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2004 J. Phys.: Condens. Matter 16 499

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# The dielectric behaviour of single-shell spherical cells with a dielectric anisotropy in the shell

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Received 9 October 2003

Published 9 January 2004

Online at [stacks.iop.org/JPhysCM/16/499](http://stacks.iop.org/JPhysCM/16/499) (DOI: 10.1088/0953-8984/16/3/026)

## Abstract

Recent experiments on cells treated with hydrophobic ions showed that the mobile charges adsorbed to the plasma membrane contributed significantly to the low-frequency dielectric behaviour of cells. Due to the different transport properties of the mobile ions along the radial and tangential directions within the membrane, there is a dielectric anisotropy in the plasma membrane. In this work, we adopted a single-shell spherical cell model with an intrinsic dispersion in the membrane, which can be isotropic or anisotropic. We developed a dielectric dispersion spectral representation (DDSR) and expressed the Clausius–Mossotti factor in terms of a series of sub-dispersions. This representation enables us to assess the effects of the permittivities and conductivities in cells. We further assessed the effects of a dielectric anisotropy on the dispersion spectrum in the DDSR. To this end, we interpreted the results as a change in the dispersion strength, as well as a shift of the characteristic frequency. Moreover, the changes are indeed small and the weak-anisotropy expansion is justified.

## 1. Introduction

Biological cells can be modelled as conductive spheres (cytosol) with a thin insulating outer shell (membrane), assuming the shell is an *isotropic, non-dispersive* dielectric with conductive losses. When a biological cell is exposed to an applied electric field, a dipole moment is induced in it. The interaction of the dipole moment of biological cells with the applied fields has resulted in a wide range of practical applications from manipulation and trapping to the separation of biological cells [1].

The Clausius–Mossotti (CM) factor determines the polarization of a biological particle in a surrounding medium, and is a measure of the dielectric contrast between the particle and the medium. The CM factor is important in biophysical research because it is closely related to the alternating current (ac) electrokinetic behaviour of biological cells, namely,

dielectrophoresis [2], electrorotation [3], electro-orientation [4], electrofusion [5], as well as electrodeformation [6]. Any change in the cell's properties such as the mobile charges (in the membrane), or particle shape, as well as the variation of medium conductivity or medium permittivity, will change the CM factor, which is in turn reflected in the ac electrokinetic spectra. These spectra show characteristic frequency-dependent changes amongst other complicated features [7–16].

In this work, we will establish a dielectric dispersion spectral representation (DDSR) for the single-shell spherical cell model with an intrinsic dielectric dispersion in the shell. While the DDSR was proposed earlier by Lei *et al* [17] and further elaborated by Gao *et al* [18] for cell models without shells, the single-shell model has been widely used to mimic a living biological cell as a homogeneous, nondispersive spherical particle surrounded by a thin shell corresponding to the plasma membrane.

However, complications arise if there exists a dielectric anisotropy in the plasma membrane, due to the different transport properties of the mobile ions along the radial and tangential directions within the membrane [8]. We will assess the effects of the dielectric anisotropy on the dispersion spectrum, again in the general framework of a DDSR.

The DDSR enables us to express the CM factor in terms of a series of sub-dispersions, each of which with analytic expressions for the dispersion strengths and their corresponding characteristic frequencies expressed in terms of the various parameters of the cell model [17–19]. It is known that the CM factor of a colloidal spherical particle can be expressed in terms of a series of sub-dispersions by using various techniques [20], like the one in [19]. In this work, we will adopt a somewhat different approach through the DDSR.

The paper is organized as follows. In the next section, we review the DDSR for the CM factor of an unshelled spherical cell model [17]. We express the dispersion strength and the characteristic frequency of the CM factor in terms of the parameters of the cell model. Then an intrinsic dielectric dispersion is included in the cell [18]. In section 3, we analyse the single-shell model with an intrinsic dielectric dispersion in the shell. We apply the DDSR to the CM factor to obtain analytic expressions for the dispersion strengths and characteristic frequencies. These expressions enable us to assess the influence of various model parameters on the electrokinetics of cells. More precisely, we examine the influence of the permittivities and conductivities of the external medium and the cytosol on the dispersion spectra. In section 4, a weak-anisotropy expansion is employed to discuss the effect of a dielectric anisotropy in the membrane. A discussion and conclusion will be given.

