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The potential of a dielectrophoresis activated cell sorter (DACS) as a next generation cell sorter

Dongkyu Lee, Bohyun Hwang and Byungkyu Kim*

Abstract

Originally introduced by H. A. Pohl in 1951, dielectrophoretic (DEP) force has been used as a striking tool for biological particle manipulation (or separation) for the last few decades. In particular, dielectrophoresis activated cell sorters (DACSes) have been developed for applications in various biomedical fields. These applications include cell replacement therapy, drug screening and medical diagnostics. Since a DACS does not require a specific bio-marker, it is able to function as a biological particle sorting tool with numerous configurations for various cells [e.g. red blood cells (RBCs), white blood cells (WBCs), circulating tumor cells, leukemia cells, breast cancer cells, bacterial cells, yeast cells and sperm cells]. This article explores current DACS capabilities worldwide, and it also looks at recent developments intended to overcome particular limitations. First, the basic theories are reviewed. Then, representative DACSes based on DEP trapping, traveling wave DEP systems, DEP field-flow fractionation and DEP barriers are introduced, and the strong and weak points of each DACS are discussed. Finally, for the purposes of commercialization, prerequisites regarding throughput, efficiency and recovery rates are discussed in detail through comparisons with commercial cell sorters (e.g. fluorescent activated and magnetic activated cell sorters).

Keywords: Dielectrophoresis, Dielectrophoretic force (DEP force), Dielectrophoresis activated cell sorter (DACS), Microfluidics, Cell sorting

Background

Since dielectrophoresis was first reported by H. A. Pohl in 1951, it has been employed as a biological particle manipulating tool in various fields (e.g. cell replacement therapy, drug screening, medical diagnostics, particle filtration and microfluidics) [1–10]. Dielectrophoretic (DEP) phenomena occur when micro/nano-particles in a medium are exposed to a non-uniform electric field, causing polarization for particular particles according to their dielectric property [11, 12]. DEP force is classified into two types according to correlations of the dielectric properties of the particles and medium. Positive DEP (p-DEP) force pulls particles toward a higher electric gradient, and negative DEP (n-DEP) force repels particles away from the higher electric gradient. Therefore, various target cells with different dielectric properties can be manipulated by controlling the medium properties or the input voltage condition. In order to manipulate biological particles, consequently, various dielectrophoresis-based techniques, including DEP trapping, DEP field-flow fractionation (DEP-FFF), traveling wave DEP (TwDEP) force and DEP barrier, are performed within a micro fluid channel [13–21]. DEP trapping techniques are mainly used to isolate particles within a still fluid utilizing p-DEP force [22–25]. The TwDEP force, DEP-FFF and DEP barrier techniques are realized via angled or vertical electrode pairs, and they are generally implemented with n-DEP force within the micro channel with fluidic flow [26–32]. The latter techniques have a striking advantage in terms of throughput since the continuous loading of target cells along the fluidic flow allows for continuous cell separation. Therefore, there have been many studies on the separation of

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various biological particles, including blood cells [red blood cells (RBCs) and white blood cells (WBCs)], cancer cells [circulating tumor cells (CTCs), leukemia cells and breast cancer cells], submicron particles (bacteria, yeast cells), spermatozoa, stem cells, protein and DNA. Dielectrophoresis activated cell sorters (DACSes) differ from conventional fluorescent activated cell sorters (FACSes) and magnetic activated cell sorters (MACSes) in that they do not require the additional financial and time expenditure necessary for immune-labeling [33–38]. In addition, DACSes achieve high separation efficiency owing to the continuous separation in the micro fluid channel. Nevertheless, there are still big hurdles to be overcome with respect to their low throughputs and recovery rates.

In this article, therefore, we explore current DACS capabilities worldwide and look at recent developments intended to overcome particular limitations. First, the basic theories are reviewed. Then, the configurations and characteristics of four representative DACSes are compared, and the strong and weak points of each DACS are discussed. Finally, a commercialization strategy is suggested.

Theory

Dielectrophoresis is a phenomenon that occurs in a non-uniform electric field as a result of polarization, as shown in Fig. 1. DEP force is generated by the interaction between the induced dipoles and a non-uniform electric field [11, 12]. The magnitude and direction of the DEP force is determined by the intrinsic dielectric properties of the particles and the medium. As mentioned, the characteristics of DEP force differ from those of other cell sorters that require an antibody antigen reaction. The magnitude and direction of the DEP force is expressed with the below equation [11, 12, 39].

$$\boldsymbol{F}_{\mathrm{DEP}} = 2\pi r^3 \varepsilon_m \varepsilon_0 \mathrm{Re}[f_{CM}] \nabla |\boldsymbol{E}_{rms}|^2 \quad (1)$$

where r indicates the radius of the target particle, ε_m and ε_0 are the permittivity of the medium and the vacuum state, the term $\mathrm{Re}[f_{CM}]$ indicates the real parts of f_{CM}. f_{CM} is the Clausius–Mossotti (CM) factor, and $\boldsymbol{E}_{rms}$ is the root-mean-square of the electric field. Researchers transform Eq. 1 as necessary to various forms according to technique. For example, in the case of TwDEP force (Fig. 1c), the magnitude of the acting force on a particle can be expressed as [16, 17].

