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IN-DEPTH THEORETICAL AND EXPERIMENTAL REVIEW ON DIELECTROPHORETIC MANIPULATION OF BIOLOGICAL CELLS

BY

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Abstract. Dielectrophoresis (DEP) is a powerful and well-established technique that allows label-free, non-invasive manipulation, and characterization of biological cells by leveraging their electrical properties. DEP has become a promising technique to separate, isolate and identify biotargets suspended within a medium based on their dielectric properties, fact which might be essential in development of future biomedical applications.

The herein review is aiming to provide an in-depth collection of experimental studies on utilization of DEP in handling various biological cells. Thus, starting from the classical setup of DEP, several literature-proposed technological configurations for cells sorting have been discussed. The literature is presenting a plethora of studies with respect to electrical evaluation of cells, and this review is reporting a collection of information regarding the functioning principles of different types of dielectrophoresis set-ups and electrical investigation. The interpretation of electrical characteristics against frequency is discussed with respect to interfacial/Maxwell–Wagner polarization. Nonetheless,

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technological challenges and future scientific directions to be approached for ensuring medium-term large-scale uptake of DEP in clinical studies are discussed while clearly differentiating the influence of electrodes' geometry and architecture, medium conductivity, DEP parameters against cells electrophysiology.

Keywords: dielectrophoresis, biological cells, electrodes, medium conductivity, non-uniform electric field.

1. Introduction

Within the last decades, dielectrophoresis (DEP) has been successfully employed in numerous cancer research studies as of its capacity of allowing one to distinguish between the abnormal and healthy states of cells by means of exploiting their dielectric properties.

Due to its unique characteristics, including speed, ease of use and affordability, DEP may find its way into future diagnostic techniques used in standard pre-clinical and/or clinical laboratory procedures. First used to separate and manipulate cells and introduced to the biological and chemical fields by Pohl in 1951 (Zhizhong *et al.*, 2020), DEP has attracted the interest of researchers worldwide as of its simplicity and free-labeling operation.

Drug delivery and discovery (Pethig, 2013), identification of healthy and diseased/unhealthy cells (Yafouz *et al.*, 2016), differentiation of living from dead yeast cells (Matbaechi *et al.*, 2021) red blood cells (RBCs), (Sang *et al.*, 2016) and bacteria (Zhu *et al.*, 2018), identification and isolation of cancer cells (Yao *et al.*, 2019), DNA (Li *et al.*, 2015), protein molecules (Liao *et al.*, 2012), and enrichment of stem cells (Yoshioka *et al.*, 2018) are just a few of the previous medical applications where DEP manipulation was convincingly used. Over the past few years, the use of DEP has evolved considerably, particularly in relation to biological research and technologies. Within the herein paper, we are presenting an updated review on the progress of DEP in respect to both set-up and functionality as well as from the viewpoint of its multiple application opportunities regarding evaluation of biological cells (targets).

2. Dielectrophoresis (DEP)

2.1. Theory

DEP explains the behavior of particles that move under the influence of a non-uniform electric field due to their polarizability. Because of its precise selectivity, high sensitivity and minimally non-invasive nature, DEP offers several advantages when working with neutral bioparticles. The method is capable of capturing, transforming, concentrating, splitting and characterizing chemical, biological and inorganic target objects suspended within a fluid

medium. Dielectrophoresis (DEP) operates based on the difference in dielectric properties between particles and the medium in which they are suspended and this principle applies to both charged and neutral particles (Pesch and Du, 2021).

DEP is a nonlinear electrokinetic (EK) phenomenon resulting from Maxwell–Wagner interfacial polarization, which arises when an external electric field causes the displacement of a particle within a suspending medium (Giduthuri *et al.*, 2020).

A mismatch in electrical polarizability connecting a particle and its surrounding medium leads to the formation of surface charges under an external electric field. These charges produce ponderomotive forces, causing the particle to migrate within a non-uniform field toward areas of greater or lesser intensity based on its polarizability (Pethig, 2016).

Several factors influence how strong the DEP force is and in which direction it acts, including the particle's electrical characteristics, the nature of the fluid it's in the irregular distribution of the electric field and the frequency of the applied voltage (Pethig, 2013).

The motion of particles under dielectrophoresis is influenced by more than just their dielectric characteristics. Factors such as the conductivity of the surrounding fluid, the intensity of the electric field with the particle's geometry and dimensions all play crucial roles. Central to the process is the dielectric contrast, the disparity in how the particle and medium polarize in response to the field. Moreover, the spatial distribution and frequency of the electric field are essential in determining both the orientation and extent of particle movement (Turcan and Olariu, 2020).

