

Electrokinetics in Micro Devices for Biotechnology Applications

Pak Kin Wong, Tza-Huei Wang, Joanne H. Deval, and Chih-Ming Ho

Abstract—Electrokinetics is the study of the motion of bulk fluids or selected particles embedded in fluids when they are subjected to electric fields. With the recent developments in microfabrication, electrokinetics provides effective manipulation techniques in the micro and nano domains, which matches the length scale of various biological objects. The ability to manipulate objects down to molecular levels opens new avenues to exploit biological science and technology. Understanding of the fundamental characteristics and limitations of the forces becomes a crucial issue for successful applications of these force fields. In this paper, we review and examine the range of influence for electrokinetically manipulated biological objects in microdevices, which can lead to interesting applications in biotechnology.

Index Terms—AC electroosmosis, bio-nano fluidic system, dielectrophoresis, electrokinetics, molecular manipulation.

I. INTRODUCTION

THE DEVELOPMENT of microfluidic devices enables the integration of miniaturized components for accomplishing bio/chemical processes or medical diagnostics. Performing these procedures in a microfluidic system allows automatic biochemical analysis to be carried out at a volumetric scale several orders of magnitudes below conventional practice. Diagnosis in microdevices can greatly reduce the amount of reagents and samples needed. Automatic biochemical analysis eliminates labor-intensive bench top processes and the possible error associated with it. Above all, the technology provides great promise in improving sensitivity, specificity and the processing time required, which are the key requirements for biomedical analysis [1].

For automated total analysis systems, the samples are usually processed in liquid. Fluid delivery, mixing, concentration, and separation are fundamental fluidic processes in biomedical analyses. The overall system performance depends on the effectiveness of each process. Due to the reduction in length scale, some of the techniques used in laboratory bench top processes become ineffective and cannot be directly applied in microfluidic systems. For example, the small transverse length scale leads to a large velocity gradient and dominance of vis-

cus forces. The inertia of fluid mass is insignificant when comparing with the viscous force and, thus, the Reynolds number is usually very small (much less than 1 in a typical microfluidic system). Hydrodynamic pressure can become inefficient for driving fluids inside microchannels. The large pressure drop associated with the small transverse dimensions makes this approach impractical in some cases.

Length scale matching is important for efficient momentum and energy transfer for controlling the motion of desired fluids and molecules. Most of the biological objects of interest, such as DNA, proteins, and cells have a characteristic length from nanometer to micrometer. Electrokinetics are especially effective in this domain by taking advantage of the small length scale. With the development of MEMS fabrication technology, integration of micro or nano scale electrodes in fluidic device is a relatively simple procedure. Therefore, electrokinetic forces are ideal for manipulating biological objects and performing fluidic operations. In this paper, the principles of several electrokinetic phenomena and the applications of electrokinetic manipulation for biological analysis will be reviewed. First, we will examine electrothermal forces, which act on the bulk fluid. Second, we will discuss forces that are effective in driving fluid near surface boundaries, such as electroosmosis and AC electroosmosis. Then, electrowetting, which is an interfacial electrokinetic effect, is described. We also will present forces that display effects on embedded particles, such as electrophoresis and dielectrophoresis. Finally, a comparison of the magnitudes of forces at different length scales will be presented.

II. ELECTROTHERMAL FLOWS

Electrothermal flow arises from the temperature gradient in the medium generated by joule heating of the fluid. This temperature gradient induces local changes in the conductivity, permittivity, viscosity, and density of the solution. These gradients can generate forces, which act on the fluid [2]. For example, conductivity gradients produce free volume charge and Coulomb forces while a permittivity gradient produces dielectric forces.

Ramos *et al.* [3] have provided an order-of-magnitude estimation of the electrothermal flow. The power dissipation per volume is given by σE^2 . In order to calculate the temperature rise, the energy equation has to be solved and the temperature rise, ΔT , can be approximated by

$$\Delta T \approx \frac{\sigma V_{\text{rms}}^2}{k} \quad (1)$$

where σ is the electrical conductivity, V_{rms} is the root mean square voltage, and k is the thermal conductivity. An analytical

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expression of the force generated is given for parallel electrodes. The order of magnitude of the force on the fluid can be estimated by

$$f_e = -M(\omega, T) \left(\frac{\varepsilon \sigma V_{\text{rms}}^4}{2k\pi^3 r^3 T} \right) \left(1 - \frac{2\phi}{\pi} \right) \quad (2)$$

with $M(\omega, T)$ being

$$M(\omega, T) = \left(\frac{T}{\sigma} \frac{\partial \sigma}{\partial T} - \frac{T}{\varepsilon} \frac{\partial \varepsilon}{\partial T} + \frac{1}{2} \frac{T}{\varepsilon} \frac{\partial \varepsilon}{\partial T} \right) \quad (3)$$

where ω is the angular frequency, ε is the fluid permittivity, r and ϕ are the polar coordinates with reference to the middle of the electrode gap. $M(\omega, T)$ is a dimensionless factor describing the variation of the electrothermal force as a function of applied frequency. τ is the charge relaxation time. Detailed calculations and experimental verifications of electrothermal flow can be found in [4], [5].

By properly designing the electrodes and microstructures, micropumping based on electrothermal flow can be achieved [6]–[8]. Electrothermal pumps have the advantage of being free of moving parts while only requiring a simple fabrication process. In addition, electrothermal flow can operate with an ac potential at high frequency, which prevents electrochemical dissociation of the fluid and accumulation of impurities on the electrode surface.

