Electrorotation and levitation of cells and colloidal particles

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ABSTRACT We review dielectrophoretic forces on cells and colloidal particles, emphasizing their use for manipulating and characterizing the electrical properties of suspended particles. Compared with dielectric spectroscopy, these methods offer a measure of independence from electrode artifacts and mixture theory. On the assumption that the particles can be modeled as uniform dielectric objects with effective dielectric properties, a simple theory can be developed for the frequency variation in the field-induced forces. For particles exhibiting counterion polarization, dielectrophoretic forces differ considerably from predictions of this theory at low frequencies, apparently because of double layer phenomena.

INTRODUCTION

The dielectric permittivity ϵ_p and conductivity σ_p of particles in suspension have long interested biophysicists and colloid scientists, for basic scientific reasons and for technological applications. Most commonly, an investigator measures the bulk dielectric properties of suspensions (i.e., the permittivity ϵ_s and conductivity σ_s) and deduces the electrical properties of individual particles (Schwan, 1957; Schwan 1967).

We consider the mechanical forces exerted by a field on a suspended particle, through interaction with its induced dipole moment. These include translational (dielectrophoretic) forces (Kaler and Jones, 1990) or torques (Glaser and Fuhr, 1987; Arnold et al., 1987; Arnold and Zimmermann, 1988). We emphasize the relation of these forces to the electrical properties of cells and colloidal particles; obvious applications include the study of their electrical properties, and the dielectrophoretic manipulation of particles.

THEORETICAL BACKGROUND

The forces exerted by an electric field E on an uncharged dielectric particle have been reviewed by several authors (Sauer 1983, 1985; Chizmadzhev et al., 1985; Glaser and Fuhr, 1987; Arnold and Zimmermann, 1988; Pastushenko et al., 1988; Kaler and Jones, 1990). For a spherical particle of radius r in field E, which possesses no permanent dipole moment, the time-averaged force F is:

$$F = 2\pi\epsilon_m r^3 \nabla(E^2) Re(u^*),\tag{1}$$

where u^* is the Clausius-Mossotti ratio:

$$u^* = \frac{(\epsilon_p^* - \epsilon_m^*)}{(\epsilon_p^* + 2\epsilon_m^*)} = \frac{(\sigma_p^* - \sigma_m^*)}{(\sigma_p^* + 2\sigma_m^*)}\tag{2}$$

and ϵ^* and σ^* are the complex permittivity and conductivity defined as

$$\sigma^* = \sigma + j\omega\epsilon\tag{3}$$

$$\epsilon^* = \epsilon - j\sigma/\omega.\tag{4}$$

(Complex quantities are denoted with asterisks). The subscripts p and m refer to the particle and medium, respectively.

Thus, the dielectrophoretic force depends on the gradient of the field, which is assumed constant over the particle. The force can be directed towards a region of higher (positive dielectrophoresis) or lower field strength (negative dielectrophoresis) depending on the sign of $Re(u^*)$.

If the particle is placed in a circularly polarized electric field it will experience a time-averaged torque τ, given by (Sauer and Schlögl, 1985):

$$\tau = -4\pi\epsilon_m r^3 E^2 Im(u^*).\tag{5}$$

The torque can be in the same or opposite direction as the rotation of the field vector (cofield or counterfield rotation) depending on the sign of $Im(u^*)$. The corresponding forces on a cylinder are given by Sauer and Schlögl (1985).

Thus, the linear force and torque on the particle are both proportional to the volume of the particle, the real part of the complex permittivity of the medium, and the dielectric properties of the medium and particle as contained in u^*. This factor is a bilinear function of ϵ_p^* and ϵ_m^*, and its frequency dependence can be related to those of the individual phases. Jones and Kaler (1990) have described the use of plots of u^* on the complex plane. We present a complementary analysis, based on partial fraction expansion of u^* for several cases.

(a) Nondispersive particle and medium. For this case the dielectric properties of the particle and medium (ϵ_p, ϵ_m, σ_p, σ_m) are independent of frequency. By expanding Eq. 2 by partial fractions, u^* can be written in the form

$$u^* = \frac{\Delta u}{(j\omega/\omega_m + 1)} + u_\infty,\tag{6}$$

where

$$\Delta u = \frac{3(\epsilon_m\sigma_p - \epsilon_p\sigma_m)}{(\epsilon_p + 2\epsilon_m)(\sigma_p + 2\sigma_m)}\tag{7}$$

$$u_\infty = \frac{\epsilon_p - \epsilon_m}{\epsilon_p + 2\epsilon_m}.\tag{8}$$

Thus, u^* shows a single dispersion at frequency ω_m

$$\omega_m = (2\sigma_m + \sigma_p)/(2\epsilon_m + \epsilon_p).$$

This relaxation (the so-called Maxwell-Wagner effect) is associated with the charging of the interface between the two phases, due to differences in their bulk electrical properties. It occurs even if the dielectric properties of the individual phases are independent of frequency.

The real and imaginary parts of u^* are

$$Re(u^*) = \frac{\Delta u}{(\omega/\omega_m)^2 + 1} + u_\infty \qquad (9)$$

$$Im(u^*) = \frac{-\Delta u \omega/\omega_m}{(\omega/\omega_m)^2 + 1}. \qquad (10)$$

Thus, $Re(u^*)$ varies monotonically between the limiting values

$$(\sigma_p - \sigma_m)/(\sigma_p + 2\sigma_m) \quad \text{(low frequencies)}$$

and

$$(\epsilon_p - \epsilon_m)/(\epsilon_p + 2\epsilon_m) \quad \text{(high frequencies)},$$

with the midpoint of the transition at ω_m. In contrast, $Im(u^*)$ has a broad peak of amplitude $\Delta u/2$ that may be positive or negative. On the complex plane, u^* describes a semicircle of radius Δu, rotating clockwise with increasing frequency.

(b) Dispersive particle, nondispersive medium. A more interesting case is a dispersive particle in a nondispersive medium. We consider a particle undergoing a relaxation with time constant τ' (corresponding to relaxation frequency $\omega' = 1/\tau'$), suspended in a nondispersive medium. The dielectric properties of the particle can be written

$$\sigma_p^* = \sigma_{p,0} + (\sigma_{p,\infty} - \sigma_{p,0})\frac{j\omega/\omega'}{1 + j\omega/\omega'} + j\omega\epsilon_{p,\infty}, \qquad (11)$$

where $\epsilon_{p,\infty}$ is the permittivity of the particle in the limit of high frequencies, and $\sigma_{p,0}$ and $\sigma_{p,\infty}$ are the conductivities of the particle in the low and high frequency limits. This is equivalent to a dispersion in permittivity:

$$\epsilon_p^* = \epsilon_{p,\infty} + \frac{\epsilon_{p,0} - \epsilon_{p,\infty}}{1 + j\omega/\omega'} - \frac{\sigma_{p,0}}{j\omega}, \qquad (12)$$

where $(\sigma_{p,\infty} - \sigma_{p,0}) = (\epsilon_{p,0} - \epsilon_{p,\infty})\omega'$.