## 2. The dielectric dispersion spectral representation

In this section, we review the dielectric dispersion spectral representation (DDSR) for the Clausius–Mossotti (CM) factor of an unshelled spherical cell model [17]. A similar representation was attempted by Foster *et al* [19]. The dipole moment of a single sphere in a uniform electric field [21] is

$$p = \epsilon_e R^3 U E_0, \quad (1)$$

where  $\epsilon_e$  is the permittivity of the external medium,  $R$  the radius of particle,  $E_0$  the electric field strength, and  $U$  is the CM factor due to the dielectric discontinuity

$$U = \frac{\epsilon_i - \epsilon_e}{\epsilon_i + 2\epsilon_e}, \quad (2)$$

where  $\epsilon_i$  is the permittivity of particle. In ac applied fields, the real constants  $\epsilon_e$  and  $\epsilon_i$  are replaced by their complex counterparts [1]

$$\epsilon_e \rightarrow \epsilon_e^* = \epsilon_e + \frac{\sigma_e}{i\omega}, \quad (3)$$

**Table 1.** The parameters used for isotropic mobile charge model calculations [8].

Parameter	Symbol	Numerical value
Cell radius	$R_c$	$9.5 \mu\text{m}$
Membrane thickness	$d$	$8 \text{ nm}$
External permittivity	$\epsilon_e$	$80\epsilon_0$
External conductivity	$\sigma_e$	$1 \text{ mS m}^{-1}$
Cytosolic permittivity	$\epsilon_i$	$120\epsilon_0$
Cytosolic conductivity	$\sigma_i$	$0.25 \text{ S m}^{-1}$
Membrane permittivity	$\epsilon_m$	$7.23\epsilon_0$
Membrane conductivity	$\sigma_m$	$4 \times 10^{-7} \text{ S m}^{-1}$
Mobile charge concentration	$N_t$	$20 \text{ nmol m}^{-2}$
Translocation rate	$k_i$	$10^4 \text{ s}^{-1}$

$$\epsilon_i \rightarrow \epsilon_i^* = \epsilon_i + \frac{\sigma_i}{i\omega}, \quad (4)$$

where  $i = \sqrt{-1}$ , and  $\sigma_i$  and  $\sigma_e$  are conductivities. Then the CM factor becomes complex:

$$U \rightarrow U^* = \frac{\epsilon_i^* - \epsilon_e^*}{\epsilon_i^* + 2\epsilon_e^*} = U + \frac{B_0}{1 + A_1 w}, \quad (5)$$

where  $w = i\omega$ ,

$$B_0 = \frac{\sigma_i - \sigma_e}{\sigma_i + 2\sigma_e} - \frac{\epsilon_i - \epsilon_e}{\epsilon_i + 2\epsilon_e}, \quad A_1 = \frac{\epsilon_i + 2\epsilon_e}{\sigma_i + 2\sigma_e}.$$

This gives the dielectric relaxation of a single spherical particle

$$U^* = U + \frac{\Delta\epsilon_1}{1 + i\omega/\omega_1}, \quad (6)$$

where the characteristic frequency  $\omega_1$  and dispersion strength  $\Delta\epsilon_1$  are given by

$$\omega_1 = A_1^{-1} = \frac{\sigma_i + 2\sigma_e}{\epsilon_i + 2\epsilon_e}, \quad (7)$$

$$\Delta\epsilon_1 = B_0 = \frac{\sigma_i - \sigma_e}{\sigma_i + 2\sigma_e} - \frac{\epsilon_i - \epsilon_e}{\epsilon_i + 2\epsilon_e}. \quad (8)$$

Using typical values for the permittivities and the conductivities (see table 1),  $\epsilon_e = 80\epsilon_0$ ,  $\epsilon_i = 120\epsilon_0$ ,  $\sigma_e = 10^{-3} \text{ S m}^{-1}$ , and  $\sigma_i = 0.25 \text{ S m}^{-1}$ , we obtain  $\omega_1 = 10^8 \text{ Hz}$ .

For electrorotation, the angular velocity  $\Omega$  of the particle is given by [1]

$$\Omega = -\frac{\epsilon_e E_0^2}{2\eta} \text{Im } U^*, \quad (9)$$

where  $\eta$  is the coefficient of viscosity. When  $\text{Im } U^* < 0$  ( $\text{Im } U^* > 0$ ) or  $\Delta\epsilon_1 > 0$  ( $\Delta\epsilon_1 < 0$ ), we have a co-field rotation (anti-field rotation).

Then, when an intrinsic dielectric dispersion is included in the cell [18],

$$\epsilon_i^* = \epsilon_i + \frac{\Delta\epsilon_i}{1 + i\omega/\omega_c} + \frac{\sigma_i}{i\omega}, \quad (10)$$

its corresponding complex CM factor  $U_{\text{int}}^*$  can be expressed in the dispersion form as

$$U_{\text{int}}^* = U_{\text{int}} + \frac{B_0 + B_1 w}{1 + A_1 w + A_2 w^2} = U_{\text{int}} + \sum_{n=1}^2 \frac{\Delta\epsilon_n}{1 + i\omega/\omega_n}, \quad (11)$$

where  $U_{\text{int}} = (\epsilon_i - \epsilon_e)/(\epsilon_i + 2\epsilon_e)$ . In equation (11), the characteristic frequency  $\omega_n$  and dispersion strength  $\Delta\epsilon_n$  are given by

$$\omega_1 = \frac{1}{2(2\epsilon_e + \epsilon_i)} [2\sigma_e + \sigma_i + (\Delta\epsilon_i + 2\epsilon_e + \epsilon_i)\omega_c + \sqrt{\Gamma}], \quad (12)$$