III. ELECTROOSMOSIS

Electroosmosis can occur due to the formation of electrical double layer at charged surfaces [9]. The surface charge is balanced by counter ions in the medium. There is a layer of ions absorbed on the charged surface called the Stern layer. The outer region, where ions are in rapid thermal motion, is called the diffuse electrical double layer that spans a distance on the order of the Debye length. If a potential is applied along the channel, the diffuse electrical double layer will move due to the electrostatic force. Due to the cohesive nature of the hydrogen bonding of water molecules, the entire buffer solution is pulled. Therefore, the velocity profile is uniform across the channel.

A typical application of electroosmosis is nonmechanical pumping of fluid. The velocity v in a circular capillary of radius a is given by [10]

$$v(r) = \frac{P_z}{4\mu} (a^2 - r^2) - \frac{\varepsilon \zeta}{\mu} \left(1 - \frac{\phi(r\kappa)}{\zeta} \right) E \quad (4)$$

where r represents the distance from the center of the capillary, P_z is the pressure gradient in the flow direction z , μ is the fluid viscosity, ε is the fluid permittivity, ζ is the zeta potential, κ is the reciprocal Debye length, E is the applied electric field, ϕ is the potential in the capillary, and ϕ/ζ is the nondimensional potential, which can be calculated by solving the Poisson–Boltzmann equation. The analytical study of electroosmotic velocity in a channel with rectangular cross section can be found in [11]. Electroosmotic flow is commonly used for sample injection in electrophoresis-based separation [12]–[14]. If silica particles are packed in a fused silica capillary [15], the porous glass structure provides a high surface-to-volume ratio, which maximizes the electroosmotic effect. In microanalytical systems, wide and

shallow channels are usually fabricated. If the distance between surfaces is compatible to the Debye length, the effect of the electrical double layer overlap has to be taken into consideration [16], [17]. Typically, glass substrates are used due to their well-documented surface properties and well-developed surface modification techniques. Recently, the technique has also been demonstrated in other polymeric materials [18], [19].

Electro-osmotic pumping has been demonstrated in complex networks of intersecting capillaries. The fluid flow can be controlled quantitatively by simultaneously applying potentials at several locations [20], [21]. The electroosmotic flow is directly related to the electric current and can be estimated by considering the equivalent resistive circuit and electroosmotic mobility [13], [22], [23]. On the other hand, surface properties are the key feature for controlling electroosmotic flow. A perpendicular electric field can be applied to alter the zeta potential [24]. Spatial modifications of electroosmotic mobility have been reported with protein adsorption [25] and viscous polymer channel sidewall coatings [26]. In addition, the flow pattern can be regulated by the surface charge. Bidirectional electroosmotic flow and out-of-plane vortices have been demonstrated with different surface charge patterns [27], [28]. The capability of generating flow patterns offers the potential for achieving microscale mixing.

IV. AC ELECTROOSMOSIS

AC electroosmosis is a recently identified electrokinetic phenomenon observed at frequency ranges below 1 MHz [3]. This observation has been reported for aggregation of yeast cells in interdigitated castellated electrodes [29]. AC electroosmosis has an origin similar to dc electroosmosis, which exerts a force on the electrical double layer by a tangential electric field. Electric potential within the electrode causes charges to accumulate on the electrode surface, which changes the charge density near surface and forms the electrical double layer. The process is called electrode polarization. The electrical double layer interacts with the tangential component of the electric field and generates a net force. The force acts on the double layer and cause fluid movement (Fig. 1). In alternating electric field, the sign of charges in the electrical double layer changes with the applied electric field and the tangential component. Therefore, the direction of the driving force for the fluid remains the same in alternative electric potential.

Ramos *et al.* [30] has modeled AC electroosmosis by considering the electrolyte and the electrical double layer as impedances in series. The model predicts the AC electroosmotic velocity v on parallel electrodes with small gap distance to be

$$\langle v(r) \rangle = \frac{1}{8} \frac{\varepsilon V_0^2 \Omega^2}{\mu r (1 + \Omega^2)^2} \quad (5)$$

where ε is the permittivity of the electrolyte, V_0 is the potential applied to the electrodes, μ is the viscosity of the electrolyte, and r is the distance from the center of the electrode gap. The nondimensional frequency Ω is given by

$$\Omega = \omega r \frac{\varepsilon}{\sigma} \frac{\pi}{2} \kappa \quad (6)$$

where ω is the angular frequency of the applied field, σ is the conductivity of the electrolyte, and κ is the reciprocal Debye

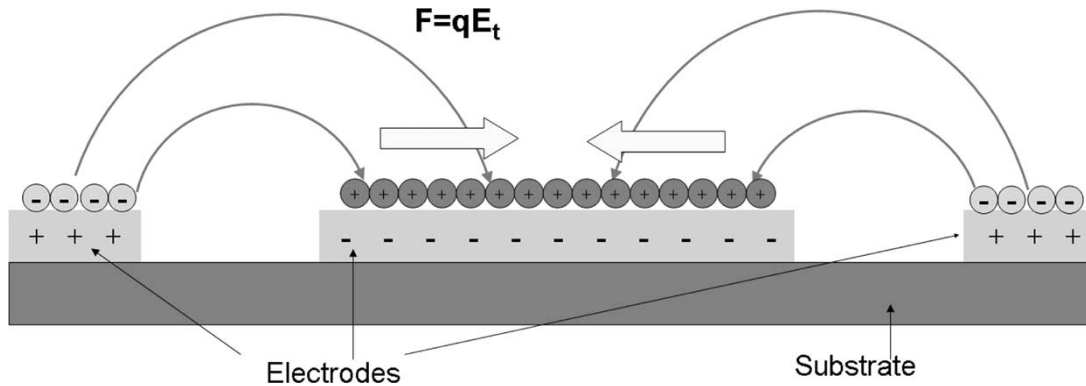


Fig. 1. Principle of an AC electroosmosis.