Inserting Eq. 11 into Eq. 2 and expanding by partial fractions yields:

$$u^* = \frac{\Delta u_1}{1 + \dfrac{j\omega}{\omega_1}} + \frac{\Delta u_2}{1 + \dfrac{j\omega}{\omega_2}} + u_\infty, \qquad (13)$$

where

$$u_\infty = \frac{\epsilon_{p,\infty} - \epsilon_m}{\epsilon_{p,\infty} + 2\epsilon_m}.$$

The locus of u^* on the complex plane is then the superposition of two semicircles of radii Δu_1 and Δu_2.

The coefficients Δu_1 and Δu_2 and center frequencies ω_1 and ω_2 can be obtained in closed form by computer algebra, although the results are complicated in form. An interesting limit is when $\omega_1 \ll \omega_2$, which applies for most experiments on cells or colloidal particles. The parameters of the dispersion are:

$$\Delta u_1 = -\frac{3\sigma_m(\sigma_{p,\infty} - \sigma_{p,0})}{(\sigma_{p,\infty} + 2\sigma_m)(\sigma_{p,0} + 2\sigma_m)} \qquad (14)$$

$$\Delta u_2 = \frac{3(\sigma_{p,\infty}\epsilon_m - \epsilon_{p,\infty}\sigma_m)}{(\epsilon_{p,\infty} + 2\epsilon_m)(\sigma_{p,\infty} + 2\sigma_m)} \qquad (15)$$

$$\omega_1 = \frac{\omega'(\sigma_{p,0} + 2\sigma_m)}{\sigma_{p,\infty} + 2\sigma_m} \qquad (16)$$

$$\omega_2 = \omega_m + \frac{\omega'(\sigma_{p,\infty} - \sigma_{p,0})}{\sigma_{p,\infty} + 2\sigma_m}, \qquad (17)$$

where

$$\omega_m = \frac{\sigma_{p,\infty} + 2\sigma_m}{\epsilon_{p,\infty} + 2\epsilon_m}.$$

The above expressions are valid to zero order (Eqs. 14 and 15) or first order in ω'/ω_m (Eqs. 16 and 17).

Thus, a dispersive particle shows two dispersions, both of which depend on the dielectric properties of the particle and medium. If $\sigma_{p,\infty} > \sigma_{p,0}$ (which is nearly always the case) then $\Delta u_1 < 0$ and the low frequency dispersion is negative; the high frequency dispersion might have either sign. For a nondispersive particle, $\Delta u_1 = 0$ and the dispersion is identical to that given in Eq. 6.

Membrane-covered spheres. The theory can be extended to the case of a membrane-covered sphere, used to model a biological cell. The effective conductivity σ_c^* of the cell is obtained from the solution of Laplace's equation for the particle (Schwan, 1957):

$$\frac{\sigma_c^* - \sigma_{mem}^*}{\sigma_c^* + 2\sigma_{mem}^*} = \frac{(R - d)^3}{R^3} \frac{\sigma_i^* - \sigma_{mem}^*}{\sigma_i^* + 2\sigma_{mem}^*}, \qquad (18)$$

where σ_i^* and σ_{mem}^* are the complex conductivities of the cell interior and membrane, and d and R are the thickness of the membrane and radius of the sphere. If the membrane is thin ($d \ll R$) and $|\sigma_{mem}| \ll |\sigma_i|$ this reduces to

$$\sigma_c^* = \frac{\sigma_i^* - \dfrac{2d}{R}(\sigma_i^* - \sigma_{mem}^*)}{1 + \dfrac{d}{R}\dfrac{(\sigma_i^* - \sigma_{mem}^*)}{\sigma_{mem}^*}}. \qquad (19)$$

Defining the membrane capacitance and conductance:

$$C_{mem} = \epsilon_m/d$$

$$G_{mem} = \sigma_m/d$$

leads to the result

$$\frac{1}{\sigma_c^*} = \frac{1}{\sigma_i^*} + \frac{1}{R(G_{mem} + j\omega C_{mem})}. \quad (20)$$

This can be written in the form of Eq. 11 with

$$\omega' = \frac{\sigma_i + RG_{mem}}{C_{mem}R} \approx \frac{\sigma_i}{C_{mem}R} \quad (21)$$

$$\sigma_{p,0} = \frac{RG_{mem}\sigma_i}{\sigma_i + RG_{mem}} \approx RG_{mem} \quad (22)$$

$$\epsilon_{p,\infty} = \epsilon_i \quad (23)$$

$$\sigma_{p,\infty} = \sigma_i. \quad (24)$$

Inserting this into Eqs. 14–17 gives, to first order in RG_m/σ_m,

$$\omega_1 = \frac{G_{mem}}{C_{mem}} + \frac{1}{RC_{mem}}\left[\frac{1}{\sigma_i} + \frac{1}{2\sigma_m}\right]^{-1} \quad (25)$$

$$\Delta u_1 \approx \frac{3\sigma_i^2\sigma_m}{(RG_{mem}(\sigma_i + 2\sigma_m) + 2\sigma_i\sigma_m)(\sigma_i + 2\sigma_m)} \quad (26)$$

$$\omega_2 = \frac{\sigma_i + 2\sigma_m}{\epsilon_i + 2\epsilon_m} + \omega'\frac{\sigma_i - RG_{mem}}{\sigma_i + 2\sigma_m} \quad (27)$$

$$\Delta u_2 \approx \frac{3(\epsilon_m\sigma_i - \epsilon_i\sigma_m)}{(\epsilon_i + 2\epsilon_m)(\sigma_i + 2\sigma_m)} \quad (28)$$

$$u_\infty = \frac{\epsilon_i - \epsilon_m}{\epsilon_i + 2\epsilon_m}. \quad (29)$$

