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On the analytical description of transmembrane voltage induced on spheroidal cells with zero membrane conductance

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Abstract We present analytical equations for the transmembrane voltage ($\Delta\Phi$) induced by a homogeneous field on oriented cells of spheroidal shape in spherical coordinates. For simplicity, a nonconductive membrane and a highly polarizable cytoplasm were assumed. Under these conditions, the cell's polarizability is determined by the nonconductive membrane. For symmetry reasons the surface of the highly polarizable cytoplasm can be assumed to be at 0 V. Since the cell is of ellipsoidal shape its effective local field, i.e. the field of its Maxwellian equivalent body, must be constant. This allows for a simple description of the potential at the external membrane side, directly leading to $\Delta\Phi$. The dependence of $\Delta\Phi$ on cell size and shape as well as on the location of the considered membrane site is described for both possible orientations of the symmetry axis, parallel and perpendicular to the external field, respectively.

Keywords Membrane polarization · Maxwell's equivalent body · Depolarizing factor · Dielectric breakdown · Electroporation

Introduction

To our knowledge, Fricke (1953) was the first to express the transmembrane voltage ($\Delta\Phi$) induced at the poles of a cell of general ellipsoidal shape for the DC steady-state case. The frequency and cell parameter dependency of $\Delta\Phi$ was considered by Schwan (1957) and explicit equations were given by Bernhardt and Pauly (1973). Analytical $\Delta\Phi$ equations are commonly named after Schwan (see e.g. Marszalek et al. 1990). Several attempts to improve the equation for cells of nonspherical geometry exist (Jerry et al. 1996; Gimsa and Wachner 1999). Recently, Kotnik and Miklavcic (2000) presented analytical equations for the angle dependence of $\Delta\Phi$ of spheroidal cells. These authors derived an expression for oblate and prolate spheroidal cells but restricted their derivation to the parallel orientation of the symmetry axis and the field. Their extensive derivation started from the very basis of the problem and considered the DC steady-state polarization of a cell with negligible membrane conductivity and a highly polarizable cytoplasm.

Physicists have been dealing with the potential induced on the surface of spherical, spheroidal and ellipsoidal bodies or cavities for a long time (Maxwell 1873; Stratton 1941; Stille 1944; Osborn 1945; Stoner 1945). Nowadays, the problem is described in textbooks (see e.g. Landau and Lifschitz 1985). The so-called depolarizing factors were introduced to describe the dependence of the local field deviation on the shape of the bodies or cavities. In our $\Delta\Phi$ derivation, we start from this physical knowledge and use a straightforward approach to derive an analytical expression for the perpendicular orientation of the symmetry axis and the field for oblate and prolate spheroidal cells.

Biological cells are usually negligibly magnetizable and they are small with respect to the wavelength at frequencies below a few GHz. Under these conditions, the potential distribution can be directly obtained by solving Laplace's equation. Nevertheless, an explicit solution requires closed surfaces of the second degree, i.e. ellipsoids (Maxwell 1873; Stratton 1941). The most complex but finite surface of the second degree is the general ellipsoid. A feature of spheroidal and ellipsoidal models with confocal shells is that homogeneous equivalent bodies of the same external geometry can be found for all frequencies. These bodies possess certain properties and exhibit the same external field distribution as the shelled model. The effective internal field of

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this Maxwellian equivalent body is constant. Its surface potential is identical to the potential at the external membrane side.

In the following paper we will consider the DC steady-state polarization of an oriented spheroidal cell with zero membrane conductance and a highly polarizable cytoplasm. In this case, the effective polarizability and, consequently, the external field distribution of the cell model are determined by the nonconductive membrane. The cytoplasmic field vanishes owing to polarization charges on its surface. As a result, the whole cytoplasmic surface will be at the same potential that can (for simplicity) be assumed as 0 V (note that this condition cannot as easily be met at AC; at higher frequencies, when the membrane impedance decreases by capacitive bridging, "metallic" cytoplasmic properties or an infinitely high permittivity are required). With every surface point of the cytoplasm being at 0 V, another simplification of the problem is possible: $\Delta\Phi$ for a given membrane point is identical to the potential at the surface of the equivalent body.

Theory and results

DC steady-state polarization of an oriented spheroidal cell

Let us assume a spheroidal single-shell model oriented in the field direction with one of its principal axes. In this case, also the constant, effective local field of its Maxwellian equivalent body is oriented in parallel to the external field (Fig. 1). The symmetry plane of the model, oriented perpendicularly to the fields, will be at 0 V. Thus, the potential of any surface point can be calculated from the constant local field of the equivalent body and its distance to the symmetry plane. Since all surface points of the cytoplasm are at 0 V, the derivation of $\Delta\Phi$ can be split into two problems that can be solved separately: first, to determine the constant local field; and second, to determine the distance of every surface point to the symmetry plane.