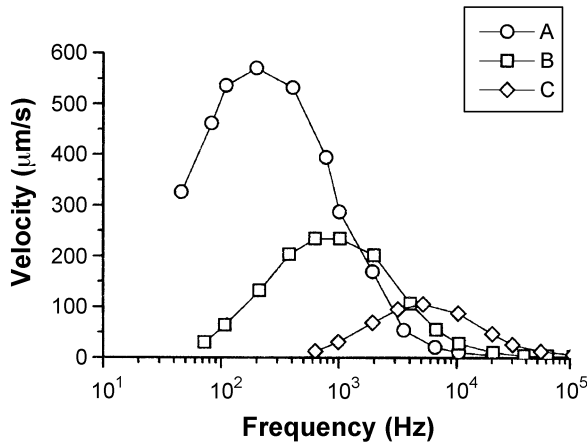


Fig. 2. Frequency dependence of AC electroosmotic velocities within three different medium conductivities from [33] with permission. Conductivities of medium A: 2.1 mS/m, B: 8.6 mS/m, C: 84 mS/m.

length of the electrical double layer. A similar expression is also given by using linear electrical double layer analysis [31]. The bulk fluid motion driven by the surface velocity can be calculated numerically [32].

Green *et al.* [33] have performed detailed experimental measurements of the velocity on parallel electrodes. AC electroosmotic flow velocity displays strong dependences on applied frequency and medium conductivity (Fig. 2). The AC electroosmotic velocity is related to the charge density in the electrical double layer and the tangential electric field. At low frequency, the space charges can quickly respond to the electric field and most of the electric potential drops along the double layer. The tangential electric field is at a minimum at such frequencies and generates small AC electroosmotic velocities. At high frequencies, the net charge in the double layer is small and the impedance across the electrolyte dominates. Therefore, the AC electroosmotic velocity tends to be zero at high and low frequency and has a maximum at an intermediate frequency.

Clustering of particles is usually observed on top of the electrode in AC electroosmosis experiments. The clusters are pushed toward the electrode center by the fluid flow [3], [30]. Discussion of particle–particle interactions is given in Section VII. Based on AC electroosmosis and the clustering properties, we have developed a molecular concentrator for concentrating samples in microanalysis systems [34]. Fig. 3

shows the experimental results of concentrating 200-nm-fluorescence latex particles. With optimizations of the operating parameters, we have also successfully demonstrated concentration of different small biological objects, such as *E. coli* bacteria, λ phage DNA (48 kbp), and single-strand DNA fragments as small as 20 bases [34].

AC electroosmosis has been proposed to be the driving mechanism for an electrokinetic ratchet pump in a microfluidic channel [35], [36]. Asymmetric shaped electrode pairs are used to generate fluid flow in microchannels [37], [38]. The main advantage of this approach is that only very low driving voltage is required. Furthermore, more complex flow patterns can be generated for fitting the needs of other applications.

V. ELECTROWETTING

Instead of driving the bulk fluid inside microchannels with mechanical or electrokinetic pumps, another approach is to perform fluidic operations in droplet based digital fluidic circuits. It is envisioned that the entire biological analysis can be performed in digital fluidic circuits [39]. It eliminates many problems, such as leakage and bounding, associated with channel-based microfluidics. Digital fluidic circuits are made possible by the ability to manipulate fluid droplets (from pl to μ l) with different mechanisms, such as thermocapillaries [40], [41], dielectrophoresis [42], electrostatic force [43], voltage [44] or light [45] mediated surface wetting.

Among those mechanisms, electrowetting on dielectric (EWOD) has been studied most extensively due to the low power consumption, high reversibility, and wide applicability to different fluids. In EWOD, a dielectric coating is used to cover the electrodes, eliminating the direct electrochemical interaction between the fluid and the electrode with a tradeoff of higher driving voltage [46], [47]. Contact angles of liquid droplets on the electrode surface can be controlled by electric potential according to the Lippman–Young equation

$$\cos \theta(V) - \cos \theta(0) = \frac{\epsilon}{2\gamma_{LV}t} V^2 \quad (7)$$

where $\theta(V)$ is the contact angle under electric potential V , γ_{LV} is the surface tension at the liquid-vapor interface, ϵ and t is the permittivity and thickness of the insulating layer. If ac voltage is applied, V is replaced by the root-mean-square (rms) voltage. Good agreement has been obtained between the