$$\omega_2 = \frac{1}{2(2\epsilon_e + \epsilon_i)} [2\sigma_e + \sigma_i + (\Delta\epsilon_i + 2\epsilon_e + \epsilon_i)\omega_c - \sqrt{\Gamma}], \quad (13)$$

$$\Delta\epsilon_1 = \frac{3(-\epsilon_i\sigma_e\omega_1 + \epsilon_e\sigma_i\omega_1 + \epsilon_i\sigma_e\omega_c - \epsilon_e\sigma_i\omega_c + \Delta\epsilon_i\epsilon_e\omega_1\omega_c)}{(2\epsilon_e + \epsilon_i)^2\omega_1(\omega_1 - \omega_2)}, \quad (14)$$

$$\Delta\epsilon_2 = \frac{3(\epsilon_i\sigma_e\omega_2 - \epsilon_e\sigma_i\omega_2 - \epsilon_i\sigma_e\omega_c + \epsilon_e\sigma_i\omega_c - \Delta\epsilon_i\epsilon_e\omega_2\omega_c)}{(2\epsilon_e + \epsilon_i)^2\omega_2(\omega_1 - \omega_2)}, \quad (15)$$

with  $\Gamma = -4(2\epsilon_e + \epsilon_i)(2\sigma_e + \sigma_i)\omega_c + [2\sigma_e + \sigma_i + (\Delta\epsilon_i + 2\epsilon_e + \epsilon_i)\omega_c]^2$ . It is worth remarking that there are two dispersion terms in equation (11), one of which (namely, the first term,  $n = 1$ ) is due to the dielectric contrast between the cell and the medium, while the other (i.e., the second term,  $n = 2$ ) is due to the presence of the intrinsic dispersion inside the cell.

To summarize, our objective here is to establish a dielectric dispersion spectral representation for the  $U^*$  factor. Generally,  $U^*$  can be written as

$$U^* = U + \sum_{k=1}^n \frac{\Delta\epsilon_k}{1 + i\frac{\omega}{\omega_k}}, \quad (16)$$

where  $\Delta\epsilon_k$  is the dielectric dispersion strengths, and  $\omega_k$  is the characteristic frequencies. The actual number of terms in the summation depends on the nature of the model. In the next section, we will consider the single-shell spherical cell model with an intrinsic dispersion. We will show that the summation consists of four terms corresponding to four sub-dispersions. We should remark that similar representation has been done, for example, in [19] for these simple cases. Although different formulae have been obtained, these are similar formulae. The analytic expressions for the single-shell model with an intrinsic dispersion in the shell will be the object of the next section.

### 3. The single-shell spherical model

Following Roth and Dignam [22], the CM factor for a single-shell spherical cell with *isotropic, lossless* dielectric membrane is

$$U_{\text{iso}} = \frac{(2\epsilon_m + \epsilon_i)(\epsilon_m - \epsilon_e)R_e^3 + (\epsilon_i - \epsilon_m)(2\epsilon_m + \epsilon_e)R_i^3}{(2\epsilon_m + \epsilon_i)(2\epsilon_e + \epsilon_m)R_e^3 + 2(\epsilon_i - \epsilon_m)(\epsilon_m - \epsilon_e)R_i^3}, \quad (17)$$

where  $\epsilon$  is permittivity and  $R$  the radius; the subscripts e, m and i correspond to the external medium, the membrane and the cytosol, respectively.

The intrinsic dielectric dispersion of the membrane is caused by the presence of mobile hydrophobic ions within the plasma membrane. It involves ionic diffusion in the diffuse double layer surrounding the membrane [23]. As stated in Sukhorukov and Zimmerman [7], the diffusion process can be slow compared to the translocation process within the membrane, and the intrinsic dispersion is dominated by the translocation of ions through the membrane. Thus the area specific concentration of the adsorbed ions  $N_t$  is related to the dielectric increment  $\Delta\epsilon_m$  by the following equation:

$$\Delta\epsilon_m = \frac{N_t F^2 d}{2RT} \quad (18)$$

where  $F$  is Faraday's constant,  $d$  is the membrane thickness,  $R$  is the universal gas constant,  $T$  is the temperature, and  $\Delta\epsilon_m$  is one of the factors in the complex membrane permittivity  $\epsilon_m^*$ .

The translocation rate of the adsorbed ions  $k_i$  is related to the circular frequency of the membrane dispersion  $\omega_d$  by the following equation:

$$\omega_d = 2k_i, \quad (19)$$

and  $\omega_d$  is one of the factors in  $\epsilon_m^*$ .

Thus the real constants  $\epsilon_e$ ,  $\epsilon_m$  and  $\epsilon_i$  are replaced by their complex counterparts [1]

$$\epsilon_e^* = \epsilon_e + \frac{\sigma_e}{i\omega}, \quad (20)$$

$$\epsilon_m^* = \epsilon_m + \frac{\Delta\epsilon_m}{1 + i\omega/\omega_d} + \frac{\sigma_m}{i\omega}, \quad (21)$$

$$\epsilon_i^* = \epsilon_i + \frac{\sigma_i}{i\omega} \quad (22)$$

to give the complex CM factor  $U_{iso}^*$ , where there are in fact four parameters in the membrane permittivity.

