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Numerical study of the electrical conductivity and polarization in a suspension of spherical cells

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Abstract

The spatial distribution of electrical potential and current in a suspension of spherical cells under an applied electric field was numerically obtained using the equivalent circuit method (ECM). The effect of the proximity of the cells was studied in a set of simulations where the volumetric fraction varied from 0.24 to 0.66. The results show that the transmembrane potential for cells in the suspension is lower than the theoretically predicted value for a single dielectric membrane under a uniform electric field. It was also observed that as the volumetric fraction is increased, the transmembrane potential on the pole of the cells decreases linearly. Furthermore, the conductivity of the suspension was also observed to be a function of the volumetric fraction and this result is in a good agreement with the Maxwell's model for spherical particles suspended in a volume conductor.
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1. Introduction

The biological cell exposed to an electric field produce transiently cell membranes porous and permeable to otherwise ions, DNA, proteins, drugs and impermeable substances [1–3]. This phenomenon is named membrane electropermeabilization or electroporation, this electrical stimulation of the plasmatic membrane may have important effects on the morphology and physiology of the cell. The study how electric fields interact with the cell suspension presents significant theoretical aspects and it can help us to understand the basis of the electroporation phenomenon [4–6].

Cell membranes are very thin structures containing a bi-layer of lipidic molecules. Due to the low permittivity of the lipidic matrix, there is a high energy barrier hindering the ionic movement across the membrane (Bohr energy) [7]. Then, the electrical conductance of the cell membrane is usually very low.

When a biological tissue or suspension of cells is excited by an electric field, ionic currents are established and ions from the electrolyte accumulate on both sides of the cell membranes. Therefore, membranes are polarized and the transmembrane potential depends, mainly, on the strength of the applied field, geometry of the cells, density of the suspension, cells organization and extracellular medium conductivity [4,5,8,9].

For a single spherical membrane of radius a and thickness h immersed in a conductor liquid under an uniform electric field of strength E_o applied in $t=0$, the transmembrane potential is given by Eq. (1), extracted from [10]:

$$V_m = -F\ a\ E_o \cos\theta\left(1 - e^{-t/\tau}\right) \quad (1)$$

where, $V_m = V_i - V_o$, V_i and V_o is the inside and outside membrane potential, respectively. θ is the angle between the direction of the field and the position vector of the point on the membrane, relative to the centre of the cell. Newmann et al. [11] present F like a function of the conductances of the external solution (σ_o), of the cell interior (σ_i), of the membrane (σ_m) and of the ratio h/a. When $a>>h$, $\sigma_m<<\sigma_i$, $\sigma_i>>\sigma_o$ (low conductivity media), but still $\sigma_o>>\sigma_m$ such that $F=1.5[1+0.5(a\ \sigma_m)/(h\ \sigma_o)]^{-1}$. Kotnik et al. [8] calculated V_m by solving the Laplace equation and the $F=1.5\sigma_o[3ha^2\sigma_i+(3h^2a-h^3)(\sigma_m-\sigma_i)]/$

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$[a^3(\sigma_m+2\sigma_o)(\sigma_m+0.5\sigma_i)-2(a-h)^3(\sigma_o-\sigma_m)(\sigma_i-\sigma_m)]$, and the time constant is $\tau=aC_m/\{[2\sigma_o\sigma_i/(2\sigma_o+\sigma_i)]+(\sigma_m a/h)\}$, C_m is the capacitance per unit area of the membrane. This analytical calculation is used where cells are surrounded by a medium of low conductivity ($\sigma_o<10^{-2}$ S m^{-1}), but it does not apply in case of a charged membrane surface. In case of a single nonconductive spherical cell in an infinite volume conductor, $a>h$ and $\sigma_m=0$, $F=1.5$. The time constant is reduced to (2), from [12]:

$$\tau = aC_m\left(\frac{1}{\sigma_i}+\frac{1}{2\sigma_o}\right). \tag{2}$$

For cells suspended in an electrolytic solution, the transmembrane potential is different from the cosine distribution given by Eq. (1) because the proximity between cells distorts the current distribution in the interstitial space close to the membranes [4,5]. The transmembrane potential is also a function of the volumetric fraction occupied by the cells and it is quite hard to obtain it by analytical methods. Numerical approaches are better to do it. Miklavcic et al. [13] present a numerical model validated through experimental observation determined the induced transmembrane voltages. They estimated the transmembrane potential difference in a single cell of the rabbit liver to be 394±75 and 694±136 mV for reversible and irreversible electroporation threshold. Schemeer et al. [6] show experimental data of reduction in the conductivity of cell suspension, before the electroporative field pulse, when the volume fraction increases.