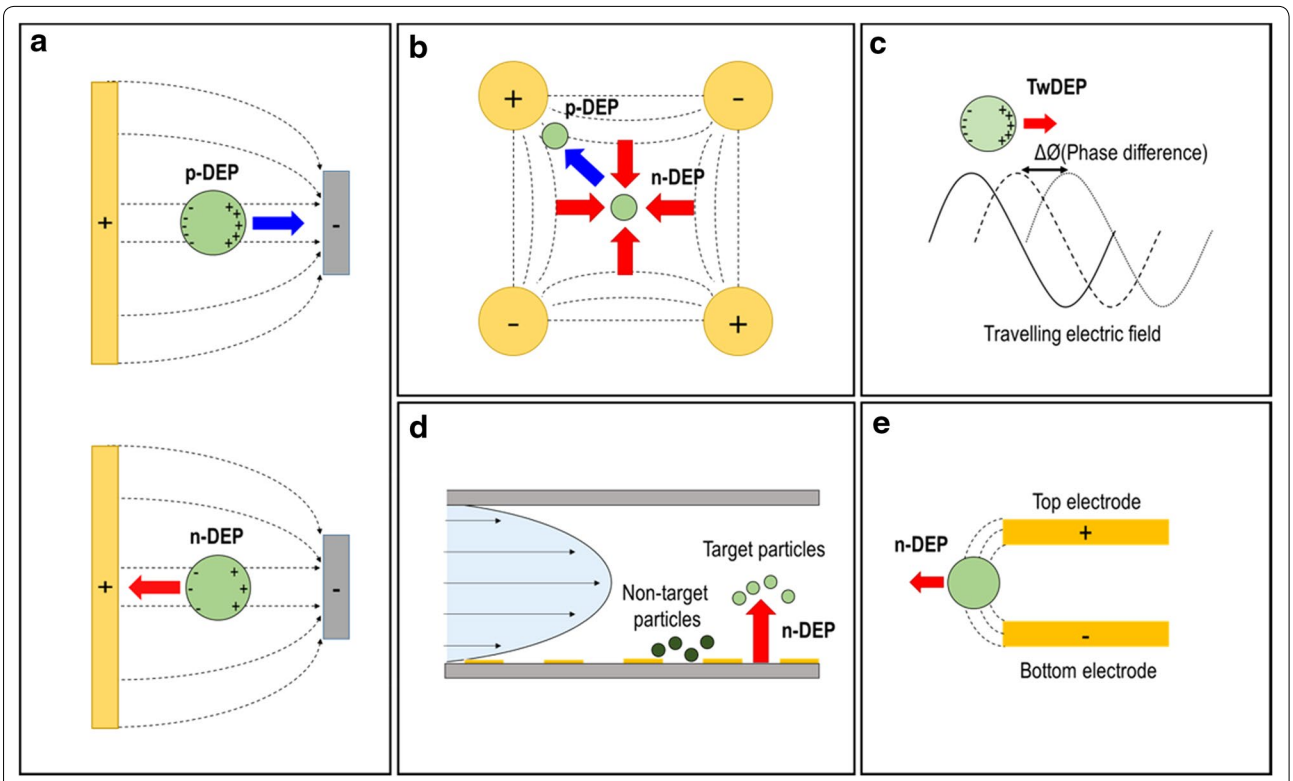

Fig. 1 Schematic diagram of dielectrophoresis. **a** a particle in a non-uniform electric field experiencing positive DEP force and negative DEP force, **b** a particle experiencing DEP trapping, **c** a particle in an electric field with a phase gradient (traveling wave dielectrophoresis), **d** target and non-target particles experiencing DEP-FFF, **e** a particle experiencing DEP barrier

$$\boldsymbol{F}_{TWD} = -\frac{4\pi\varepsilon_m\varepsilon_0 r^3 \mathrm{Im}\left(f_{CM}\right)\boldsymbol{E}^2}{4\left(w+g\right)} \quad (2)$$

where the term $\mathrm{Im}[f_{CM}]$ indicates the imaginary part, w is the width of the electrode, and g is the spacing between each electrode. Also, the force of the DEP barrier (Fig. 1e), which is generated between top and bottom electrodes, can be approximated as [19, 40].

$$F_{DEP} = \frac{27}{32}\pi^2\varepsilon_m \mathrm{Re}[f_{CM}]r^3\frac{U^2}{a^3}\left[1+O\left(\frac{r^2}{a^2}\right)\right] \quad (3)$$

where U is the applied root-mean-square voltage, and a is the channel height, which is the same as the spacing between the top and bottom electrode pair.