Using *Mathematica*, the  $U_{iso}^*$  factor can readily be expressed in the dielectric dispersion spectral representation. The solution consists of a few steps: after calculating the real  $U_{iso}$  factor, we replace the real permittivities with their complex counterparts, and that gives the complex  $U_{iso}^*$  factor. To solve for the summation part, assume it is of the form

$$U_{iso}^* = U_{iso} + \frac{B_0 + B_1w + B_2w^2 + B_3w^3}{1 + A_1w + A_2w^2 + A_3w^3 + A_4w^4} \quad (23)$$

$$= U_{iso} + \frac{B_0 + B_1w + B_2w^2 + B_3w^3}{(1 + w/\omega_1)(1 + w/\omega_2)(1 + w/\omega_3)(1 + w/\omega_4)}, \quad (24)$$

where  $w = i\omega$ , and the  $A_i$  and  $B_i$  are constants. These constants can be expressed in terms of the permittivities and conductivities of various different regions (as well as the cell radius and membrane thickness).

By partial fraction, this term can be expressed as a summation of four terms, each of which takes on the form  $\frac{\Delta\epsilon_k}{1+i\omega/\omega_k}$ , where  $\Delta\epsilon_k$  and  $\omega_k$  can be solved easily.

For this model,  $\Delta\epsilon_1$  in terms of the constants  $B_i$  turns out to be

$$\Delta\epsilon_1 = \frac{(-B_0 + \omega_1(B_1 + \omega_1(-B_2 + B_3\omega_1)))\omega_2\omega_3\omega_4}{(\omega_1 - \omega_2)(\omega_1 - \omega_3)(\omega_1 - \omega_4)}. \quad (25)$$

The rest of the  $\Delta\epsilon_k$  follow by cyclic permutation of the variables, namely,  $1 \rightarrow 2, 2 \rightarrow 3, 3 \rightarrow 4, 4 \rightarrow 1$ .

To solve for  $\omega_k$ , one must solve the quartic equation

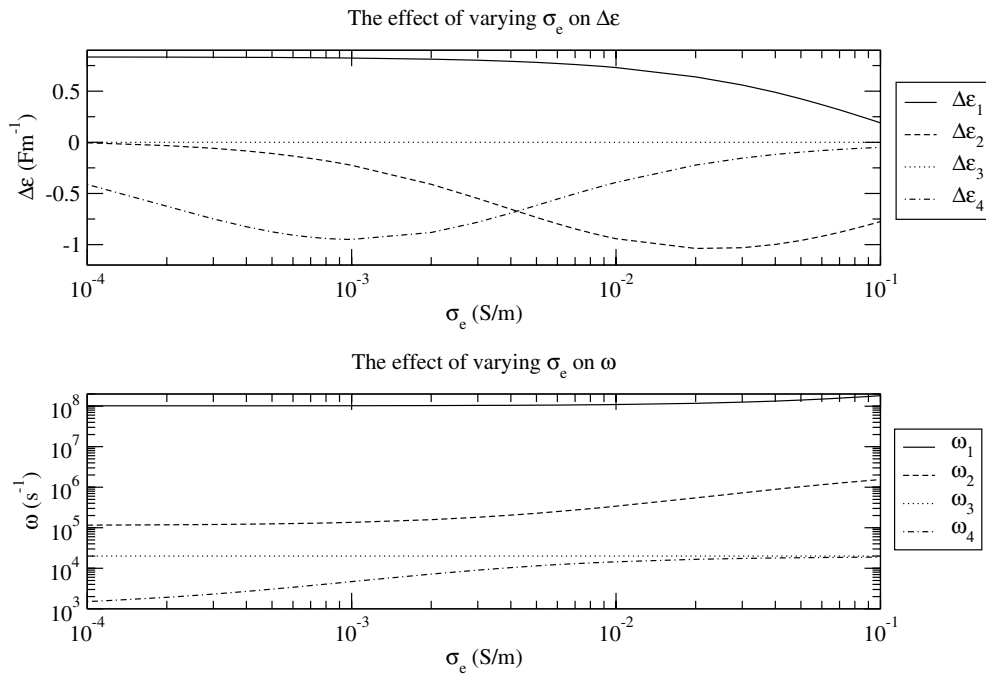
$$1 + A_1w + A_2w^2 + A_3w^3 + A_4w^4 = 0 \quad (26)$$

with the constants  $A_i$  replaced by their numerical values. Then  $\omega_k$  are *minus* the solutions to this equation.

The constants  $A_i$  and  $B_i$  are complicated expressions of the parameters of the model; therefore it is essential to evaluate their numerical values first before solving for  $\Delta\epsilon_k$  and  $\omega_k$  in order to simplify the calculations.

We will report the influence of the conductivities on the dispersion spectra in this section. Using *Mathematica*, the dielectric dispersion strengths and the characteristic frequencies can be calculated easily with the parameters incremented individually in turn while the values of other parameters remain as stated in table 1. The results were tabulated and graphs were plotted, as shown below.