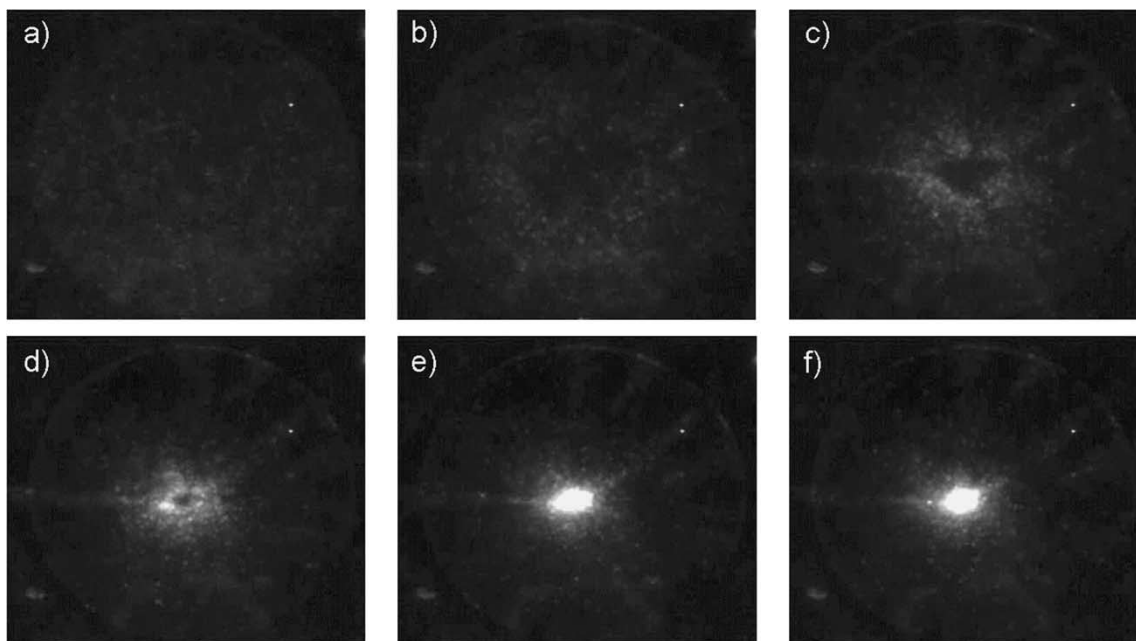


Fig. 3. Video time series demonstrating concentrating of 200 nm fluorescence particles on the central electrodes.

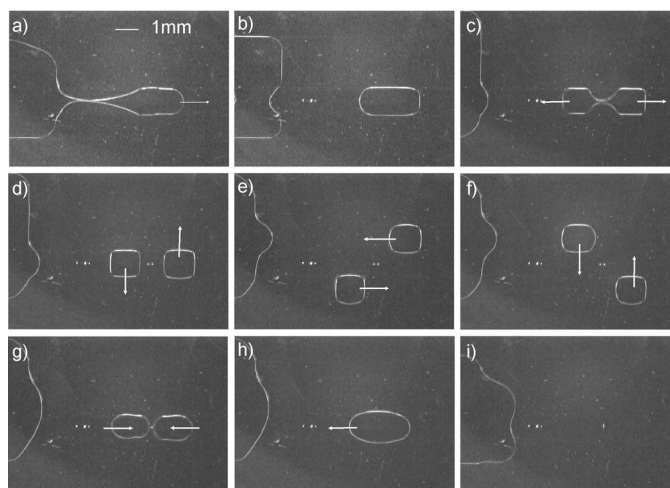


Fig. 4. Droplet operations in digital fluidic circuit from [52]. (a) and (b) Droplet creation from reservoir; (c) droplet cutting; (d)–(f) simultaneous and independent transportation of two droplets; (g)–(i) merging of the droplets and return to reservoir.

Lippman–Young equation and the experimentally measured contact angles. The required driving voltage, therefore, can be minimized accordingly by using a thin layer of dielectric and a high-permittivity material [48].

As the contact angle changes due to the applied voltage, surface wettability changes. By applying voltage at one end of the droplet to decrease the surface tension, a difference in force between the ends of the droplet can be created, which causes droplet motion [49]. Different methods have been developed for driving droplets on a two-dimensional (2-D) space to realize the digital fluidic concept [50], [51]. Recently, Cho *et al.* [39] demonstrated creation, transportation, cutting, and merging of fluid droplets. All these droplet operations can be done on a single chip (Fig. 4) [52]. Mixing of fluorescence dye [52], [53] and separation of particles [54] in digital fluidic chips has also been demonstrated.

VI. ELECTROPHORESIS

Electrophoresis describes the movement of charged particles in a liquid medium under an external electric field. When a particle with charge q is under a steady electric field E , the particle experiences an electrostatic force qE . The electrical force is balanced by a friction force, which can be estimated by Stoke's law, $6\pi\mu Rv$ for a spherical object. The steady state velocity v of the charged particle can be estimated as

$$v = \frac{q}{6\pi\mu R} E \quad (8)$$

where R is the effective hydrodynamic radius of the particle and μ is the medium viscosity.