The direction of DEP force depends on the sign of the CM factor in Eq. 1, and it is defined as.

$$f_{CM} = \frac{\varepsilon_p^* - \varepsilon_m^*}{\varepsilon_p^* + 2\varepsilon_m^*} \quad (4)$$

$$\varepsilon_i^* = \varepsilon_0\varepsilon_i - j\frac{\sigma_i}{\omega}, where, i = m, p \quad (5)$$

where ε_p^* and ε_m^* denote the complex permittivity of the particle and the medium, j is the imaginary vector ($j = \sqrt{-1}$), σ_i is the conductivity of i, and ω is the angular frequency ($\omega = 2\pi f$) of the applied AC electric field. In the case of $\mathrm{Re}[f_{CM}] > 0$, particles in a non-uniform AC electric field move toward the higher electric field, and this is called p-DEP force. The blue arrow in Fig. 1a indicates its direction. In the case of $\mathrm{Re}[f_{CM}] < 0$, particles in an electric field are repelled from the higher electric field, and this is called n-DEP force. The red arrow in Fig. 1a indicates its direction. Hence, the input frequency is an important factor. In particular, the condition in which the frequency at the CM factor is zero is called cross-over frequency. This is expressed as [41, 42].

$$f_{CO} \approx \frac{\sigma_m}{\sqrt{2}\pi r C_{mem}} \quad (6)$$

where σ_m is the medium conductivity, and C_{mem} is the capacitance per unit area of the cell plasma membrane. In other words, when an application employs n-DEP force, the input frequency should be selected properly to ensure that $\mathrm{Re}[f_{CM}] < 0$. Consequently, DEP force-based cell manipulating tools in the microfluidics can be designed based on the above equations.

DEP trapping

Dielectrophoretic trapping is an application suitable for dealing with submicron particles such as bacteria and viruses. Its concept is shown in Fig. 1b. In order to separate submicron particles, DEP trapping generally harnesses p-DEP force in a still fluid. Suehiro et al. [13] implemented a DEP impedance measurement (DEPIM) employing p-DEP to trap suspended biological cells [e.g. *Escherichia coli* (*E. coli*) and *Serratia marcescens* (*Serratia*)]. They trapped target cells within a still fluid and washed the non-target cells after agglutinating the target cells by antigen–antibody reaction. Also, they employed interdigitated patterned electrode arrays and trapped target cells spaced between electrodes deposited in parallel. Lapizco-Encinas et al. [43] presented insulator-based (electrodeless) dielectrophoresis (iDEP) to separate live and dead *E. coli*. In their paper, p-DEP and n-DEP force were selective1y utilized. Since dead cells show much lower DEP mobility than live cells, dielectrophoresis is a more appropriate technique than those using other electrokinetic phenomena. Their DACS was designed to have numerous micron-sized posts, as shown in Fig. 2 (i.e. extruded electrodes). Although DEP trapping is a useful tool to differentiate target particles, it has limitations. Rather than separating biological particles continuously, DEP tapping is a one-shot method. In addition, DEP trapping requires flushing to collect trapped target cells (or wash un-trapped non-target cells). These limitations cause low throughput and recovery rates in DEP tapping-based DACSes. In order to overcome these limitations, transporting techniques (TwDEP force) and particle sorting in a continuous flow (e.g. DEP-FFF) have been proposed [16, 44–46].

Traveling wave dielectrophoresis

Unlike other DACS techniques, traveling wave dielectrophoresis utilizes an AC electric field with a phase gradient. It is suitable for separating micron-sized particles such as blood cells. The phase shifts induce particle transportation along or against the direction of the travelling wave. For cell separation, it is a more adequate method than DEP trapping because the phase shifts enable particle motion even in a still fluid. Morgan et al. [16] introduced TwDEP force-based cell sorting by employing a multilayered electrode on a large area to achieve high throughput. Although they separated the components of whole blood, the large area of the configuration caused a resistance increase at the microelectrode. Therefore, Choi et al. proposed a unique multilayered bus bar design to deliver an improved TwDEP force-based DACS, as shown in Fig. 3. They exploited a quadrature phase (0°, 90°, 180° and 270°) with four microelectrode tracks. In addition, in order to implement size-based particle sorting, a microelectrode track was designed with gradually increasing gaps from 10 to 40 μm. Consequently, they demonstrated separation feasibility by fractionating four different diametric latex particles (i.e. 3, 6, 10 and 20 μm) successfully. In order to break through the limitations

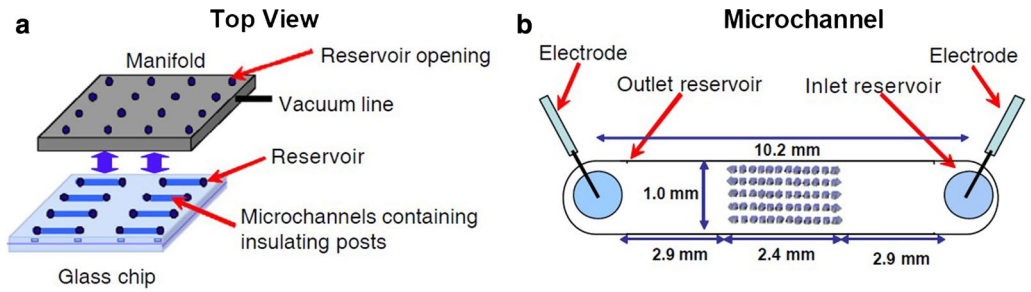

Fig. 2 DEP trapping configuration by Lapizco-Encinas et al. [43]. **a** Top view of the DACS, **b** the electric lines being squeezed between the insulating posts

