Induced-charge electrokinetic (ICEK) development and applications in microfluidics

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Abstract

Applying an external electric field over a polarizable electrode or object within microchannels can induce an electric double layer (EDL) around channel walls and create induced-charge electrokinetics (ICEK) within channels. The primary consequence of the induced charge is the generation of micro-vortices around the polarizable electrode or object, presenting a great potential for various microfluidic applications. This review presents the advances in theoretical, numerical and experimental studies on the physics and applications of ICEK within microfluidics. In particular, the characteristics and performance of ICEK-based microfluidic components in active micromixers, micropumps, and microvalves are critically reviewed, followed by discussing the applications of ICEK in electrophoresis and particle/cell manipulation within microfluidics. Furthermore, the opportunities and challenges of ICEK-based microfluidic devices are highlighted. This work facilitates in recognizing deliverable ICEK-based microfluidic technologies with unprecedented functionality for the next generation of biomedical applications with predictable manufacturability and functionality.

1. Introduction

Lab-on-chip (LOC) microfluidic devices have been developed for various biomedical and biochemical applications (Azarmanesh et al., 2019; Sackmann, Fulton, & Beebe, 2014; Shamsi, Mohammadi, Manshadi, & Sanati-Nezhad, 2019; Jing Wu, He, Chen, & Lin, 2016). Components, such as micromixers, micropumps, and microvalves are integrated into LOC devices to automate their function (Bhagat et al., 2010). While passive platforms operate without any external energy source, active systems operate mainly based on one of thermophoretic (Vigolo, Rusconi, Stone, & Piazza, 2010), acoustophoretic (Barani et al., 2016; Lenshof, Magnusson, & Laurell, 2012), magnetophoretic (S. Kim et al., 2013; M. K. Manshadi et al., 2018), electrokinetic (Mohammadi, Madadi, Casals-Terré, & Sellarès, 2015; C. Zhao & Yang, 2013) or centrifugal forces (Kinahan et al., 2016; Mohammadi, Kinahan, & Ducrée, 2016; Tang, Wang, Kong, & Ho, 2016). Electrokinetic techniques have become one of the most popular active methods for chemical analysis and biomedical diagnostics due to their inherent characteristics, including their high controllability, flat velocity profile in microchannels, independency form channel size, and function without need to moving parts (Cunlu Zhao & Yang, 2012).

Electrokinetics refers to fluid or particle motion in liquid electrolytes under an external electric field (Bazant & Squires, 2010). In classical electrokinetics, the main assumption is a linear response to the applied electric potential within microchannels that have constant surface charge (Todd M Squires & Bazant, 2004). Therefore, classical electrokinetic phenomena are also called linear electrokinetics. However, the possible drawbacks of linear electrokinetics are: i) weak flow rate, ii) zero time-averaged liquid flow under alternating current (AC) electric fields, and iii) the need to a high electric potential along the microchannel (with the length order of centimeter) to generate a strong electric field strength (Bazant & Squires, 2004, 2010). These drawbacks have been improved by introducing non-linear electrokinetics (Ajdari, 2000; Ramos, Morgan, Green, & Castellanos, 1999). Such non-linearity was first examined by Ramos et al. (Ramos et al., 1999) around locally asymmetric polarizable electrodes where they observed AC electroosmotic (ACEO) fluid flow over a pair of adjacent metal microelectrodes fabricated on planar glass substrates (Ramos et al., 1999). Ajdari (Ajdari, 2000) further employed locally asymmetric arrays of electrodes to demonstrate low-voltage ACEO micro-pumping. Non-linear AC electrokinetics was further used for particle manipulation (Mirzajani et al., 2016), DNA concentration (Bown & Meinhart, 2006), and micromixing (Sasaki, Kitamori, & Kim, 2010).

Bazant and Squires (Bazant & Squires, 2004) first generalized ACEO fluid flow to dielectric and conducting structures by introducing the term of induced-charge electroosmosis (ICEO) in a weak DC or AC electric field. The ICEO describes the interactions between the applied electric field and the induced ionic charge near the polarizable surface (electrode or object) (Todd M Squires & Bazant, 2004). The induced-charge electrokinetic (ICEK) theory and applications, as well as theoretical and experimental advances on ICEK, were further presented (Bazant, Kilic, Storey, & Ajdari, 2009; Bazant & Squires, 2010). Then, Bazant (Bazant, 2011), in his book chapter, introduced the basic physical concepts of ICEK. Zhao and Yang's review article (Cunlu Zhao & Yang, 2012) then focused on the breakthrough in electrokinetics and its physical mechanisms in micro and nanofluidics. Ramos et al. (Ramos, García-Sánchez, & Morgan, 2016) studied AC electrokinetic characteristics of polarizable microparticles with a focus on the theory and experimental observations. The field of non-linear ICEK has expanded rapidly over the past few years to various microfluidic and LOC applications, such as induced-charge electrophoresis (ICEP) (Todd M Squires & Bazant, 2006), ICEO micropump (Paustian, Pascall, Wilson, & Squires, 2014), ICEO microvalve (C. Wang, Song, Pan, & Li, 2016), ICEK micromixer (M. K. D. Manshadi, Khojasteh, Mansoorifar, & Kamali, 2016; M. K. D. Manshadi, Nikookar, Saadat, & Kamali, 2019), and recently in two-phase flow research studies (Bazant, 2015; W. Liu et al., 2017; Ren, Liu, Liu, et al., 2018).

This work reviews theoretical, numerical and experimental studies on the physics and applications of ICEK within microfluidics. The characteristics and performance of ICEK-based microfluidic components in active micromixers, micropumps, and microvalves are then reviewed, Furthermore, the opportunities and challenges of ICEK-based microfluidic devices are highlighted.

2. Theory of ICEK within microfluidics

In classic electrokinetics, the interaction between the applied electric field and the non-conducting microchannel walls results in a linear relationship between the induced zeta potential and the applied electric field (Z. Wu & Li, 2008a). However, in non-linear ICEK, such correlation behaves differently. Theoretically, upon applying an electric field (E) around a polarizable object immersed in an electrolyte, the field lines intersect with the conducting surfaces (Todd M Squires & Bazant, 2004). Due to the electrolyte's conductivity (σ), a current of J = σE is induced in the solution which therefore drives positive ions toward one side of the object and negative ions into the other side (**Fig. 1A, i**). The ions movement continues until the field lines are expelled by the screening charge cloud around the object and the steady state condtion is achieved (**Fig. 1A, ii**).

The changes in surface charge density (q) over time for an ideal polarizable object with no electrochemical reactions at the solid/liquid interface is obtained from equation (1) (Todd M Squires & Bazant, 2004).

$$\frac{dq(\theta)}{\mathrm{dt}} = \sigma \mathbf{E} \bullet \mathbf{r} \quad (1)$$

where surface charge density (q) and zeta-potential (ζ) have a linear relationship as equation (2).

$$\zeta \equiv \frac{q}{e_w k} \quad (2)$$

where ew is dielectric permittivity of the solvent and$k$ -1 ($\lambda\Delta$) is Debye screening length. Therefore, the change in zeta-potential over time until achieving a steady-state condition is obtained from equation (3).

$$\frac{d\zeta(\theta)}{\mathrm{dt}} = \frac{\sigma}{e_w k}\mathbf{E} \bullet \mathbf{r} \quad (3)$$

In the steady-state mode, since the normal component of the electric field to the charge cloud is zero, its tangential component induces the ICEO flow. The ICEO around a polarizable object (**Fig. 1A, iii**) or electrode (**Fig. 1B**) can induce micro-vortices (MVs) around the object.