As stated above, particles moving through a material in reaction to an uneven electric field is identified as dielectrophoresis. Standard time-averaged DEP theory comes from utilizing Maxwell's equations to a uniform particle in a large, ideal medium. It assumes the electric field does not change much across the particle, which makes the math easier. With this approach, the standard DEP force ($\langle \overrightarrow{F_{DEP}} \rangle$) could be calculated using Eq. (1). If the result is positive, the particle will be directed toward areas where the electric field is most intense. The angled brackets indicate a time-averaged value, as the dielectrophoretic force arises from a time-varying,

$$\langle \overrightarrow{F_{DEP}} \rangle = 2\pi R^3 \varepsilon_m \text{Re}[\widetilde{f_{CM}}] \nabla |\overrightarrow{E_{rms}}|^2 \quad (1)$$

where ε_m is the absolute permittivity of the theoretically infinite and uniform medium, $[\widetilde{f_{CM}}]$ is the frequency-dependent Clausius–Mossotti factor concerning to the polarizability of the particle and medium, Re is the real part of the expression inside the brackets, R is the particle radius, E_{rms} is the root-mean-

square of the electrical field and $\nabla |\overrightarrow{E_{rms}}|^2$ is the gradient of the squared magnitude of the *RMS* electric field. Dielectrophoresis, in contrast to electrophoresis which requires particles to carry an electric charge, can influence both neutral and charged particles by exploiting variations in polarizability relative to the ambient medium. This interaction is explained by the Clausius–Mossotti factor in Eq. (2), a dimensionless parameter that reflects the distinction in complex permittivity in relation to the particle–fluid interface. It governs both the strength and orientation of the DEP force, ultimately determining whether particles are drawn to or pushed out of zones with high field strength. The equation is:

$$f_{CM} = \frac{\varepsilon_p^* - \varepsilon_m^*}{\varepsilon_p^* + 2\varepsilon_m^*} \text{ or } f_{CM} = \frac{\sigma_p^* - \sigma_m^*}{\sigma_p^* + 2\sigma_m^*} \quad (2)$$

where both the complex permittivity of the particle (ε_p^*) and the media (ε_m^*) and the complex conductivity of the particle (σ_p^*) and of the media (σ_m^*) are frequency dependent (Weng *et al.*, 2016). The frequency-dependent behavior of the Clausius–Mossotti factor is defined by the unique electrical properties of both the particle and the surrounding medium (Deivasigamani *et al.*, 2022).

The Clausius–Mossotti factor (f_{CM}) illustrates the part of a particle's polarization that is in sync with the electric field. Its size and sign are shaped by the variation in dielectric properties of the particle relative to the solution, as well as by how the electric field varies in space, which determines how the particle reacts in a non-uniform field:

$$f_{CM} = \frac{\varepsilon_p^* - \varepsilon_m^*}{\varepsilon_p^* + 2\varepsilon_m^*} \quad (3)$$

Equation (3) shows that the f_{CM} is governed by the inherent dielectric characteristics of the particle and the fluid. These properties together establish the particle's crossover frequency (f_{XO}), where its dielectrophoretic response changes behavior. In this context, ε_p^* and ε_m^* represent the complex permittivities of the particle and the surrounding medium. The value of $Re[f_{CM}]$ bands from $-0.5 \leq f_{CM} \leq 1$ (Md Ali *et al.*, 2016). The value of f_{CM} is influenced by the dielectric characteristics of both the cell and the surrounding fluid, in combination with the angular frequency (Giduthuri *et al.*, 2020). Two distinct crossover frequency points exist: at the first (f_{XO1}), the response shifts from negative DEP to positive DEP, while at the second (f_{XO2}) indicates a transition back from positive to negative dielectrophoretic behavior (Fig. 1). By modifying the electric field frequency, it is feasible to differentiate target cells from non-target ones based on their specific DEP responses (Pethig, 2016).

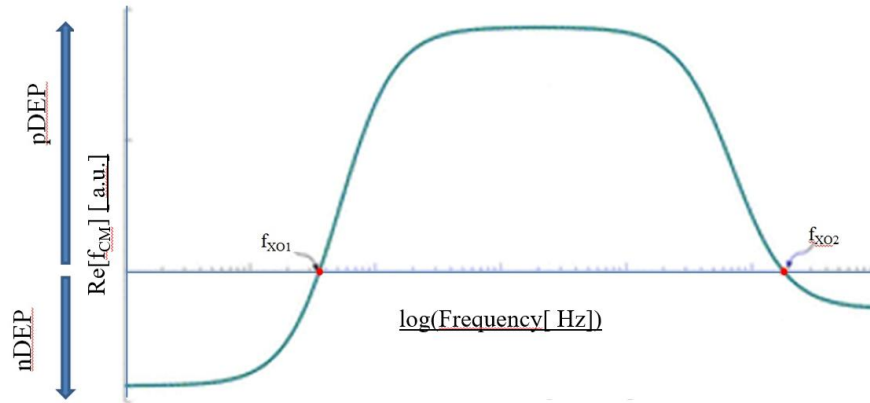


Fig. 1 – Representation for $\text{Re}[f_{CM}]$ against frequency.