In experimental studies the cell is frequently suspended in a low conductivity medium (to reduce heating effects), i.e., $\sigma_i \gg \sigma_m$. Eqs. 25 and 26 reduce to

$$\Delta u_1 \approx \frac{-3\sigma_m}{2\sigma_m + RG_{mem}}$$

$$\omega_1 \approx \frac{1}{RC_{mem}}[RG_{mem} + 2\sigma_m]. \quad (30)$$

Particle with frequency-dependent surface admittance. Another interesting case is that of a nonconductive particle surrounded by a shell with a complex admittance. This problem is discussed by Schwan (1985) and (for frequency-independent surface conductance) by Chizmadzhev (1985). Eq. 19 then reduces to

$$\sigma_p^* = \sigma_i^* + 2\sigma_{shell}^*\frac{d}{R} = \sigma_i^* + 2\frac{Y_{shell}^*}{R}, \quad (31)$$

where $Y_{shell}^* = G_{shell} + j\omega C_{shell}$ is the surface admittance, and G_{shell} and C_{shell} are the surface conductance and capacitance. The effective dielectric properties of the particle are then

$$\sigma_p = \sigma_i + 2G_{shell}/R$$

$$\epsilon_p = \epsilon_i + 2C_{shell}/R.$$

Any dispersion in Y_{shell}^* will give rise to a corresponding dispersion in u^*. The surface admittance might be associated with counterions near the surface of the particle.

Typically, cell membranes have a high surface charge density, and a correspondingly high and possibly frequency-dependent surface admittance. Thus, the field–force spectra might exhibit separate dispersions associated with the surface admittance and with the charging of the membrane capacitance. In addition, a dispersion arising from the Maxwell-Wagner effect will occur, typically at much higher frequencies.

Thus, the dielectrophoretic forces on a cell vary greatly with frequency range. Below the relaxation frequency for membrane charging (ω_1 given in Eq. 25), the cell is electrically equivalent to a nonconducting particle with a frequency-dependent surface admittance, in a conductive medium. At higher frequencies it is equivalent to a conductive particle in a conductive medium; and at still higher frequencies (above ω_2 given in Eq. 27) to a dielectric particle in a dielectric medium.

Double layer effects

This treatment assumes that the particle can be modeled as an electrically homogeneous body in a homogeneous medium, and is based on solutions of Laplace's equation. For particles with space charges (i.e., colloidal particles or cells in electrolyte), this approach requires that the Debye length of the medium be small compared with the radius of the particle or the thickness of the cell membrane.

Colloidal particles and cells exhibit large polarizabilities at low frequencies due to counterion displacement (e.g., Schwan et al., 1962). These effects are characterized by distance scales that include the Debye screening length $1/\kappa$, and the distance an ion can diffuse in a period of the field, $\sqrt{4D/\omega}$, where D is the ion diffusion coefficient and ω is the radian frequency (Dukhin, 1974; Chew and Sen, 1982; Fixman, 1983; Mandel and Odijk, 1984; Grosse and Foster, 1987). For a 1–1 electrolyte of 10^{-3} S/m and at 1 kHz, these distances are ~40 and 500 nm, respectively. In contrast, the hydrodynamic slip plane (for micron-sized vesicles) is within 1 nm of the surface (Alvarez et al., 1983).

Thus, for colloidal particles and cells, the simple theory might break down, particularly with low conductivity solutions and at low frequencies. In effect, the field exerts forces both on the particle and the surrounding electrolyte, which are free to move with respect to each other, and Stoke's law does not apply. Similar complications arise in electrophoretic mobility of colloidal particles, which departs from simple theory when $\kappa a < 1$ (O'Brien and White, 1978; Gaigalas et al., 1990).

So far, no rigorous theory is available for dielectrophoretic forces that accounts for counterion effects. Such a theory would entail the combined solution of the Poisson and Navier-Stokes equations, and mass balance equations for the ions.

For different reasons, the high frequency (Maxwell-Wagner) dispersion is also sensitive to ionic diffusion effects when $\kappa a < 1$. The simple theory for the Maxwell-

Wagner effect is based on the assumption that the charge accumulation at the interface occurs in an infinitely thin region. An extended theory, that takes into account ionic diffusion effects, leads to large corrections to the simple theory when $\kappa a < 1$ (Garcia et al., 1985).

More complicated systems. The above analysis can be extended to more complicated systems that exhibit multiple dispersions. The case of multishelled spheres (used to model cells with intracellular organelles) was discussed by Turcu and Lucaciu (1989) and Fuhr and Kuzmin (1986) for rotation, and Kaler and Jones (1990) and Glaser and Fuhr (1985) for dielectrophoretic forces, and Pastushenko (1988) for both force and torque.

For these more complicated systems, the algebra becomes very complex. However the qualitative results are clear: u^* exhibits several dispersions, equal in number to the number of different interfaces in the system (Hanai et al., 1988). Unfortunately, the problem of extracting relaxation parameters from data exhibiting multiple relaxation is notoriously ill conditioned (Colonomos and Gordon, 1979), particularly when the individual relaxation times are not widely separated in frequency. This difficulty is exacerbated by the fact that the individual relaxations might not be characterized by single time constant behavior, because of polydispersity in particle geometry or other factors.

Relation to dielectric spectra

The dielectric properties of a suspension (ϵ_s^*, σ_s^*) are related to those of the particles (ϵ_p^*, σ_p^*) and continuous phase (ϵ_m^*, σ_m^*) by mixture theory. Despite many years of study, no rigorous solution to this problem exists that is generally valid. One simple and useful result is that of Maxwell. If p is the volume fraction of the suspension,

$$\frac{(\epsilon_s^* - \epsilon_m^*)}{(\epsilon_s^* + 2\epsilon_m^*)} = pu^*, \tag{32}$$

or equivalently

$$\frac{(\sigma_s^* - \sigma_m^*)}{(\sigma_s^* + 2\sigma_m^*)} = pu^*. \tag{33}$$

The Maxwell theory is rigorous only in the limit of small p. However, Eqs. 32–33 are surprisingly accurate even at high volume fractions of suspended particles (Cole et al., 1969) provided that no aggregation occurs. Various alternate mixture theories have been proposed, based on a virial expansion (Chiew and Glandt, 1983) or ad hoc corrections for interparticle interactions (Dukhin, 1971; Grosse and Greffe, 1979). The former approach is rigorous but requires more information about the structure of the suspension than is usually available; the latter are of uncertain accuracy.

In the limit of small p, Eqs. 2 and 32 can be combined to yield

$$\sigma_s^* = \sigma_m^*(1 + 3pu^*). \tag{34}$$

In this approximation, σ^* and u^* have poles (and thus dispersions) at the same frequencies. Therefore, for dilute suspensions the dielectric and field–force spectra have the same relaxation frequencies. Other mixture theories, or the Maxwell theory applied to more concentrated suspensions, yield slightly different dispersion frequencies for the dielectric and field–force spectra.

