Modelling effective dielectric properties of materials containing diverse types of biological cells

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Abstract
An efficient and versatile numerical method for the generation of different realistically shaped biological cells is developed. This framework is used to calculate the dielectric spectra of materials containing specific types of biological cells. For the generation of the numerical models of the cells a flexible parametrization method based on the so-called superformula is applied including the option of obtaining non-axisymmetric shapes such as box-shaped cells and even shapes corresponding to echinocytes. The dielectric spectra of effective media containing various cell morphologies are calculated focusing on the dependence of the spectral features on the cell shape. The numerical method is validated by comparing a model of spherical inclusions at a low volume fraction with the analytical solution obtained by the Maxwell–Garnett mixing formula, resulting in good agreement. Our simulation data for different cell shapes suggest that around 1 MHz the effective dielectric properties of different cell shapes at different volume fractions significantly deviate from the spherical case. The most pronounced change exhibits \( \varepsilon_{\text{eff}} \) between 0.1 and 1 MHz with a deviation of up to 35% for a box-shaped cell and 15% for an echinocyte compared with the sphere at a volume fraction of 0.4. This hampers the unique interpretation of changes in cellular features measured by dielectric spectroscopy when simplified material models are used.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

In order to assess the range of observable deviations due to certain changes in cellular properties numerical models of realistically shaped biological cells are needed. Besides the development of an efficient modelling framework, the main target of this work is the quantification of changes in the geometric properties such as cellular volume fraction and cell shape. The investigations are carried out in order to estimate how, at which frequencies and with which magnitude the dielectric spectra depend on shape variations only. Before realizing a measurement setup this knowledge is advantageous in order to optimize it or to answer the question if an effect is measurable at all.

Due to the availability of increased computational power, in particular larger working memory, it becomes feasible to numerically investigate three-dimensional models of single cells where large aspect ratios occur if the membrane and eventually other small features are included.

A common way to describe the spectral dispersion of cell suspensions or tissue between 1 Hz and 1 GHz is to fit Cole–Cole or Cole–Cole-type relaxation models to measurement data [1–3]. Such relaxation models can be represented as equivalent circuits [4]. However, using this kind of
representation even in the presence of pronounced differences among tissue types the assignment of spectral features to specific tissue microstructure parameters is difficult, if not impossible. Very different combinations of dielectric and geometric parameters can generate the same spectra of the effective dielectric parameters. The dominating feature in the dielectric spectra of biological cell suspensions and tissues in the megahertz range is the $\beta$-dispersion caused by interfacial polarization of the cell membrane. However, even as the expected changes due to variations in microstructure are smaller compared with the mentioned general characteristic variation of cellular volume fraction, dielectric properties of intra- and extracellular medium (e.g. ion concentration, the presence of organelles) or cell shape still have a measurable influence on the dielectric spectrum. In order to uniquely correlate cellular features and features of the dielectric spectrum a sophisticated model of cell suspensions or tissues is required. A detailed flexible modelling approach for the dielectric spectra for the investigation of the range of the expected changes is the main focus of this work.

The principal approach consists of implicitly representing the cell suspension as a periodic assembly of unit cells, each containing a single centred particle (biological cell). The unit cell is consecutively exposed to an external homogeneous electric field in all three spatial directions and the dielectric tensor of the unit cell is extracted. In the following, the derived dielectric tensor can be used in order to describe the bulk material in an either micro- or macroscopic model.

An application of this idea was presented in [5] for the dielectric spectroscopy of the human skin in the megahertz region, employing a fringing-field sensor. The skin is subdivided into three layers parallel to the skin surface, while each layer is described as a suspension of a defined cell type. For all three cell types the effective dielectric properties of a suspension of aligned single-shelled ellipsoidal particles are analytically calculated using the Maxwell–Garnett (MG) formula. The so-obtained dielectric tensor is then inserted into a macroscopic multi-layer model of the skin. This first approach provided promising results, sufficiently approximating the spectral characteristic. However, in order to improve the reproduction and especially explanation power of measured data a more sophisticated cell model than obtained by the MG formula is required.