Particles more polarizable than their surroundings are drawn into regions of maximum electric field intensity, a phenomenon called positive DEP (pDEP). On the other hand, particles having a lower polarizability compared to the medium move away from these high-field regions, exhibiting negative DEP (nDEP), (Habaza *et al.*, 2016). pDEP occurs when the particle is drawn to regions with the highest field if $\text{Re}(f_{CM}) > 0$. Despite the presence of strong electric fields, certain particles are pushed away from these areas. This repulsive behavior occurs due to dielectrophoretic forces and is referred to as negative dielectrophoresis (nDEP), where particles are guided toward zones with lower electric field intensity (Fig. 2).

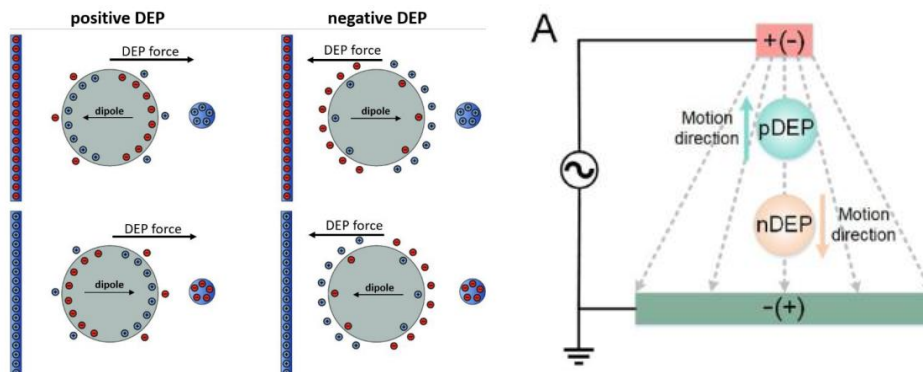


Fig. 2 – The polarization behavior of particles, the resulting dipole moment and the orientation of the dielectrophoretic force vary founded on whether the particles exhibit higher or lower polarizability compared to the surrounding fluid. The upper and lower diagrams illustrate these effects under two opposite orientations of the applied electric field (adjusted from ref. (Ramos *et al.*, 2011)).

Particles exposed to an external electric field undergo forces that cause motion within the medium. The non-uniform field causes the particle's side facing the stronger field region to be pulled more, leading to net movement independent of the field's orientation. Consequently, the particle undergoes motion when subjected to alternating electric fields, where the electric potential applied by external electrodes varies over time (Gascoyne *et al.*, 2009).

Therefore, the particle will also move in the presence of alternating electric fields. This applies to situations where the electrical bias on the external electrodes fluctuates over time (Hughes *et al.*, 2002).

2.2. Classification

From the traditional DEP setup, various modified configurations for cell sorting have been introduced and extensively described in scientific studies:

- Electrode-Based Dielectrophoresis (DEP or eDEP)
- Insulator-Based Dielectrophoresis (iDEP)
- Contactless Dielectrophoresis (cDEP)
- Traveling Wave Dielectrophoresis (twDEP)
- Optically Induced Dielectrophoresis (oDEP)
- Dielectrophoretic Field-Flow Fractionation (DEP-FFF or dFFF)

a. (Electrode-based) dielectrophoresis (DEP or eDEP), the most commonly employed DEP approach, uses metal electrodes (e.g., Au, Au/Cr, Pt, Pt/Ta) integrated into a microchannel, directly interacting with the suspension medium and the cells.

Electrode-based dielectrophoresis (eDEP) devices traditionally generate non-uniform fields using electrode configurations such as narrowly spaced “fingers” (Alazzam *et al.*, 2011). Most DEP systems described in scientific studies are employing microfabricated electrodes, which allow generation of strong local electric fields fact which might increase the price and difficulty of production. Electrode-based dielectrophoresis (eDEP) operates by integrating sets of microelectrodes embedded in a microchannel and applying AC voltages at different frequencies to generate intense electric fields and gradients, while minimizing electrochemical reactions on the electrode surfaces (Park *et al.*, 2009).

DEP offers the capability to differentiate between cells of comparable size but varying structural origins, presenting a substantial improvement over traditional size-based filtration methods in capturing circulating tumor cells. The accelerated progress in this area is largely attributed to the benefits of microfluidic systems, which include faster analysis, minimal sample requirements, high processing rates, ease of automation and portability features not typically available in conventional macroscale fluidic approaches.