However, the amplitudes of these spectra are quite different, even in terms of the simple Maxwell theory. A full analysis, based on Maxwell's mixture analysis, was presented by Pauly and Schwan (1959). The results in this case are quite complicated. For dilute suspensions, the analysis is much easier. Expansion of Eq. 34 by partial fractions yields an expression of the form

$$\epsilon_s^* = \frac{\Delta\epsilon_1}{1 + j\omega/\omega_1} + \frac{\Delta\epsilon_2}{1 + j\omega/\omega_2} + \epsilon_\infty - \frac{j\sigma_0}{\epsilon_r\omega}, \tag{35}$$

where (for small p) the coefficients reduce to

$$\Delta\epsilon_1 \approx \frac{9pRC_{mem}}{4(1 + RG_{mem}(1/\sigma_i + 1/2\sigma_m))} \approx \frac{9pRC_{mem}}{4} \tag{36}$$

$$\Delta\epsilon_2 \approx \frac{(9p/2)(\epsilon_i\sigma_m - \epsilon_m\sigma_i)^2}{(\epsilon_i + 2\epsilon_m)(\sigma_i + 2\sigma_m)^2} \tag{37}$$

$$\epsilon_\infty \approx \epsilon_m\left(1 + 3p\frac{\epsilon_i - \epsilon_m}{\epsilon_i + 2\epsilon_m}\right) \tag{38}$$

$$\sigma_0 \approx \sigma_m\left(1 - \frac{3p}{2}\frac{1 + RG_{mem}(1/\sigma_i - 1/\sigma_m)}{1 + RG_{mem}(1/\sigma_i + 1/2\sigma_m)}\right) \tag{39}$$

and the relaxation frequencies (ω_1, ω_2) are the same as those given in Eqs. 25 and 27.

The dielectric and field–force spectra, for a dispersive particle in nondispersive medium, are compared in Figs. 1–3. The dielectric properties of the particle are reminiscent of those of a micron-sized polystyrene sphere in dilute electrolyte, showing a dispersion at 1 kHz from counterion polarization.

Sensitivity considerations

An important consideration is the relative sensitivities of field–force and dielectric spectra to the dielectric properties of the particle.

Some insight can be gained from the form of u^*. At low and high frequencies, u^* approaches the real functions $(\sigma_p/\sigma_m - 1)/(\sigma_p/\sigma_m + 2)$ and $(\epsilon_p/\epsilon_m - 1)/(\epsilon_p/\epsilon_m + 2)$, respectively. Thus, the torque will vanish, and the translational force will depend only on the ratios σ_p/σ_m or ϵ_p/ϵ_m. This dependence will be very weak unless the ratios are close to unity.

At intermediate frequencies, the question of sensitivity becomes more complicated. To explore this further, we define the sensitivity of the force $F(x)$ to parameter x to be the partial derivative

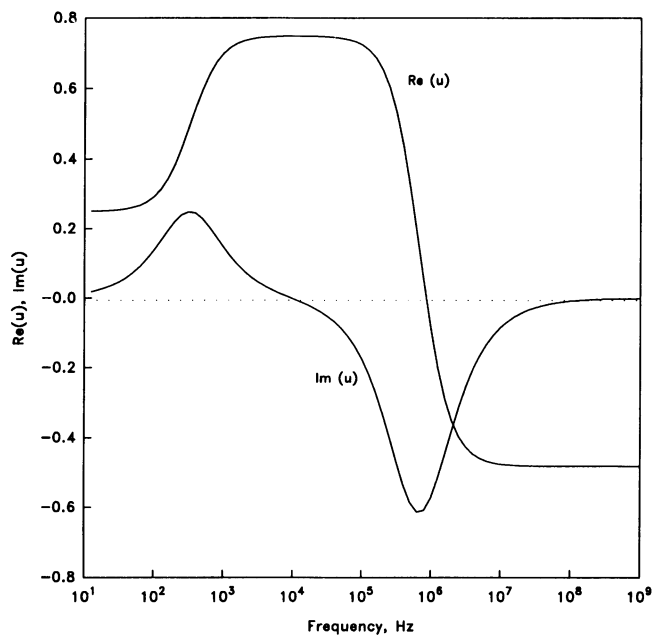$$S_x^F \doteq \frac{x}{F(x)}\frac{\partial F(x)}{\partial x}. \tag{40}$$

FIGURE 1 Frequency dependence of dielectrophoretic force and torque. The particle has a dispersion in its conductivity, with parameters $\sigma_{p,0} = 0.001$, $\sigma_{p,\infty} = 0.005$, $\sigma_m = 0.0005$, $\epsilon_m = 78\epsilon_r$, $\epsilon_{p,\infty} = 2\epsilon_r$, and $2\pi\tau' = 0.001$ (center relaxation frequency 1,000 Hz). Conductivity values in S/m; ϵ_r is the permittivity of free space. These properties are typical of a micron-sized particle exhibiting counterion polarization.

Fig. 4 shows the sensitivity of the force and torque for the particle of properties given in Figs. 1–3, which were evaluated numerically. In the dispersion region, the torque is considerably more sensitive to the permittivity of the
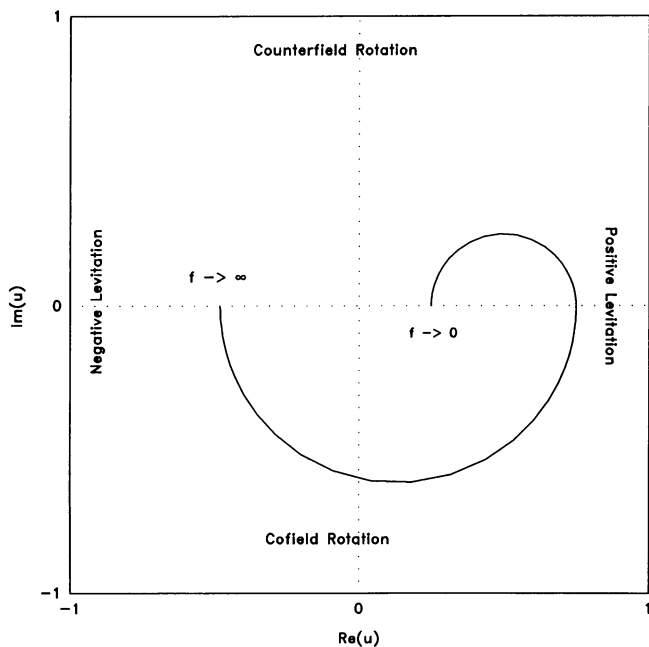

