A NEW BEM MODEL OF THE POLARIZATION PROPERTIES OF NON-SPHERICAL CELLS

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ABSTRACT

Valuable information about the morphology and physiology of biological cells can be obtained by combining measurements of polarizability with theoretical modelling of the dielectric behaviour of cells. We propose a new BE method, based on an integral equation for computing the charge density induced on the dielectric interfaces. The approach is free of numerical instabilities and gives a direct computation of the surface charges and the polarizability of the cell as well as of the field and transmembrane voltage. The results show the importance of a realistic simulation of shape and structure lacking in the analytical approaches to the subject.

INTRODUCTION

The recent introduction of microelectrode technology in biomedical industries has facilitated the development of sophisticated methods for manipulating, trapping and separating bio-particles, from bacteria to viruses, by means of electric fields [1,2]. The electrokinetic response of cells to non-uniform or rotating AC fields allows to characterize the type of cell, its physiological state as well as possible functional alterations caused by physical or chemical agents [3,4]. Besides these applications, the effects of electromagnetic fields on biological cells have been the subject of considerable concern because of their possible harmful influence on human health. For all these reasons, the theoretical modeling of the electrical response of a cell to an external field is essential.

Classical models of cells based on shelled spheres or ellipsoids provide relatively simple and useful analytical solutions However, they have severe limitations: cell shape may differ considerably from spherical or ellipsoidal geometry. Even for ellipsoids, it is necessary to assume a confocal shell, which results in a cell membrane of non-uniform thickness. To overcome these drawbacks, we propose a new numerical technique pertaining to the class of boundary element methods (BEM), based on an integral equation for the polarization charge density induced on the dielectric interfaces, in quasi-static approximation. Using this method we have examined shape effects on the polarizability of non-spherical cells and shown the importance of a faithful representation of the cell geometry.

INTEGRAL EQUATION FOR THE INDUCED CHARGE DENSITY

In a layered model of cell immersed in an external field, the quasi-static electric field may be obtained by superposition of the contributions of external sources and that of free and polarization charges. The complex total charge density at the interface between media i and j , $\tilde{\zeta}$, is in turn related to the normal component of the field through

$$\tilde{\zeta} = \left(\tilde{\varepsilon}_i - \varepsilon_0\right)\tilde{E}_{ij} + \left(\tilde{\varepsilon}_j - \varepsilon_0\right)\tilde{E}_{ji} = \varepsilon_0 \frac{\tilde{\varepsilon}_i - \tilde{\varepsilon}_j}{\tilde{\varepsilon}_j}\tilde{E}_{ij}\,. \qquad (1)$$

In this way, and after considering the discontinuity in the integral containing the contribution of the charge density to the field, the following Fredholm integral equation of the second kind for $\tilde{\zeta}$ is obtained

$$\tilde{\zeta}(\boldsymbol{r}) = 2\frac{\tilde{\varepsilon}_i - \tilde{\varepsilon}_j}{\tilde{\varepsilon}_i + \tilde{\varepsilon}_j}\varepsilon_0 \tilde{E}_{0n}(\boldsymbol{r}) - \frac{1}{2\pi}\frac{\tilde{\varepsilon}_i - \tilde{\varepsilon}_j}{\tilde{\varepsilon}_i + \tilde{\varepsilon}_j}\sum_{S_k}\int_{S_k}\tilde{\zeta}(\boldsymbol{r}')\frac{\partial}{\partial n}\left(\frac{1}{R}\right)dS' \ , \tag{2}$$

where $\boldsymbol{r}$ represents a point at the interface between media *i*, *j* and $R = |\boldsymbol{r} - \boldsymbol{r}'|$. The sum in the last term extends to all the interfaces. $\tilde{E}_{0n}$ is the normal component of the external field and $\tilde{\varepsilon}_i$, $\tilde{\varepsilon}_j$ are complex permittivities of media *i*, *j*, respectively.

For the numerical solution of Eq. (2), the interfaces S_k are divided into suitable elements $\Delta^k_1, \cdots, \Delta^k_{n_k}$, resulting in a set of linear complex equations whose coefficients A_{ij} are proportional to the normal component of the electric field created at $\boldsymbol{r}_i$ by a uniform distribution of charge on the element Δ_j, with unit density. We restrict the analysis to cases of rotational symmetry around the external field direction and, consequently, the elements Δ_j are zones with this symmetry. The field that they produce is calculated by numerical integration of the elementary field created by a charged circumference.