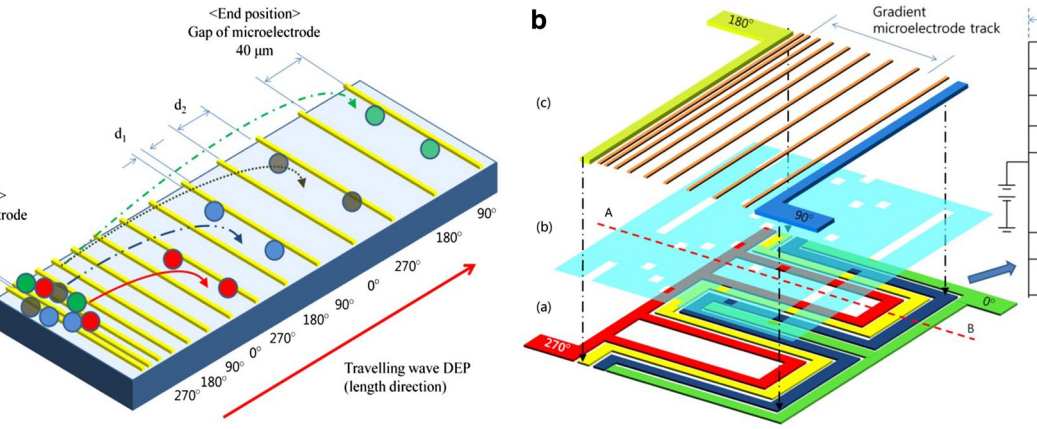

Fig. 3 The proposed electrode with three layers by Choi et al. [17]. **a** Schematic view of the high-throughput gradient TwDEP device, **b** three layers of the TwDEP device

of conventional DACSes, Cheng et al. [47] proposed a transformed cell sorting device employing two different electrode arrays that generated TwDEP force, as shown in Fig. 4. They achieved an approximate fourfold velocity increase by using a focusing mechanism that employed TwDEP force within a continuous flow. Conclusively, they showed that a TwDEP system could achieve a higher throughput than DEP trapping. However, since it required complicated electrode structures, they had difficulty in improving the recovery rate and reproducibility.

DEP field flow fractionation

The working principle of the DEP field-flow fractionation is shown in Fig. 1d. DEP-FFF is an outstanding technique because it was originally proposed to separate biological particles within a continuous fluidic flow. In other words, a DACS that harnesses DEP-FFF is able to perform continuous cell separation with the unceasing injection of target particles. Particle movement in the microchannel depends on three acting forces—DEP force, hydrodynamic force, and gravity. Particles passing through the main channel can experience sedimentation and levitation due to the gravity and n-DEP force, respectively. When the DEP force is stronger than gravity, the particles levitate diagonally rather than vertically due to the hydrodynamic force of the fluidic flow. Since DEP force depends on dielectric properties and the radius of the particles, multiple particle types with different sizes or dielectric properties can be fractionated. A detailed analysis concerning the acting force for different particles with DEP-FFF was implemented by Gascoyne et al. and Wang et al. [8, 48]. Lewpiriyawong et al. [49] fabricated a PDMS-based micro-device utilizing DEP-FFF, and they demonstrated simulation studies. They selected an AgPDMS composite as their electrode material. In order to select the proper input voltage, they implemented a separation test under various voltage conditions (0, 25, 50 and 55 V) with latex polystyrene microspheres (5, 10 and 15 μm), as shown in Fig. 5. Since the AgPDMS caused voltage drops, they were able to select a higher voltage than in the simulation analysis. Consequently, they demonstrated size-dependent