Helmholtz–Smoluchowski formula can be used to find the local slip ICEO velocity around the conducting object (equations 4) (Todd M Squires & Bazant, 2004).

$$(6)$$

$$\zeta_i = -\varnothing_e + \varnothing_c$$

$$\varnothing_c = \frac{\int_S \varnothing_e \mathrm{dA}}{A}$$

where **Et** is a tangential electric field, µeo is electroosmotic mobility, and µ is fluid viscosity. Various equations have been proposed to define the induced charges over polarizable objects. For instance, equation (5) was derived to describe the correlation between the potential in the polarizable dielectric domain and the bulk of the fluid domain (Cunlu Zhao, 2012).

$$\lambda_D \frac{e_d}{e_f} n \bullet \nabla \Phi_d \Big|_{n=0} = 2\frac{K_B T}{\mathrm{ze}} \sinh\left[\frac{ze(\ \Phi_f|_{n=\lambda_D} - \ \Phi_d|_{n=0})}{2K_B T}\right] + \zeta_{d0} \quad (5)$$

where ed is dielectric constant of the dielectric block, ef is dielectric constant of the electrolyte, Φd, and Φf are potentials in the bulk fluid and dielectric block, respectively, KB is Boltzmann constant, T is absolute temperature, e is elementary charge, z is valence of ions, and ζd0 is zeta potential corresponding to surface charge density (qd0). Wu and Li (Z. Wu & Li, 2008b) suggested a numerical calculation for the induced zeta potential on the surface of an arbitrary polarizable object (equations 6).

where Øe is external electric potential and Øc is constant correction potential for a conducting surface with an area of A. This correction equation is based on the assumption that the conducting object is initially uncharged and the magnitude of the local strength of the induced field on the surface is equal to the externally applied electrical field magnitude with opposite directions. These correlations have been widely used to explain the ICEK phenomena employed in various microfluidics applications. In the following sections, these applications are discussed.

3. Application of ICEK microfluidics

ICEK-based microfluidic systems have contributed tremendously to developing different LOC components, such as micropumps, micromixers, microvalves, as well as particle manipulation and two-phase flow studies, which are addressed in this section.

3.1. ICEK micropumps

Inducing of controlled fluid flow in microchannels without the need for expensive and bulky injection systems is one of the hurdles of designing LOCs, particularly for developing miniaturized and high-throughput (HT) platforms (Dehghan Manshadi, Khojasteh, Mohammadi, & Kamali, 2016). Electrokinetic-based micropumps have a high potential in maintaining the pressure drop along the microchannels due to their simple structure with no need for a moving part, easy fabrication, and integrability on a chip. More importantly, these pumps can generate continuous and precise flow with high controllability and long-term perfusion (Kamali, Manshadi, & Mansoorifar, 2016; Zhou, Zhang, Li, & Wang, 2016). Unlike the conventional electroosmotic flow (EOF) micropumps, ICEK micropumps induce fluid flow in microchannels deliberately with the capability of rapid change of fluid flow with minimal intertia by designing proper polarizable objects/electrodes in both DC and AC electric fields (Todd M. Squires, 2009). Here, the advances in ICEK micropumps are discussed, wherein these pumps are classified as ACEO-based (around polarizable electrodes) and ICEO-based (around polarizable objects) micropumps.

3.1.1. ACEO micropumps

ACEO phenomena employed non-linear electrokinetics by using a locally asymmetric polarizable electrode to induce fluid flow in microchannels (Ajdari, 2000). Brown et al. (Brown, Smith, & Rennie, 2000) utilized a pair of planar electrodes with different edge sizes to induce fluid flow in channels. This work was further optimized by Studer et al. (V Studer, Pepin, Chen, & Ajdari, 2002) to improve the flow control within microchannels (**Fig. 2A**). This design configuration showed that breaking the electrode symmetry created an asymmetry charge distribution along the channel's axis, which led to a frequency-dependent pumping. The asymmetry pair of a planar electrode array was also used for micro-pumping thanks to its ease of fabrication, low-voltage operation, and capability in local flow control (Jie Wu, 2008). Theoretical modeling of the frequency-dependent pumping was further developed (Ramos, Gonzalez, Castellanos, Green, & Morgan, 2003) and used to simulate different aspects of the ACEO pumping (Debesset, Hayden, Dalton, Eijkel, & Manz, 2004; Vincent Studer, Pépin, Chen, & Ajdari, 2004). Furthermore, the effect of several parameters and pumping configurations were investigated, such as studying the effect of channel height, electrochemical reactions, and non-linear surface capacitance of the Debye layer (Olesen, Bruus, & Ajdari, 2006); controlling the pumping direction by switching the voltage using an inclined electrode array (Hilber, Weiss, Saeed, Holly, & Jakoby, 2009; Loucaides, Ramos, & Georghiou, 2007), pumping of two different electrolytes simultaneously through microchannels (Morgan, Green, Ramos, & García-Sánchez, 2007), bubble-free pumping (Kuo & Liu, 2008; Tawfik & Diez, 2017) as well as ACEO pumping using biased AC/DC signals (Islam & Reyna, 2012; Lian & Wu, 2009; Piñón et al., 2017; Jie Wu, 2008; Yang Ng, Ramos, Cheong Lam, & Rodriguez, 2012), pulse voltage waveforms (Tawfik & Diez, 2017), square pole-slit electrode arrays (Yoshida, Sato, Eom, Kim, & Yokota, 2017), and arrays of asymmetric ring electrode pairs in the cylindrical microchannels (Gao & Li, 2018). Also, the comparison between fluid velocity on arrays of identical electrodes with AC voltage and a traveling-wave potential demonstrated that traveling-wave potential resulted in a higher fluid velocity (Ramos et al., 2005; Yang, Jiang, Ramos, & García-Sánchez, 2009).

Besides using a planar array of electrodes, Urbanski et al. (Urbanski, Thorsen, Levitan, & Bazant, 2006) introduced the first nonplanar ACEO pump by using three-dimensional (3D) stepped electrodes. They demonstrated the capability of higher flow rate pumping compared to planar ACEO pumps (**Fig. 2B**). Senousy and Harnett (Senousy & Harnett, 2010) introduced a less expensive and an easy fabrication method for constructing 3D stepped electrodes. Rouabah et al. (Rouabah et al., 2011) further studied the performance of a new set of 3D high-aspect-ratio electrodes for ACEO pumping while Huang et al. (C.-C. Huang, Bazant, & Thorsen, 2010) employed these 3D electrode micropumps for liquid manipulation in portable biomedical microfluidic devices.

3.1.2. ICEO micropumps

Bazant and Squires (Bazant & Squires, 2004; Todd M Squires & Bazant, 2004) suggested that the ICEO flow around polarizable obstacles has the potential for liquid pumping in microchannels. Zhang et al. (Kai Zhang, Tian, & Yu, 2012) numerically demonstrated that ICEO around conducting/Janus cylinders immersed in a microchannel could be used for efficient liquid pumping. Zhang et al. (Kai Zhang, Mi, & Sheng, 2013) showed, in a numerical study, the capability of inducing the ICEO-based pumping by employing a Janus cylinder in a T-shape microchannel. Nobari et al. (Nobari, Movahed, Nourian, & Kazemi, 2016) used a similar numerical strategy but using a conducting cylinder in a T-junction to drive fluid flow in microchannels. Paustian et al.