CONFOCAL VERSUS UNIFORMLY SHELLED ELLIPSOIDS

We consider the case of a cell immersed in a uniform field. The dispersive behaviour of cells is much more complex than that of homogeneous particles, due to the combined Maxwell-Wagner polarizations at the different interfaces. Dielectrophoretic and electrorotational spectra reflect the dependence of the polazirability on the frequency. The unique solution of the inverse problem, i.e., obtaining the dielectric parameters of a cell from the observed frequency response, requires the relationship between effective polarizability and dielectric model to be accurately established. Variations in the assumed characteristics of the membrane may produce significant alterations to the calculated polarizability [5]. Therefore, it can be expected that removal of the restriction of confocal surfaces of the layer and the use of more realistic descriptions of membrane and cell shapes would lead to significantly better descriptions of the electrical behaviour of cells. In order to check the limitations of the usual analytical model which assume ellipsoidal and confocal surfaces, we have applied our numerical BEM to confocal and uniformly shelled ellipsoids. The geometrical and electrical parameters used in the calculations are: $a = 1$, $b = c = 0.2$ for the semi-axes lengths, membrane thickness in the major and minor axis direction $\delta a = 0.01$ and $\delta b = 0.058$ respectively; permittivity and conductivity of cytoplasm, membrane and external medium are $\varepsilon_1 = 50\ \varepsilon_0$, $\sigma_1 = 0.1$ Sm^{-1}, $\varepsilon_2 = 10\ \varepsilon_0$, $\sigma_2 = 1$ mSm^{-1}, $\varepsilon_3 = 80\ \varepsilon_0$, and $\sigma_3 = 0.5$ Sm^{-1}. For the more realistic case of membrane of uniform thickness δ, both possibilities $\delta = \delta a$ and $\delta = \delta b$ are studied. Results for the real part of the polarizability are shown in Fig. 1. In the same figure, analytical and numerical values for the confocal model are plotted, showing the high accuracy of the BEM approach. It can be realized that the results obtained using the confocal approximation differ greatly from those predicted by a more realistic model of the membrane. At each frequency, the analytical value for the confocal model is intermediate between the results obtained for spheroids with membranes of uniform thickness δa and δb respectively. This suggests that, besides shape effects, volume effects due to the contribution of the polarization of the different dielectric phases, are important.

Fig. 2 depicts values of the induced charge density at both interfaces for a confocal and a uniform membrane models of spheroidal cell. The difference between the results using both models is important in the region close to the cell poles and explains the difference of polarizabilities represented in Fig. 1. The fact that $\zeta_{12} \neq -\zeta_{23}$ shows that the field in the membrane is not uniform, especially for a uniformly shelled spheroid. This warns against the use of the approximation of uniform field in certain numerical models.

CILINDER AND ROD-LIKE MODELS OF ELONGATED CELLS

Different types of cells have been frequently modeled as shelled ellipsoids to allow for the use of analytical solutions. Our previous analysis shows that the error in the calculated charge densities at the poles is very sensitive to shape details. Therefore it is important to incorporate more realistic structure descriptions to the dielectric modeling of cells. To this aim, we have next studied the dielectric behaviour of shelled cylinder and rod-like particles. Commercial programmes, using FEM with adaptive meshing have been successfully applied to obtain field values at the different regions in a layered structure [6,7], but our BEM is better adapted to the direct computation of polarizability, surface charges or electric forces which would involve additional treatment of data and associated errors in other methods.

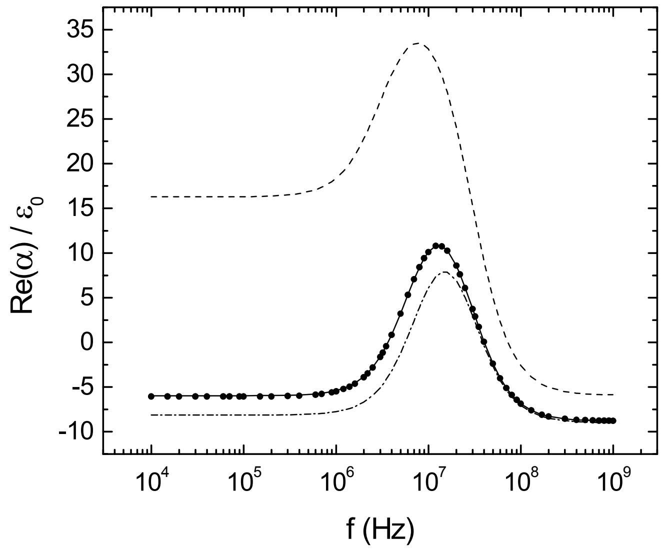

Fig. 1. Real part of the effective longitudinal polarizability of a spheroidal cell. Solid line: spheroid with confocal layer, analytical solution; solid circles: numerical solution; dashed line: spheroid with layer of uniform thickness $\delta = \delta a$ = 0.01; dash-dotted line: spheroid with layer of uniform thickness $\delta = \delta b = 0.058$.

