various challenges faced by the detection system are as follows:

Size: AC field cage (ACC) is unsuitable for particles with a small size compared to electrode distance. Positive DEP is unsuitable for separating the larger bead (6μm) & red blood cells. In addition, fabricating more complicated 3D microelectrodes and integrating nanostructures on DEP cells is challenging.

Technology: YAC laser during focussing can damage E- coli cells. UV laser also causes a chemical change in DNA, which is not preferable for a polymerase chain reaction. Constant driving voltage may cause an extraordinary increase in chamber field strength & resulting force. Planner electrode surface levitation of particles at a large axial distance has been affected by Joule heating & convective fluid flow. Frequency-dependent separation caused by electrohydrodynamic flow has a foundation for the chip's design.DEP is enhanced with increased DNA length, so there is a problem separating small-length DNA. Trapping chamber no increase & feedback control electronics is also a design challenge.

Performance: DEP enhanced with increased DNA length, so there is a problem separating small-length DNA. Its manipulation in the case of DNA charge double layer is inconsistent for the experiment. Frequency-dependent separation caused by electrohydrodynamic flow has a foundation for the chip's design. There should be reduced noise. Biocompatibility of chip surfaces is a significant challenge. The seal is formed between the cell membrane & orifice, which is responsible for the blockage. Sensitivity of DEP chip Different DEP elements are integrated in a sequential flow manner. Limitation in separating a cell with a concentration of 8.3 ng/ml. Thermal expansion, medium's flow, and surface modification prevent electrochemical adhesion.

7. Conclusions

The DEP concept has been applied to various designs like nanosensors, MEMS, lithographically fabricated, microfluidic devices, stacked micro laboratory, 3 –D fabricated IC technology-based chips. This review highlights many problems like heating, noise problems, and separating tiny beads in DEP chips. DEP-based chips have many applications in biotechnology, the biomedical engineering field, microbiology, and nanoscience. The 3D numerical computational model can be applied in the simulation, focusing & separation of bioparticles. Microfluidic chip electrophoresis (MCE) has applications in DNA analysis, multiple tumor marker (TM) detection, and tumor cell diagnosis from blood-based on physical properties. Drug resistance analysis of leukemia cells study has been studied by coupled dielectrophoretic detection and impedimetric counting. Ultra-micro electrodes fabricated by electron beam lithography solved the issue of heat production and improved heat repellence. Microfluidic free-flow electrophoresis (μFFE) separation technique works on liquid support medium and mild separation conditions, but applications are restricted due to bubble production restrictions. The electrode is attached to a glass slide and a microchannel enriched X-sperm for increasing female offspring in dairy farms. Microfluidic free-flow electrophoresis (μFFE) separation technique works on liquid support medium and mild separation conditions, but applications are restricted due to bubble production restrictions.

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Conflict of interest

The authors declare no conflict of interest.

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