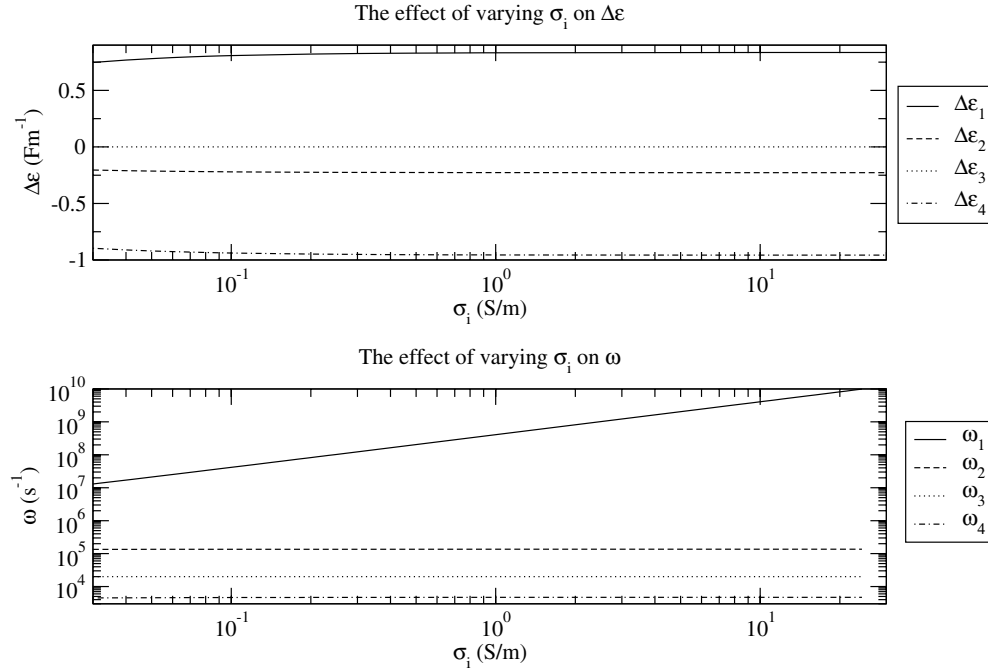
As is shown in figures 1–3, there are four sub-dispersions: namely,  $\omega_1$  is the co-field peak of electrorotation corresponding to the cytosol,  $\omega_2$  corresponds to the anti-field membrane



**Figure 1.** The dispersion strengths ( $\Delta\epsilon_1 \dots \Delta\epsilon_4$ ) and the characteristic frequencies ( $\omega_1 \dots \omega_4$ ) plotted as a function of the conductivity of the external medium  $\sigma_e$ .

peak, while  $\omega_4$  refers to the anti-field mobile charge peak.  $\omega_3$  shows some trace of the original mobile charge dispersion. These descriptions are in accord with Sukhorukov and Zimmermann [7].  $\Delta\epsilon_3$  has a very small magnitude compared with other dielectric dispersion strengths, of the order  $10^{-6}$ – $10^{-15}$ . Its corresponding characteristic frequency is relatively constant ( $\omega_3 = 20\,000 \text{ s}^{-1}$ ), only changing significantly when the translocation rate of the adsorbed ions  $k_i$  (and hence the circular frequency of the membrane dispersion  $\omega_d$ ) is varied. Therefore it is not important, and this is why it did not show up in the previous calculations [7, 8] of the dispersion spectra.

In figure 1, increasing the medium conductivity  $\sigma_e$  causes the co-field dielectric dispersion strength  $\Delta\epsilon_1$  to remain roughly constant before starting to decrease at about  $\sigma_e = 0.01 \text{ S m}^{-1}$ . At a higher medium conductivity beyond this value,  $\Delta\epsilon_1$  decreases rapidly with the increase of  $\sigma_e$ , owing to a significant reduction in the conductivity contrast between the cytosol and the external medium as the medium conductivity increases. The corresponding characteristic frequency remains relatively constant despite the slight increase towards the high  $\sigma_e$  end. On the other hand, the anti-field peaks show interesting non-monotonic behaviour. At a small medium conductivity, the membrane peak is not significant, signified by a small  $\Delta\epsilon_2$ , owing to a small conductivity contrast between the membrane and the external medium. The increase of  $\sigma_e$  causes the anti-field dielectric dispersion strengths  $\Delta\epsilon_2$  and  $\Delta\epsilon_4$  to swap magnitudes, with  $\Delta\epsilon_2$  decreasing to a minimum while  $\Delta\epsilon_4$  increases from a minimum. Their corresponding characteristic frequencies show a converge–diverge pattern: both of them increase, but with  $\omega_4$  increasing faster than  $\omega_2$  they come to a closest point at about  $\sigma_e = 0.006 \text{ S m}^{-1}$ ; then  $\omega_2$  increases faster than  $\omega_4$  and their values diverge. This level-repulsion phenomenon is a general spectral property, common in many physical systems.