FIGURE 2 Polar plot of u^*, showing regions of positive and negative levitation and counter- and cofield torque. The same dielectric properties of the particle and medium as in Fig. 1.
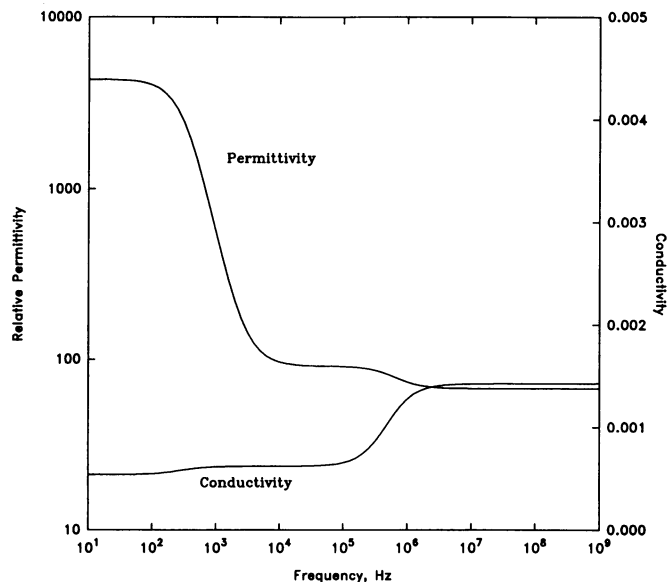

FIGURE 3 Calculated dielectric properties of a 10% suspension of particles with dielectric properties given in Fig. 1.

particle, whereas the linear force is slightly more sensitive to the conductivity of the particle.

Dielectric measurements using field-force techniques

Over a century ago, Hertz discussed the mechanical forces exerted by an electric field on a dielectric object (Hertz, 1881). Since then, several investigators have studied these phenomena as a means of determining the electrical properties of materials. For example, Quincke (1883) and Pellat (1896) measured the dielectric properties of liquids using field–force techniques. During the 1920s, Furth developed an ingenious method for measuring the permittivity of concentrated electrolyte solutions, by measuring the field-induced torques on ellipsoidal metal particles suspended in the solution (Furth, 1924). At about the same time, Lertes studied electrically-induced rotation of spherical particles in air (Lertes, 1921). These investigators interpreted their results in terms of the simple theory presented above.

In the past two decades, investigators have used field-induced forces to manipulate cells and study their electrical properties. We summarize these new developments.

(a) Electrorotation. The rotation of cells in an electric field was first described in 1971 by Pohl and Crane (1971). Pohl speculated that the effect resulted from an oscillating electric dipole in the cell (1981a, b). In retrospect, the phenomenon clearly arises from field-induced torque on the cells, which is of nonbiological origin. Electrorotation spectra have been reported for: protoplasts (Lovelace et al., 1984), mammalian oocytes (Arnold et al., 1987, 1989), platelets (Egger et al., 1988),

quency ω. The particle, which is suspended in a low conductivity, neutrally buoyant solution, is observed with a microscope or video camera, and its speed of rotation is measured as a function of the field frequency ω. The required field strength depends on the size of the particle; for micron-sized particles it is typically in the range of 10–100 V/cm. The range of particle sizes is limited by the need to visually observe the rotation, and the difficulty in suspending larger particles.
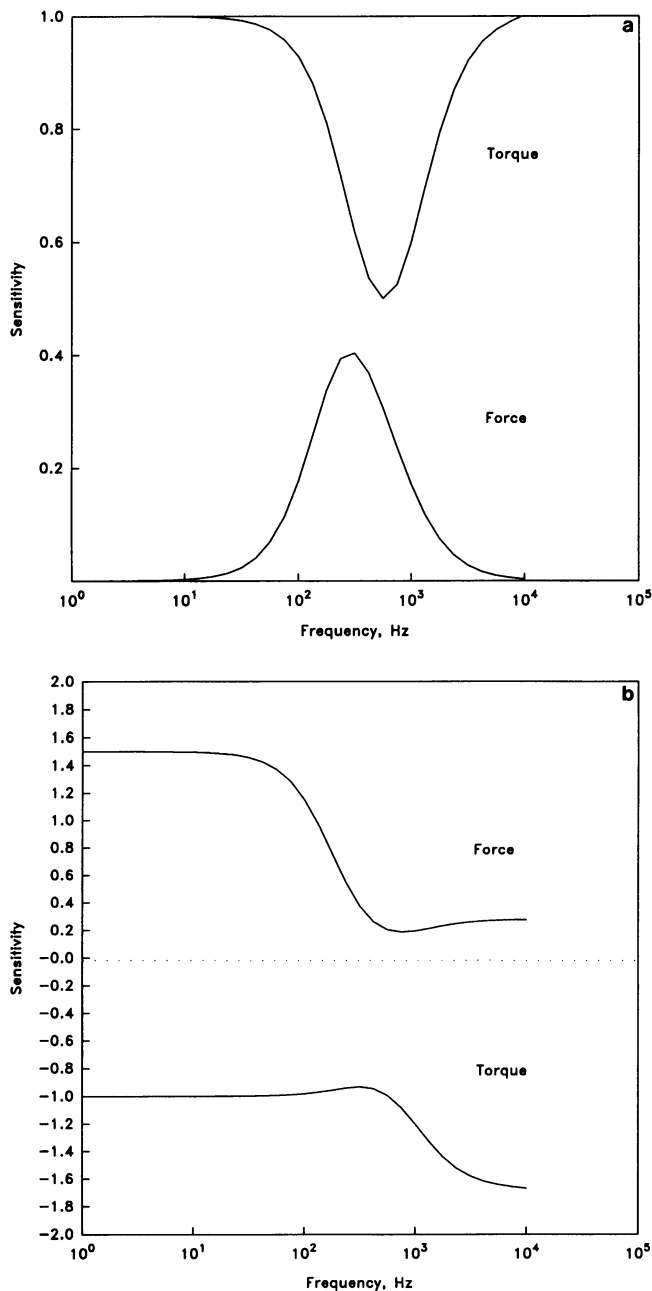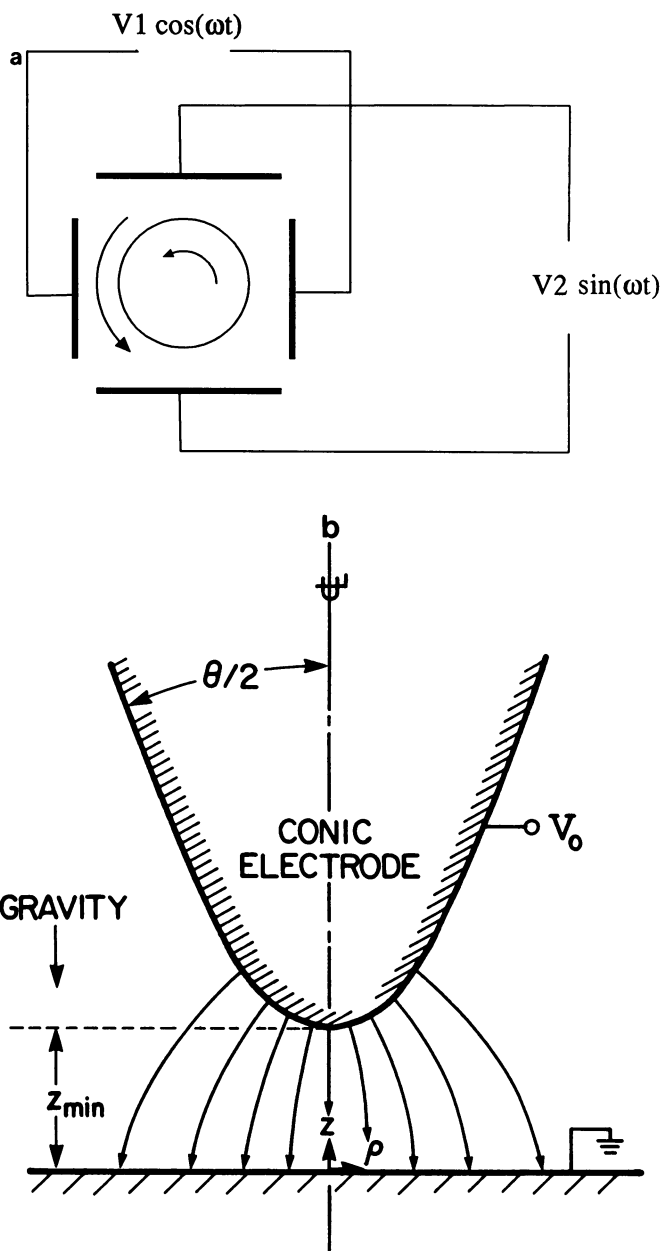

