Effective Conductivity of Cell Suspensions

Mojca Pavlin*, Tomaž Slivnik, and Damijan Miklavčič

***Abstract*—Using finite-element method (FEM) effective conductivity of cell suspension was calculated for different cell volume fractions and membrane conductivities. Cells were modeled as spheres having equivalent conductivity and were organized in cubic lattices, layers and clusters. The results were compared to different analytical expressions for effective conductivity and they showed that Maxwell theory is valid also for higher volume fractions.**

***Index Terms*—Cell suspension, effective conductivity, finite-element modeling, theory.**

I. Introduction

With the development of new methods such as electroporation [1], [2], theoretical aspects of conductivity of cell suspensions are becoming more important. In this paper, we introduce a finite-element model which enables us to calculate the effective (bulk) conductivity of cell suspensions, cell layers and cell clusters for different values of cell parameters. Knowledge of effects of the cell organization on effective conductivity and dielectric constant should also offer better understanding of bioimpedance measurements, which are difficult to interpret due to the geometry and nonhomogeneity of measured tissues.

Effective medium theories give us approximate analytical solutions for the effective conductivity of a cell suspension, however, they are exact only for dilute suspension [3]–[7]. Analytical solutions for dense suspensions and complex structures are not obtainable (with exception of some special cases) so numerical methods have to be applied. Numerical models of two cells [8] and few connected cells [9], [10] have been reported in the literature. However, due to complex geometry, numerical modeling with detailed cell structure is limited to problems with few cells and cannot be extended to tissue like structures. So we combined numerical modeling and equivalent sphere approach to calculate the effective conductivity of different cell structures like layers and clusters.

In the first part of our study, we modeled cell suspensions using a finite-element method (FEM) for different volume fractions, ordering and membrane conductivity in order to determine the range of cell volume fraction where the approximate analytical solution are valid. To examine changes between different arrangements, cells of uniform size were organized into simple-cubic (sc), body-centred cubic (bcc) or face-centred cubic (fcc) lattice. In addition, we used FEM to calculate the effective conductivity of cells arranged in layers and clusters in order to extend this approach to more tissue-like structures and to estimate the effect of cell organization on the effective conductivity.

The calculation of effective (bulk) conductivity of an inhomogeneous medium is theoretically a complex problem due to the mutual interactions between the particles. The effective medium theories use an average field and neglect local field effects [3]–[7] to obtain approximate analytical solutions. Maxwell was the first to derive an equation for the effective conductivity σ of a dilute suspension [11]. He realized that the potential due to N spheres placed in the external field having conductivity σ_p and dispersed in a medium having conductivity σ_e [Fig. 1(a)] is equal to the potential of an equivalent sphere having the effective conductivity σ [Fig. 1(b)]. With this he derived equation

$$\frac{\sigma_e - \sigma}{2\sigma_e + \sigma} = f\frac{\sigma_e - \sigma_p}{2\sigma_e + \sigma_p}\ , \quad f = \frac{N\,R^3}{D^3} \tag{1}$$

where f is the volume fraction of the particles dispersed in the medium and D denotes the radius of the equivalent sphere.

Bruggeman extended Maxwell's equation to concentrated suspensions by a mathematical procedure [3]–[5] and obtained the result known as Bruggeman's formula

$$\frac{\sigma - \sigma_p}{\sigma_e - \sigma_p}\left(\frac{\sigma_e}{\sigma}\right)^{1/3} = 1 - f. \tag{2}$$

For a special case of the heterogeneous medium with spherical particles arranged in a sc lattice, Rayleigh calculated the approximate result [12]

$$\sigma = \sigma_e\left(1 + \frac{3f}{\frac{\sigma_p + 2\sigma_e}{\sigma_p - \sigma_e} - f - a\frac{\sigma_p - \sigma_e}{\sigma_p + \frac{4}{3}\sigma_e}f^{\,10/3}}\right) \tag{3}$$

where a is the numerical factor, which according to Rayleigh is 1.65. Later, Tobias and Meredith obtained the same formula with the value of the numerical factor a being 0.523 instead of 1.65 [5]. All these theories are exact in the first order of f (for dilute suspensions), however, for higher volume fractions they give only approximate values.