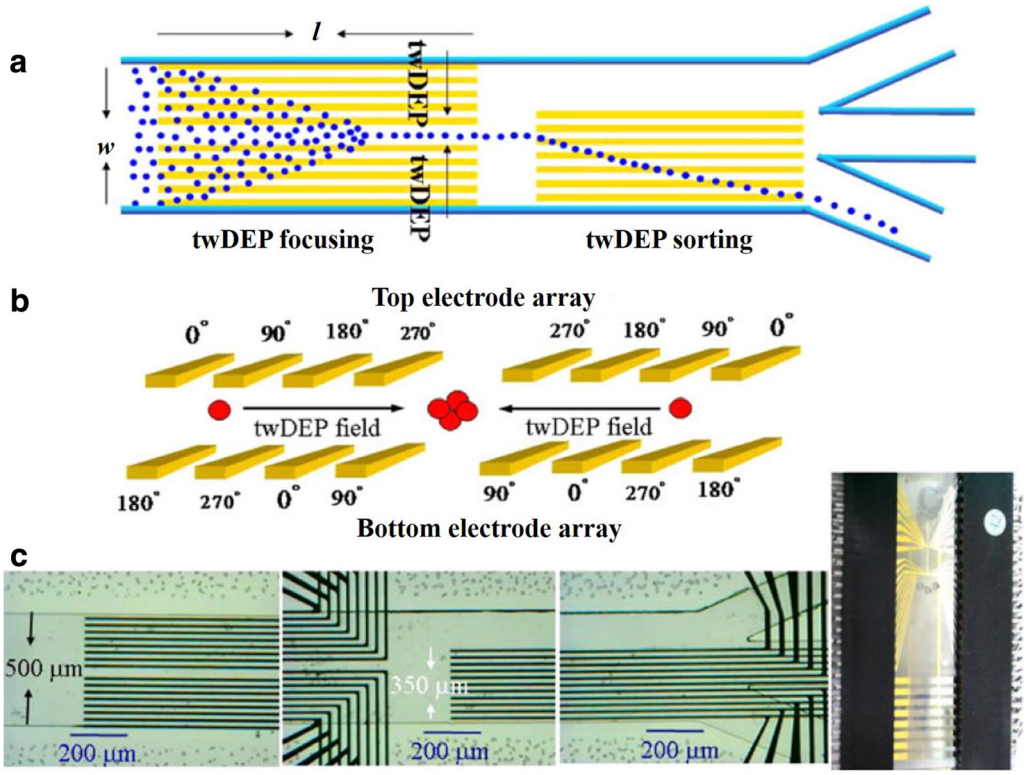

Fig. 4 Schematic diagram of TwDEP force-based cell sorter by Cheng et al. [47]. **a** Top view of electrode arrangement, **b** side view of electrode structure, **c** images of TwDEP focusing electrodes, TwDEP sorting electrodes and packaged chip

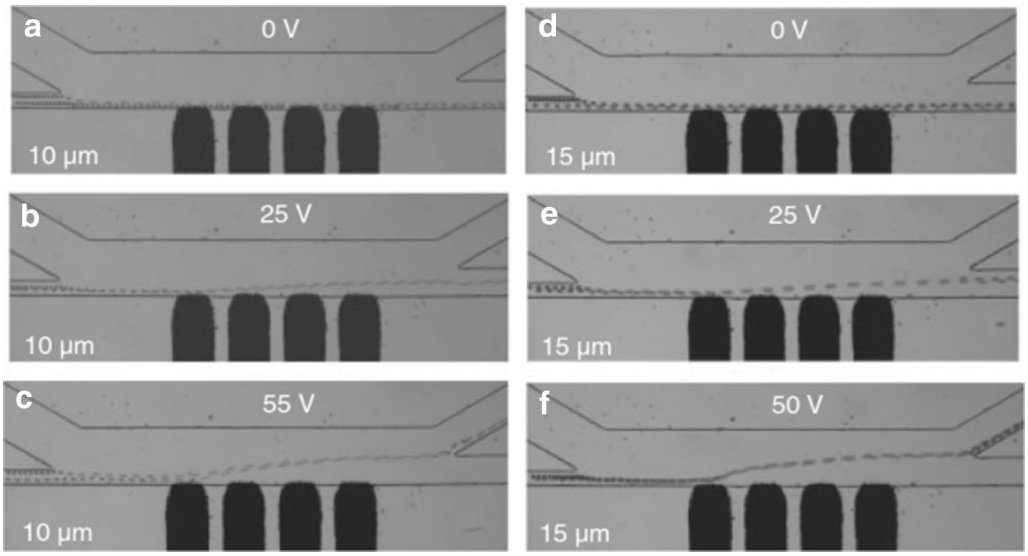

Fig. 5 Video clip of particle levitation according to input voltage (10 μm particle at **a** 0 V, **b** 25 V, **c** 55 V, and 15 μm particle at **d** 0 V, **e** 25 V and **f** 50 V) by Lewpiriyawong et al. [49]

particle sorting within a continuous microfluidic flow. Piacentini et al. [50] performed the size-based separation of platelets from red blood cells, as shown in Fig. 6. In the same manner as that used by Lewpiriyawong et al. 48 they investigated the trajectory in the microchannel through a numerical simulation. Their device employed

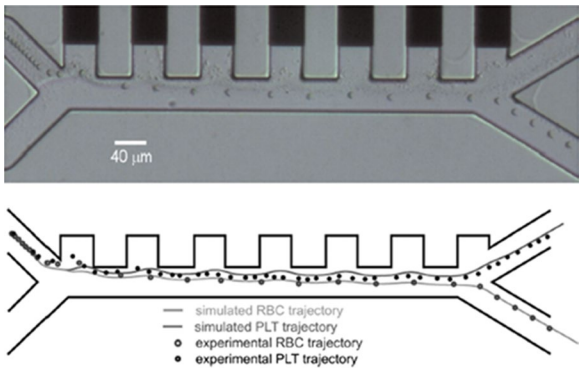

Fig. 6 Trajectory of RBCs and PLTs in the device and graphical representation of trajectory between simulation and experiment by Piacentini et al. [50]

a "liquid electrode" defined by Demierre et al. [46] which is a kind of planar electrode deposited at the bottom of the empty zone positioned vertically from the main channel. They achieved striking results, with a recovery rate of over 98 %. On the other hand, Gupta et al. developed a device named ApoStream® to separate circulating tumor cells (CTCs) from normal and healthy blood cells in a microfluidic flow [47, 51]. They not only separated various CTCs (e.g. SKOV3 and MDA-MB-231), but also confirmed the viability of the completely separated cells. As a result, the viability of the cancer cells fractionated by Apostream® (see Fig. 7) was greater than 97.1 %, and the throughput was reported as 5000 cells/s. Also, Apostream® has come close to being commercialized, and the device has been utilized in research fields. Recent news regarding its commercialization is continually being reported on their website (ApoCell).