Non-invasive diagnostics require a unique correlation between observed quantities and variation of geometrical and constitutional parameters of cells or tissues. In order to fulfil this criterion knowledge about the relation between changes in cellular features and their manifestation in the dielectric spectra as well as a sensitive experimental setup are indispensable. Especially for the development of instrumentation for single-cell monitoring, the probe geometry and the specific measurement configuration also become relevant.

2. Modelling

Up to the lower gigahertz region the dielectric spectrum of cell suspensions, tissues or a single cell exhibits three main dispersion mechanisms: the electrode polarization due to diffusion of counterions through the electrical double-layer ($\alpha$-dispersion) below 1 MHz, capacitive charging/short-circuiting of the poorly conductive cell membrane ($\beta$-dispersion) at 1–10 MHz and the dipolar relaxation free water molecules ($\gamma$-dispersion) above 1 GHz. Additionally, sometimes a weak dispersion above 100 MHz originating from relaxation of small dipolar segments of biomolecules (e.g. proteins) and bound water ($\delta$-dispersion) can be observed [6]. As already mentioned, in the megahertz region the $\beta$-dispersion yields the dominating spectral feature. Since the cell membrane thickness and dielectric parameters as well as the dielectric contrast between extracellular medium, membrane and cytoplasm are similar in all cells in a first attempt a single-shelled sphere is chosen as a first approximation [7–9]. The advantage of confocal ellipsoidal shapes is that the dielectric spectra can be calculated analytically. The MG formula provides a good approximation for dilute solutions, meaning for an inclusion volume fraction limit of $f < 0.1$ [10–14]. For higher volume fractions MG is less accurate since interparticle interactions are neglected. The Hanai–Bruggeman (HB) formula, an extension of MG taking mutual particle interactions into account was shown to provide good agreement with measurements for $f < 0.8$ [13]. Besides those theoretical validity bounds in practice the spherical or ellipsoidal shape implies an upper volume fraction limit that can be reached. The volume fraction limit for simple cubic (sc) packing of spheres is $f = \pi/6 \approx 0.5236$. A higher limit of $f = \pi/\sqrt{18} \approx 0.7405$ is obtained by spheres forming lattices with hexagonal closest packed (hcp) or face centre cubic (fcc) unit cells. The so far known maximum of $f = 0.7707$ can be reached with a specific crystal (i.e. non-random) packing of ellipsoids with certain semi-axis ratios [15]. These volume fraction limits are often exceeded in tissues since cells often do not have spherical or ellipsoidal geometry and are tightly packed. For example in the basal layer of the human epidermis the volume fraction of cells is $f = 0.83$ [16]. Deviations from the spherical shapes clearly have an impact on the dielectric spectra. These and other shape effects were already studied in [10, 11, 17–20]. In [21, 22] a piece of tissue is modelled as a brick-like structure. Composites described by the MG and HB formulae also exhibit a drastic change in dielectric properties if the inclusion exceeds the percolation limit yielding the formation of connected regions. The microstructure of tissues has already been described within the framework of percolation theory [23]. However, if cells are not interconnected via gap junctions each cell is properly separated so theoretically no percolation occurs. Therefore, a percolation model has to be set up very carefully and might not be suitable for every kind of tissue. In another approach in [24, 25] tissue is represented by a fractal structure. The modelling approaches in [23–25] do not explicitly involve single cells but are mentioned here for completeness.

Another analytical method for modelling various kinds of shapes is the spectral decomposition method or the spectral density function approach (e.g. [11, 26, 27]). Although this method is relatively fast since it does not require a discretization of the geometry, first, it uses experimental data ($\Delta\varepsilon_1/\Delta\varepsilon_2$ in [26]) and second, the analytical description gets very cumbersome with increasing complexity of the cell shape [27].
Consequently, the largest flexibility concerning shape generation provide numerical simulations. Moreover, implementation of interparticle interactions is straightforward: Stacking and packing of single cells enable the calculation of the dielectric tensor of the tissue’s microstructure as already mentioned for the skin or cell suspension (blood). Once the geometry and a corresponding mesh is set up the calculation of the cell’s properties is almost entirely limited by the size of the system of equations and therefore by the available computer memory.