Maxwell's equation (1) can also be used to obtain equivalent conductivity of a cell cluster. From the Maxwell's theory of polarization, it follows that the field outside the equivalent sphere will be the same as that of the cluster. For this reason, a cluster can be replaced with an equivalent sphere having the conductivity σ_c determined by Maxwell's equation

$$\frac{\sigma_e - \sigma_c}{2\sigma_e + \sigma_c} = f_c\frac{\sigma_e - \sigma_p}{2\sigma_e + \sigma_p}\quad , \qquad f_c = \frac{N\,R^3}{D^3} \tag{4}$$

where D is the cluster radius and N the number of the particles aggregated in the cluster. The volume fraction f_c of particles aggregated in the cluster is calculated according to the above expression.To model the suspension of heterogeneous particles, an equivalent conductivity of the particle has to first be determined. A biological cell is an example

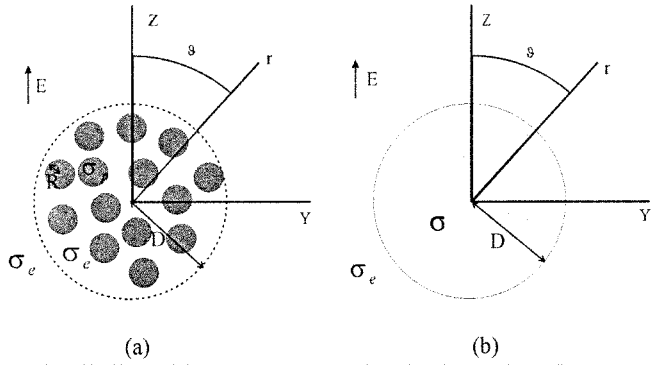

Fig. 1. Maxwell's derivation of conductivity for a dilute suspension of particles. (a) N spheres having conductivity σ_p dispersed in a medium with σ_e induce the same potential in the external field E as (b) one sphere of a radius D having the effective conductivity σ.

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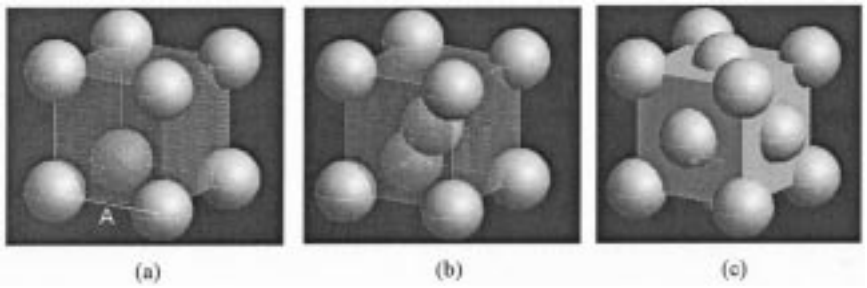

Fig. 2. Unit cells for (a) sc, (b) bcc, and (c) fcc lattices. A is the length of the unit cell side shown in Fig. 1(a).

of such a heterogeneous particle having different values of dielectric constant and conductivity of membrane compared to cytoplasm. By solving Laplace equation for a cell surrounded with the membrane Pauly and Schwan [13] were first to derive analytical solution for the potential and the polarization of a spherical cell in the external field. With the assumption that the membrane thickness – d is much smaller than the cell radius– R (valid for biological cells) the solution is simplified to some extent. If the cell has the conductivity of a membrane σ_m and the conductivity of a cytoplasm σ_i it follows that the field outside the cell will be the same as the field of a homogeneous sphere with the equivalent conductivity σ_p

$$\sigma_p = \sigma_m \frac{2(1-\nu)\sigma_m + (1+2\nu)\sigma_i}{(2+\nu)\sigma_m + (1-\nu)\sigma_i} \quad \nu = \left(\frac{1-d}{R}\right)^3. \tag{5}$$