FIGURE 4 (a) Sensitivity of the force and torque to changes in the permittivity of the particle. (b) Sensitivity to changes on the conductivity of the particle. The dielectric properties of the particle are as in Figs. 1–3. Note that the scales in a and b are different.

liposomes (Wicher and Guendel, 1989), and latex microspheres (Arnold, et al., 1987). The theory and experimental techniques have been described by Arnold and colleagues (1988), Fuhr and colleagues (Glaser and Fuhr, 1986; Fuhr et al., 1986), and Schwan (1989).

Fig. 5 a illustrates a simple experimental technique for producing electrorotation. The rectangular array of electrodes is excited by two sine waves in quadrature to produce a circularly polarized electric field at angular fre-

FIGURE 5 Schematic illustration of electrode arrangements to study electrorotation (a) and levitation (b). In a, the direction of rotation of the field and particle are shown by the large and small arrows, and illustrates cofield rotation. Fig. 5 b was reprinted from Kaler and Jones (1990) with permission.

Fig. 6 shows the rotation spectra of a single latex microsphere (from Arnold, 1987). As expected, the spectrum shows the two dispersions. The high frequency dispersion shows a peak at ~300 kHz; a second dispersion is indicated by the increase in torque at low frequencies, which suggests a relaxation frequency below 100 Hz.

There is, however, a remarkable discrepancy with the theory presented above: the direction of rotation of the low frequency peak is opposite to that predicted by the simple theory (cf. Figs. 1-3 and 6). This anomaly might arise from hydrodynamic effects, as discussed above.

(b) Levitation and dielectrophoresis. Herbert Pohl was largely responsible for the renewed interest in field-induced forces for manipulating biological cells (Pohl, 1978); he coined the term dielectrophoresis. Pohl and Pethig designed a three-electrode chamber with fields of constant gradient, which they used to study the electrical properties of cells (Pohl and Pethig, 1977). These investigators measured the permittivity of small particles by varying the composition of the suspending medium until the dielectrophoretic force vanished. More recently, Burt et al. described an elaborate spectrometer to measure dielectrophoretic movement of particles by light scattering (Burt et al., 1989).

An ingenious method for studying dielectrophoretic forces was introduced by Jones and Kaler, working both together and separately, in which particles are stably suspended (levitated) in an inhomogeneous electric field (Fig. 5 *b*). These investigators used the technique to study the electrical properties of cells and other particles (Jones and Loomans, 1983; Kaler and Pohl, 1983; Jones and Kraybill, 1986). Kallio and Jones (1980) measured the dielectric properties of various fluids by levitating trapped air bubbles. The levitation technique was used

by Tombs and Jones (1991) to measure the induced dipole moment of chains of metal spheres.

To levitate a particle, the dielectrophoretic and gravitational forces must balance. If z is the vertical direction, this requires that

$$Re(u^*) = \frac{2g|\gamma_p - \gamma_m|}{3\epsilon_m|\partial E^2/\partial z|}, \tag{41}$$

where $(\gamma_m - \gamma_p)$ is the difference in density between the particle and the medium, and g is the gravitational constant. One advantage is that the particles are (nearly) motionless in the field.

Levitation is most easily accomplished for low permittivity particles (more precisely, for which $Re(u^*) < 0$), which are drawn towards a local minimum of the field. In that case, stable levitation can be achieved by very simple apparatus. In contrast, when $Re(u^*) > 0$, the particle is propelled towards regions of greater field strength, and can only be stably levitated if some form of active feedback control is employed. A system employing digital feedback techniques was recently described by Tombs and Jones (1991). Fig. 7 shows the threshold for levitation of *Canola* protoplasts, suspended in isotonic sorbitol of varying conductivity (Kaler and Jones, 1990). The two dispersions predicted by the simple theory are clearly shown.

For any particle, the sign of $Re(u^*)$ depends on the frequency and conductivity of the surrounding medium. Thus, two different sets of apparatus are needed to study particles over wide ranges of frequency, a significant disadvantage of the method. Kaler and Jones recently described an ingenious way to overcome this limitation, in which the particle is stably levitated with a strong alternating field at one frequency, and a second alternating field at a different frequency is used to perturb the suspended particle (Kaler et al., 1991).

