LAB ON CHIP FOR CELL MANIPULATION

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Contents

Summary

This chapter reviews the cell manipulation techniques using Dielectrophoresis (DEP). It provides a mathematical model of DEP and the particle movement under

Dielectrophoresis forces. It also shows the application of Lab-on-Chip using DEP and the Manipulation Techniques. The DEP is shows a promising technique for micro and nano-particle manipulation.

1. Introduction

Cell Manipulation is the process in which cells or particles are manipulated to change their behavior. Some techniques for cell manipulation include changing their physical shape, adding foreign particles into a cell (such as dying or tagging), transporting cells to a location, separating or sorting cells. There are several techniques proposed for cell manipulation as outlined in the following.

1.1. Dielectrophoresis

With the exposure of a particle to a non-uniform electric field, the particle will have a dipole and interacts with the electric field that results in external force which in turn results in a rotation, displacement or simply a movement of the particle. This force is called dielectrophoresis DEP. It is a function of the frequency and magnitude (specifically the gradient of square of intensity) of electric field, electric properties of medium and particle, shape and volume of the particle. DEP is also used in transportation and separation of micro particles.

DEP is only a polarization of the particle so it does not change the structure of the particle which allows further processing or analysis of the actual particle. Although DEP has a higher throughput, it has a small selectivity as it depends on the relative dielectric value of the cells and medium. Several methods have been developed such as traveling-wave dielectrophoresis (TWD) and electrorotation to enhance the DEP separation.

1.2. Electrophoresis

Electrophoresis is a motion of the polarized particles in a medium under uniform electric field (compare with DEP). A particle in liquid polarized by a surface charge under Coulomb's electrostatic force is formed and causes a motion of the particle. Like charges repel and unlike charges attract each other. Electrostatic method manipulates large object with 5–400 microns in diameter. A parallel electrode structure was used with multiphase high voltages with amplitude 0.2–2 kV peak-to-peak. Coulomb force moved the particles in the plane parallel to the electrodes as traveling field moves.

1.3. Optical Tweezers

Using focused laser beam, the incident light exerts several forces on the particle, the force resulting from photon momentum. Radiation force is in propagation direction. Gradient force is in the direction of the intensity gradient. The particle acts as a lens and rays are refracted on its interface, a force is exerted as photons change direction. The sum of these forces is the gradient force. The particle will repel/attract to the maximum intensity. The optical tweezers can only be used with particles bigger than the wavelength of the light. It is suitable for precise trapping and is used for particles with dimensions in tens of nanometers to tens of micrometers but the manipulation area is limited.

1.4. Ultrasonic Manipulation

Ultrasonic technique is used to excite particles and particles move to an areas where oscillation is zero, which are the nodes of wave. Standing wave is at the interference of two waves with similar amplitude and frequency traveling in the opposite direction. As a result of the wave, the medium oscillates at the same phase but amplitude is varying. Two active sources are used to create two waves traveling in opposite directions.

1.5. Magnetic Tweezers

A magnetic tweezer is a means used for separation similar to electrical field or laser but using a magnetic field gradient. Transport and separation use special beads filled with super-magnetic particles. The beads interact with a bio-marker. Particles attach to the bio-marker and then move or sort by the magnetic field.

1.6. Optoelectronic Tweezers

Optical beams are used to pattern virtual electrodes on a photoconductive material. Spatial light modulator, such as micro-mirror device, is used to generate optical images with million-pixel resolution. The image is projected onto the photoconductive material for parallel manipulation of particles. Complex array of electrodes is used ***and wiring of such an array is challenging. Projected light illuminates the photoconductive layer; it turns on the virtual electrodes creating non-uniform electric fields and enabling particle manipulation via DEP forces.

1.7. Fluid Flow

Motion is induced by the fluid and the fluid draws the particles. Flows of fluid can be caused by increasing the pressure in the inlet to the chamber.