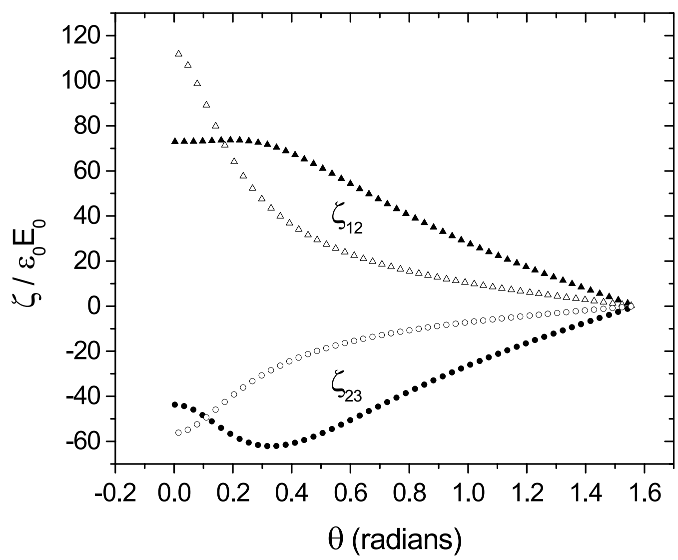

Fig. 2. Charge density at the interfaces: external medium-membrane (12, triangles) and membrane-cytoplasm (23, circles), in a uniformly shelled spheroid (solid symbols) and a spheroid with confocal shell (open symbols). θ is the angular coordinate of the point along the surface contour.

Fig. 3 shows results of polarizability corresponding to particles of different shapes, with equal external length and radius. Again the difference among the results for possible models of an elongated cell can be important at low frequency.

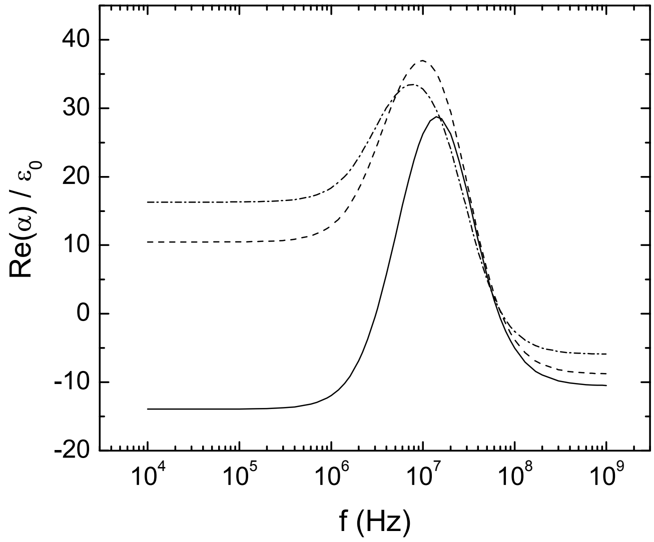

Fig. 3. Real part of the longitudinal polarizability of cells with different shapes and the same length and radius. Solid line: circular cylinder; dashed line: rod ended by hemispheric caps; dash-dotted line: spheroid with shell of uniform thickness. Electrical and geometric parameters are the same as in Fig. 1.

CONCLUSIONS

Dielectric modeling constitutes an important tool for the development of techniques for selective handling and characterization of biological cells. We have shown the importance of a numerical approach to obtain an accurate solution of the dielectric response of cells using realistic models. Our BE approach allows a reliable computation of polarizability, surface charges or electric forces without involving any additional treatment of data. Presumably producing a considerable error. The technique could be used for analysing a variety of phenomena, i.e., DEP, ER, pearl chaining, including multipole contributions not considered in the usual approximation or the deformation of cells by an electric field. When applied to different elongated particles uniformly shelled, we have shown that the influence of shape and membrane structure cannot be ignored. Although we have restricted ourselves to case of axial symmetry, extension of this work to treat force and torque effects on arbitrary shaped and oriented cells is straightforward and will be the subject of future research.

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