From this equation, one can obtain the equivalent conductivity of the cell which is $\sigma_p = 2 \times 10^{-4}$ S/m for physiological values of parameters ($\sigma_m = 10^{-7}$ S/m, $\sigma_i = 0.5$ S/m). However, the increase of the membrane conductivity due to the electroporation causes an increase of the equivalent conductivity [14], [15]. DC conductivity of a cell suspension can be calculated combining (5) and (1), whereas for the calculation of frequency-dependent conductivity the conductivity has to be replaced with complex conductivity [16]: $\sigma^* = \sigma + j\,\omega\,\varepsilon$. However, in many low-frequency measurements of bioelectric phenomena second term in (6) is much smaller than the first one, and in the special case of astatic direct current (dc) problems we simply deal with the first term, whereas the second term influences only the transition phenomenon. In this paper, we shall limit ourselves only to the analysis of conductivity for the static direct current, which holds also for low frequencies (under 1MHz).

II. Methods of Analysis

An idealised model of biological cell is a sphere consisting of a cell cytoplasm surrounded by a very thin, low conducting membrane, which is placed in a conductive medium. Under normal conditions membrane conductivity is many orders smaller than that of the external medium and, therefore, normal cells were modeled as nonconductive spheres. However, for the increased membrane conductivity, which models changes due to electroporation, cells were modeled as spheres having value of the "equivalent" conductivity calculated from (5); for $\sigma_m = 10^{-4}$ S/m and $\sigma_i = 0.5$ S/m is $\sigma_p = 0.143$ S/m. We used two values for the conductivity of external medium: 1.2 S/m for physiological saline and 0.01 S/m for the low conductive medium, which is often used to reduce the heating of the medium [17].

In the first part of the study, a finite-element model of cell suspension was developed. Cells were organized either into sc, bcc, or fcc lattice shown in Fig. 2. Maximum volume fractions for hard spheres are 0.52 for sc, 0.64 for bcc, and 0.74 for fcc lattice.

Using the symmetry of cubic lattices and applying appropriate boundary conditions, we were able to model infinite cubic lattices with a model of a primitive cell [18]. In all our models, voltage V was applied on the face normal to z axis. Varying sphere radius

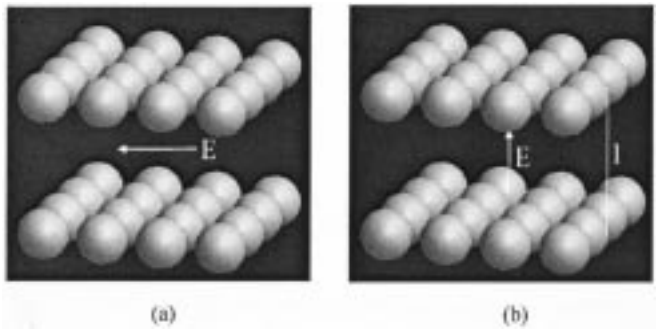

Fig. 3. Cells arranged in (a) layers parallel and (b) perpendicular to the external electrical field.

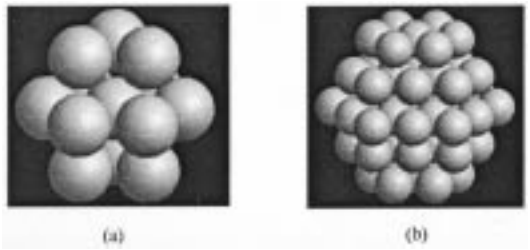

Fig. 4. Hexagonal-close packing of spheres in clusters of (a) 13 and (b) 47 spheres having volume fractions $f_c = 0.4367$ and $f_c = 0.334$, respectively.

calculations were performed for different cell volume fraction f, where $f = 4\pi/3N(R/A)^3$, A is the length of the unit cell side shown in Fig. 3(a) and N number of the spheres in the unit cell.

In the second part of our study, infinite layers of cells were modeled (Fig. 3). Cells were arranged in sc lattice and while the distance l between the layers was varied, the volume fraction was kept constant. In this way, it was possible to examine the effects of the cell arrangement at the same volume fraction.

