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Theoretical Analyses of Cellular Transmembrane Voltage in Suspensions Induced by High-frequency Fields

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ABSTRACT

A change of the transmembrane voltage is considered to cause biophysical and biochemical responses in cells. The present study focuses on the cellular transmembrane voltage ($\Delta\varphi$) induced by external fields. We detail analytical equations for the transmembrane voltage induced by external high-frequency (above the relaxation frequency of the cell membrane) fields on cells of a spherical shape in suspensions and layers. At direct current (DC) and low frequencies, the cell membrane was assumed to be non-conductive under physiologic conditions. However, with increasing frequency, the permittivity of the cytoplasm/extracellular medium and conductivity of the membrane must be accounted for. Our main work is to extend application of the analytical solution of $\Delta\varphi$ to the high-frequency range. We first introduce the transmembrane voltage generated by DC and low-frequency exposures on a single cell. Then, we focus on cell suspensions exposed to high-frequency fields. Using the effective medium theory and the reasonable assumption, the approximate analytical solution of $\Delta\varphi$ on cells in suspensions and layers can be derived. Phenomenological effective medium theory equations cannot be used to calculate the local electric field of cell suspensions, so we raised a possible solution based on the Bergman theory.

1. Introduction

Exposure of a biological cell to an external electric field can cause profound biophysical and biochemical responses (e.g., neurotransmitter release, enzymatic activity, intracellular signal transduction, gene expression). Under physiological conditions, the cell membrane is subjected to a voltage (resting membrane voltage) that ranges from −10 mV to −90 mV caused by a system of ion pumps and channels in the membrane [1,2]. If a cell is exposed to electromagnetic fields, an additional induced transmembrane voltage, denoted by $\Delta\varphi$, will emerge across the membrane. $\Delta\varphi$ is superimposed onto the resting voltage. This phenomenon can lead to various applications, such as transferring various molecules into cells [3], electrochemotherapy [4,5], and study of the biological effects of electromagnetic fields [6]. Therefore, investigation of cellular-induced transmembrane voltage is essential for study of the responses of cells exposed to electric magnetic fields.

Analytical equations for cellular transmembrane voltage induced by external electric field have been studied for several decades. In the early 1950s, the classical theory of transmembrane voltage was developed by Schwan [7]. For a single spherical cell with no surface charge exposed to an external direct current (DC) electric field, the steady-state value of $\Delta\varphi$ can be calculated by solving the Laplace partial differential equation and is described as

$$\Delta\varphi = F_s E_e R\cos(\theta) \tag{1}$$

where E_e is the strength of the electric field, R is the cell radius, θ is the polar angle measured with respect to the direction of the field, and F_s (as given by Kotnik et al. [8]) is a function reflecting the electrical and geometrical properties of the cell. F_s is described by the following equation

$$F_s = \frac{3\sigma_e\left[3dR^2\sigma_i + \left(3d^2R - d^3\right)(\sigma_m - \sigma_i)\right]}{2R^3(\sigma_m + 2\sigma_e)\left(\sigma_m + \frac{1}{2}\sigma_i\right) - 2(R-d)^3(\sigma_e - \sigma_m)(\sigma_i - \sigma_m)} \tag{2}$$

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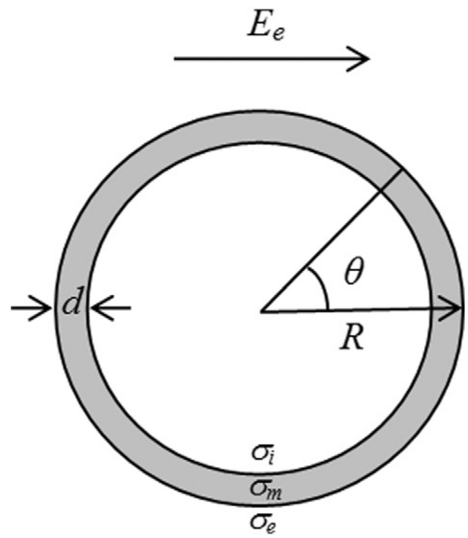

Fig. 1. The single-shell model, which ignores the nuclear envelope and organelles. E_e is the strength of the electric field, R is the cell radius, θ is the polar angle measured with respect to the direction of the field, σ_i, σ_m, and σ_e are the conductivities of the cytoplasm, membrane and extracellular medium, respectively, and d is the thickness of the cell membrane.

where σ_i, σ_m, and σ_e are the conductivities of cytoplasm, membrane and extracellular medium, respectively, and d refers to the membrane thickness (see also Fig. 1). The analytical equations mentioned above are valid only for spherical cells. For cells of arbitrary shape, only numerical methods can be used to calculate the induced transmembrane voltage [9].

Under physiological conditions where $R \gg d$; $\sigma_i, \sigma_e \gg \sigma_m$, the term F_s approximates to a constant 3/2, that is $F_s \approx 3/2$. In this scenario, Eq. (1) can be written as $\Delta\varphi = 3/2 E_e R \cos(\theta)$. This is the well-known Schwan equation that describes the transmembrane voltage of a single spherical cell with a non-conductive membrane exposed to DC fields.

Nevertheless, if the same cell is exposed to alternating current (AC) fields in low frequencies, the membrane capacitance should also be accounted for. Therefore, Eq. (1) should be modified and expressed as

$$\Delta\varphi = F_{s1} E_e R \cos(\theta) \tag{3}$$

where F_{s1} is obtained from F_s by replacing membrane conductivity with membrane admittivity $(\sigma_m + j\omega\varepsilon_m)$. With a feasible approximation [10], Eq. (3) can be approximated by

$$\Delta\varphi = F_s E_e R \cos(\theta) \frac{1}{1 + j\omega\tau_m} \tag{4}$$

where ω denotes the angular frequency of the external field, and τ_m is the time constant of the membrane, which can be approximated by:

$$\tau_m = \frac{\varepsilon_m}{\frac{d}{R}\frac{2\sigma_i\sigma_e}{\sigma_i + \sigma_e} + \sigma_m}. \tag{5}$$

Typically, for a single spherical cell under physiological conditions, Eqs. (4) and (5) can be reduced to

$$\Delta\varphi = \frac{3}{2} E_e R \cos(\theta) \frac{1}{1 + j\omega\tau_m} \tag{6}$$

$$\tau_m = R\frac{\varepsilon_m}{d}\left(\frac{1}{\sigma_i} + \frac{1}{2\sigma_e}\right). \tag{7}$$

At higher frequencies (below the relaxation frequency of the cell membrane), the capacitive properties of the cytoplasm and extracellular medium should be taken into account. By replacing conductivities σ_i, σ_m, and σ_e with the corresponding admittivities $\sigma_i + j\omega\varepsilon_i$, $\sigma_m + j\omega\varepsilon_m$, and $\sigma_e + j\omega\varepsilon_e$, we obtain another F_{s2}. This leads to the following equation:

$$\Delta\varphi = F_{s2} E_e R \cos(\theta). \tag{8}$$

Also, Eq. (8) can be approximated as

$$\Delta\varphi = \frac{3}{2} E_e R \cos(\theta) \frac{1 + j\omega\tau_{m2}}{1 + j\omega\tau_{m1}} \tag{9}$$