1.8. Electro-osmosis

At the interface of the electrode and the liquid, an inner layer (Stern layer) consisting of ions is strongly bonded to the solid and outer layer (diffuse layer)**. Ions in the outer layer move under the influence of electric field parallel to the electrode-liquid interface. A force drives the fluid at the level of the electrodes and the direction remains the same and independent of the sign of the electrode potential. This mechanism is called *AC electro-osmosis*.

1.9. Electro-thermal Fluid Flow

When a fluid is heated, the variation in temperature changes the density, viscosity and properties of conductivity and permittivity. Difference in density causes buoyancy force, and electro-thermal forces. Change in conductivity produces Coulomb force, and dielectrophoretic force.

2. Dielectrophoresis

Dielectrophoresis "DEP" was demonstrated by suspension of droplets of water in midair. DEP is applied to neutral particles that are "larger than molecules". It uses AC field to manipulate biological particles such as bacteria, virus, mammalian cells, yeast, DNA, protein, and polystyrene beads.

DEP is modeled using a standard dipole as shown in Figure 1 with at a distance d, while r the distance of the dipole under a nonuniform electric field represented as $E(r)$. The dipole position is measured relative to the origin, *O*.

To simplify the model, we assume that $d \ll r$ and $+q$ and $-q$ are equal charges. The dipole will be under a force that is measured under the positive charge can be computed as

$$\vec{F}_{\mathrm{p}} = q\vec{E}(\vec{r}+\vec{d}) \tag{1}$$

and under the negative charge is

$$\vec{F}_{\mathrm{n}} = q\vec{E}(\vec{r}) \tag{2}$$

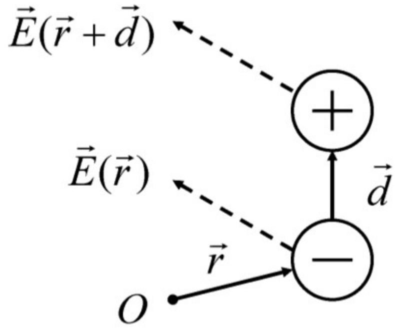

Figure 1. Dipole model with distance d under nonuniform electric field represented $E(r)$, r is the relative distance from the origin, *O*.

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The total force can be computed as

$$\vec{F} = q\vec{E}(\vec{r}+\vec{d}) - q\vec{E}(\vec{r}) \quad (3)$$

Using Taylor expansion Eq. (3) will lead to

$$q\vec{E}(\vec{r}+\vec{d}) = q\vec{E}(\vec{r}) + q\vec{d}\cdot\nabla\vec{E}(\vec{r}) + \text{[illegible]}\,q\vec{E}(\vec{r}+\vec{d}) \quad (4)$$

and d is too small so

$$\Delta_1 q\vec{E}(\vec{r}+\vec{d}) \text{[illegible]} \quad (5)$$

From Eq. (3) and (4)

$$\vec{F} = q\vec{d}\cdot\nabla\vec{E} \quad (6)$$

The moment p is defined as

$$p = qd \quad (6)$$

The force defined in Eq. (5) to

$$\vec{F} = p\cdot\nabla\vec{E} \quad (7)$$

The moment of the dipole p measures the polarity of the electric charges.

The electrostatic potential $\varnothing$ for a small spherical neutral particle of a radius r in a dielectric medium with permittivity ε_m is defined as

$$\varnothing = \frac{p\cdot\text{[illegible]}}{4\pi\varepsilon_\mathrm{m} r^3} \quad (8)$$

If the dipole is replaced with a small neutral sphere with radius a and permittivity of ε_p, the new electrostatic potential is,

$$\phi = \frac{(\varepsilon_\mathrm{p} - \text{[illegible]}}{(\varepsilon_\mathrm{p} + 2\varepsilon_\mathrm{m})r^3} \quad (9)$$

Comparing Eq. (8) and Eq. (9)

$$\vec{p}_\mathrm{eff} \text{[illegible]}\, a^3\varepsilon_\mathrm{m}\cdot K\cdot\vec{E} \quad (10)$$

where K is the Clausius-Mossotti factor

$$K = \left(\frac{\varepsilon_{\mathrm{p}} + \varepsilon_{\mathrm{m}}}{\varepsilon_{\mathrm{p}} + 2\varepsilon_{\mathrm{m}}^{*}} \right) \tag{11}$$