**Figure 2.** The same as figure 1, but as a function of the conductivity of the cytosol  $\sigma_i$ . Typical  $\sigma_i$  values range from 0.2 to 1 S m<sup>-1</sup>.

In figure 2, varying the cytosol conductivity  $\sigma_i$  has the greatest effect on  $\Delta\epsilon_1$  and  $\omega_1$  because they are related to the cytosol. All other dielectric strengths and characteristic frequencies remain roughly constant.

In figure 3, varying  $N_t$  does not affect the cytosolic factors  $\Delta\epsilon_1$  and  $\omega_1$  significantly. Increasing  $N_t$  causes  $\Delta\epsilon_4$  to become more negative, and thus showing more significance, because it is related to the mobile charges; while  $\Delta\epsilon_2$ , related to the membrane, increases towards zero, showing less significance. For their corresponding characteristic frequencies,  $\omega_2$  increases while  $\omega_4$  decreases.

#### 4. Weak-anisotropy expansion

For the anisotropic model, the  $U_{\text{ani}}$  factor is a non-analytic expression [22]:

$$U_{\text{ani}} = -\frac{-R_i^{1+2\delta}(\epsilon_i - \delta\epsilon_{\text{mr}})(\epsilon_e + \epsilon_{\text{mr}} + \delta\epsilon_{\text{mr}}) + R_e^{1+2\delta}(\epsilon_e - \delta\epsilon_{\text{mr}})(\epsilon_i + \epsilon_{\text{mr}} + \delta\epsilon_{\text{mr}})}{R_i^{1+2\delta}(\epsilon_i - \delta\epsilon_{\text{mr}})(-2\epsilon_e + \epsilon_{\text{mr}} + \delta\epsilon_{\text{mr}}) + R_e^{1+2\delta}(2\epsilon_e + \delta\epsilon_{\text{mr}})(\epsilon_i + \epsilon_{\text{mr}} + \delta\epsilon_{\text{mr}})}, \quad (27)$$

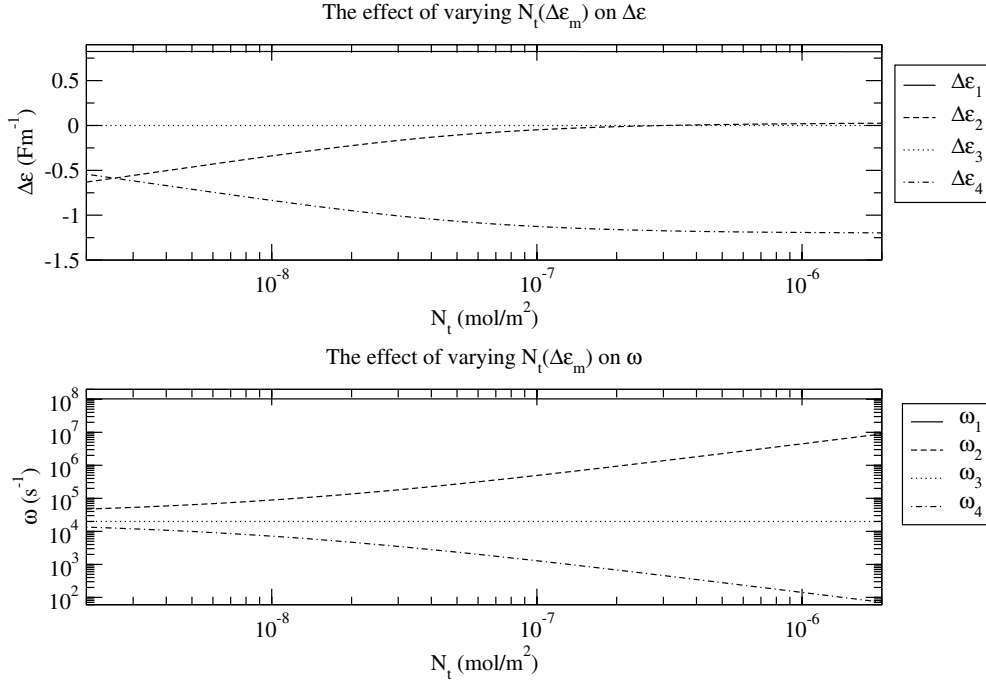
where

$$\delta = -\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{2\epsilon_{\text{mt}}}{\epsilon_{\text{mr}}}} \quad (28)$$

and  $R$  is the radius,  $\epsilon$  is the permittivity; the subscripts e, i, m, r and t represent the external medium, the cytosol, the membrane, radial direction and tangential direction respectively.

Since  $\delta$  contains the terms  $\epsilon_{\text{mt}}$  and  $\epsilon_{\text{mr}}$ , which are complex in the anisotropic model, the  $U_{\text{ani}}$  factor cannot be expanded in the same way as in the isotropic mobile charge model.