In this work we propose a new framework in order to efficiently model cell-like structures comprising the steps depicted in figure 1. In the past, cells exposed to electromagnetic fields were usually modelled numerically using the finite-difference method (FDM) [28–30]. The finite-element method (FEM) was also employed for biological cells [7, 10, 31] and dielectric mixtures in general [32]. In this work, FEM is preferred to FDM because FEM can handle the most delicate part of the model, the cell membrane. In FEM material boundaries coincide with element boundaries and therefore each element belongs to a defined medium. No averaging or interpolation of material parameters is needed and the only error concerning this aspect is caused by the domain discretization error [33, 34]. Furthermore, FEM provides a more flexible approximation of curved boundaries by an unstructured grid, resolving small features. Non-regular, non-Cartesian grid refinement is usually not implemented in the FDM software on a standard basis [35]. The mentioned issues can cause accuracy problems, especially in the case of thin layers with curved boundaries, which are present in the form of cell membranes. Even though FEM requires larger computational effort compared with FDM the former is preferred since it offers higher accuracy [36].

2.1. Cell shape parametrization

Since the parameter space can be arbitrarily large it would be convenient to describe e.g. the cell shape with as few parameters as possible while being able to cover a wide variety of cell morphologies. Parametrization of cells (red blood cells (RBCs), fission yeast cells) from images has already been described in [37, 38] with appropriate combinations of spherical harmonics. Another analytical parametrization of an echinocyte, a particularly shaped RBC was given in [28]. Discocytes, also a form of RBCs, were represented by rotated Jacobi elliptic functions e.g. in [30] or [31] and references therein. References [17, 18] used rotated Cassini curves in order to model RBCs and rotation of combined trigonometric functions provided pear-shaped models of cells during division. In [18] the effect of geometrical variations of the cell shape on the dielectric spectra has been explicitly investigated. Except for the method in [37], the mentioned parameterizations have rather restricted flexibility in shape variation, i.e. they offer only a small number of symmetry groups compared with the method presented in this work.

Another approach to modelling biological structures was suggested in [39, 40]. The presented so-called superformula (SF) is a simple geometric equation able to reproduce the morphology of many plants, flowers, animals (e.g. snail shells) generating a wide variety of surfaces that are dependent on only six parameters. The SF is a generalization of superquadrics and superellipses [39, 40]. Each point \( p(\phi, \theta) = (x, y, z) \) where
An example of a shape generated by the SF using two different discretizations is given in figure 2. The discretization parameter $d$ indicates the number of equidistantly distributed points in the $\phi$- and $\theta$-intervals. By adjusting the parameters many different cell shapes can be generated, e.g. different types of RBCs, box-shaped tissue cells, oval cells and as a special case the simple spheres or ellipsoids. Also a filling of the space beyond the mentioned limit for randomly oriented tightly packed ellipsoids can be obtained: setting the parameters to $[a \ b \ m \ n_1 \ n_2 \ n_3] = [1 \ 1 \ 2 \ -0.1 \ 2 \ 3]$, $d = 20$ (a) and $d = 50$ (b).

![Figure 2](image)

In order to ensure that the new surface is not self-intersecting $d_m$ has to be smaller than the distance from an arbitrary point to the medial axis (for a definition of the medial axis see [41]) illustrated in figure 4 as a simplified 2D sketch. In other words, the theoretical minimal radius of curvature of such features is thus $d_m$. At the $d_m$-limit two parts of the inner membrane surface touch each other. If the radius increases the protuberance also contains a small volume of cytoplasm. If the diameter of this small volume is on the same scale as $d_m$ or even smaller, model geometry and/or mesh generation might potentially fail due to numerical problems. Although the a priori determination of $d_m$ from the supershape parameters is difficult, $d_m$ is about two orders of magnitude smaller than the actual cell dimensions. Most cells tend to have a flat surface and the offset surface can be easily generated by aforementioned simple linear translations. Exceptions might be cells with stellae, such as fibroblasts or neurons.