(Paustian et al., 2014) used arrays of Janus micropillars to produce a pressure gradient in a microchannel under the AC electric field. Furthermore, Wu et al. (X. Wu, Ramiah Rajasekaran, & Martin, 2016) fabricated a conical-pore polyethylene terephthalate conducting membrane immersed in an electrolyte and used it for micro pumping in microfluidics under AC electric field.

The ICEK micropumps introduced so far are categorized as ACEO micropumps where the fluid velocity in the order of 0.1-2.5 mm/s has been reported with applying DC electric signals (Lian & Wu, 2009; Yang Ng et al., 2012). Huang et al. (C.-C. Huang et al., 2010) used ACEO micropumps functioning under AC voltage (V<1.5 amplitude) to generate fluid velocity in microchannels as high as 1.3 mm/s. Among the existing ICEO micropumps, Nobari et al. (Nobari et al., 2016) demonstrated an average fluid velocity of 1750 µm/s using DC electric field with E= 300V/cm strength in a microchannel. Altogether, both ACEO and ICEO micropumps can produce a wide range of fluid velocities and are exceptionally applicable for high-speed liquid pumping in microchannels.

3.2. ICEK micromixers

Rapid and homogeneous mixing of different solutions in microfluidics is vital for numerous LOC applications, such as biochemical reactions (S.-J. Kim, Wang, Burns, & Kurabayashi, 2009), drug delivery (X. Jia et al., 2016), biological agent detection (Cho, Chung, Kim, Jung, & Seo, 2015), and DNA hybridization (R. H. Liu, Lenigk, & Grodzinski, 2003). Diffusion is the primary mechanism of fluid mixing in microscale due to the low convective mass transfer (M. K. D. Manshadi et al., 2019). Various types of passive and active micromixers have been developed to increase the contact surface area (interface) and reduce the mixing path, therefore enhancing the mixing in microchannels (Lee, Chang, Wang, & Fu, 2011; Lee, Wang, Liu, & Fu, 2016). Electrokinetic micromixers have demonstrated to be one of the most effective mixing methods in microfluidics where their performance is dependent on mixing time, length, and index (Lee et al., 2011; Rashidi, Bafekr, Valipour, & Esfahani, 2018). ICEK electrokinetic-based micromixers, in specific, have shown their potential for active mixing in microchannels due to their high flexibility, controllability, and easy usage (Harnett, Templeton, Dunphy-Guzman, Senousy, & Kanouff, 2008; Rashidi et al., 2018). The generated MVs around polarizable surfaces (electrodes or objects) increase chaotic movement in the electrolyte and therefore induce notable mixing. Similar to ICEK micropumps, two primary categories of ACEO and ICEO have shown high performance for microfluidic applications and are discussed below.

3.2.1. ACEO micromixer

The MVs produced around polarizable electrodes have been employed for the ACEO-based mixing of different solutions in microchannels. The first theoretical ACEO mixers were developed by Squires and Bazant (Bazant & Squires, 2004; Todd M Squires & Bazant, 2004) and Sasaki et al. (Sasaki, Kitamori, & Kim, 2006), where they introduced a pair of meandering electrodes for rapid mixing of liquids inside microchannels. The results demonstrated 90% mixing efficiency, where one-millimeter length of mixing using the active ACEO was equivalent to 25 mm length of passive mixing using the diffusional mechanism. The effective mixing in this system lasts 0.18 s which was 20 folds faster than diffusional mixing. Kim et al. (B. J. Kim, Yoon, Sung, & Smith, 2007) further employed asymmetric microelectrodes for simultaneous pumping and mixing within microfluidics, where the efficiency of 94.9% mixing was demonstrated under the flow rate of 0.27 m2/s. Yoon et al. (Yoon, Kim, & Sung, 2008) employed asymmetric electrode arrays to generate pumping and mixing flow modes with 80% efficacy within 350 µm mixing length under the flow rate of 0.01 m2/s. The performance of various ACEO micromixers developed so far is detailed in**Table 1** .

3.2.2. ICEO micromixer

Following the suggestion of Squires and Bazant (Bazant & Squires, 2004; Todd M Squires & Bazant, 2004) on demonstrating the capability of MVs generated around polarizable objects for ICEO mixing, Harnett et al. (Harnett et al., 2008) proved this capability numerically and experimentally. A numerical model was developed to determine optimal design parameters of ICEO mixing followed by fabricating the optimal design array of gold-coated hurdles of the triangular cross-section in microchannels under a low-frequency AC field applied on the sidewalls. A rapid increase in mixing from zero to almost perfectly mixed state

(100%) in a small length scale was demonstrated (**Fig. 3A**).

Wu and Li (Z. Wu & Li, 2008b) further simplified the design configuration to a triangle conducting hurdle pair on microchannel walls while enhanced the mixing performance. They optimized the system parameters and demonstrated 92% mixing efficiency. It was shown that the rectangular conducting objects placed on the microchannel walls generated the highest mixing efficiency (**Fig. 3B**). Nevertheless, Jain et al. (Jain, Yeung, & Nandakumar, 2009) showed that a pair of near tight triangle hurdle present even a better mixing performance as 99% efficiency. The performance of various ICEO micromixers developed so far are highlighted in **Table 2** .

The ICEK Micromixers have become popular for LOC applications due to their mixing efficiency (above 90%), simplicity and rapid mixing. However, the majority of studies are still limited to numerical studies to optimize electrodes shape and arrangement. Further experimental studies are needed to evaluate the performance of proposed mixing systems. Among various designs, the model of Daghighi and Li (Daghighi & Li, 2013) (**Fig. 3C**) is attractive due to its simple structure and straightforward fabrication method (Kazemi, Nourian, Nobari, & Movahed, 2017; M. K. D. Manshadi et al., 2019; Shamloo, Madadelahi, & Abdorahimzadeh, 2017). Further experimental characterization on this design configuration would guarantee an affordable and scalable technique for high-performance ICEK mixing within microfluidics.

3.3. ICEK microvalves

Microvalves are vital elements of complex microfluidic devices to control fluid flow along with a network of microchannels. Various types of microvalves have been developed for basic fluid flow mechanistic studies (Shoji & Kawai, 2011), *in vitro* diagnostics (Tikka, Faulkner, & Al-Sarawi, 2011), and biological sample delivery (Samiei, Tabrizian, & Hoorfar, 2016). Rapid response and ability to be integrated into microfluidic systems are the essential criteria for selecting appropriate microvalves. The potential of ICEK phenomenon for controlling the direction of fluid flow through microchannels was first demonstrated by Sugioka (Sugioka, 2010). A rotating elliptical metal cylinder placed within a normally open microchannel was actuated using MVs around it under both DC and AC electric fields. This actuation induced the closure of the liquid flow in microchannels (**Fig. 4A**). In another design, Daghighi and Li (Daghighi & Li, 2011) utilized a Janus particle within a microchamber with three side channels, where the direction of fluid flow inside the channels was controlled under the motion of the Janus particle in the microchamber as a result of external electric field actuation (**Fig. 4B**). Zhang et al. (Capretto, Cheng, Hill, & Zhang, 2011) employed electrically a series of conducting surfaces embedded at the corners of a microchannel network to use ICEK actuation for controlling the flow direction toward desired outlets (**Fig. 4C**). A similar technique was used by Wang et al. (C. Wang et al., 2016) to control fluid motion in a more complex fluidic network. Applying the electric field to the flow using conducting surfaces placed on a Y-junction wall generated MVs to control the flow direction toward the outlets (**Fig. 4D**). Li et al. (Li & Li, 2018) employed an electrically induced Janus droplet to produce ICEK microvalves functioning under DC electric field and to control fluid flow direction within a microchamber with several outlets (**Fig. 4E**). The Janus droplet was made of an oil droplet coated with aluminum oxide nanoparticles. Among different ICEK microvalves, this new system was demonstrated to be highly controllable and easy to manipulate for adjusting the fluid flow in microfluidics.