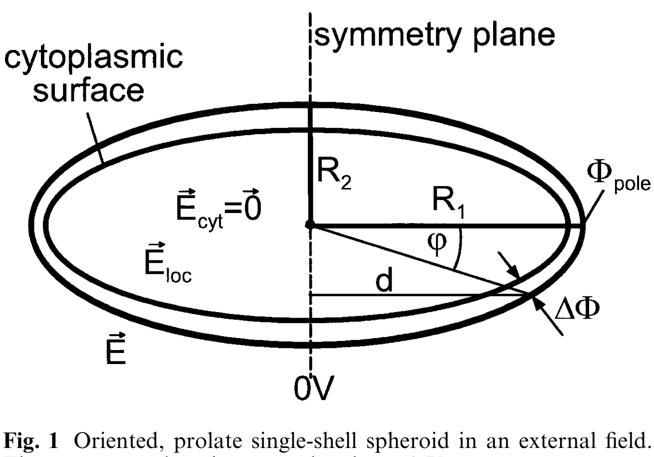

Fig. 1 Oriented, prolate single-shell spheroid in an external field. The symmetry plane is assumed to be at 0 V

For a nonconductive membrane at DC, the effective polarizability of the cell is very low in comparison with the aqueous suspension medium. Consequently, the local field is amplified with respect to the external field (see Landau and Lifschitz 1985). Along a given principal axis oriented in the field direction, the field amplification factor is related to the spheroid's axis ratio and can be expressed by the depolarizing factors (Eq. 3 below; for details on field amplification, see Gimsa and Wachner 1999). Analytical equations for the depolarizing factors were first derived by Stratton (1941) for spheroids and later in more detail by Stille (1944). The depolarizing factors were extended to the general ellipsoidal shape independently by Stoner (1945) and Osborn (1945).

The depolarizing factor n_1 of an oblate spheroid ($R_1 < R_2$) along the symmetry axis is:

$$n_1 = \frac{1+e^2}{e^3}(e - \arctan e) \quad \text{with} \quad e = \sqrt{\left(\frac{R_2}{R_1}\right)^2 - 1} \qquad (1)$$

and in the prolate case ($R_1 > R_2$):

$$n_1 = \frac{1-e^2}{2e^3}\left(\ln\frac{1+e}{1-e} - 2e\right) \quad \text{with} \quad e = \sqrt{1 - \left(\frac{R_2}{R_1}\right)^2} \qquad (2)$$

In Eqs. 1 and 2, "e" stands for the eccentricity of the spheroid. For spheres ($R_1 = R_2$), $n_1 = 1/3$. For the general ellipsoid the sum of the depolarizing factors along the three principal axes is always unity ($n_1 + n_2 + n_3 = 1$). For spheroids, it follows that if n_1 is the depolarizing factor along the symmetry axis, the depolarizing factors along the other two principal axes will be $n_2 = n_3 = (1-n_1)/2$.

Along the semiaxis R_1, the maximum field amplification factor f is given by the depolarizing factor, n_1, along this axis as:

$$f = 1/(1 - n_1) \qquad (3)$$

(for details, see Gimsa and Wachner 1999). Under the above assumptions, the maximum field amplification applies and the potential at the spheroid's pole pointing in the field direction, Φ_{pole} (e.g. along semiaxis R_1, Fig. 1), can be calculated directly from the external field amplitude, E, as $\Phi_{pole} = f \times E \times R_1$. Owing to the co-orientation of one principal axis of the spheroid and the external field, the constant local field of the equivalent body, E_{loc}, is also parallel to the external field. Its amplitude is $E_{loc} = \Phi_{pole}/R_1$. To obtain the potential at a given surface point, E_{loc} must be multiplied by the distance of that point from the symmetry plane. In the following, the two possible orientations of the spheroidal cell, with the symmetry axis in parallel and perpendicular to the field, respectively, will be considered.

