Realistic models of cultured cells for electroporation simulations starting from phase images

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OBJECTIVES

- Cell models for electroporation EP simulations obtained using holographic microscopy
- Digital reconstruction of phase images
- Import of phase images in dedicated finite element software Comsol Multiphysics
- Design and validation of 2D numerical models for circular and realistically shaped single cell stuctures exposed in uniform electric field for the evaluation of EP potential
- Assessment of membrane thickness and cell shape influences on induced transmembrane voltage
- Analysis of induced transmembrane voltage distribution, under low vs. high frequency applied electric field

THEORY

Laplace equation for the electric potential V (complex form for time-harmonic electric field)

$$-\nabla[(\sigma + j\omega\varepsilon)\nabla \underline{V}] = 0$$

Complex form of the dielectric properties
$\underline{\sigma}$ - complex conductivity; $\underline{\varepsilon}$ - complex permittivity;
$\underline{\varepsilon} = \varepsilon_0 \underline{\varepsilon}_r$

$$\underline{\sigma} = \sigma + j\omega\varepsilon = j\omega\underline{\varepsilon}$$
$$\underline{\varepsilon} = -j\,\underline{\sigma}/\omega \text{ and } \underline{\varepsilon}_r = -j\,\underline{\sigma}/(\omega\,\varepsilon_0)$$

Debye relaxation model for the dielectric properties of cellular components, considered as dispersive media [Merla, 2009], [Liberti, 2009]; the electrical conductivity and the dielectric constant are functions of frequency - $\sigma_{(f)}$, $\varepsilon_{r(f)}$

$$\underline{\varepsilon}_{r}(f) = \frac{\sigma_s}{j\omega\varepsilon_0} + \frac{\varepsilon_s - \varepsilon_\infty}{1 + j(f/f_r)}$$

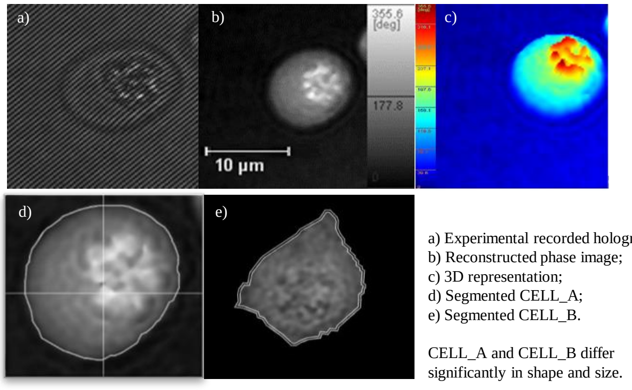
$$\underline{\varepsilon}_{r(f)} = \varepsilon_{r(f)} - j\sigma_{(f)}/(\omega\varepsilon_0)$$

$$\sigma_{(f)} = \sigma_s + \frac{\omega\varepsilon_0(\varepsilon_s - \varepsilon_\infty)}{1 + (f/f_r)^2} \cdot (f/f_r)$$

$$\varepsilon_{r(f)} = \varepsilon_\infty + \frac{\varepsilon_s - \varepsilon_\infty}{1 + (f/f_r)^2}$$

f = frequency
$\omega = 2\pi f$ – angular frequency
f_r - relaxation frequency
σ_s - static electrical conductivity
$\varepsilon_0 = 8.854 \cdot 10^{-12}$ F/m – vacuum permittivity
ε_s and ε_∞ - static and residual relative permittivities

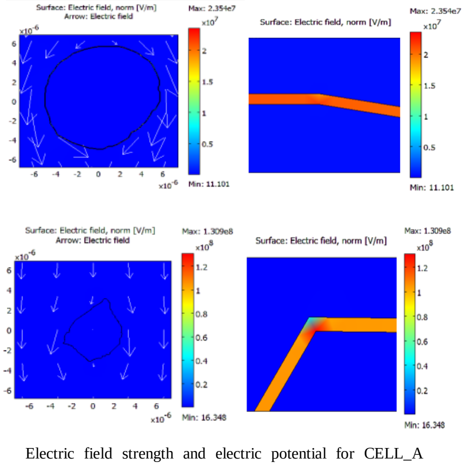
EXPERIMENT



a) Experimental recorded hologram;
b) Reconstructed phase image;
c) 3D representation;
d) Segmented CELL_A;
e) Segmented CELL_B.

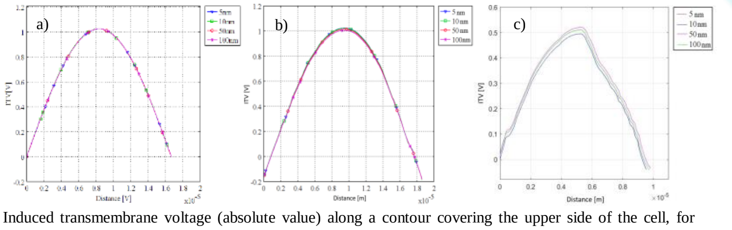
CELL_A and CELL_B differ significantly in shape and size.

SIMULATION

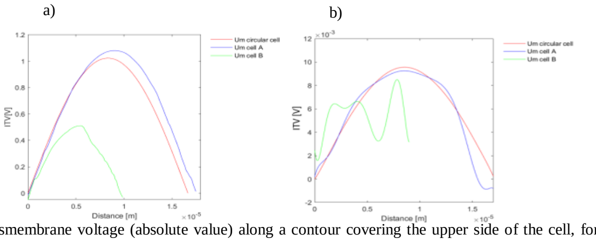


Electric field strength and electric potential for CELL_A (uppper row) and CELL_B (down row) exposed to low frequency electric field: the whole cells (left column) and details (right column)

RESULTS



Induced transmembrane voltage (absolute value) along a contour covering the upper side of the cell, for various membrane thicknesses within the range of 5 to 100nm for: a) circular cell, b) CELL_A, c) CELL_B (1 kV/cm, 50 Hz applied electric field). Membrane thickness has not a significant influence on the low frequency induced voltage, as the shape and size of the cell do have.



Induced transmembrane voltage (absolute value) along a contour covering the upper side of the cell, for three cellular models:
circular cell, CELL_A and CELL_B at a) low frequency (50Hz) and b) high frequency (1GHz)
The induced transmembrane voltage becomes much lower in amplitude and less sensitive to the shape and size of the cell, at high compared to low frequency values of the applied electric field (same strength).

CONCLUSIONS

Numerical simulations of realistic cells models obtained from the reconstruction of optical images were made to:

- analyze the differences between the cells responses to low and high frequency electrical stress;
- discover and highlight the dissimilarities among the behaviors of cells with various shapes exposed to the same electric field;
- determine locally induced transmembrane voltage magnitude and anticipate membrane sensitivity and response to electric field stress specific to the EP process;

With numerical simulation we could easily adapts the model to different electric field waveforms and frequency ranges.
Numerical simulation and analysis allow us to identify the membrane regions susceptible to electroporation and we could consider that approach as an useful research tool, complementary to biophysical laboratory experiments.

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