After obtaining the cell’s inner and outer surface this geometry has to be introduced to the FEM software. Although some FEM solvers as e.g. COMSOL™ and HFSS™ are capable of generating parametric surfaces in 2D and 3D the ‘singularities’ (namely points with coordinates $(0, 0, \pm z)$) may cause problems. For the mentioned $\phi$ and $\theta$ intervals the locations $(0, 0, +z)$ and $(0, 0, -z)$ are degenerated according to the roots of sin and cos. While visual representation of the surface is straightforward, problems with the mentioned singular points occur if the surface has to be transformed into a ‘water-tight’ boundary or solid geometry object and used for further calculations. If the FEM software does not contain high-level geometry modelling functions a possibility is to reconstruct the shape from a surface triangulation. Since COMSOL™ provides appropriate functions (after removal of $\pi/2$ and $-\pi/2$ from the $\theta$-interval) a valid geometry for further processing can be obtained using a procedure similar to the one suggested for generating solid models from MRI or CT scan data [42].

### 2.2. Calculation of dielectric spectra

After parametrization of the shape the cell has to be placed in a unit cell filled with extracellular medium. The absolute dimensions of the (biological) cell and the desired volume fraction determine the dimensions of the unit cell. The biological cell is centred in the unit cell. In other words, the walls of the unit cell in the $x$-direction are equidistant from $x_{\text{min}}$ and $x_{\text{max}}$ of the biological cell, the same applies for the $y$- and $z$-directions. An electric field is applied between unit cell walls placed opposite each other, the remaining four walls...
Simulations were carried out for two different volume fractions, $f = 0.1$ and 0.4. The effective permittivity $\varepsilon_{\text{eff}}$ and conductivity $\sigma_{\text{eff}}$ refer to the definitions given in equations (11) and (12). The static conductivity is denoted as $\sigma_{\text{dc}}$ and the complex permittivity is $\varepsilon^* = \varepsilon_0 \varepsilon' - j \varepsilon''$. Consequently

$$\varepsilon = \varepsilon', \quad \sigma = \sigma_{\text{dc}} + \omega \varepsilon''.$$

The dielectric parameters (relative permittivity and conductivity) for the phases of the cell models were assumed to be frequency independent with $\varepsilon_c = 80$ and $\sigma_c = 0.12 \text{S m}^{-1}$ for the extracellular medium, $\varepsilon_m = 9.04$ and $\sigma_m = 1 \times 10^{-6} \text{S m}^{-1}$ for the membrane and $\varepsilon_l = 50$ and $\sigma_l = 0.53 \text{S m}^{-1}$ for the cytoplasm. Here, the dielectric parameters were kept fixed for all models. Variations of dielectric parameters and the resulting impact on the spectra were e.g. investigated in [43]. The frequency range was chosen from 100 kHz up to 1 GHz. Since for this frequency range the electrical cell dimensions are much smaller than the wavelength of the electromagnetic field and the Laplace equation can be solved for the electrostatic potential within the quasi-static limit. Within the chosen frequency range the $\beta$-dispersion occurs between 1 and 10 MHz [44]. The $\beta$-dispersion is caused by the short-circuiting of the thin, almost insulating cell membrane. As already mentioned the effects of free surface charge due to diffusion of electrolytes [18] occur below 100 kHz and are therefore not included in the presented model.

As a reference for the simulation results the complex effective permittivity $\varepsilon_{\text{eff}}$ for a suspension of shelled spheres with concentric surfaces (a special case of confocal ellipsoids) is calculated by the MG formula [45] given by equation (13):

$$\frac{\varepsilon_{\text{eff}} - \varepsilon_c}{\varepsilon_{\text{eff}} + 2 \varepsilon_c} = f \frac{\varepsilon_m^* - \varepsilon_c^*}{\varepsilon_m^* + 2 \varepsilon_c^*} \frac{\varepsilon_m^*}{\varepsilon_m^* + \varepsilon_m^*} \frac{\varepsilon_l^*}{\varepsilon_l^* + \varepsilon_l^*} \frac{\varepsilon_l^*}{\varepsilon_l^* + \varepsilon_l^*} \frac{\varepsilon_{\text{eff}} - \varepsilon_m^*}{\varepsilon_{\text{eff}} + 2 \varepsilon_m^*} \frac{\varepsilon_{\text{eff}} - \varepsilon_l^*}{\varepsilon_{\text{eff}} + 2 \varepsilon_l^*}.$$