In a typical experiment, the investigator does not directly measure the dielectrophoretic force but rather its variation with frequency. Kaler and Jones (1990) analyzed the levitation spectra of *Canola* protoplasts plant cells in terms of the breakpoints of the spectra, defined as the frequencies at which the levitation threshold had changed by 3 decibels; Marszalek et al. (1991) used instead "critical frequencies" at which the dielectrophoretic force vanishes. These endpoints are experimentally convenient to determine but more complex to analyze than the relaxation frequencies and dispersion amplitudes given above.

FIGURE 6 Rotation spectrum of single latex microspheres, from Arnold et al. (1987). The spectrum shows a peak at ~300 Hz, with suggestions of a second peak below 100 Hz. The ratios of particle radius to Debye screening length of the media (κa) are (O) 84, (X) 123, ($\triangle$) 153. (Reprinted with permission from the Journal of Physical Chemistry, Copyright 1987, American Chemical Society.)

Nonspherical particles

The theory described above applies only to spherical particles. For nonspherical particles, dielectrophoretic forces, and torques depend on the orientation of the particle and the theory must be expressed in terms of the polarizability tensor of the particle (Schwan, 1957; Saito
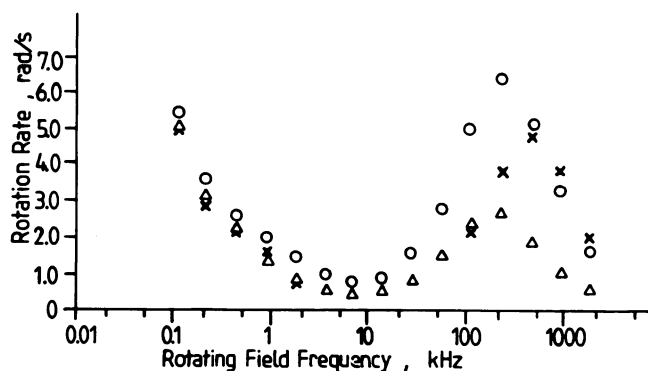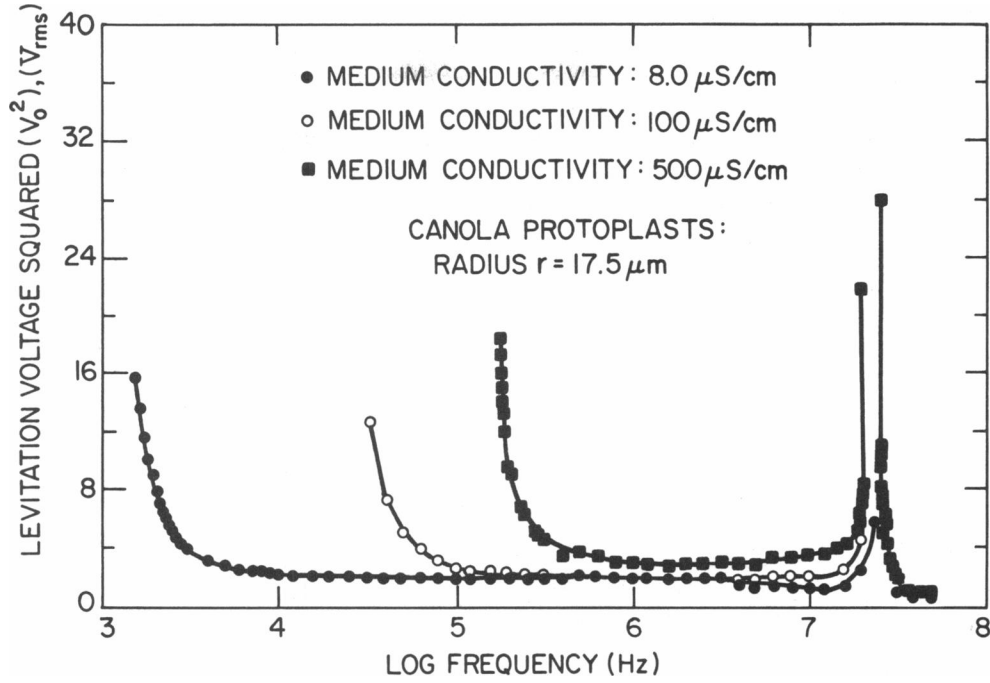
FIGURE 7   Frequency dependence of threshold for levitation of *Canola* protoplasts, suspended in sorbitol solutions of different electrical conductivities. Reprinted, with permission, from Kaler and Jones (1990).

et al., 1966; Pastushenko et al., 1988). Paul and Otwinowski (1991) obtained the frequency response of ellipsoidal biological cells in rotating electrical fields; the results are mathematically complicated.

A simple model can be used to describe the mean orientation of a spheroid of revolution in a constant electric field (Saito et al., 1966). In this formulation, the potential energy W of the particle when oriented with its ith axis parallel to the external field is

$$W_i = \frac{E^2}{2} Re(\lambda_i),\qquad(42)$$

where E is the peak field strength, and

$$\lambda_i = v\left[\tilde{\epsilon}_m^* \frac{(\epsilon_m^* - \epsilon_p^*)}{\epsilon_m(1 - L_i) + L_i\epsilon_p^*}\right],\qquad(43)$$

where v is the volume of the particle. For prolate ellipsoids of revolution, the constants L_i are given by (O'Konski, 1960), where a and b are the major and minor axes, and e is the eccentricity given by

$$L_a = \frac{b^2}{2a^2e^3}\left[-2e + \ln\left(\frac{1+e}{1-e}\right)\right]\qquad(44)$$

$$L_b = \frac{b^2}{2a^2e^3}\left[\frac{e}{1-e^2} - \frac{1}{2}\ln\left(\frac{1+e}{1-e}\right)\right]\qquad(44)$$

$$e = \sqrt{1 - \frac{b^2}{a^2}}.\qquad(45)$$

(For a sphere these constants are both one-third). For a prolate ellipsoid of revolution, the mean orientation is proportional to the difference in potential energy along the a and b axes. The mean orientation can be observed visually (for cells and other micron-sized particles) or indirectly for smaller particles, for example by electrically-induced birefringence.