Unlike many other On/Off or disposable valves used in microfluidic systems, most ICEK microvalves act like a control valve to control the flow direction in microchannels. Among different electrode configurations used for ICEK microvalves, the polarizable plates patterned on the microchannel walls are shown to be a simple and effective ICEK method for controlling the fluid flow direction in microchannels (**Figs. 4C** and **4D**). The response time for switching the flow direction reaches down to one second with the capability of controlling the flow direction in desired branches (Capretto et al., 2011; Daghighi & Li, 2011; Li & Li, 2018). All ICEK microvalves so far functioned based on the ICEO mechanism. There have not been any ACEO-based microvalves yet proposed.

3.4. ICEK for two-phase liquid flow systems

Two-phase flow microfluidic devices have been widely used for chemical filtration, pharmacology and drug delivery (Azizian et al., 2019; Bazazi, Sanati-Nezhad, & Hejazi, 2018). When a leaky dielectric droplet immersed in another immiscible leaky dielectric liquid, four symmetric MVs are induced inside and outside the droplet (Lin, Skjetne, & Carlson, 2012). This phenomenon was first observed by Taylor (Taylor, 1966) in his experimental work. Small deformation of the droplet was predicted theoretically by calculating the exerted electrical stress on droplet-medium interface (Taylor, 1966). This deformation is generated due to the distribution of the interfacial polarization charge on the interface (Lin et al., 2012). The induced charge on the interface of the liquid and the generated MVs around the droplet have a resemblance to the generated MVs around polarizable solid cylinder immersed in the electrolyte under an external electric field (Bazant, 2015). Squires and Bazant (Todd M Squires & Bazant, 2004) utilized this analogy to determine radial and azimuthal fluid velocities of the ICEO flow around a conducting cylinder. Jung et al. (Jung, Oh, & Kang, 2008) calculated the amount of induced charge in a leaky dielectric water droplet oscillated between two fixed electrodes. Flittner and Přiby (Flittner & Přibyl, 2017) proposed a mathematical model for such oscillatory behavior of water droplets. Wuzhang et al. (Wuzhang, Song, Sun, Pan, & Li, 2015) investigated oil droplet motion in different ionic surfactant solutions and observed that an increase in surfactant concentration led to a higher droplet velocity due to the enhancement in surface charge density. It was also found that two MVs are generated around the oil droplet as a consequence of the redistribution of the mobile surface charges on the droplet surface (Daghighi, Gao, & Li, 2011). Li et al. (Li & Li, 2016a) studied this phenomenon more precisely and proposed an analytical presentation for the local zeta potential distribution on the oil droplet. Furthermore, they experimentally observed the accumulation of passivated aluminum nanoparticles on one side of the droplet, which confirmed the charge redistribution on the droplet (Li & Li, 2016b). Mori and Young (Mori & Young, 2018) further improved the Taylor model (Taylor, 1966) and simulated the droplet deformation using electro-diffusion theory, as an essential tool for describing electrokinetic phenomena by considering the charge diffusion model.

Besides the above studies for describing ICEK occurrence in two-phase flows, this phenomenon has also been employed in various microfluidic applications, such as electric separation of droplets (Guo et al., 2010), droplet coalescence (Xiaodong Chen, Song, Li, & Hu, 2015; Y. Jia et al., 2018), emulsion micro-pumping (Bhaumik, Roy, Chakraborty, & DasGupta, 2014), controlling microdroplet generation (Azizian et al., 2019; Kamali & Manshadi, 2016), regulating the micro reactions (Y. Jia et al., 2017), droplet separation (Li & Li, 2017; K. Zhao & Li, 2018), controlling multiphase flow systems (W. Liu et al., 2017), particle flow-focusing (Ren, Liu, Liu, et al., 2018), droplet motion in water-air and water-oil interfaces (C. Wang, Li, Song, Pan, & Li, 2018; C. Wang, Song, Pan, & Li, 2018a, 2018b), and microvalves (Li & Li, 2018).

3.5. Induced-charge electrophoresis (ICEP)

The ICEP concept was first introduced by Bazant and Squires (Bazant & Squires, 2004). It was suggested that asymmetries on polarizable objects such as polarizable Janus particles or tear shape objects immersed in an electrolyte result in non-uniform charge distribution on the surface. Therefore, ICEO on one part of the surface is dominant and drives the particle in the electrolyte under either AC or DC electric fields (Bazant & Squires, 2004). Squires and Bazant (Todd M Squires & Bazant, 2006) further studied the effective asymmetries on the conducting particle motion, including inhomogeneous surface properties on the particle, nearly and highly asymmetry objects, and symmetric body in an electric-field gradient.

The inhomogeneity in surface properties of particles was considered in some studies. Gangwal et al. (Gangwal, Cayre, Bazant, & Velev, 2008) observed the motion of a surface-coated Janus particle perpendicular to the axis of the applied AC electric field. Kilic and Bazant (Kilic & Bazant, 2011) then numerically validated such motions. Boymelgreen and Miloh (Boymelgreen & Miloh, 2012) derived a theoretical presentation for the motion of inhomogeneous Janus particles. Daghighi et al. (Daghighi, Sinn, Kopelman, & Li, 2013) experimentally characterized the motion of Janus particles under DC electric field and observed that particles, unlike under the AC field, are aligned with the axis of the DC electric field.

The particle motion under an electric field was further studied for different types of particle geometries, including non-spherical particles (Yariv, 2005), colloidal rods (Saintillan, Darve, & Shaqfeh, 2006), striped micro rods (Rose, Meier, Dougherty, & Santiago, 2007), cylindrical particles (H. Zhao & Bau, 2007), and slender particles (Yariv, 2008). Characterizing the translational and rotational motions of these particles has shown that the rods or slender objects tend to align properly with the electric field (Saintillan, Darve, et al., 2006; Yariv, 2008).

The ICEP phenomenon was also studied within microfluidics, where the attraction and repulsion of particles from the channel walls were characterized in different conditions (Saintillan, 2008; Z. Wu & Li, 2009). Wu et al. (Z. Wu, Gao, & Li, 2009) numerically simulated the motion of an ideally polarizable particle in a microchannel and demonstrated that the velocity of these particles was equal to the electrophoretic velocity of a non-conducting particle. However, the polarizable particles were repelled from the microchannel wall by the generated MVs around them, transporting the particles toward the centerline. The ICEP motion of conducting particles has been used for developing microsensors (Gangwal et al., 2008) microvalves and microactuators, (Daghighi & Li, 2011; Sugioka, 2010), micropumps (Nobari et al., 2016), micromixers (Daghighi & Li, 2013), and stabilization of sedimenting rods (Saintillan, Shaqfeh, & Darve, 2006). In most of these studies, spherical conducting particles were employed within microfluidics, though further investigation is needed to characterize how other particle shapes contribute to enhancing the performance of ICEK-based microfluidic systems.

3.6. ICEK-based particle manipulation

Particle manipulation is an urging demand in biology and analytical chemistry (Haghighi, Talebpour, & Nezhad, 2018; Hassanpour-Tamrin et al., 2017; Khetani, Mohammadi, & Nezhad, 2018). Among various active and passive methods used for particle manipulation within microfluidics, the micro-vortices induced around conducting surfaces have attracted the attention for particle/cell manipulation. Here, we categorize particle manipulation into particle/cell focusing, trapping, and sorting.