**Figure 3.** The same as figure 1, but as a function of the area specific concentration of the adsorbed ions  $N_t$ .

Anisotropy in the membrane occurs when the permittivity in the radial direction is different from that in the tangential direction, i.e.  $\epsilon_{mt} \neq \epsilon_{mr}$ . Therefore we introduce a small correction term  $h$ , so that

$$\epsilon_{mt} = \epsilon_{mr}(1 + h). \quad (29)$$

We found that if the anisotropy is weak, we can expand  $U_{ani}$  using Taylor's series, neglecting second and higher order terms. The zeroth order term is the same as  $U_{iso}$ , while the first order term is equivalent to the summation term in the isotropic mobile charge model.

As before, we replace the permittivities with their complex counterparts.  $\epsilon_e^*$  and  $\epsilon_i^*$  remain the same, but  $\epsilon_m^*$  is split into radial part and tangential part to account for the dielectric anisotropy:

$$\epsilon_{mr}^* = \epsilon_m + \frac{\Delta\epsilon}{1 + i\omega/\omega_d} + \frac{\sigma_{mr}}{i\omega}, \quad (30)$$

$$\epsilon_{mt}^* = \epsilon_m + \frac{\sigma_{mt}}{i\omega}. \quad (31)$$

The real permittivities  $\epsilon_m$  of the two parts are the same, while their conductivities are different. Also, there is a dispersion term ( $\frac{\Delta\epsilon}{1+i\omega/\omega_d}$ ) in the radial direction but not in the tangential direction.

Assume the first order term is of the form

$$U_{ani}^* = U_{iso}^* + \frac{C_0 + C_1w + C_2w^2 + C_3w^3 + C_4w^4 + C_5w^5 + C_6w^6 + C_7w^7}{1 + D_1w + D_2w^2 + D_3w^3 + D_4w^4 + D_5w^5 + D_6w^6 + D_7w^7 + D_8w^8} \quad (32)$$

$$= U_{iso}^* + \frac{C_0 + C_1w + C_2w^2 + C_3w^3 + C_4w^4 + C_5w^5 + C_6w^6 + C_7w^7}{((1 + w/\omega_1)(1 + w/\omega_2)(1 + w/\omega_3)(1 + w/\omega_4))^2}, \quad (33)$$

where  $w = i\omega$  and the  $C$ s and  $D$ s are constants.

**Table 2.** The parameters used for anisotropic model calculations [8].

Parameter	Symbol	Numerical value
Cell radius	$R_c$	9.5 $\mu\text{m}$
Membrane thickness	$d$	8 nm
External permittivity	$\epsilon_e$	$80\epsilon_0$
External conductivity	$\sigma_e$	4 $\text{mS m}^{-1}$
Cytosolic permittivity	$\epsilon_i$	$120\epsilon_0$
Cytosolic conductivity	$\sigma_i$	0.25 $\text{S m}^{-1}$
Membrane permittivity	$\epsilon_m$	$7.23\epsilon_0$
Radial membrane conductivity	$\sigma_{mr}$	$4 \times 10^{-7} \text{ S m}^{-1}$
Tangential membrane conductivity	$\sigma_{mt}$	$4 \times 10^{-7} \text{ S m}^{-1}; 0.4 \text{ S m}^{-1}$
Mobile charge concentration	$N_t$	20 $\text{nmol m}^{-2}$
Translocation rate	$k_i$	$10^4 \text{ s}^{-1}$

It turns out that the characteristic frequencies remain the same, but because of the differentiation performed in the Taylor expansion, each frequency is now a repeated root. Therefore, after doing the partial fraction, the complex  $U_{\text{ani}}^*$  factor becomes

$$U_{\text{ani}}^* = U_{\text{iso}}^* + \sum_{j=1}^m \frac{\Delta\epsilon_j}{1 + \frac{i\omega}{\omega_j}} + \sum_{j=1}^m \frac{\Delta^2\epsilon_j}{(1 + \frac{i\omega}{\omega_j})^2}, \quad (34)$$

where the two summation terms come from the first order term of the Taylor expansion. To avoid confusion, it should be remarked that  $\Delta^2\epsilon_j$  does not equal the square of  $\Delta\epsilon_j$ .

In the anisotropic model,  $\Delta\epsilon_k$ s and  $\Delta^2\epsilon_k$ s turn out to be complicated expressions in terms of the constants  $C$ s and  $D$ s and the characteristic frequencies  $\omega_k$ s. Using the above anisotropic model, we produced some numerical results in order to access the strength of the anisotropy. The parameters used are given in table 2. The results are given in table 3 for both equal and unequal radial and tangential membrane conductivities.

For both cases, the corrections in the dielectric dispersion strengths are much smaller: of magnitude  $10^{-8}$  when  $\sigma_{mt} = \sigma_{mr} = 4 \times 10^{-7} \text{ S m}^{-1}$ , and of order  $10^{-3}$  when  $\sigma_{mt} = 0.4 \text{ S m}^{-1} \gg \sigma_{mr}$  in the anisotropic model.