Furthermore, cells arranged in clusters were modeled. We chose hexagonal-close packing of spheres to form clusters of 13 ($f_c = 0.437$) and 47 spheres ($f_c = 0.334$), respectively (Fig. 4). In hexagonal close packing, layers of the spheres are packed so that the spheres in alternating layers overlie one another. As for fcc packing, in hexagonal close packing each sphere is also surrounded by 12 neighboring spheres. The cluster was enclosed in a cubic box, which due to the same reasons as above (periodic boundary conditions) produces an infinite suspension of clusters. By increasing cube length we simulated increasing distance between clusters. In the limit of large A with respect to D, we, thus, have a case of an isolated cluster.

Numerical calculations were performed by the commercial finite-element modeling software EMAS (Ansoft, Pittsburgh, PA) using FEM. Details of this program and FEM method are described elsewhere [9], [10]. FEM solves partial differential equation by dividing the volume into smaller elements and solving differential equation on the elements.

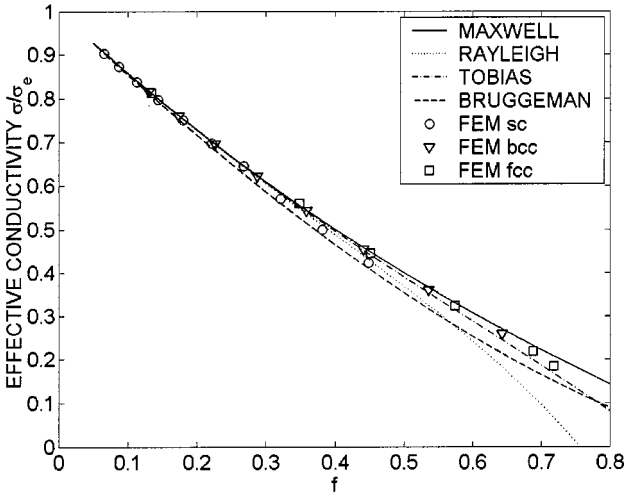

Fig. 5. Comparison of FEM results with analytical solution of Maxwell, Rayleigh, Tobias, and Bruggeman. The normalized effective conductivity σ/σ_e of cell suspension for different values of volume fraction f is shown. Different lines represent theoretical curves; numerical calculations for sc, bcc, and fcc lattices are represented with symbols.

These elements have various shapes and sizes so that complex geometries can be modeled. The static current flow analysis was chosen to calculate the current density distribution for the geometries described in the above section. The effective conductivity was obtained using Ohms law: $\sigma = j/E$.

III. Results

We used FEMs to calculate the effective (bulk) conductivity of cell suspensions. In Fig. 5, results for the normalized effective conductivity σ/σ_e of the FEM model for the cells ordered into the sc, bcc, and fcc lattice are compared to the different analytical expressions. As stated before, the analytical theories are exact for smaller values of f, however, we can see larger deviations for higher volume fractions. For the cells arranged in the sc lattice, FEM results are closest to the predicted values of Tobias and Rayleigh formulae. In general, FEM results lay closest to the Tobias's and Maxwell's theoretical curves. The difference between different lattices modeled is expected since sphere arrangement affects mutual interactions between the cells due to different numbers of nearest neighbors which are six for sc, eight for bcc, and 12 for fcc lattice. In general, our FEM results show good agreement with experimental results performed on different model systems [3]. In the case of the ordered spheres of uniform sizes, the experimental results fit best to Maxwell's and Tobias's equations.

Furthermore we analyzed the effective conductivity of the cells having the increased membrane conductivity. In Fig. 6, the results for the suspension of the cells arranged in fcc lattice having the increased membrane conductivity is shown for two different external mediums: physiological saline (a) ($\sigma_e = 1.2$ S/m) and (b) low conductive medium ($\sigma_e = 0.01$ S/m). It can be seen for the later case [Fig. 6(b)] that Rayleigh's solution fails at high volume fraction and that Maxwell's solution is closest to our FEM results. For the physiological conditions, all theories are fairly close to our FEM results.

Results obtained in the case of the cells arranged in the infinite layers are shown in Fig. 7. Since the conductivity mainly depends on the cell volume fraction f, we changed the distance l between the layers while keeping the parameter f constant. In layers of cells perpendicular to the electric field, the effective conductivity is reduced whereas in the case of parallel layers the conductivity is increased.