3.6.1. Particle focusing

Particle/cell focusing inside a microchannel is a crucial pre-step for downstream particle/cell counting, detection and sorting (Kung, Huang, Chong, & Chiou, 2016; X. Wang, Zandi, Ho, Kaval, & Papautsky, 2015). Jia et al. (Y. Jia, Ren, & Jiang, 2015), for the first time, demonstrated particle focusing in generated MVs under the AC electric field around the planar floating electrode placed at the bottom of a microchannel (**Fig. 5A**). Chen et al. (Xiaoming Chen et al., 2017) employed this focusing method for the pre-focusing of particles in different solutions prior to their dielectrophoretic separation. Song et al. (Song, Wang, Li, Pan, & Li, 2016) demonstrated particle focusing under DC electric field at the desired location in the microchannel by the induced MVs around a polarizable plate located near the microchannel walls (**Fig. 5B**). Ren et al. (Ren et al., 2016) developed a continuous-flow microfluidic device in which the desired number of focused particles were isolated at the target outlets using the generated MVs around asymmetric electrodes placed at the bottom of the microchannel (**Fig. 5C**). Liu et al. (W. Liu et al., 2016) presented a flow-focusing device in which a suspension of particles was forcused within a cylindrical volume with a diameter range of 1-8 μm (nominal diameter of 4 μm) and conducted toward the desired outlet by the induced MVs around a floating electrode (**Fig. 5D**).

3.6.2. Particle trapping

Particle trapping and enrichment have tremendous applications in clinical diagnostics (Hammarstrom, Nilson, Laurell, Nilsson, & Ekstrom, 2014), water quality management (Zeng, Chen, Vedantam, Tzeng, & Xuan, 2013) and drug development (Collins et al., 2015). The ICEK flow has also been utilized for particle/cell trapping. Yalcin et al. (Yalcin, Sharma, Qian, Joo, & Baysal, 2011) were the first to demonstrate the capability in particle trapping under DC electric field using the ICEO MVs around the floating electrodes placed on the microchannel wall. The trapping of particles down to 500 nm in diameter was demonstrated under induced MVs. Ren et al. (Ren et al., 2015) developed a particle enrichment device in which the particles were trapped at the desired location within the microchannel by applying an electric field around a floating electrode (**Fig. 6A**). Tao et al. (Tao et al., 2016) demonstrated that increasing in size of several floating electrodes or enlarging the width of a single floating electrode enhanced the trapping efficiency (**Fig. 6B**). Harrison et al. (Harrison et al., 2015) utilized the two counter-rotating MVs generated around two dielectric corners of a reservoir–microchannel junction for concentrating the particles of 1 µm diameter. Wu et al. (Y. Wu, Ren, Tao, Hou, & Jiang, 2016) used a rotating electric field for trapping polystyrene (PS) microspheres with 5-20 µm in diameter on a central electrodes array (**Fig. 6C**). Last but not the least, Zhao and Yang (Cunlu Zhao & Yang, 2018) used ICEK-based micro-vortices around a polarizable plate located on the microchannel wall for the enrichment of 50-1900 nm fluorescent particles under combined AC/DC electric field (**Fig. 6D**).

3.6.3. Particle sorting

Particle sorting is an essential procedure for biological analysis and treatment (Gómez-Pastora, Karampelas, Bringas, Furlani, & Ortiz, 2017), diagnostic (D. Kim, Luo, Arriaga, & Ros, 2018), and targeted drug development (Antfolk, Kim, Koizumi, Fujii, & Laurell, 2017). Although the ICEK flow demonstrated its high capability for particle/cell manipulation, there are a few researches with the focus on particle/cell sorting. Zhang and Li (F. Zhang & Li, 2014) used a numerical model to simulate ICEO MVs around a pair of metal plates located on opposite sides of the microchannel walls and evaluated their ability to sort particles based on the applied electric field, polarizability and size of the particles. A similar model was developed to assess sorting of Janus particles (F. Zhang & Li, 2015), where the model tuned dominant determinants of the particle's path through the microchannels (relative polarizability ratio and the size of Janus particles) to sort them by steering their streamline path to the desired branch outlets under DC electric field (F. Zhang & Li, 2015). There are still limited numbers of studies on ICEK particle/cell manipulation, especially for particle trapping and sorting. Further experimental works and characterizations are needed to demonstrate the inexpensive, easy fabrication, and high-performance ICEK particle/cell manipulation.

4. Conclusion

This paper reviews the breakthrough in microfluidic-based applications of induced-charge electrokinetic (ICEK) phenomenon for developing various lab-on-chip (LOC) components, including micromixers, micropumps, and microvalves as well as applications in induced charge electrophoresis (ICEP) and particle/cell manipulation. The ICEK micropumps provided ultrafast pumping capability in a wide range of flow rates for LOC applications. The most efficient AC electroosmotic (ACEO) micropumps operate based on either biased AC/DC signals or three-dimensional stepped electrode arrays. The most efficient ICEO micropumps utilized a circular conducting cylinder for pumping purposes. The ACEO and ICEO micromixers made based on ICEK have shown above 90% mixing efficiency. The ACEO micromixers used mostly floating electrodes on the microchannel walls. Among various ICEK-based mixers, employing a conducting circular cylinder or a floating conducting particle inside a microchamber has been widely studied. However, further experimental characterization is needed to optimize its performance. Besides, ICEK microvalves can operate as both On/Off and control valves, which are highly desirable for microfluidic applications. Among the ICEK-based microvalves developed, the ones that employed conducting plates on the microchannel walls showed the fastest switching response. There is still no ACEO microvalve developed operating based on the ICEK.

Despite the broad scope of the applications for ICEK microfluidics, there are still challenges in technology scaling up. The primary challenge is the costly fabrication of 2D and 3D electrodes within microchannels. To address this challenge, new inexpensive, scalable, and easy to fabricate methods are to be developed to assemble electrodes with the microchannels. Extensive studies are still needed to enhance the efficiency of this method and reduce the power required to implement the system in a feasible point-of-care setting. For example, it would be worthy to characterize the effect of charged particles (conducting or Janus) on the ICEO flow and the generated MVs; the effect of conducting surface properties such as hydrophobic and hydrophilic surfaces on the slip velocity around the object; the role of ion concentrations in the electrolyte solution on ICEO flow; and the influence of polarizability of the induced charges on the object and the flow around it. Most studied have employed spherical particles in the ICEK microfluidic devices and the effect of particle shape has not been yet considered for investigating the ICEP systems. Also, further studies are needed to characterize the effect of different particle configurations on the performance of ICEP systems. Moreover, research works have to delve into the potential of ICEK for particle/cell manipulation. The results showed that the induced MVs in ACEO and ICEO flows could be utilized for focusing, trapping, and sorting of particles as small as 50 nm in size. However, the challenge of separating and sorting of defined particle size from a wide variety of particulates in complex biofluids needs further investigation.

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Table list:

Table 1. The efficiency of AC electroosmotic (ACEO) micromixers demonstrated using either numerical (N) or experimental (E) studies, or both.