Negatively charged DNA molecules can migrate under the influence of an external applied electric field. In free solution electrophoresis, a DNA molecule behaves as a free draining coil,

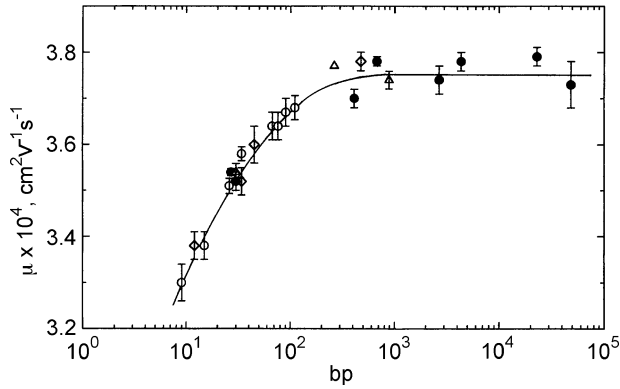


Fig. 5. Mobility of DNA molecules of different lengths in Tris–Acetate–EDTA (TAE) buffer. Reproduced from [62] with permission.

which means the friction coefficient is proportional to the length [55], [56]. On the other hand, the net charge of a DNA molecule can be described by counterion condensation theory [57]–[59]. A constant fraction of the molecule’s charge is neutralized by the counterions. Therefore, the DNA mobility is independent of the length at a given medium condition for large DNA molecules (longer than 400 base pairs) [60]–[62]. Fig. 5 shows free solution mobility of DNA molecules of various lengths, which were reported [62]. It is suggested that the length dependence of small DNA molecules is due to the relative significance of counterion relaxation [62], [63]. Detailed discussion on the topic can be found in [55], [56], and [63]. In order to achieve a size-based separation by electrophoresis, a sieving matrix can be employed to alter the size dependent frictional properties of the DNA molecules [64], [65].

For protein or peptides, the molecules can be positively or negatively charged. The mobility depends on the side chain of the amino acid, the pH value of the medium, and the detailed structure of the protein [66]. At low pH, amino side chains are protonated to give a positive charge; at high pH, carboxylic acid side chains ionize to give a negative charge. The pH value where the protein has no net charge is called the isoelectric point (pI). Proteins can be separated according to their mobility or isoelectric point [67], [68]. For example, protein extract from an HT29 cell line can be separated by capillary zone electrophoresis (Fig. 6) [69]. In addition, the protein expression of a live cell can also influence the cell pI value. For example, yeast cells at various growth stages display different pI [70].

Gel electrophoresis and capillary electrophoresis are invaluable tools in modern biological analysis, such as DNA fragment sizing, DNA sequencing, and protein analysis [71], [72]. Capillary array electrophoresis chips with a large number of separation channels producing high throughputs have been reported [73]–[75]. Isoelectric focusing is a method of the separation of analytes based on the isoelectric point of the molecule. It requires the development of a pH gradient between two electrodes [66]. Cabrera *et al.* have demonstrated generation of a pH gradient by electrolysis-driven production of H^+ and OH^- ions in a microfluidic device [76]. Concentration and separation of different proteins in microfluidic channels has been demonstrated [77], [78]. In addition to the separation of molecules, electrophoretic forces can position molecules to desired locations with properly designed electrodes. For example,

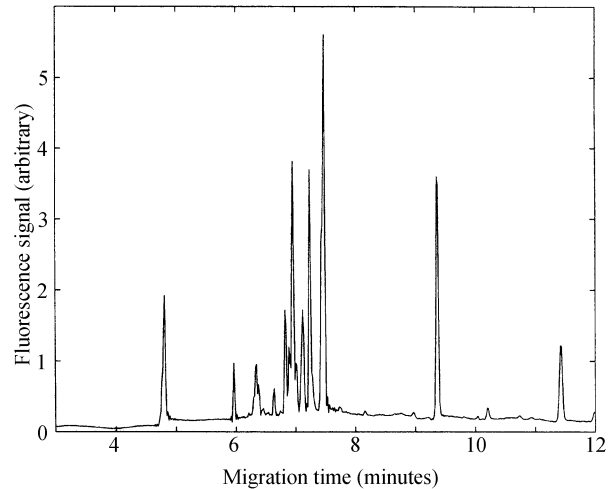


Fig. 6. Capillary zone electrophoresis coupled with laser induced fluorescence for the analysis of protein extract from an HT29 cell line. From [69] with permission.

we have developed an electromolecular focusing technique that enhances the detection efficiency of a laser induced fluorescence (LIF) system [79]. The electrokinetic force is able to focus flowing DNA molecules into a small region, which is comparable with the probe size of the LIF system. Therefore, the detection efficiency can be significantly enhanced.

VII. DIELECTROPHORESIS

When a polarizable particle is subjected to an electric field, a dipole is induced in the particle. If the electric field is diverging, the particle experiences a force that can move it toward the high- or low-electric field region, depending on the particle polarizability compared with the suspending medium. The process is termed dielectrophoresis (DEP) and is described in detail by Pohl [80], [81]. If the polarizability of the particle is higher than the medium, the force is toward the high field strength region (positive DEP). In the other case, the force is toward the lower field region (negative DEP).

The time average dielectrophoretic force is given by [81], [82]

$$F_{DEP} = 2\pi R^3 \epsilon_m \operatorname{Re}\{K(\omega)\} \nabla |E_{rms}|^2 \quad (9)$$

where R is the particle radius, E_{rms} is the root mean square electric field, r is the particle radius, ω is the angular field frequency, $\operatorname{Re}\{K(\omega)\}$ represents the real part of $K(\omega)$, and $K(\omega)$ is the Clausius–Mossotti factor at angular frequency ω . The Clausius–Mossotti factor is a measure of the effective polarizability of the particle in the medium and is given by

$$K(\omega) = \frac{\epsilon_p^* - \epsilon_m^*}{\epsilon_p^* + 2\epsilon_m^*} \quad (10)$$

where $\epsilon_{p,m}^*$ are the complex permittivities of the particle and medium, respectively. For homogeneous particle and medium, the complex dielectric constant is given by