For neutral sphere and for all $|r|$ [illegible] when placed in the dielectric medium, the dielectrophoretic force due to the electrical losses is

$$\left(F_{\mathrm{DEP}}\right) = 2\pi a^{3}\varepsilon_{\mathrm{m}} \,\mathrm{Re}\left[K^{*}\right]\nabla E_{\mathrm{rms}}^{2} \tag{12}$$

The complex Clausius-Mossotti factor, is

$$K^{*} = \left(\frac{\varepsilon^{*} - \varepsilon_{\mathrm{m}}^{*}}{\varepsilon^{*} + 2\varepsilon_{\mathrm{m}}^{*}} \right) \tag{13}$$

where

$\varepsilon_{\mathrm{p}}^{*} =$ [illegible] ω (14)

and

$$\varepsilon_{\mathrm{m}}^{*} = \varepsilon_{\mathrm{m}} - j\frac{\sigma_{\mathrm{m}}}{\omega} \tag{15}$$

where σ_{p} is the conductivity of the particle p , σ_{m} is the conductivity of the medium m , respectively, and ω is the angular frequency of the electric field. From Eq. (14) and Eq. (15), $\mathrm{Re}[K]$ from Eq. (12) is

$$\mathrm{Re}[K] = \frac{\varepsilon_{\mathrm{p}} - \varepsilon_{\mathrm{m}}}{\varepsilon_{\mathrm{p}} + 2\varepsilon_{\mathrm{m}}} + \frac{3\left(\varepsilon_{\mathrm{m}}\sigma_{\mathrm{p}} - \varepsilon_{\mathrm{p}}\sigma_{\mathrm{m}}\right)}{\tau_{\mathrm{MW}}\left(\sigma_{\mathrm{p}} + 2\sigma_{\mathrm{m}}\right)2\left(1 + \omega^{2}\tau_{\mathrm{MW}}^{2}\right)} \tag{16}$$

where τ_{MW} is the Maxwell-Wagner charge relaxation time:

$$\tau_{\mathrm{MW}} = \frac{\varepsilon_{\mathrm{p}} + \varepsilon_{\mathrm{m}}}{\sigma_{\mathrm{p}} + 2\sigma_{\mathrm{m}}} \tag{17}$$

The high frequency response when ω [illegible] is

$$\mathrm{Re}[K] = \frac{\varepsilon_{\mathrm{p}} - \varepsilon_{\mathrm{m}}}{\varepsilon_{\mathrm{p}} + 2\varepsilon_{\mathrm{m}}} \tag{18}$$

and the low frequency response when $\omega \rightarrow 0$ is

$$\mathrm{Re}\left[K\right] = \frac{\sigma_\mathrm{p} - \sigma_\mathrm{m}}{\sigma_\mathrm{p} + 2\sigma_\mathrm{m}} \tag{19}$$

We noted that the permittivity dominates in high frequencies while the conductivity dominates at low frequencies.

The DEP effects can be discussed into two scenarios. The first one, when the medium conductivity is much higher than the conductivity of the particle and the particle's permittivity of dominates the medium permittivity $\sigma_\mathrm{p} < \sigma_\mathrm{m}$ and $\varepsilon_\mathrm{p} > \varepsilon_\mathrm{m}$. The frequency response is shown in Figure 2a. $\mathrm{Re}\left[K\right]$ has a negative value at low frequencies and a positive value at high frequencies.