Authors	Research method	Mixing time (s)	Mixing length (µm)	Flow condition	Mixing index
Chen et al. (J.-L. Chen, Shih, & Hsieh, 2013)	E, N	0.75	64	NA	90%
Huang et al. (K.-R. Huang, Hong, & Chang, 2014)	E, N	NA	700	100 (µm/s)	98%
Park and Song (Park & Song, 2012)	E	NA	100	4 (µL/min)	95%
Hu et al. (Hu et al., 2017)	E, N	NA	6,000	50 (µL/min)	85%
Wu et al. (Y. Wu et al., 2017)	E, N	NA	2,300	2.16 (µL/min)	84%
Hu et al. (Hu, Guo, Cao, & Jiang, 2018)	N	NA	3,000	NA	98%
Zhang et al. (Kailiang Zhang et al., 2018)	E, N	NA	3,200	1,500 (µm/s)	95%
Du et al. (Du et al., 2018)	N	NA	NA	10 (mm/s)	95%
Tatlisoz and Canpolat (Tatlısoz & Canpolat, 2018)	N	10	700	NA	96%

Table 2. Efficiency of different induced-charge electroosmosis (ICEO) micromixers for mixing liquids within microfluidics.

Authors	Object type/position/Electric field type	Mixing length (µm)	Mixing efficiency (index)
Jain et al. (Mranal Jain, Anthony Yeung, & Krishnaswamy Nandakumar, 2010)	Rectangular and right triangle /near wall/DC	2,000	98% mixing efficiency for the right triangle shape

Authors	Object type/position/Electric field type	Mixing length (µm)	Mixing efficiency (index)
Jain et al. (Mranal Jain, Anthony Yeung, & K Nandakumar, 2010)	Circular/near wall/DC	1,000	NA
Daghighi and Li (Daghighi & Li, 2013)	Conducting particle/free/DC	80	100%
Manshadi et al. (M. K. D. Manshadi et al., 2016)	Rectangular/near wall/center-DC	500	95% mixing efficiency for near-wall object
Alipanahrostami and Ramiar (Alipanah & Ramiar, 2017)	Conducting edges /near wall/AC	20	99%
Azimi et al. (Azimi, Nazari, & Daghighi, 2017)	conductive flexible link /near wall/DC	156	90%
Kazemi et al. (Kazemi et al., 2017)	Conducting particle/free/DC	140	98%
Shamloo et al. (Shamloo et al., 2017)	Circular/triangular/square-inside a microchamber-DC	2,000	81% mixing efficiency for circular hurdle in a rectangular chamber
Ren et al. (Ren, Liu, Tao, Hui, & Wu, 2018)	semiconductor block array/near wall/AC	2,000	100%
Manshadi et al. (M. K. D. Manshadi et al., 2019)	Circular/inside a microchamber/DC	500	96.89%

Figure list:

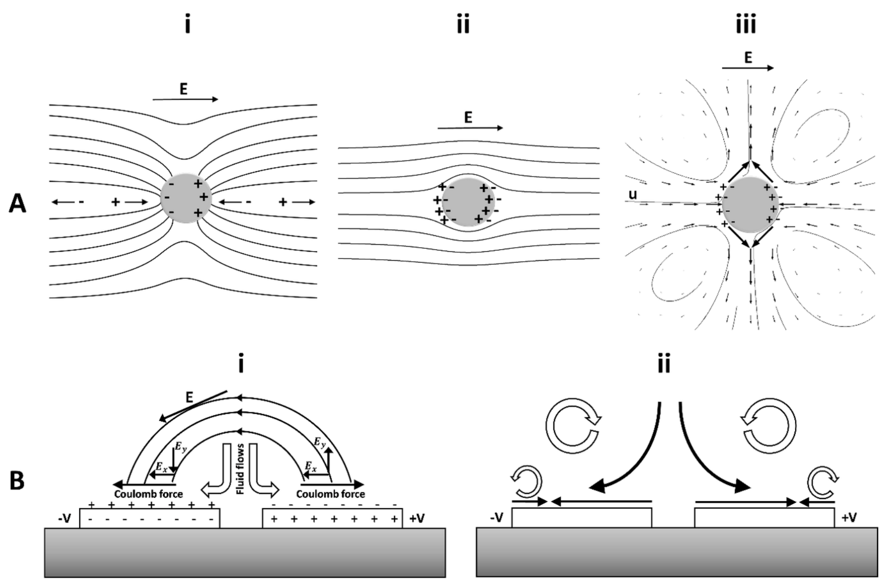


Figure 1. Non-linear Induced-charge electrokinetic (ICEK) phenomena. **A)** Polarizable cylinder, **i)** applying an electric field, **ii)** induced potential in the object, and**iii)** induced micro vortices around the object. **B)**Polarizable electrode**:** **i)** the induced electric potential,**ii)** the generated micro vortices around the electrode.

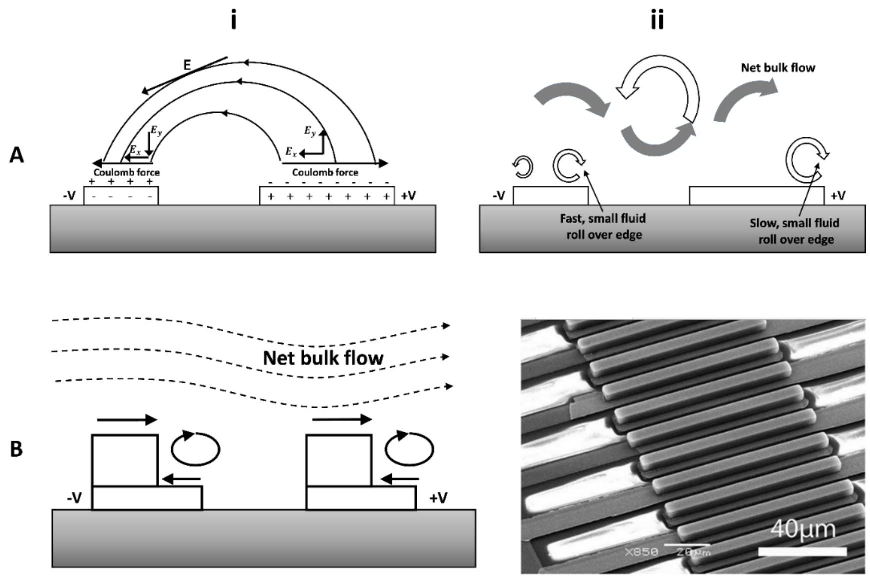


Figure 2 . Schematic view of AC electroosmotic (ACEO) micropumps to induce fluid flow in microchannel by (**A**) a planar array of electrodes with different edge sizes s (Brown et al., 2000; V Studer et al., 2002) and (**B**) a nonplanar configuration of 3D stepped electrodes (Urbanski et al., 2006).