$$\epsilon_{p,m}^* = \epsilon_{p,m} + \frac{\sigma_{p,m}}{j\omega} \quad (11)$$

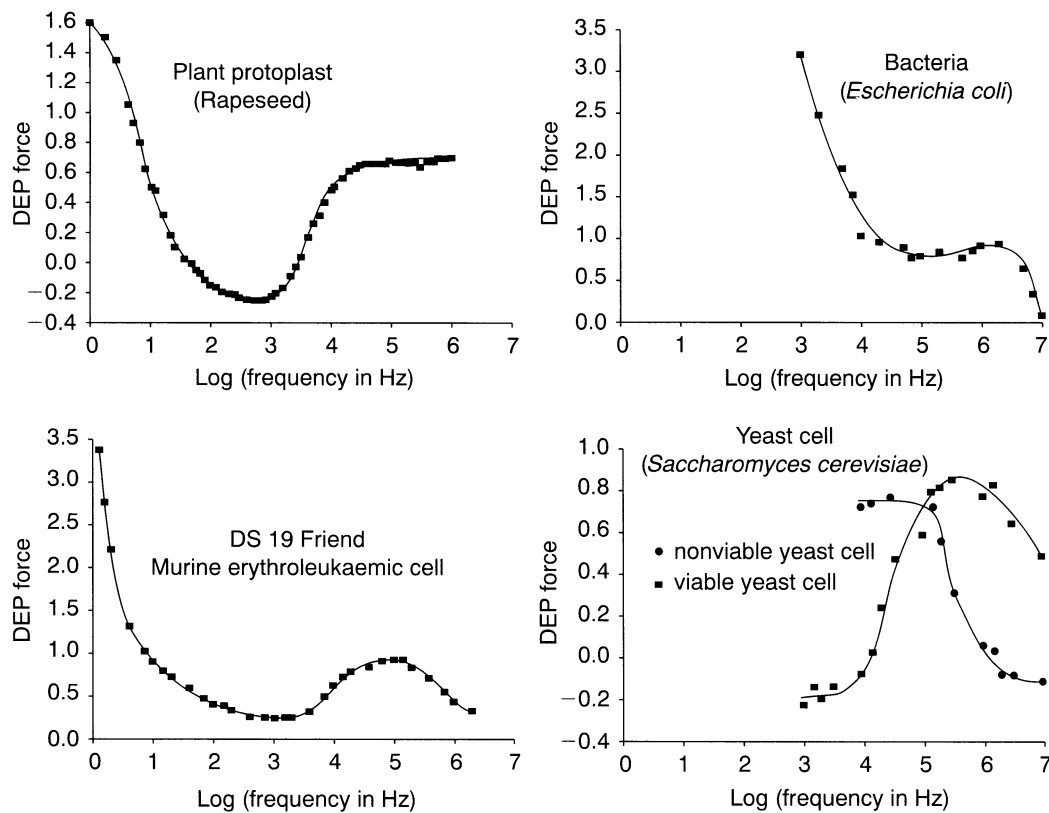


Fig. 7. Dielectrophoretic spectra of different cell types from [83] with permission.

For a more general description, the complex permittivities of the particle and medium have to be replaced by frequency-dependent values [82]. The frequency-dependent description is especially important for the modeling of a biological cell. This is because cells consist of various materials and structures. Each material has very different electrical properties, leading to large interfacial polarizations at the boundaries between structures [83], [84]. Different DEP spectra with strong frequency dependence are observed for different cell types [83] (Fig. 7). Review of DEP spectra for live cells can be found in [81]–[83].

DEP is commonly used for generating translational motion of different objects [85]–[88]. It is possible to discriminate different cell types according to their properties [89], [90]. A detailed discussion of different DEP particle separation techniques can be found in [91]. For example, it has been demonstrated that a mixture of major human leukocyte subpopulations can be separated by DEP [90]. DEP has also been demonstrated for manipulating submicron objects, such as viruses, DNA, and proteins [92]–[95]. For small objects, it is likely that the thermal randomization will dominate over the dielectrophoretic interactions. The condition for DEP potential exceeds the thermal energy, which is given by

$$2\pi R^3 \epsilon_m \operatorname{Re}\{K(\omega)\} E_{\text{rms}}^2 > kT \quad (12)$$

where k is the Boltzmann constant and T is the temperature. Translational motion generated by DEP can also be used to enhance mixing in microchannel flow. We have developed a chaotic mixer based on dielectrophoretic force [96]. Fig. 8 shows the result of mixing enhancement with dielectrophoretic actuation.

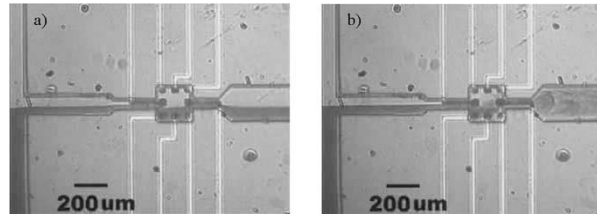


Fig. 8. Micromixing by dielectrophoretic force. (a) Before DEP actuation and (b) after DEP actuation.

Electro-orientation occurs for anisotropic objects [97], [98]. Anisotropic polarization yields orientation torque, which aligns the dipole to the electric field. Electrorotation of particles can be generated by the interaction of a rotating electric field and the dipole moment, which has a certain phase delay [99], [100]. An electrode array in a radial pattern can be used to generate a rotating electric field. Electrorotation has been extensively applied for studying the dielectric properties of different objects [84], [101]–[103]. The principle has also been utilized for measuring the torque–speed characteristic of the flagella motor of salmonella typhimurium [104].