In this work, we present a numerical study using the equivalent circuit method (ECM) [14,15] for analysis of the induced membrane voltage on spherical cells in dense suspension.

2. Method

The ECM is a numerical approach suitable for field calculation in inhomogeneous and anisotropic media. It is based on the modelling of the transport properties of the media by means of an electric circuit whose elements are associated to a discrete mesh of regular blocks that fill the analyzed space (Fig. 1a). Each block is modelled as a node of the equivalent circuit. In the cell scale model (Fig. 1b), which is suitable for analysis around the cells, the total current between two adjacent blocks in the mesh is described as having three components: conduction, diffusion and shift currents, and it is given by Eq. (3), from [15]:

$$I_{ox} = \sum_n [g_{nox}(V_o - V_x) + k_{nox}(\rho_{no} - \rho_{nx})] + \sum_x c_{ox}\frac{\delta}{\delta t}(V_o - V_x) \tag{3}$$

where the nodes are identified by 'o' and 'x' and n indicates summation over all types of ions in the media surrounding the cells. V and ρ are the voltage and charge density in the node, respectively, while g, k and c are the conductance, diffusion coefficient and capacitance of the connection, respectively. These parameters are given by Eq. (4), extracted from [15]:

$$g_n = \mu_n\rho_n A/L,\ k_n = f_n D_n A/L,\ c = \varepsilon A/L \tag{4}$$

where μ_n and D_n are the mobility and diffusion coefficient of the ion 'n', respectively, and ε is the electrical permittivity of the media. A and L are the area and length of the connection between two adjacent nodes, respectively. f_n is a function of the voltage difference between the nodes [15]. It is obtained from the spatial averaging of the Nernst–Planck equation, supposing that the current density is uniform in the area A and the voltage varies linearly along the length L. Its value is given by:

$$f_n = \frac{\Delta V}{2v_n}\frac{\exp(\Delta V/v_n)+1}{\exp(\Delta V/v_n)-1} \tag{5}$$

where $v_n=KT/ez_n$ is a constant for each type of ion in the media and $\Delta V=V_o-V_x$.

The ECM consists in obtaining and analyzing the equivalent circuit of the media aiming to obtain the electric potential and charge density distribution in the space with known initial and boundary conditions. We obtained the potential distribution by computing the node equations system and the charge distribution by finite integration of the continuity equation for each block of the mesh.

The body centred cubic (BCC) diagram of the cells suspended into the electrolytic solution is shown in Fig. 2. We built the discretization mesh for two levels of resolution. A

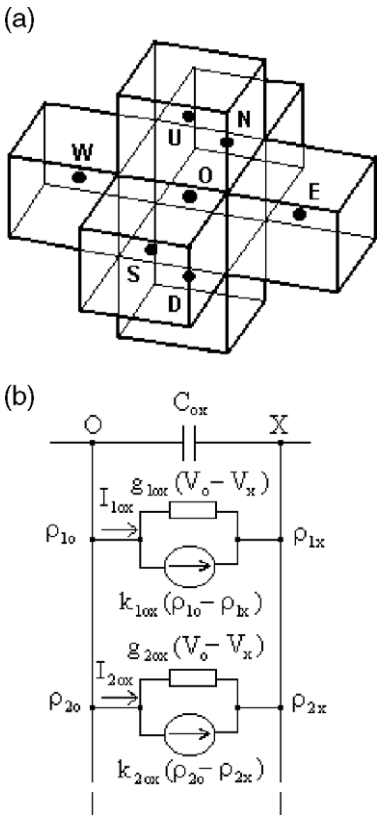

Fig. 1. (a) Discretization scheme used in the MCE. Each block is represented by a node in the equivalent circuit. (b) Equivalent circuit with the lumped elements modelling the transport process in the media.

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