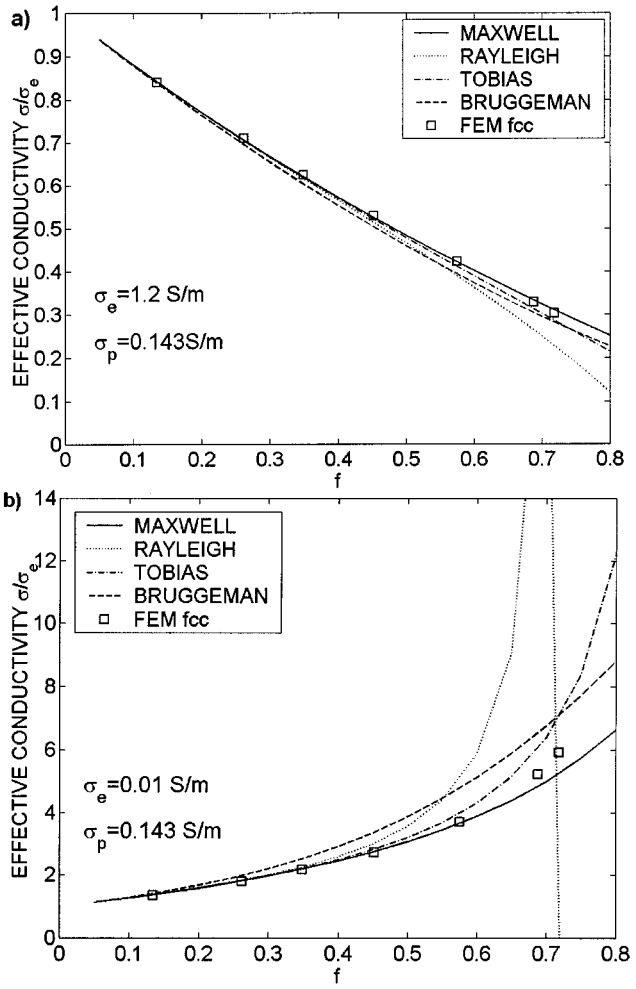

Fig. 6. Comparison of FEM results for fcc lattice with analytical solution of Maxwell, Rayleigh, Tobias and Bruggeman. The effective conductivity σ/σ_e for suspension of cells arranged in fcc lattice having the increased membrane conductivity ($\sigma_m = 10^{-4}$ S/m $\Rightarrow$ $\sigma_p = 0.143$ S/m) is shown for two different external mediums: physiological saline (a) $\sigma_e = 1.2$ S/m and (b) low conductive medium $\sigma_e = 0.01$ S/m.

In Fig. 8, FEM results of the effective conductivity σ/σ_e of the cells packed in the clusters of 13 and 47 spheres (Fig. 4) are shown. Curves in Fig. 8 represent Maxwell's solution for a suspension of the clusters replaced by the equivalent spheres. The two equivalent conductivities σ_c of these spheres (representing the clusters) having f_c 0.4367 ($\mathrm{N} = 13$) and 0.334 ($\mathrm{N} = 47$) were calculated using (6).

IV. Discussion

We studied the effective (bulk) conductivity of cell suspensions analytically and numerically. The aim of our study was to compare FEM results with the approximate analytical for different volume fractions and for increased cell membrane conductivity. Furthermore, the dependency of the effective conductivity on cell arrangements was studied. In order to study the effect of cell organization on effective conductivity, cells arranged in layers and clusters were modeled.

For a suspension of cells arranged into an sc, a bcc, and a fcc lattice, theories of Maxwell, Rayleigh, Tobias, and Bruggeman show good agreement for the range of volume fraction up to 0.74. Our results agree with the experimental results of other authors where measured values are somewhere between Maxwell's and Bruggeman's theory [3], [5]. As expected the effective conductivity mainly depends on the cell volume fraction. From this, we conclude Maxwell's theory can be