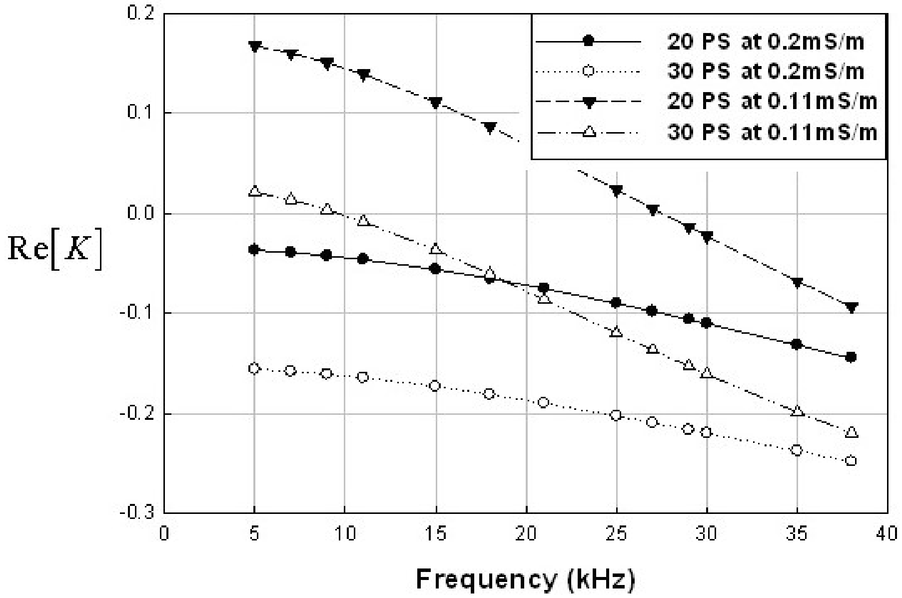

Figure 2. The polarity factor for two different values of medium conductivity, 0.11mS/m and 0.2mS/m, both 20 and 30μm diameter in size polystyrene particles experience only negative dielectrophoresis.

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Biographical Sketch

Bio: Prof. Wael Badawy. (Ph.D., M.Sc. University of Louisiana at Lafayette 2000, 1998; M.Sc., B.Sc., Alexandria University, 1997, 1994)

Dr. Badawy is currently a professor at Umm Al Qura University, prior to that he was at the helm of IntellliView in the role of President and is navigating the company through commercialization into both local and international markets. Dr. Badawy conducted his research at the U of Calgary, Canada where he was a Professor and iCore Chair Associate.

He has more than 400 journal and conference papers in addition to 2 books in the area of Lab on chip and system on chip. He led the development of the hardware reference with 50+ contributions to develop the ISO standards, which represent more than 75% of the hardware reference model for the H.264 compression standard. He also was listed as "Primary contributor" in the VSI Alliance™ developing the "Platform-Based Design Definitions and Taxonomy, (PBD 11.0), 2003". VSI Alliance is an industrial organization that aimed at the development of a standard for IP Cores. This standards is used as a reference by all companies developing electronic chips for different application mainly communication and video.

He has 6 issued patents and 14 pending patent applications. He is received 51 national and international awards including also a recipient of the Canadian Immigrants of Distinction – Distinguished Professional, the Standards Council of Canada (SCC) Awards – Award of Excellence Avenue Magazine and the Top 40 Under 40.

He is also the 2008 Chairman of the Canadian Delegation, ISO/JTC1/SGSN, Study Group on Sensor Networks, Member of the IEEE Health IT Standards Study Group, Co-editor of the ISO/IEC JTC1/SC29/WG11 MPEG. Part 9, Chairman of the Canadian Advisory Committee (CAC) on ISO/IEC/JTC1/SC6 "Telecommunications and Information Exchange Between Systems" and head of the Canadian Delegation, 2006 – 2008 Chairman of the Canadian Delegation, ISO/JTC1/WSSG, Web Service Study Group , 2006 - 2007Chairman of the Canadian Delegation, ISO/JTC1/TW, Technology Watch Study Group and an active Member of the Canadian Advisory Committee (CAC) and a Canadian Delegate in: ISO/JTC 1/TCIT - Information Technologie, ISO/JTC1 Privacy Study Group., ISO/JTC1/SC24 - Computer Graphics and Image Processing, ISO/JTC1/SC29 - Coding of Audio, Picture Multimedia and Hypermedia Information.