Another effect of polarization is the stretching of the objects, such as deformable cells or DNA molecules. Fig. 9(a) and (b) show a stretch-and-relax experiment of a *Brassica oleracea* (cabbage) protoplast with dielectrophoretic force [88], [105], [106]. It is also possible to break the cell membrane with excessive electric field [Fig. 9(c)]. On the other hand, stretching of long DNA molecules with dielectrophoretic force can also be done. The length of long DNA molecules can be directly observed by stretching (1 base pair is roughly 0.34 nm) [107].

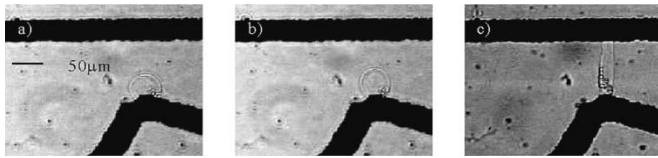


Fig. 9. Stretch-and-relax experiment of a single *Brassica oleracea* protoplast. a) The protoplast is relaxed under no electric field; b) deformed under dielectrophoretic force; c) cell membrane has ruptured under excessive high electric field.

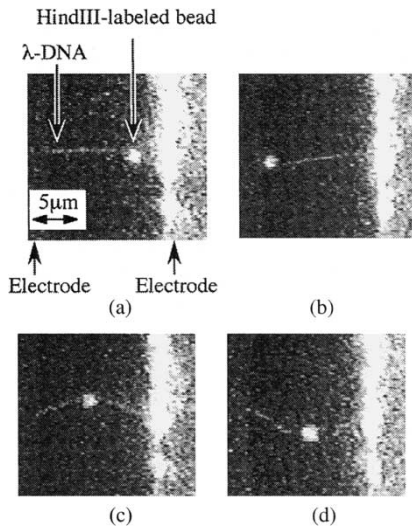


Fig. 10. Molecular surgery with restriction enzyme labeled microbead from [108] with permission. (a) A lambda phage DNA was stretched and anchored on electrodes. (b)–(d) The bead was moved along the DNA and selectively cut the DNA.

In another experiment, DNA molecules are stretched-and-anchored onto electrode surfaces. Molecular surgery can be performed to cut selective portions of the molecules with an AFM tip, UV laser or restriction enzymes [107], [108] (Fig. 10).

Aggregation and pearl-chain formation are frequently observed in ac and dc electrokinetic experiments [81], [82]. The interparticle electromechanics can be explained by the dipole-dipole interactions and the local distortion of the electric field due to the existence of the particles [109], [110]. If two identical particles are parallel to the electric field, the induced dipoles attract each other, independent of the sign of the Clausius-Mossotti factor. Furthermore, the existence of the particle enhances the nonuniformity of the electric field. If particles have a permittivity higher than that of the surrounding medium, the electric field tends to concentrate to the particle and cause mutual attraction between particles. Efforts have been applied to model the mutual interaction between particles under external electric field [111]–[114]. On the other hand, it has been suggested that the particles can introduce inhomogeneities in the ion distribution of the electrical double layer on the electrode surface [115]–[118]. The mutual interaction between particles is critical for the process of live cell electrofusion [119] (Fig. 11). The cell fusion process has been applied for studying membrane properties [120] and formation of hybridoma for monoclonal antibody production [121], [122]. Review of electrofusion can be found in [106].

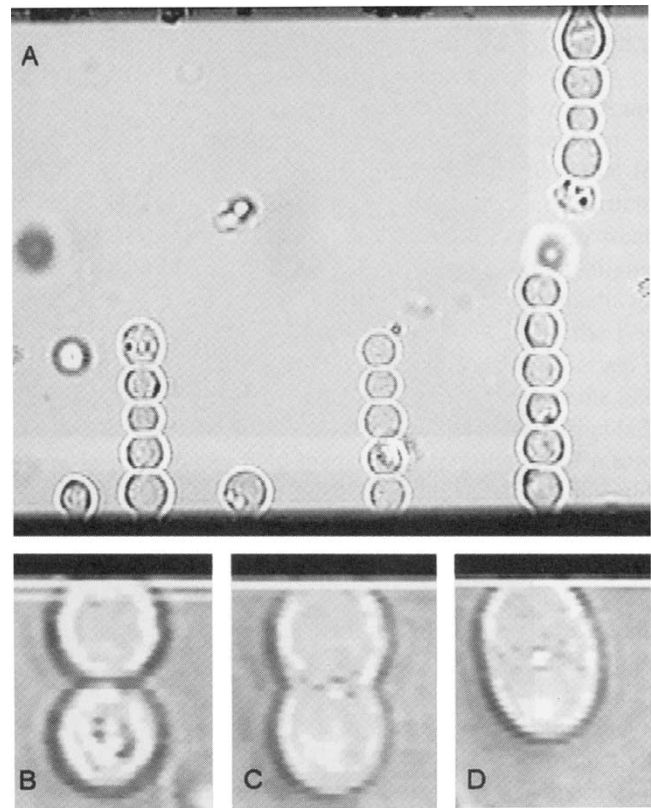


Fig. 11. (a) Dielectrophoretic alignment. (b)–(d) Electrofusion of aligned cells suspended in medium. Reproduced from [106] with permission.