### 3. Results

Three different cell types with their parametrized shapes are given in figure 5. The first two cell types occur in the human body on a regular basis. The subcutaneous fat or adipose tissue consists of spherical or slightly deformed fat cells as shown in figure 5(a). Epithelial tissue lines almost the entire body from inside as well as from the outside. An example is the
cuboidal epithelium cell in the kidney given in figure 5(b). The third example in figure 5(c) depicts a special form of an RBC, an echinocyte. Echinocytes are crenated RBCs characterized by convex rounded protrusions or spicules. The shape transformation from normal RBCs (discocytes) is e.g. induced by anionic amphipaths, high salt concentration, high pH, ATP depletion, cholesterol enrichment and proximity to a glass surface [46].

The simulated dielectric spectra for the box-shaped, echinocyte-like and spherical cell and the analytically calculated spectra obtained from the MG formula in equation (13) for the spherical cell for volume fractions \( f = 0.1 \) and \( f = 0.4 \) are given in figure 6. The purpose of the displayed spectra is to show occurring differences on a larger scale.

In order to quantify deviations between the non-spherical shapes and the spherical cell figure 7 shows the relative difference of permittivity and conductivity of the box-shaped cell and echinocyte with respect to the spherical cell.

Considering figure 7 again the upper frequency limit up to which an influence of the non-sphericity can be seen is located at approximately 3 MHz for \( f = 0.1 \) and at 20 MHz for \( f = 0.4 \) for the presented shapes. Above this frequency limit the relative deviation for \( \varepsilon_{\text{eff}} \) of the non-spherical shapes with respect to the spherical shape is below 5%. For \( \sigma_{\text{eff}} \) and a volume fraction of \( f = 0.1 \) the deviation is smaller than 5% throughout the entire frequency region from 100 kHz up to 1 GHz and for \( f = 0.4 \) the limiting frequency is 2 MHz. The short-circuiting eliminates the influence of the geometry and the effective quantities are almost exclusively governed by the volume fractions of the materials. The effective dielectric properties are very similar for all models since the volume fraction of the membrane material is much smaller than those of cytoplasm and extracellular medium. As observed in [18, 47] the obtained results demonstrate a clear dependence of the dielectric spectra on the shape. At higher frequencies the effects are more pronounced when increasing the volume fraction.

The known inaccuracy of the MG formula at higher inclusion volume fractions is demonstrated in figure 6(b) by comparing the values with those from numerical simulations for the spherical cell. Analytical solution and simulation are practically identical at \( f = 0.1 \). However, at \( f = 0.4 \) MG deviates by up to 10% from the numerical simulation due to neglected interparticle interactions.

In order to investigate the characteristics of the membrane only, a simplified serial equivalent circuit of the single-cell model’s materials is set up: extracellular medium–cell membrane–cytoplasm–cell membrane–extracellular medium. The thickness of the membrane is the same as in the single-cell models, \( d_m = d_{\text{m}} \). The scaling of the thickness of the cytoplasm- and extracellular medium layer was performed via the total cell volume \( V_{\text{tot}} \) and the corresponding volume fraction. The remaining layer thicknesses are \( d_c = \sqrt{V_i - 2d_{\text{m}}} \approx \sqrt{V_{\text{cytoplasm}} - 2d_{\text{m}}} \) for the cytoplasm and \( d_e = \sqrt{(1-f)V_{\text{extracellular}}}/2 \) for each extracellular medium layer. The dielectric spectra are given in figure 8. The magnitude of \( \varepsilon_{\text{eff}} \) at the lower end of the spectrum is almost two times higher (for \( f = 0.1 \) and the box-shaped model) than for the single-cell models. However, the relaxation frequency occurs at a lower frequency of 400 kHz. For \( \sigma_{\text{eff}} \) the values cover a wider range than for the single-cell models and especially the second relaxation at around 100 MHz is much more pronounced. It is demonstrated that mainly the cell membrane setting is responsible for the spectral characteristic in the considered...
frequency range. Nevertheless, the actual cell shape has as expected a large impact on the absolute values of the dielectric parameters.