The DEP-based devices may potentially experience Joule heating in the surrounding medium affected by spatially concentrated electric field around microelectrodes. Metallic electrodes have the disadvantage of charging and occurrence of electrolysis at high frequencies, which can lead to the electrode degradation and deterioration of the biological material (Pohl *et al.*, 1951).

These systems are often affected by drawbacks like electrode fouling, electrolysis, Joule heating, and the need for close proximity ($\approx 30\text{ }\mu\text{m}$) between cells and electrodes, which limits efficiency and throughput. Although DEP achieves strong electric field gradients at low AC voltages, its use is restricted by expensive fabrication methods, electrode degradation caused by electrolysis, and potential negative effects on biological samples.

b. Insulator-Based Dielectrophoresis (iDEP)

In insulator-based dielectrophoresis, electrodes are positioned at either ends of a microfluidic device and are in physical interface with the sample solution. Insulator-based DEP (iDEP) utilizes structural features, for example channel constrictions, serrated geometries, or post arrays positioned between electrodes within the microchannel. These features manipulate the electric field configuration, concentrating it surrounding the insulators to produce the non-uniform fields essential for DEP activity. Nevertheless, iDEP systems typically require high operating voltages and are susceptible to electrolysis-related issues (Shafiee *et al.*, 2009).

Insulator-based dielectrophoresis (iDEP) microfluidic systems have been utilized to control a variety of particles, cells, viruses, bacteria, and synthetic beads. These devices utilize either DC or AC voltages, across a broad frequency range, delivered to distal electrodes positioned in terminal channel reservoirs, allowing effective particle transport and control within the microchannel (Nakano and Ros, 2013).

In comparison to classical DEP, iDEP exhibits a simpler and more cost-effective production procedure due to elimination of expensive multimetal fabrication of electrode arrays. Additionally, iDEP is highly robust and can be used multiple times, making it suitable for mass production. Furthermore, there is absence of gas formation within the microchannel caused by electrolysis, making it chemically inert. The fluid travels via the electroosmotic flow (EOF) process inside the microchannel, eliminating the need for a micropump for fluid transport (Davalos *et al.*, 2008).

The application of electric voltages along the full length of microchannels in iDEP devices can result in considerable thermal accumulation (Sabounchi *et al.*, 2008). Joule heating may occur within the suspending medium due to concentrated electric fields around insulating structures, potentially compromising the integrity or viability of biological samples. Elevated temperatures pose a risk in biological contexts, as they can alter sample properties or reduce cell survival rates.

Therefore, iDEP microchips are well-suited for the isolation of biological particles that are vulnerable to Joule heating, including yeast cells (approximately 3 μm diameter) and bacteria (ranging from 0.5 to 5 μm diameter).

c. Contactless Dielectrophoresis (cDEP)

Contactless dielectrophoresis (cDEP) represents a modified approach to conventional DEP, utilizing fluid electrodes which are removed from the primary microfluidic channel by a narrow insulating membrane. This configuration enables the generation of the required electric field without allowing direct interaction of the electrodes with the sample (Martinez-Duarte *et al.*, 2012). Contactless dielectrophoresis (cDEP) is a method of cell manipulation that uses physically isolated electrodes to manipulate cells. This setup helps overcome several limitations commonly encountered in conventional dielectrophoresis systems, such as electrode fouling, gas bubble generation, and delamination. Contactless DEP (cDEP) platforms can be produced using replication techniques from a single etched mold, making them compatible with scalable manufacturing processes like those used for iDEP, while preventing interaction between the electrodes and the sample. By leveraging capacitive coupling, contactless DEP (cDEP) avoids common drawbacks of traditional DEP. While both cDEP and iDEP rely on insulating barriers to produce field non-uniformities, cDEP isolates its electrodes from the sample channel via an insulating layer. This setup minimizes electrolysis and electrode degradation, making cDEP especially advantageous for biological applications due to reduced heat generation and contamination risks (Shafiee *et al.*, 2009).

Fabricating and replicating the device consistently can be challenging due to small defects that may occur during casting, de-molding, and bonding. This can result in the need of multiple casts to produce a functioning device. Conventional cDEP systems typically generate the electric potential gradients essential for particle manipulation via DEP within the 100 kHz to 1 MHz frequency range. However, advancing cDEP technology will require extending this capability to operate effectively at lower frequencies, particularly between 1 and 100 kHz.

d. Traveling Wave Dielectrophoresis (twDEP)

Traveling wave dielectrophoresis (twDEP) or four-phase twDEP, emerged in the early 1990s as a method to improve the control and discrimination of cells. It employs multiple electrodes energized in sequence with phase-shifted voltages (0° , 90° , 180° , and 270°) to create a traveling electric field. In the case of twDEP, the magnitude of dielectrophoretic force causes cells levitation and move parallel to the microelectrodes.