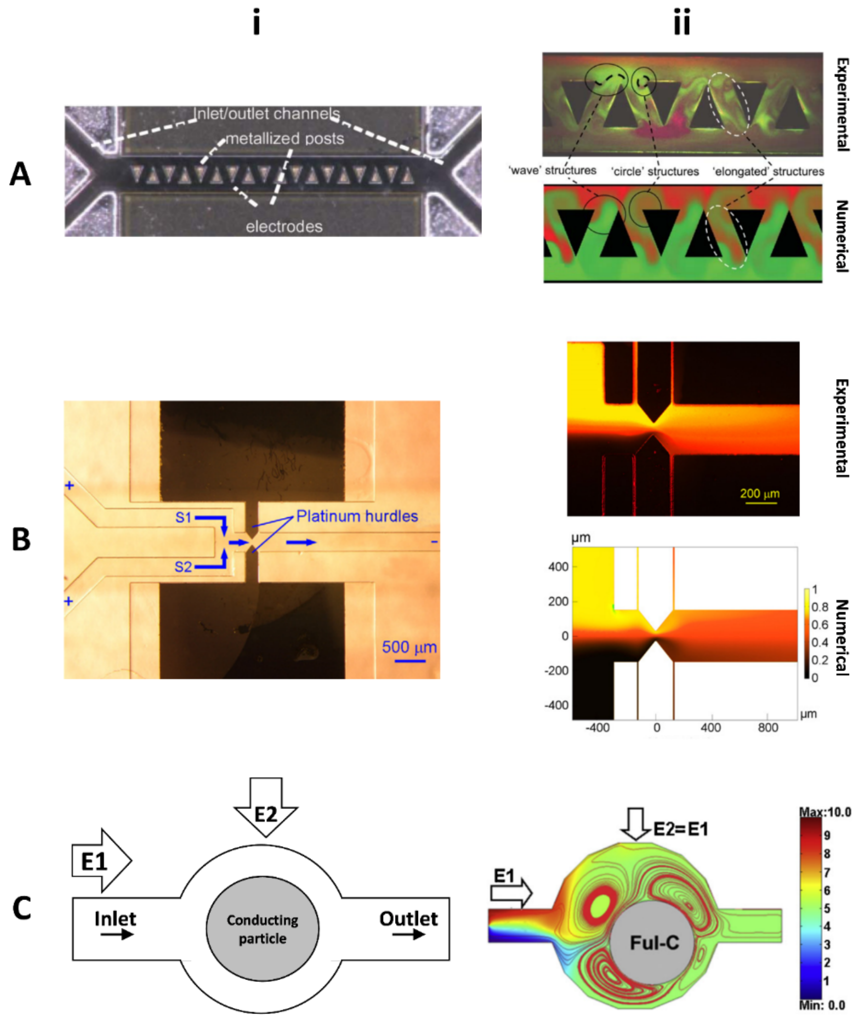


Figure 3. The schematics of induced-charge electroosmosis (ICEO) micromixers, **(A)** numerical and experimental results for rapid mixing state from zero to 100% under AC electric field applied on the sidewalls, **(B)** symmetry pair of triangle conducting hurdles on microchannel walls for inducing micromixing (Z. Wu & Li, 2008a), (**C**) fully conducting particles in the micro-chamber for inducing micromixing (Daghighi & Li, 2013).

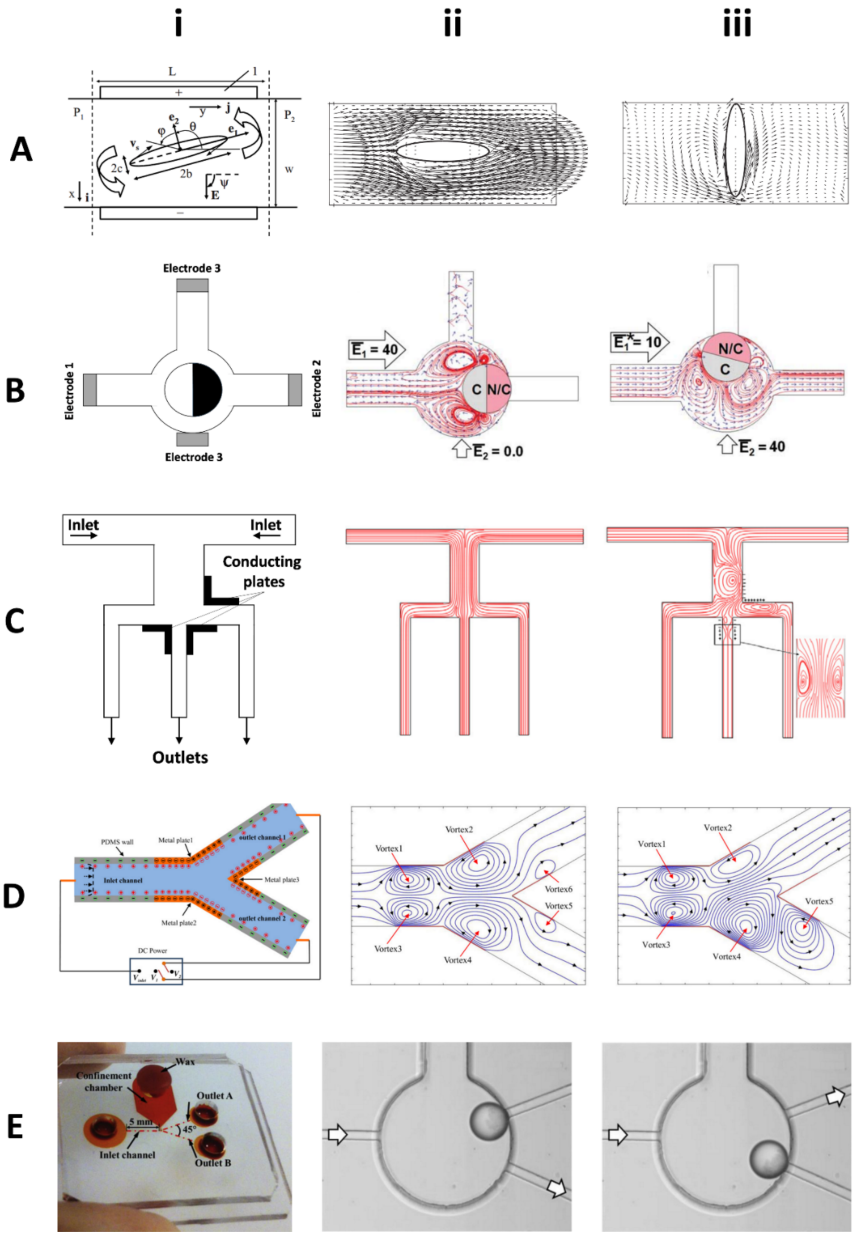


Figure 4. The ICEK microvalves utilizing, **(A)** rotary elliptical metal cylinders as an actuator within a microchannel (Sugioka, 2010), **(B)** a Janus particle actuated within a microchamber with three-side channels (Daghighi & Li, 2011),**(C)** electrically conducting surfaces placed at the corners of a microchannel network for generating actuation MVs, **(D)**Y-junction walls for generating actuation MVs (C. Wang et al., 2016), and **(E)** electrically induced Janus droplet actuated within a chamber with one inlet and two outlets (Li & Li, 2018).