4. Discussion

The results indicate that non-spherical cell shape has an influence on the dielectric spectra in the lower megahertz region and has to be accounted for in modelling, depending on the desired accuracy. Consequently, cell shape changes can be potentially tracked with single-cell dielectric spectroscopy in the mentioned frequency region. In contrast to most other works where the shape effects are investigated in terms of quantities derived from the Cole–Cole relaxation model (such as e.g. $\Delta \varepsilon$) the presented quantitative study is more general due to its very emphasis on the actual cell geometry.

For the given overall shape and volume parameter range the presented work provides a robust and flexible method for the calculation of the dielectric spectra of cells. Nevertheless, certain limitations have to be mentioned. The large aspect-ratio between cell membrane thickness and cell dimensions requires a high mesh resolution and therefore large computational power. A model incorporating the cell membrane only in terms of boundary conditions is in preparation. Another issue, advantage and limitation at the same time concerns the large parameter ranges for $a, b, m, n_1, n_2$ and $n_3$. Sharp edges and non-spherical topologies can both be easily generated. Spike-like features may occur e.g. in neurons, which are likely to cause problems in numerical simulations and eventually require some special care, such as removal of points. Certain parameter combinations lead to self-intersection or other modifications ($n_1$ and $n_3 < 0$) so the topology is not spherical anymore. Both issues can be avoided indicating a certain parameter range if modelling biological cells. Since the computational effort for the generation of a solid object with the described software-specific procedure depends on the number of points the discretization parameter has to be chosen so the topology is not spherical anymore. Both issues can be avoided indicating a certain parameter range if modelling biological cells. Since the computational effort for the generation of a solid object with the described software-specific procedure depends on the number of points the discretization parameter has to be chosen.

From a general point of view the few parameters required in the shape representation, the flexible discretization and robustness make the procedure suitable in shape optimization of any kind. The multi-scale modelling concept for tissues can be extended by setting up minimal-size cell arrays in order to include and control interparticle interactions.

5. Conclusion

Using the presented framework for cell shape generation, the influence of geometrical variations as well as the cell volume...
Concerning measurability it can be stated that the changes are pronounced in the high kilohertz range but potentially masked by electrode polarization effects. Above the occurrence of electrode polarization, starting in the low megahertz range the magnitude of the deviations due to shape changes is smaller and would therefore require a higher sensitivity of the measurement setup.

The SF turned out to be a suitable parametrization method for non-axisymmetric shaped biological cells, also applicable to test a functional dependence between environmental changes (concentration of a species, pressure, temperature, etc) and the shape of a surface. As an example the RBC shape strongly depends on the electrolyte concentration in the blood plasma. Although completely asymmetrical shapes cannot be generated by the SF this drawback could e.g. be compensated by an additional ‘deformation’ function acting on the supershape. Furthermore, multiplying the SF with other functions or another SF would also extend the variety of possible shapes [40].

Followed by FE simulations of the dielectric spectra of the mentioned cell models the overall method is very flexible for single cell and tissue modelling, required for the design of non-invasive spectroscopic tools. However, in order to establish an efficient and reliable macroscopic tissue model the influence of other aspects such as ion channels, proteins and organelles have to be investigated as well, especially for frequencies above 50 MHz.
More detailed and accurate tissue models could significantly improve non-invasive dielectric sensing instruments. Microfluidic cytometry, dielectrophoresis and electrorotation are reviewed in [4] (for more details on a specific of the listed methods see also [7, 48, 49]). In the field of medical applications, electric impedance spectroscopy and dielectric spectroscopy are already used for inspection of cervical squamous tissue since the cell shape is subsequently modified with advancing precancerous stage [21], skin cancer [50], skin irritations [51], non-invasive glucose monitoring [52], ischemia detection [53], measurement of oedema in irritant-exposed skin [54], monitoring of in vitro tissue engineering [55] or tumour characterization [56].

On the microscopic scale itself the developed models can be used in order to analyse the local distribution of applied electromagnetic fields for the investigation of potential non-thermal effects.

References


[40] Gielis J, Beirinckx B and Bastiaens E 2003 Superquadrics with Rational and Irrational Symmetry 8th ACM Symposium on Solid Modeling SM'03 (Seattle, WA)


[42] Bai W, Zhao K S and Asami K 2006 Dielectric properties of E. coli cell as simulated by the three-shell spheroidal model Biophys. Chem. 122 136–42