DEP barrier

Another way to exploit a continuous flow is to generate a dielectrophoretic barrier to hinder cell movement at the main channel. Generally, top–bottom patterned electrodes are deposited to generate n-DEP force and

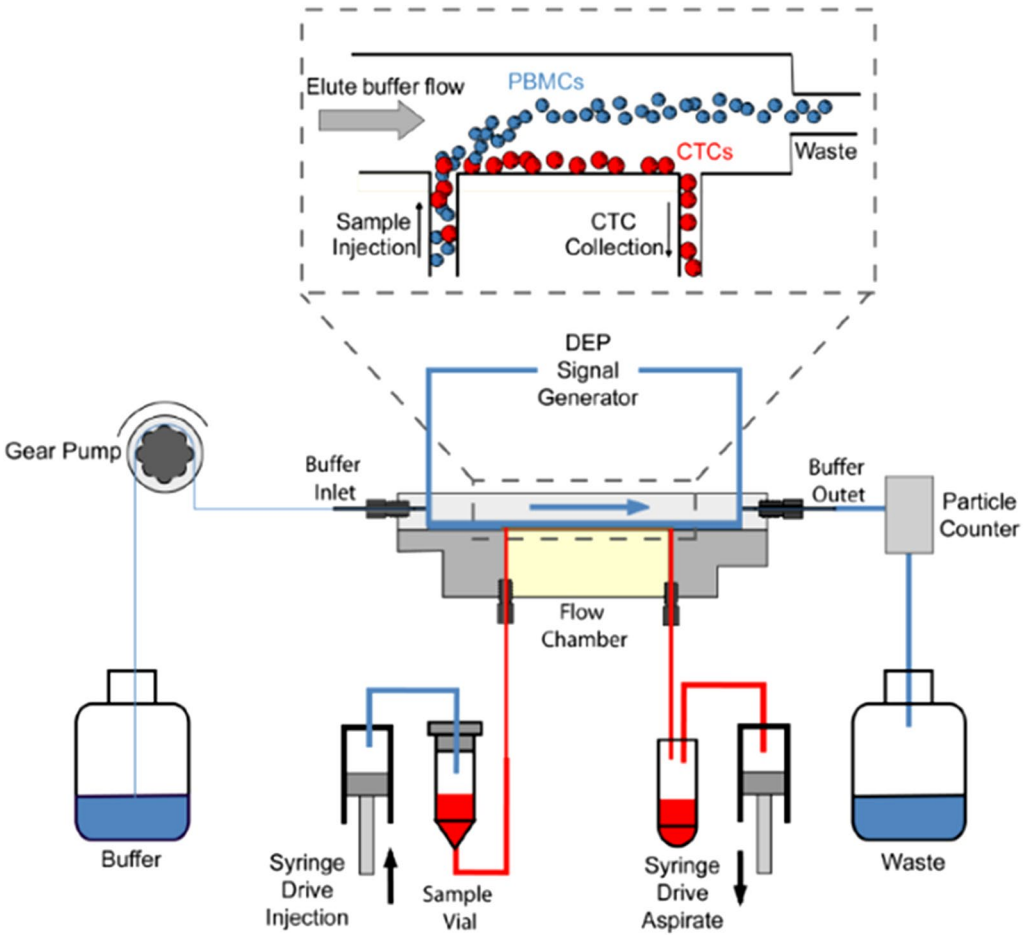

Fig. 7 Schematic diagram of the Apostream® by Gupta et al. [44]

consequently deflect target particles toward a target area. When the DEP force between the top and bottom electrodes (electrode pair) is sufficient, the angled electrode pair enables the deflection of the target particles along the electrode pair. DACSes harnessing DEP barrier always install repeated electrode pairs to guarantee high separation efficiency. This technique is convenient since it does not forcibly translocate but just switches the direction of the particles in the channel, though not against the fluidic flow. In addition, the DEP barrier technique has advantages in terms of size-based target particle selection because changes in the channel depth (distance between top and bottom electrodes) can control the magnitude of the DEP barrier under the same input conditions (input voltage and frequency), as shown in Eq. 3. Durr et al. [19] introduced a DACS that harnessed DEP barrier, as shown in Fig. 8. They reported an electrode pair as a 3-D deflector array. They analyzed the threshold velocity for particle size according to voltage variation, as well as an electric field in a numerical simulation. As shown in Fig. 9, Kim et al. [52] presented a multi-target DACS (MT-DACS), and they separated multiple biological particles (MC1061 strain of *E. coli*) harnessing the same mechanism. They confirmed their separation results using flow cytometry. Since three kinds of particles were selected as target cells, three outlets and two kinds of angled electrode groups with different angles were fabricated. Compared to single pass DACSes, they achieved a 1000-fold overall enrichment of the separated target cells. In addition, they found that there was no detectable cross-contamination near the outlet channels. Kim et al. [53] proposed a novel DACS with a vertically arrayed micro channel to harness gravity with cantilever type electrode arrays. Since the proposed DACS harnessed gravity to shunt the injected cells, they did not require an additional flow generator such as micro syringe pump (or other micro-device), which is utilized by almost DACSes. Also, for high throughput, which is a weak point in current DACSes, they designed a meso-sized channel (L × W×H = 2 mm × 0.5 mm × 2 5 mm) that differed from conventional micro-devices. They injected a mixture including three kinds of particles (10, 25 and 50 μm), and they investigated the sedimentation patterns of each colony. Consequently, they achieved a high separation efficiency of 94.7 %. Lee et al. [54] designed a simplified DACS to obtain high reliability. Their DACS consisted of a meso-sized channel (15 mm × 40 mm × 0.2 mm) encompassed by two plates that were as a patterned top–bottom electrode to generate DEP barrier as shown in Fig. 10. In the case of conventional DACSes, the large number of components complicates the assembly procedure. Hence they insisted that complex structures could cause a leaking phenomenon between components and reduce reproducibility and reliability. They determined the proper input condition based on a numerical simulation and demonstrated a separation test with K562 cells (cancer cells found in bone marrow). In the experiments, the DACS achieved a separation efficiency of 94.74 %, a throughput of 17,000 cells/min and a recovery rate of 49.42 %.