When using parallel electrodes positioned along the microfluidic chamber, suspended particles are exposed to travelling wave dielectrophoresis (twDEP), which acts perpendicularly to the pressure-driven flow. DEP and twDEP-based methods enables the manipulation and precise positioning, orientation, and velocity of submicron-scale particles. twDEP is realized by applying a traveling-wave voltage to a patterned electrode array, generating the desired electric field. The resulting separation is governed by variations in particle size or dielectric relaxation time relative to the suspending medium when exposed to a phase-shifted AC signal (Cui and Morgan, 2000).

e. Optically Induced Dielectrophoresis (oDEP)

The operational principle of oDEP-based microparticle manipulation closely parallels that of conventional DEP-based techniques, except that optical images are used as virtual electrodes instead of metal microelectrodes. This technique was first introduced in 2005 and has been well described in previous literature. In an optoelectronic dielectrophoresis (oDEP) setup, an electric field is imposed over a thin fluid layer, leading to the polarization of microparticles. When light is cast onto the photoconductive surface, the illuminated region experiences a reduction in electrical impedance, that creates a localized non-uniform electric field.

The resulting dielectrophoretic force arises from the interplay of induced particle polarization and the spatially varied electric field formed through targeted light exposure. This functionality enables more adaptable control over microparticles than traditional DEP methods, which rely on fixed, pre-patterned microelectrodes (Chu *et al.*, 2020). The oDEP approach for microparticle control has been effectively utilized in various biological applications, particularly in sorting, separating, or purifying cells. For instance, it has been employed to isolate dead and living cells, isolate rare cells in blood such as circulating tumor cells (CTCs) and sort and separate bacteria with different drug resistance (Wang *et al.*, 2020).

Evidence suggests that manipulating cells using optoelectronic dielectrophoresis (oDEP) under optimized electric field conditions does not compromise their properties or viability (Chu *et al.*, 2020). This technique has proven effective for isolating and purifying bacterial cells from complex biological samples.

f. Dielectrophoretic Field-Flow Fractionation (DEP-FFF or dFFF)

Dielectrophoretic field-flow fractionation (DEP-FFF) is a technique for cell separation that exploits variations in the dielectric properties of cells, enabling them to be suspended at varied vertical positions within a laminar flow environment. DEP-FFF separates target particles from a heterogeneous mixture of samples. The DEP-FFF method is conventionally utilized to levitate particles

to distinct vertical positions based on their dielectric properties using DEP force.

By combining microfabrication with microfluidics, DEP-FFF enables continuous, label-free separation of various analytes. Its simplicity and non-invasive nature make it suitable for isolating targets such as latex particles, blood cells, cancer cells, bacteria, yeast, DNA, complex fluids like emulsions and colloids (Frederick *et al.*, 1995).

DEP-FFF provides several advantages over two-phase methods in separation and manipulation applications, as there is a risk of sample modification with the latter. The miniaturization of DEP-FFF platforms has enabled utilization of reduced sample volumes, resulting in less sample wastage. FFF is biocompatible and has been successfully applied to various biological samples (cells, organelles, proteins, and nucleic acids). The reduction in size of DEP-FFF platforms has enabled utilization of reduced sample volumes, resulting in less sample wastage. Furthermore, DEP-FFF is a 'soft' elution process enabled by the lack of a stationary phase. This means that samples maintain their original structure and are less affected by shear-induced damage or deformation (Qureshi and Kok, 2011).

DEP-FFF has attracted considerable attention in biomedical engineering for its potential integration into point-of-care (POC) diagnostic systems. The technique has shown strong quality measured by purity, sensitivity, and recovery efficiency of cells and particles. Most DEP-FFF studies have produced exceptional results, with output parameters sometimes exceeding 99.9%.

However, the DEP-FFF technique still has several technical limitations that hinder its advancement toward establishing itself as a key industry technology. The primary limitation is that the device throughput lacks sufficient scalability for application in clinical or industrial environments. As a result, there are only a few commercial DEP-FFF devices available.

Several factors restrict the throughput of DEP-FFF systems, primarily due to the limited magnitude of the dielectrophoretic force produced by current electrode configurations and dimensions. Moreover, this technique is challenging to implement in simple, automated, and portable diagnostic devices. Consequently, there is a clear demand for enhanced cell sorting techniques capable of identifying and selectively manipulating various cell types by exploiting novel physical characteristics (Jun *et al.*, 2000).

The following table is aimed to present and summarize in an easy understandable manner the main technological differences between different DEP configurations.