In the weak-anisotropy expansion, the corrections to the DDSR are of the forms  $(1 + i\omega/\omega_j)^{-1}$  and  $(1 + i\omega/\omega_j)^{-2}$ . While the former form can readily be interpreted as a change in the dispersion strength at  $\omega_j$ , the latter form is quite problematic because it does not appear as a dispersion form. In fact, the results can be cast into a form  $\Delta\epsilon'_j/(1 + i\omega/\omega'_j)$  to first order in the expansion parameter, where  $\omega'_j$  is given by  $\omega_j(1 - \Delta^2\epsilon_j/\Delta\epsilon_j)$ . Thus, we can interpret the result as a dispersion form with a shift in the characteristic frequency. In view of the positive sign of the ratio  $\Delta^2\epsilon_j/\Delta\epsilon_j$  in table 3, there is always a red shift in the dispersion spectrum, i.e., a shift to a lower frequency due to dielectric anisotropy. The result also showed that the anisotropic effect is indeed very small, and thus justifies our weak anisotropic expansion.

## 5. Discussion and conclusion

Here a few comments are in order. We would like to spell out the advantages and limitations of the present model, and discuss why it is useful to take anisotropy into consideration. The present work makes several quantitative predictions which would stimulate further experimental work on the basic mechanisms of the interaction of hydrophobic ions and other charged molecules with biological membranes, using ac electrokinetic and related techniques.

**Table 3.** Results from the weak anisotropic model calculations.

Solution	Symbol	Absolute numerical value
Characteristic frequencies	$\omega_1$	$1.05 \times 10^8$ Hz
	$\omega_2$	$2.05 \times 10^5$ Hz
	$\omega_3$	$2.00 \times 10^4$ Hz
	$\omega_4$	$1.04 \times 10^4$ Hz
When $\sigma_{mr} = \sigma_{mt} = 4 \times 10^{-7}$ S m <sup>-1</sup> Dielectric dispersion strengths	$\Delta\epsilon_1$	$3.19 \times 10^{-8}$
	$\Delta\epsilon_2$	$3.05 \times 10^{-8}$
	$\Delta\epsilon_3$	$1.74 \times 10^{-9}$
	$\Delta\epsilon_4$	$2.43 \times 10^{-8}$
	$\Delta^2\epsilon_1$	$2.94 \times 10^{-8}$
	$\Delta^2\epsilon_2$	$1.29 \times 10^{-7}$
	$\Delta^2\epsilon_3$	$1.73 \times 10^{-11}$
	$\Delta^2\epsilon_4$	$1.36 \times 10^{-7}$
When $\sigma_{mr} = 4 \times 10^{-7}$ S m <sup>-1</sup> and $\sigma_{mt} = 0.4$ S m <sup>-1</sup> Dielectric dispersion strengths	$\Delta\epsilon_1$	0.0022
	$\Delta\epsilon_2$	0.0010
	$\Delta\epsilon_3$	$1.0 \times 10^{-6}$
	$\Delta\epsilon_4$	0.020
	$\Delta^2\epsilon_1$	0.0020
	$\Delta^2\epsilon_2$	0.0081
	$\Delta^2\epsilon_3$	$9.1 \times 10^{-7}$
	$\Delta^2\epsilon_4$	0.0087

It is useful to take anisotropy into consideration. The traditional isotropic cell models were extended to account for a dielectric anisotropy in the plasma membrane introduced by hydrophobic ions. This work could be of interest to researchers working in the fields of membrane and cell biophysics, where organic ions are widely used as field-sensitive molecular probes.

The present model is valid for the low concentration limit where the interaction between the particles can be neglected. However, we can extend this model to a high concentration case by using the Maxwell–Garnett approximation (see, for example, [18]), in an attempt to take into account the many-body (local-field) effect.

In this work, we have considered a single-shell model with a homogeneous cytosol; realistic cells must be inhomogeneous due to the compartment in the interior of cells. We can extend our consideration to a single-shell graded cell model to capture the inhomogeneous nature of the cell interior [24]. In such a model, the cytosol can have a conductivity profile which varies along the radius of the cell, and we cover the cytosol by an insulating membrane. A small conductivity-gradient expansion for the DDSR of single-shell graded cell model can be done, based on the differential effective dipole approximation [24]. Similarly to the weak anisotropy expansion, we will assess the effects of a conductivity gradient in the cytosol on the dispersion spectrum.

Since cells (e.g., human erythrocytes) can change from perfect spherical shape to oblate spheroidal shape by applying a hydrostatic pressure [25], it is also instructive to consider nonspherical cells [26]. The general framework of the DDSR can be used for this.

In summary, we showed that the Clausius–Mossotti factor of a single-shell spherical particle can actually be expressed in terms of a series of sub-dispersions by the dielectric dispersion spectral representation. This representation enables us to assess the influence of

the permittivities and conductivities in cells, including the properties of the external medium, membrane and cytosol regions of the cells, without having to analyse the full dispersion spectrum. The effects of a dielectric anisotropy on the results have been addressed in the general framework of a DDSR. The results showed that the effects are indeed small and our small-anisotropy assumption is justified.

### Acknowledgments

This work was supported in part by the RGC Earmarked Grant under project number CUHK 403303 and in part by the Direct Grant for Research. YTCK wishes to thank the Jardine Foundation Scholarship (2002) for supporting her education at the University of Cambridge.

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