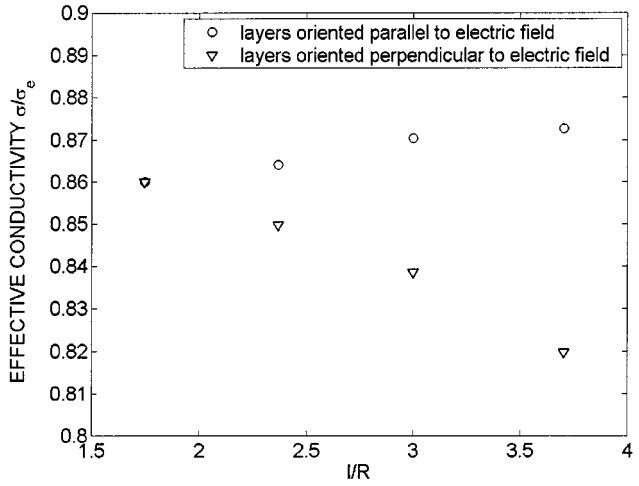

Fig. 7. Results obtained in the case of the cells arranged in the infinite layers. Keeping the volume fraction – f constant, the distance – l between the layers was increased. As expected, the layers of the cells perpendicular to the electric field reduces the effective conductivity whereas it is increased for those laying parallel to the electric field.

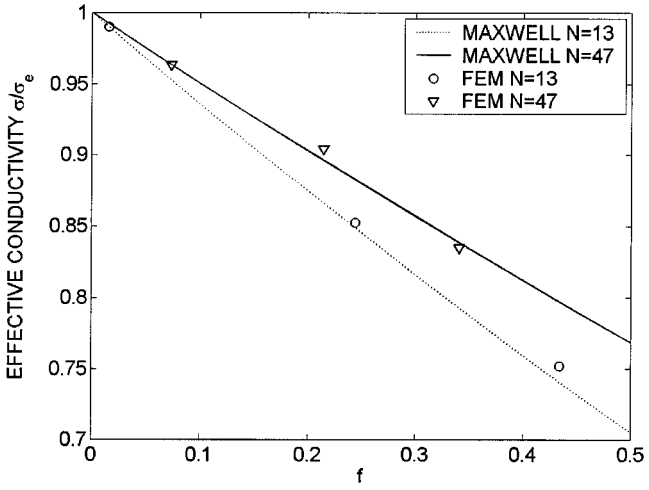

Fig. 8. Finite-element solutions calculated for clusters of 13 and 47 cells are presented with symbols. Curves in the figure represent Maxwell's solution for a suspension of the clusters replaced by the equivalent spheres. Conductivities for the two equivalent conductivities σ_c of spheres having radius D (representing the clusters) were calculated using (4). Results indicate that cells aggregated in clusters can be replaced by equivalent spheres having conductivity σ_c as predicted by Maxwell's theory.

successfully used for the explanation of conductivity measurements in cell suspensions. This is in agreement with the measurements of Cole [19] who found that Maxwell's theory could predict the low-frequency conductivity of suspension of the nonconductive cells for the volume fractions as high as 0.8. Our results also showed that for the increased membrane conductivity of few orders Maxwell's and Tobias solutions are good approximation for higher values of f.

For the cells arranged into the infinite layers, we found that the effective conductivity is either increased or decreased depending on cell arrangements. Results for the cells arranged in the clusters indicate that a cells cluster can be replaced by an equivalent sphere having conductivity predicted by Maxwell's theory similarly as shown by Raicu *et al.* [20], except that they used Bruggeman's theory to calculate equivalent conductivity.

Our approach enables modeling of infinite cell suspensions or complex structures and cells of arbitrary shapes with different cell parameters. In presented models, cells were approximated with spheres, however, for many kinds of cells, such as plated cells, cells in tissues and rod-shaped bacteria the real shapes of cells should be modeled.

The drawback of our approach is that it does not enable modeling of a realistic suspension of infinite number of randomly dispersed cells. We believe that the random or ordered arrangement does not significantly affect the effective conductivity, but for calculations of the induced transmembrane voltage this could be of some importance. Still, by modeling a finite number (a few hundred) of randomly positioned cell, this drawback can also be overcome.

Finally, we showed that by using the concept of an equivalent sphere one can calculate FEM models of many cells with high geometrical complexity by replacing a heterogeneous cell with an equivalent sphere. Our approach, thus, overcomes the limitations of the analytical solutions and the numerical calculations to simple geometries and low densities or models of only few cells.

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