Table 1
Cellular Dielectric Parameters (Cytoplasm Conductivity) of Biological Cell
Compiled from the Literature

Methods	Cell types	Electrodes	Medium conductivity (S/m)	Cytoplasm conductivity (S/m)	DEP input parameters	Ref.
Electrode-Based Dielectrophoresis (DEP or eDEP)	ESCC cell lines (CE81T, and CE81T-4)	a glass substrate, interdigitated electrodes	1.76×10^{-2} S/m	-	5 V at a frequency of 1 MHz	(Hsiang-Chen <i>et al.</i> , 2017)
	prostate cancer cells (LnCaP)	Gold interdigitated electrodes	0.7×10^{-3} , 7×10^{-2}	-	6 Vpp 10 kHz–10 MHz	(Turcan and Olariu, 2020)
	HeLa, MCF-7	vertical pin-plate micro-hump electrodes	10-2	-	10–35 Vpp 10 MHz	(Turcan and Olariu, 2020)
	OSCC cell lines, H357	DEP–microwell electrode system	5 mS/m	0.26±0.06	4 kHz to 20 MHz	(Mulhall <i>et al.</i> , 2011)
	OSCC cell lines H157	DEP–microwell electrode system	5 mS/m	0.25±0.10	4 kHz to 20 MHz	(Mulhall <i>et al.</i> , 2011)
	Human T lymphocytes	microelectrodes	40 mS/m		45 kHz	(Pethig <i>et al.</i> , 2002)
	human breast cancer cells (MCF 7)	pair of electrodes	-	-	10 MHz to 100 MHz; voltage, 7 Vp-p	(Youngho <i>et al.</i> , 2009)
	human colon cancer cells (HT-29 cells)	strip electrodes	0.01, 0.05 and 0.1	-	20 Vpp 5 kHz–20 MHz	(Turcan and Olariu, 2020)
	MDA-MB-231 cells	a set of planar interdigitated transducer electrodes	150 μ S/cm	-	15 Vpp, 40 kHz	(Anas <i>et al.</i> , 2017)
	primary human oral keratinocytes (HOK)	DEP–microwell electrode system	5 mS/m	0.71 ± 0.08	4 kHz to 20 MHz	(Mulhall <i>et al.</i> , 2011)
	human colorectal carcinoma cancer cells (HCT 116)	28 interdigitated electrodes pairs	-	-	2.55 Vpp 4 MHz	(Turcan and Olariu, 2020)
Insulator-Based Dielectrophoresis (iDEP)	Escherichia coli (E. coli) and Staphylococcus aureus (S. aureus) cells	Embedded electrodes within the microfluidic channel covered by a thin passivation layer	300 μ S/m	-	50 V peak-to-peak (Vpp), 1 kHz to 1 MHz	(Tyler <i>et al.</i> , 2013)
	human breast epithelial cells	creek-gap electrode	70 mS/m	200 mS/m	$V_{pp} = 34$ V peak-to-peak and 200 kHz–50 MHz	(Shigeru <i>et al.</i> , 2019)

	MCF-7 breast cancer cells	An electrode holder constructed of an additional PDMS slab	270 μ S/cm	1	-	(Sanchari <i>et al.</i> , 2014)
	CT26 murine colon cancer cells	Indium Tin Oxide (ITO) electrode on the top and bottom sides and a middle layer of thin PDMS	100 μ S/cm	-	1 kHz to 1 MHz, 5 V _{pp} -10 V _{pp}	(Gaurav <i>et al.</i> , 2022)
	MCF-7 breast cancer cell	integrated electrodes (designed microdevices)	0.3 to 4.9 mS/cm	-	200 V/cm was applied for two or four minutes	(Sanchari <i>et al.</i> , 2011)
	Circulating tumor cells (CTCs)	contactless electrodes	0.055 - 1.2 S/m	-	100 KHz	(Aghaamoo <i>et al.</i> , 2017)
	Viable and dead human carcinoma (HeLa) cells	interdigitated microelectrodes	1.76 $\times$ 10 ⁻³ S/m	1	1 $\times$ 10 ⁵ V/m, 500 Hz	(Chun-Ping <i>et al.</i> , 2010)
Contactless Dielectrophoresis (cDEP)	MCF10A, MCF7, and MDA-MB-231 human breast cells	aluminium electrodes	1.00E-0.2	1	100 kHz and 1 MHz	(Erin <i>et al.</i> , 2011)
	THP-1 human leukemia monocytes	fluid and sink electrodes	100 μ S/cm	0.65	300 VRMS between 50 and 100 kHz	(Michael <i>et al.</i> , 2011)
	Mouse Ovarian Surface Epithelial (MOSE) cells	self-aligned electrode	0.01 S/m	-	150 Vrms/cm at 450 kHz	(Armita <i>et al.</i> , 2020)
	THP-1 human Leukemia monocytes, MCF-7 breast cancer cells, and MCF-10A breast cells	platinum electrodes	100 μ S/cm	-	(100 V, 200 V, 350 V, and 500 V) at 85 kHz and for different frequencies (40 kHz, 85 kHz, 125 kHz, and 200 kHz) at 250 Vrms	(Hadi <i>et al.</i> , 2009)
	THP-1 human leukemia monocytes	4 metal electrodes	130 ms/cm	-	70 Vrms and 300 kHz	(Hadi <i>et al.</i> , 2010)
Traveling Wave Dielectrophoresis	T-cell leukemia	Four parallel platinum electrodes	40 mS/m	-	3.5 Vrms at 100 kHz	(Sander <i>et al.</i> , 2012)