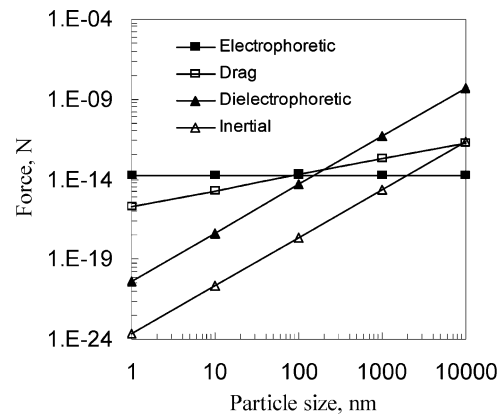


Fig. 12. Dependences of different forces on the size of the particle.

VIII. DISCUSSION

In general, the motion of biological objects in microscale is determined by many forces. Sedimentation, hydrodynamic drag, electrokinetic forces, thermal agitation, and intermolecular interactions are all important considerations for manipulating biological objects. The forces can be divided into two categories: forces that act on 1) the particle or 2) the bulk fluid. The magnitude of all these forces can be in the same order of magnitude in certain circumstances while one of them may become dominating in other situation. Fig. 12 compares the order of magnitude of forces as a function of the particle size. We estimated all the forces by assuming the characteristic length of

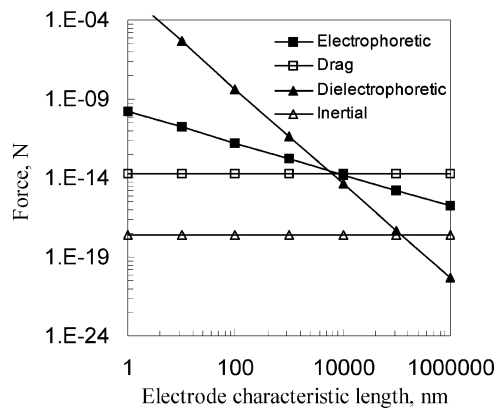


Fig. 13. General trends of different forces versus the electrode characteristic length.

the electrodes are $10\ \mu\text{m}$ and the applied voltage is 1 V. Fig. 13 shows the forces scale as a function of the characteristic distance from the electrode. The object is assumed to be a 100-nm polystyrene particle in aqueous medium with a relative permittivity of 2 and 80, respectively.

Hydrodynamic drag plays an important role in the manipulation of biological objects. All the electrohydrodynamic flows discussed express effects on the embedded molecules via hydrodynamic drag. We estimated the order of magnitude of the drag force by using Stoke's law with a fluid velocity of $10\ \mu\text{m/s}$. Since most biological objects naturally exist in fluid media, hydrodynamic force is a powerful tool for direct manipulation. We have demonstrated deforming of DNA molecules far from its natural equilibrium by generating velocity gradients in microchannel flow [123]. Reviews of microfluidics and hydrodynamic forces can be found in [1] and [124].

Electrophoretic force has strong effects and can be significant even in large scale. We calculated electrophoretic force of a one-charged particle under an external electric field of $10^5\ \text{V/m}$, which is equivalent to applying 1 V across a $10\text{-}\mu\text{m}$ electrode gap. On the other hand, DEP has a relative short-range effect, because it is a function of the potential gradient. The electric field gradient decays rapidly in position away from the electrode edges. The magnitude of force can range widely, which depends on molecule size, position from electrode and the characteristic length of the electrode. Dielectrophoretic force also depends strongly on the material properties and medium. However, it should be noted that the Clausius–Mossotti factor is bounded by 1 and -0.5 .

In most cases, inertia force is not important in small scale. The calculated buoyancy force is orders of magnitudes smaller than other forces for submicrometer particles. On the contrary, intermolecular forces are especially important in molecular scale. The intermolecular forces have the same origin as the forces discussed, such as electrostatic and dipole interaction. Detailed discussion of intermolecular force can be found in [124] and [125].

We have discussed and compared different electrokinetic forces. These forces can be coexisting and are hard to distinguish from their combined effects. They can reinforce each other or compliment each other. This feature can be problematic in designing electrokinetic force based reactors.

For example, electrode polarization can affect low-frequency dielectrophoretic manipulation [126]–[129]. On the other hand, the nature of electrokinetic forces provides rich possibilities for researches and applications. AC electroosmosis is a direct result of electrode polarization and led to the development of our molecular concentrator [34]. Moreover, it is possible to combine different forces to produce a new set of manipulation tools. Ramos *et al.* [3] have demonstrated separation of 282 and 93 nm spheres by combining electrohydrodynamic flow and dielectrophoretic force. Large particles are trapped at the electrode edge due to large dielectrophoretic force, which is proportional to the volume, while small particles are drag along with the flow, which is proportional to the radius.

IX. CONCLUSION

We have briefly reviewed the characteristics and limitations of several electrokinetic forces. We also presented applications of electrokinetics in microdevices, such as fluid delivery, cell positioning, mixing, separation, and concentration of biomolecules in microdevices. Directly manipulating molecules and cells by electrokinetic forces has provided a link to study the complex biological system from micro to nano scale. With many phenomena remaining unexplained, ample opportunities are still available in exploring the nature of electrokinetics. Future study will lead toward further understanding of the bio–nano sciences and novel tools for fast-developing biotechnology field.

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