The parallel orientation of the symmetry axis and the field

For completeness, we will first apply our approach to the case considered by Kotnik and Miklavcic (2000). The cell has semiaxes R_1, R_2, and R_2 and is oriented with R_1 in the field direction. In this case, surface points of the same potential form rings that are described by the same angle, Φ, in between the symmetry axis and lines through the spheroid's center. This feature allows for a further simplification, reducing the calculation of the distance in between a surface point and the symmetry plane to the two-dimensional case of an ellipse with semiaxes R_1 and R_2. The distance d is given by:

$$d = \frac{R_1 R_2 \cos\phi}{\sqrt{R_1^2 \sin^2\phi + R_2^2 \cos^2\phi}} \tag{4}$$

According to the above considerations, $\Delta\Phi$ at a point of distance d to the symmetry plane is given by:

$$\Delta\Phi = E_{\mathrm{loc}} d = \frac{E}{1 - n_1} d \tag{5}$$

Introducing Eq. 1 into Eq. 5 yields the potential distribution for the oblate shape:

$$\Delta\Phi = \frac{R_2^2 - R_1^2}{\frac{R_2^2}{\sqrt{R_2^2 - R_1^2}} \operatorname{arccot}\left(\frac{R_1}{\sqrt{R_2^2 - R_1^2}}\right) - R_1} \frac{d}{R_1} E \tag{6}$$

For the prolate shape, Eq. 2 must be introduced, leading to:

$$\Delta\Phi = \frac{R_1^2 - R_2^2}{R_1 - \frac{R_2^2}{\sqrt{R_1^2 - R_2^2}} \log \frac{R_1 + \sqrt{R_1^2 - R_2^2}}{R_2}} \frac{d}{R_1} E \tag{7}$$

For spheres ($R_1 = R_2$), n_1 in Eq. 5 is 1/3, directly leading to the well-known expression for a spherical cell. Equations 6 and 7 are identical to those recently published by Kotnik and Miklavcic (2000), proving the feasability of the approach.

The perpendicular orientation of the symmetry axis and the field

Obviously, the perpendicular orientation of the symmetry axis to the field is a more complex problem. Nevertheless, also for this orientation an analytical expression can immediately be derived. In spherical coordinates, the distance of each surface point to the symmetry plane of the spheroid must now be described by two angles: α, the angle relative to the symmetry plane that is oriented perpendicular to the symmetry axis, and β, the angle within this plane. With respect to these angles the field will be oriented at 0° and 0° along axis R_2. The distance d of a surface point to the symmetry plane of zero potential is now given by:

$$d = \frac{R_1 R_2 \cos\alpha \cos\beta}{\sqrt{R_1^2 \sin^2\alpha + R_2^2 \cos^2\alpha}} \tag{8}$$

The induced $\Delta\Phi$ is the product of the field amplification factor along axis R_2 [$f = 1/(1-n_2)$; Eq. 3], the field amplitude E, and d:

$$\Delta\Phi = E\mathrm{loc} d = \frac{E}{1 - n_2} d \tag{9}$$

For the new orientation the relation of the depolarizing factors must be used to obtain the depolarizing factor $n_2 = (1-n_1)/2$ along axis R_2. For spheres ($R_1 = R_2$), the depolarizing factor again is 1/3 and the angle dependence (Eq. 8) can be described by a single angle, ϕ. Nevertheless, for the oblate shape, n_2 can be introduced into Eq. 9. We obtain:

$$\Delta\Phi = \frac{2\left(R_2^2 - R_1^2\right)}{\frac{2R_2^2 - R_1^2}{R_2} - \frac{R_1 R_2}{\sqrt{R_2^2 - R_1^2}} \operatorname{arccot}\left(\frac{R_1}{\sqrt{R_2^2 - R_1^2}}\right)} \frac{d}{R_2} E \tag{10}$$

With n_2 for the prolate shape we obtain:

$$\Delta\Phi = \frac{2\left(R_1^2 - R_2^2\right)}{\frac{R_1^2 - 2R_2^2}{R_2} + \frac{R_1 R_2}{\sqrt{R_1^2 - R_2^2}} \log \frac{R_1 + \sqrt{R_1^2 - R_2^2}}{R_2}} \frac{d}{R_2} E \tag{11}$$

Discussion

For the simplified cell properties assumed, it is possible to derive closed, analytical $\Delta\Phi$ expressions in a very straightforward manner. In principle, such expressions have already existed for a long time. From a physical point of view, the equations describe the potential distribution on the surface of a spheroidal cavity in a dielectric. Consequently, they lack physiological cell properties. Nevertheless, assuming a zero membrane conductance and a highly polarizable cytoplasm is not a very serious limitation at DC (Schwan 1957, 1983; Grosse and Schwan 1992). Of course, for a non-negligible membrane conductance, e.g. after electrically induced pore formation, $\Delta\Phi$ will decrease. In this light, the above equations must be considered to describe the maximum $\Delta\Phi$ that can be induced for a given cell shape at a given membrane site. In an AC field the membrane impedance decreases with increasing frequency. The characteristic frequency of membrane polarization determines the –3dB criterion, a decrease of the induced voltage by a factor of $2^{-0.5}$. In the case of a spheroidal cell this frequency depends on shape and orientation (for explicit expressions for the characteristic frequency of spheroidal cells, see Gimsa and Wachner 1999).