Optically Induced Dielectrophoresis (oDEP)	Raji cells	optical/virtual electrode	0.01 S/m	-	10 kHz and 10 V _{pp} (35 kHz crossover frequency)	(Wenfeng <i>et al.</i> , 2017)
	B-cell lymphomas	virtual electrodes	1.3×10^{-2} S/m	-	50 kHz at 20 V _{pp}	(Wenfeng <i>et al.</i> , 2014)
	MCF-7 cells	optical/virtual electrode	0.01 S/m	-	10 kHz and 10 V _{pp} (35 kHz crossover frequency)	(Wenfeng <i>et al.</i> , 2017)
	human embryonic kidney (HEK) 293 cells	optical/virtual electrode	0.01 S/m	-	10 kHz and 10 V _{pp} (35 kHz crossover frequency)	(Wenfeng <i>et al.</i> , 2017)
	K562 cells	optical/virtual electrode	0.01 S/m	-	10 kHz and 10 V _{pp} (35 kHz crossover frequency)	(Wenfeng <i>et al.</i> , 2017)
Dielectrophoretic Field-Flow Fractionation (DEP-FFF or dFFF)	Separation of monocytes from T- or B-lymphocytes	microfabricated, interdigitated electrodes	10 mS/m	-	20 and 50 kHz for the monocyte/T-lymphocyte mixtures, and between 20 and 40 kHz for monocyte/B-lymphocyte mixtures	(Jun <i>et al.</i> , 2000)
	Separation of granulocytes from T-lymphocytes	microfabricated, interdigitated electrodes	10 mS/m	-	40 and 50 kHz for 8 min	(Jun <i>et al.</i> , 2000)
	Separation of monocytes from granulocytes	microfabricated, interdigitated electrodes	10 mS/m	-	30 and 35 kHz for 8 min	(Jun <i>et al.</i> , 2000)
	NCI-60 cells	-	30 mS/m	-	100 kHz	(Peter <i>et al.</i> , 2013)
	Breast tumor (MDA-MB) cells-peripheral blood	interdigitated 50 mM wide gold-on-copper electrodes	30 mS/m	1	2.8 V _{peak} -peak AC signal at 60 kHz	(Peter <i>et al.</i> , 2009)
	MDA_435 cells-peripheral blood mononuclear (PBMN) cells	planar, multilayer microelectrode	56 mS/m	-	frequency ^ 45 kHz, voltage ^ 8 V p-p, fluid flow rate ^ 1 ml/min	(Giovanni <i>et al.</i> , 1999)

3. Challenges in dielectrophoresis

DEP-based cell characterization has proven to be flexible and adaptable to several important biological applications. Each technique exhibits various advantages and disadvantages. It is not necessary for the target particle to carry a net electric charge, which is an asset of using DEP in particle control. The particle will behave as an electric dipole interacting with a non-uniform electric field gradient; this behavior is indicated by a generated dipole moment. According to Turcan and Olariu (2020), the application of an external electric field causes the positive and negative charges inside the neutral particle to be split and oriented in the field plane. This, in turn, causes the particular to be mobilized.

Dielectrophoresis has been widely explored within low to intermediate frequency ranges (1 kHz to 50 MHz) for cell identification based on membrane characteristics; however, studies focusing on the ultrahigh frequency spectrum (above 50 MHz) remain limited (Josie *et al.*, 2021). Although the membrane capacitance of a number of cell lines has allowed thorough characterization, the sensitivity of DEP could be improved by looking beyond surface expression variations to intracellular variations caused by organelle content, cytoplasmic changes or nuclear features.

One can address the difficulties of strong electrical conductivities over the entire spectrum from low to high frequencies. Joule heating caused by low frequency leads to significant cellular injury, dehydration, reduced device efficiency, alterations in electrolyte characteristics and diminished particle retention ability (Caglayan *et al.*, 2020). Lower frequencies can cause changes in concentration and osmolarity due to electrolysis and liquid evaporation. This can result in damages at the level of electrodes and samples, as well as formation of bubbles that can disrupt or stop DEP operation. In what it concerns the biochemical and biophysical side effects, biological cells subjected to strong electric fields can potentially undergo cell lysis and apoptosis (Puttaswamy *et al.*, 2010). Nevertheless, DEP manipulation requires sophisticated and severe electrode miniaturization in a high-frequency electric field (from 10 MHz to hundreds MHz, 50-100 kV/m).