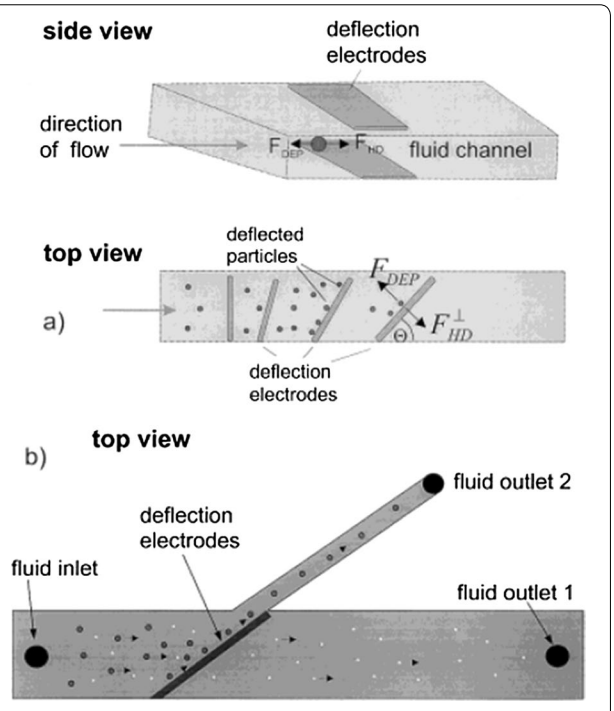

Fig. 8 Schematic diagram of DACS harnessing DEP barrier by Durr et al. [19]

Comparative analysis with a commercial cell sorter

FACSes and MACSes are representative commercial cell sorters. FACSes show high separation efficiencies of over 97 %, throughputs of 10,000 cells/s and recovery rates of over 55 % [55–57]. MACSes show similar performance characteristics—separation efficiencies of over 90 %, throughputs of 10^{10} cells/h and recovery rates near 50 % [58–60]. The results do not include the time-consuming labeling process that takes over an hour. The aforementioned DACS employing DEP-FFF and DEP barrier immediately achieved competitive results when compared to FACSes and MACSes in terms of separation efficiency. However, the throughput and recovery rate are still not at commercial levels. Even though Hu et al. [40] reported a striking throughput employing dielectrophoresis at over 10,000 cells/s, similar to that of a FACS, their sorter required a specific marker and a labeling process as prerequisites, which are also required for FACSes and MACSes. Consequently, it can be said that a

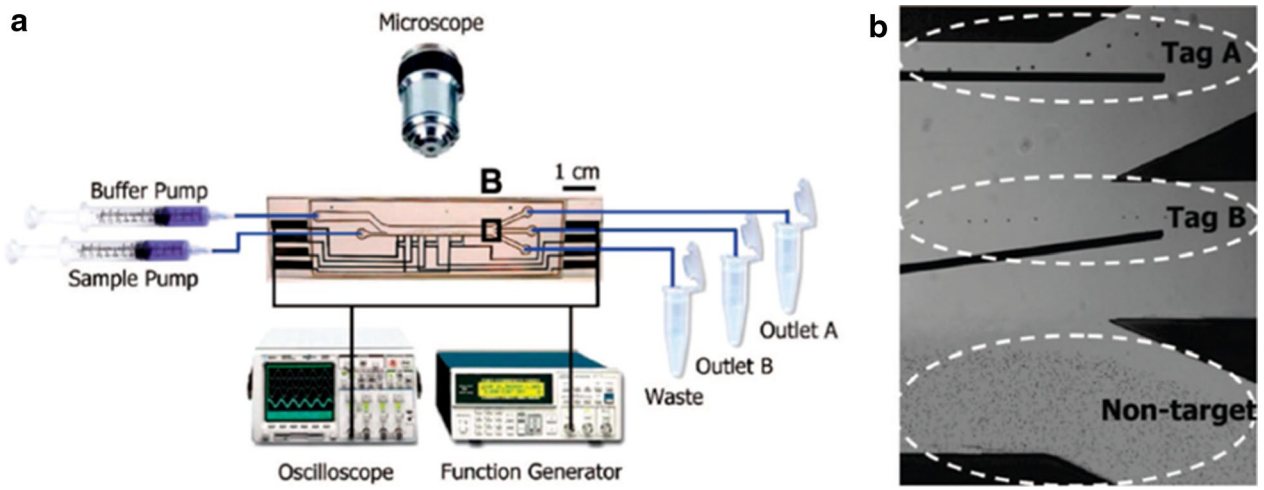

Fig. 9 Experimental setup **a** and optically captured images **b** at the crossroads by Kim et al. [52]