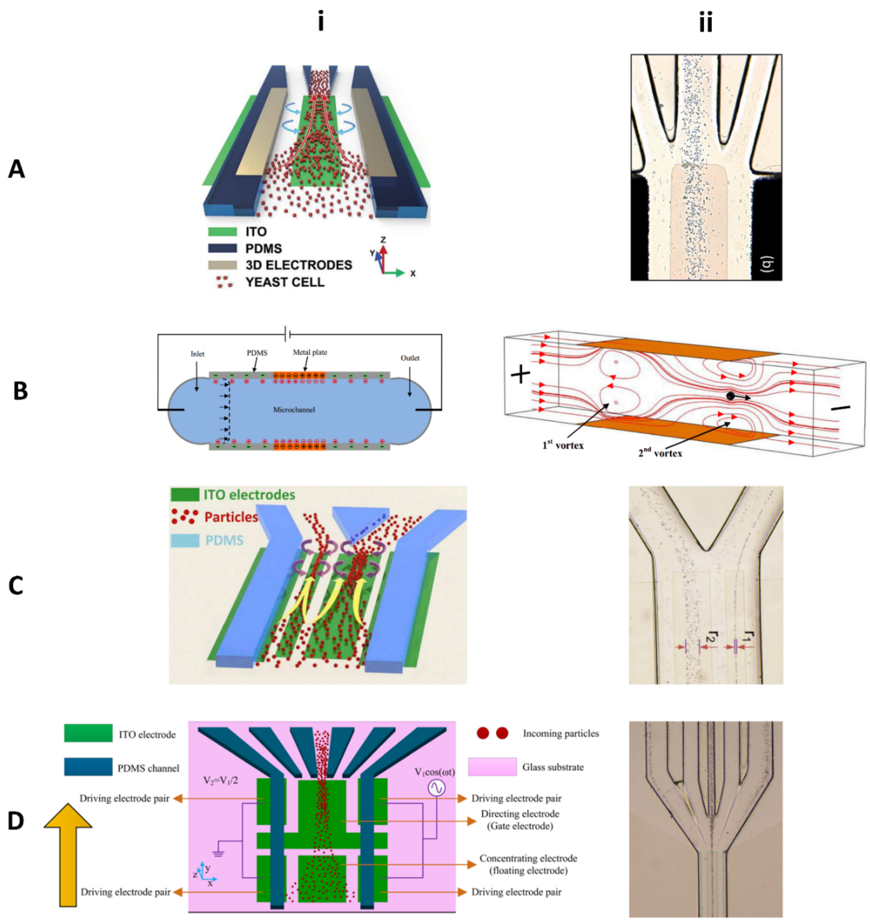


Figure 5. Different electrode design configurations in ICEK to generate MVs for particle focusing. **(A)** planar floating electrode placed at the bottom of the microchannel (Xiaoming Chen et al., 2017), **(B)** polarizable plates placed near the microchannel walls (Song et al., 2016), **(C)** asymmetric electrodes placed at the bottom of the microchannel (Ren et al., 2016), (**D**) a floating electrode placed in the flow-focusing device (W. Liu et al., 2016).

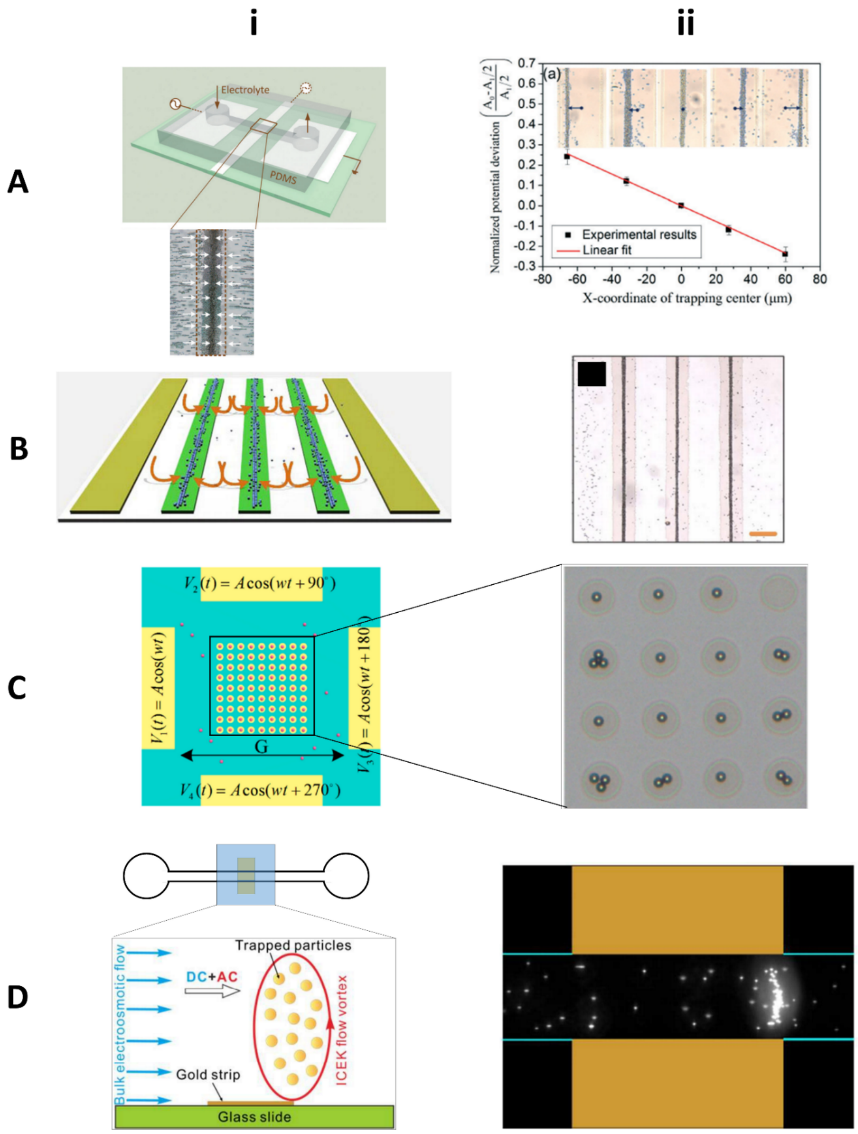
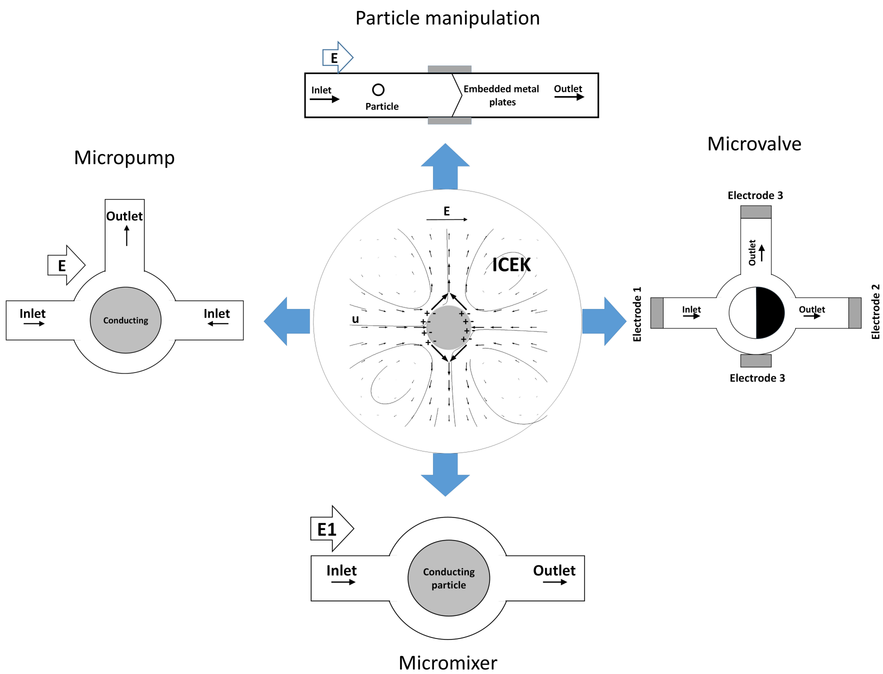


Figure 6. Different electrode design configurations in ICEK to generate MVs for particle trapping. **(A)** a floating electrode array for trapping 500 nm particles (Ren et al., 2015), **(B)**multiple floating electrodes (Tao et al., 2016), **(C)** rotating electric field and central electrodes for trapping 5-20 μm polystyrene (PS) particles (Y. Wu et al., 2016), **(D)** polarizable plate located on the microchannel wall for enrichment of 50-1900 nm particles (Cunlu Zhao & Yang, 2018).



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