The potential energy can be expanded by partial fractions to yield an expression similar to Eq. 6. This yields, after neglecting a pure imaginary term:

$$\lambda_i = \frac{\Delta\lambda_i}{1 + \left(\dfrac{\omega}{\omega_{m,i}}\right)^2} + \lambda_{i,\infty},\qquad(46)$$

where

$$\Delta\lambda_i = -v\frac{\sigma_m^2[\epsilon_m(L_i - 1) - \epsilon_p] - 2\epsilon_m\sigma_p\sigma_m(L_i - 1) + \epsilon_m L_i\sigma_p^2}{(\sigma_m(L_i - 1) - L_i\sigma_p)^2}\qquad(47)$$

$$\lambda_{i,\infty} = v\frac{\epsilon_m(\epsilon_m - \epsilon_p)}{\epsilon_m(L_i - 1) - \epsilon_p L_i}\qquad(48)$$

$$\omega_{m,i} = \frac{\sigma_m(1 - L_i) + L_i\sigma_p}{\epsilon_m(1 - L_i) + L_i\epsilon_p}.\qquad(49)$$

The above expressions show a dispersion in λ_i at radian frequency $\omega_{m,i}$. This dispersion arises from the Maxwell-Wagner effect, i.e., the collection of free charges at the particle-medium interface, rather from any frequency dependence of the dielectric properties of either phase. Additional frequency dependence in λ_i will

arise from a dispersion in the dielectric properties of the particle or medium.

It is interesting to note that the frequency dependence of W_i is similar to that of the dielectric properties of a dilute suspension of particles oriented with their ith axes parallel to the field. The Fricke mixture equation yields (Fricke, 1924):

$$\frac{\epsilon_i^* - \epsilon_m^*}{\epsilon_m^* + (\epsilon_i^* - \epsilon_m^*)L_i} = \frac{p(\epsilon_p^* - \epsilon_m^*)}{\epsilon_m^* + (\epsilon_p^* - \epsilon_m^*)L_i},$$ (50)

where p is the volume fraction of the suspension (assumed small). This can be solved for ϵ_i^* and expanded to first order in p, to yield

$$\epsilon_i^* \approx \epsilon_m^*\left[1 + \frac{p(\epsilon_p^* - \epsilon_m^*)}{\epsilon_m^* + (\epsilon_p^* - \epsilon_m^*)L_i}\right].$$ (51)

Thus, the permittivity ϵ_i^* and potential energy W_i (and hence the mean orientation) are given by similar relations (Eqs. 43 and 51). The reason is that both theories (Fricke's mixture theory for the permittivity, and Saito's calculation of the potential energy) involve the solution of Laplace's equation for the local field at the particle.

It is interesting to note that force–field studies can be considered to be an extension of electro-optic techniques, to larger particles that can be directly visualized (Stoylov, 1991). For example, electric birefringence studies, based on the Saito theory or an equivalent approach, have been used to study the surface conductance of colloidal poly(tetrafluorethylene) particles (Foster et al., 1992) and the electrical properties of DNA and tobacco mosaic virus (O'Konski and Krause, 1970). Stoylov (1991) pointed to the need to extend the theory of field–force effects to other cases (including particles with a permanent dipole moment) that have been considered in the electro-optics literature.

Aggregation of particles (pearl-chain effect)

A related phenomenon is the field-induced aggregation of particles. Under the influence of an electric field of sufficient amplitude, colloidal particles or cells will aggregate in linear arrays (so called pearl chains). The threshold for aggregation depends on the frequency of the field and dielectric properties of the particle and medium (Schwan, 1985). This is the physical basis of electrorheological fluids (Gast and Zukoski, 1989) and electrofusion of cells.

Sauer has calculated the interaction potential between two particles in suspension, using the point dipole approximation (Sauer, 1983, 1985), which applies when the separation of the particles is much greater than their diameter. In this approximation, the field-induced force between the particles is proportional to the quantity

$$r^3\epsilon_m|u^*|^2E^2,$$

i.e., to the absolute magnitude of u^*. Experimental data are in agreement with this theory (Schwan, 1985; Takashima and Schwan, 1985).

Comparison of dielectric and field-force spectra

Important points for comparison include the following.

(a) Ability to study and manipulate single particles. The ability to study and manipulate single particles is perhaps the major advantage of rotation and levitation methods. For example, Geir et al. studied the effects of low levels of mercuric salts on single yeast cells using cell rotation techniques (Geier et al., 1987). Fuhr et al. showed that rotation experiments can be used to separate individual cells according to their membrane properties (Fuhr et al., 1985).

A more subtle advantage of field–force methods is their independence from dielectric mixture theory. Dielectric studies on particle suspensions require the use of such theories for their interpretation; field–force techniques do not. Whereas useful approximations exist (e.g., the Maxwell theory), no mixture theory is both rigorous and readily applicable to concentrated suspensions.

(b) Instrumentation. Dielectric studies can make use of network analyzers and other readily available equipment that permit accurate and rapid measurements over many decades of frequency. In contrast, apparatus for field–force measurements is custom built, painstaking to use, limited in frequency range, and limited in the range of particle sizes that can be studied.

(c) Extraction of the dielectric properties of the particles. As described above, field–force measurements typically do not measure the actual force or torque on a particle, but rather their variation with frequency. This severely limits the interpretation of the experimental data.

More fundamentally, field–force experiments only provide information about one component, u^*. While these components are interrelated so that the complete response can in principle be calculated from either component, insufficient data are usually available to allow this to be accomplished in practice. In contrast, dielectric methods yield direct information about both real and imaginary parts of the response, both in amplitude and frequency dependence.

(d) Other considerations. Field–force techniques require use of strong fields, often 10–100 V/cm or even higher. Such fields might induce deformation of cells or changes in membrane permeability. To avoid excessive heating, this requires the use of low conductivity media, such as distilled water or (for cells) isotonic sucrose. A serious limitation, for cell studies, is the fact that the

parameters that are most readily obtained (membrane capacitance, internal conductivity) can be measured in other more direct ways. Field–force and dielectric techniques cannot provide the kind of detailed information obtained with patch clamp and other microelectrode techniques. On the other hand, they might be used to study the electrical properties of the cell surface, as an extension of electrophoretic techniques. They offer the possibility of manipulation of cells, with possible application in biotechnology.

CONCLUSION

The three methods we compare (dielectrophoresis, rotation, and dielectric spectroscopy) are interrelated through their dependence on the Clausius-Mossotti factor u^*. The dielectric dispersions of the particle are reflected in this factor, and thus in the field–force and dielectric spectra, but with different amplitudes. For colloidal particles at low frequencies, the simple theory is inadequate, apparently due to hydrodynamic effects. Force–field techniques appear promising methods for the study and manipulation of suspended particles.

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