Experimentally, the time-dependent charging and discharging of the membrane as well as time-dependent changes of the cell's properties are of importance, e.g. in modeling the dielectric membrane breakdown (Marszalek et al. 1990; Sukhorukov et al. 1998; DeBruin and Krassowska 1999). To model these relations, a complete expansion of Schwan's equation is required. It should not only describe the angle dependence of $\Delta\Phi$, but also its dependence on field, cell and medium properties. The complete equation must describe the $\Delta\Phi$ dependence on (1) cell size and shape, (2) field frequency, (3) the membrane capacitance, (4) the conductivities of cytoplasm, membrane and external medium, and (5) the site at the membrane, e.g. given by the angle dependence. The expression derived by Kotnik and Miklavcic (2000) (Eqs. 6 and 7) only meets points (1) and (5) of the above criteria and is restricted to spheroidal cells with a parallel orientation of symmetry axis and field. In this letter, we derived equations also for the perpendicular orientation.

We believe that the derivation of a complete $\Delta\Phi$ equation, taking into account all points (1) through (5) for oriented cells, will not only be possible for the spheroidal but also for the general ellipsoidal shape. An expression for the poles of spheroidal cell, meeting points (1) through (4) but not point (5), has already been published (Gimsa and Wachner 1999). A complete equation for ellipsoidal cells has, to our knowledge, not yet been published. A respective paper, starting from our equation for the poles of spheroidal cells, is in preparation. Still open is the problem of $\Delta\Phi$ for an arbitrarily oriented cell of the general ellipsoidal shape. We believe that this problem can also be solved.

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References

Bernhardt J, Pauly H (1973) On the generation of potential differences across the membranes of ellipsoidal cells in an alternating electrical field. Biophysik 10:89–98

DeBruin KA, Krassowska W (1999) Modeling electroporation in a single cell. II. Effects of ionic concentrations. Biophys J 77:1225–1233

Fricke H (1953) The electric permittivity of a dilute suspension of membrane-covered ellipsoids. J Appl Phys 24:644–646

Gimsa J, Wachner D (1999) A polarization model overcoming the geometric restrictions of Laplace's solution for spheroidal cells: obtaining new equations for field induced forces and transmembrane potential. Biophys J 77:1316–1326

Grosse C, Schwan HP (1992) Cellular membrane potentials induced by alternating fields. Biophys J 63:1632–1642

Jerry RA, Popel AS, Brownell WE (1996) Potential distribution for a spheroidal cell having a conductive membrane in an electric field. IEEE Trans Biomed Eng 43:970–972

Kotnik T, Miklavcic D (2000) Analytical description of transmembrane voltage induced by electric fields on spheroidal cells. Biophys J 79:670–679

Landau LD, Lifschitz EM (1985) Elektrodynamik der Kontinua, vol 8. Akademie-Verlag, Berlin (in German)

Marszalek P, Liu D-S, Tsong TY (1990) Schwan equation and transmembrane potential induced by alternating electric field. Biophys J 58:1053–1058

Maxwell JC (1873) Treatise on electricity and magnetism. Oxford University Press, London

Osborn JA (1945) Demagnetizing factors of the general ellipsoid. Phys Rev 67:351–357

Schwan HP (1957) Electrical properties of tissue and cell suspensions. Adv Biol Med Phys 5:147–209

Schwan HP (1983) Biophysics of the interaction of electromagnetic energy with cells and membranes. In: Grandolfo M, Michaelson SM, Rindi A (eds) Biological effects and dosimetry of nonionizing radiation. Plenum Press, New York, pp 213–231

Stille U (1944) Der Entmagnetisierungsfaktor und Entelektrisierungsfaktor für Rotationsellipsoide. Arch Elektrotechnik 38:91–101 (in German)

Stoner EC (1945) The demagnetizing factors for ellipsoids. Phil Mag 36:308–321

Stratton JA (1941) Electromagnetic theory. McGraw-Hill, New York

Sukhorukov VL, Mussauer H, Zimmermann U (1998) The effect of electrical deformation forces on the electropermeabilization of erythrocyte membranes in low- and high-conductivity media. J Membr Biol 163:235–245