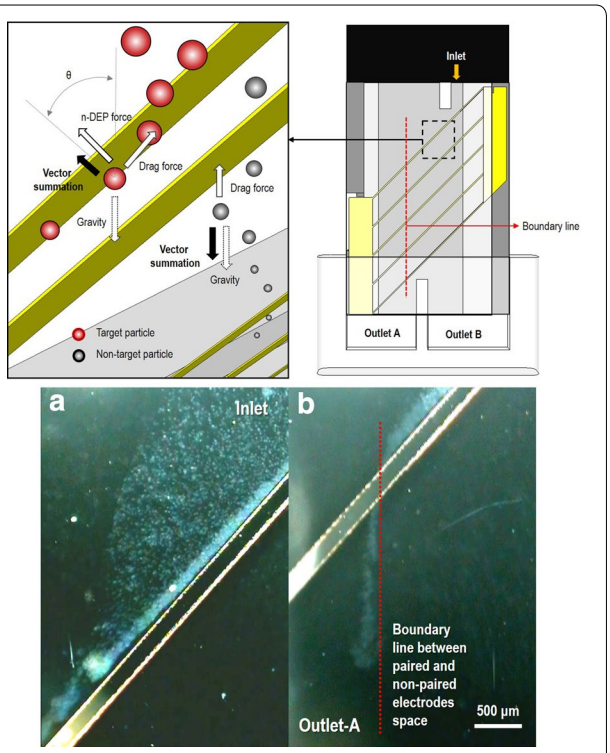

Fig. 10 Simplified DACS configuration and video clip of separation process by Lee et al. [54]. **a** Deflected K562 cells above the DEP barrier, **b** K562 cells sinks beyond boundary line

DACS without immune-labelling cannot produce the levels of performance in terms of efficiency, throughput and recovery rate when compared to FACSes and MACSes. Nevertheless, a DACS employing the intrinsic dielectric material properties of a particle obtained a high separation efficiency and high recovery rate without the labeling process. Once a high throughput can be achieved through an optimization process (e.g. employing a modular system consisting of a few of the same features as those used by MACSes, applying a higher flow rate and so on), DACSes will be sufficiently competitive with FACSes and MACSes.

Conclusion and prospects

In this review article, DEP theory and various transformed equations broadly used in DACSes were introduced. Particle sorting techniques were classified into four types—DEP trapping, DEP field-flow fractionation (DEP-FFF), traveling wave dielectrophoresis and DEP barrier. According to target particles and objects, it was shown that the appropriate technique must be selected. Even though DEP trapping techniques are outstanding with respect to isolating submicron particles such as viruses and bacteria, they still have limitations in separating micro particles when compared to other techniques. This is because DEP trapping techniques are generally performed within a still fluid, and this prohibits the increase of throughput. Throughput is a very important factor for commercialization. Although research has stressed high efficiency, throughput and recovery rate have not been dealt with in depth because almost all DACSes have failed to obtain throughputs and recovery rates that have already been achieved by commercialized tools such as FACSes and MACSes. In order to meet the prerequisites for commercialization, exceedingly high separation efficiencies, throughputs and recovery rates must be achieved. Considering commercialization,

therefore, DACS techniques within a continuous flow (DACSes based on TwDEP force, DEP-FFF and DEP barrier) have been widely studied to achieve the desired throughputs and recovery rates. However, success has not yet been achieved since the DACSes reported thus far have not only used micro-sized channels with low flow rates, but also complicated configurations. Therefore, the channel and the flow rate should be maximized for high throughput. In addition separation device configurations need to be simplified to enable high recovery rates. Furthermore, innovative electrode shapes and channel configurations must be implemented to obtain the high separation efficiencies. When high separation efficiencies, throughputs and recovery rates are guaranteed, DACSes will be able to open a new era in the fields listed below since they will not require immune-labelling related pre- and post-processes before and after separation.

- Tissue engineering to rebuild damaged organs.
- Stem cell separation for cell replacement treatment.
- In vitro fertilization or intracytoplasmic sperm injection; superior sperm selection.

Authors' contributions

DL carried out the research work and wrote the manuscript. BH carried out a survey of dielectrohporesis-based particle sorting systems. BK supervised all research work. All authors read and approved the final manuscript.

Authors' information

Dongkyu Lee received his B.S. and M.S. degrees from Korea Aerospace University in 2012 and 2014, respectively, and is now a Ph.D. candidate at Korea Aerospace University. His current research interests include microelectromechanical systems (MEMS) for bio particle sorting systems.

Bohyun Hwang received his B.S. degree from Korea Aerospace University in 2015, and is now in a Master's course at Korea Aerospace University. His current research interests include the development of cell sorting systems based on dielectrophoresis.

Byungkyu Kim received his Ph.D. in mechanical engineering from the University of Wisconsin, Madison, in 1997. From 1997 to 2000, he was a technical staff member at the Center for X-ray Lithography (CXrL) at the University of Wisconsin where he developed a computer code for the thermal modeling of a mask membrane and wafer during beam exposure. From 2000 to 2005, he worked for the Microsystem Center at KIST as a principal research scientist. He was in charge of developing the microrobot for a microcapsule-type endoscope. Currently, he is a professor in the School of Aerospace and Mechanical Engineering at Korea Aerospace University. His research interests include microelectromechanical systems (MEMS) for cell separation.

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Competing interests

The authors declare that they have no competing interests.

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