Most studies involving DEP have been conducted in low-conductivity media, typically varying from 1 to 10 mS/m. Generally, a maximum conductivity of 100 mS/m is recommended for reaching positive dielectrophoresis (pDEP) with cells. However, maintaining extremely low conductivity levels (e.g., below 1 mS/m) is unrealistic due to fluctuations over time caused by environmental CO₂ absorption, ion release from surfaces, or ion leakage from cells into the medium.

Elevated voltage and power densities in the suspending fluid may lead to adverse redox processes taking place on electrode surfaces, electrode fouling, microbubble formation causing channel blockage, Joule heating, AC

electroosmosis and other electrochemical effects. The strong electric field increases the possibility of manipulation cells, which may result in ion leakage or cell electroporation, as well as cell adhesion to the electrode edges and an increase in transmembrane potential.

4. Conclusion

Since many decades, DEP has been extensively studied as of numerous application possibilities with different domains. The difficulties have been highlighted and current applications of DEP have been reviewed in this review. (Sang *et al.*, 2016)

Enhanced biological technique are essential for effective disease identification, diagnosis, and treatment. Research involving bioparticles and dielectrophoresis (DEP) has develop from focusing on microscopic scales to exploring nanoscale applications. DEP-based electrical stimulation offers diverse functionalities, including the enrichment, separation, and therapeutic capture of bioparticles.

Particle/cell separation in general has been achieved in recent years using a variety of methods. DEP has been one of the most effective methods due to its advantages, which include simple production processes and high sensitivity. DEP is an effective method for manipulation, concentration and separation of bioparticles.

When used in DEP-based bioparticle modification, DEP is an accurate, affordable, label-free systematic, diagnostic and screening method that shows a strong relationship with cell viability and the conducting medium. Through the use of systematic screening and diagnostic tools, the DEP approach is expected to contribute to the transformation of public and medical health. DEP techniques applied in conductive media have demonstrated notable benefits for tasks such as bioparticle enrichment, cell sorting, trapping, and selective identification.

DEP offers a powerful approach for sorting and detecting biological entities in suspension by exploiting differences in their dielectric behavior, with strong prospects for future use in biomedical technologies.

The performance of dielectrophoresis (DEP) is closely tied to the electrical interaction between cells and their surrounding medium, primarily governed by Maxwell–Wagner interfacial polarization. Advances in DEP-based microfluidic platforms now enable the differentiation of normal and diseased cells by analyzing their distinct electrical responses to non-uniform electric fields. Cellular behavior in DEP systems is shaped by various factors, including membrane and cytoplasmic conductivity, cell size, and the electrical properties of the suspending fluid. Microfluidic DEP systems have proven effective in distinguishing cells according to their electrophysiological characteristics,

showing great promise for applications in clinical diagnostics and biomedical research.

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ANALIZĂ TEORETICĂ ȘI EXPERIMENTALĂ PRIVIND MANIPULAREA DIELECTROFORETICĂ A CELULELOR BIOLOGICE

(Rezumat)

Dielectroforeza (DEP) este o tehnică care permite manipularea neinvazivă și caracterizarea celulelor biologice prin valorificarea proprietăților lor electrice. DEP a devenit o tehnică promițătoare pentru a separa, izola și identifica celulele suspendate într-un mediu pe baza proprietăților lor dielectrice, fapt care ar putea fi esențial în dezvoltarea viitoarelor aplicații biomedicale.

Prezenta analiză își propune să ofere o evidență a studiilor experimentale privind utilizarea DEP în manipularea diferitelor celule biologice. Astfel, pornind de la configurația clasică a DEP, au fost discutate mai multe configurații tehnologice propuse de literatură pentru sortarea celulelor.

Literatura de specialitate prezintă o multitudine de studii cu privire la evaluarea electrică a celulelor, iar această analiză raportează o colecție de informații referitoare la principiile de funcționare ale diferitelor tipuri de configurații de dielectroforeză și investigații electrice. Interpretarea caracteristicilor electrice în raport cu frecvența este discutată cu privire la polarizarea interfacială/Maxwell-Wagner. Cu toate acestea, provocările tehnologice și direcțiile științifice viitoare care trebuie abordate pentru a asigura absorbția pe termen mediu la scară largă a DEP în studiile clinice sunt discutate, diferențiind în mod clar influența geometriei și arhitecturii electrozilor, conductivitatea medie, parametrii DEP față de electrofiziologia celulelor.