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CONSTRUCTAL COUPLINGS IN THE ELECTROPERMEABILIZATION OF THE CELL MEMBRANE

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Through electromagnetic field analysis and numerical experiments, the paper aims to explore the influence of the applied electric field frequency on the electropermeabilization (EP) conditions. The physical quantity correlated to the EP triggering is the transmembrane voltage induced before the pore generation process starts. The Constructal Law is here perceived and operates through the intrinsic couplings of the associated electromagnetic field, which may be tuned by the experiment designer, who is empowered to promote EP by adjusting the working frequency of the setup.

Keywords: Constructal law (CL); Electropermeabilization (EP); Electromagnetic field (EMF); Electric currents; Design.

1. INTRODUCTION

Electropermeabilization (EP) aims at raising the permeability of lipid membranes of cells or chemical-containing capsules to various substances, facilitating their passage between the inside and outside environment by exposure to a variable electromagnetic field (EMF); the process is highly dependent on both the characteristics of the target (cell morphology (shape and structure) and electric properties of the membrane) and the EMF (amplitude, waveform, frequency, and space-distribution) [1]. Here, the concern is related to the EMF, which may be frequency-tuned to reach the threshold of the membrane's EP: two pending electric currents – the conduction current and the displacement current – may be adjusted to assist the EP. This analysis confirms the designer's ability to utilize the constructal intrinsic nature of the EMF, which "morphs" the coupling between the electric and magnetic fields (EF – MF), such that EP is enabled through tuning the working frequency in the experiment.

2. PHYSICAL AND MATHEMATICAL APPROACH TO THE NUMERICAL EXPERIMENTS

EMF penetration in the experimental setup (Fig. 1) is described by Maxwell laws, which in **A**–*V* form (**A** – magnetic vector potential; *V*– electric scalar potential) lead to the PDEs (Lorentz gauge condition is utilized),

$$\left(\frac{1}{\mu\varepsilon}\frac{\partial^2}{\partial t^2}-\nabla^2\right)\mathbf{A}=\mu\mathbf{J},\quad \left(\frac{1}{\mu\varepsilon}\frac{\partial^2}{\partial t^2}-\nabla^2\right)V=0,\quad \nabla\cdot\mathbf{A}+\frac{1}{\mu\varepsilon}\frac{\partial V}{\partial t}=0, \tag{1}$$

where **A** [m·T] is the magnetic vector potential, *V* [V] is the electric scalar potential, **J** [A/m^2] is the electric current density (conduction), μ [H/m] is the magnetic permeability, and ε [F/m] is the electric

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permittivity. In this 2D model, the cells are represented as disks, the distance L = 3 μm = 30% d between adjacent cells, under the 1 kV/cm, continuous wave (CW) applied electric field (V_0 = 6 V).

The electric properties of the cell parts are frequency-dependent, following a Debye model

$$\varepsilon_r(f) = \varepsilon_\infty + \frac{\varepsilon_s - \varepsilon_\infty}{1 + (f/f_r)^2}\,, \sigma(f) = \sigma_s + \frac{\omega\varepsilon_0(\varepsilon_s - \varepsilon_\infty)}{1 + (f/f_r)^2}(f/f_r) \tag{2}$$

where ε_r is the dielectric constant, ε_r , and ε_∞ are the respective residual and static values, ε_0 [F/m] is the dielectric permittivity of free space, f_r [Hz] is the relaxation frequency, f [Hz] is the incident EMF frequency, σ [S/m] is the electrical conductivity with its static value σ_s. Figure 2 shows the frequency dependence of the dielectric properties, and Table 1 gives the values used here.

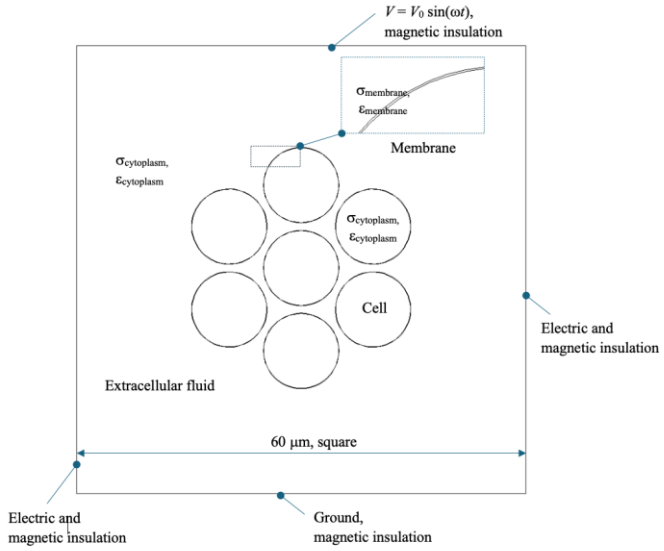


Fig. 1 – The 2D model – numerical experiment design and EMF constraints.

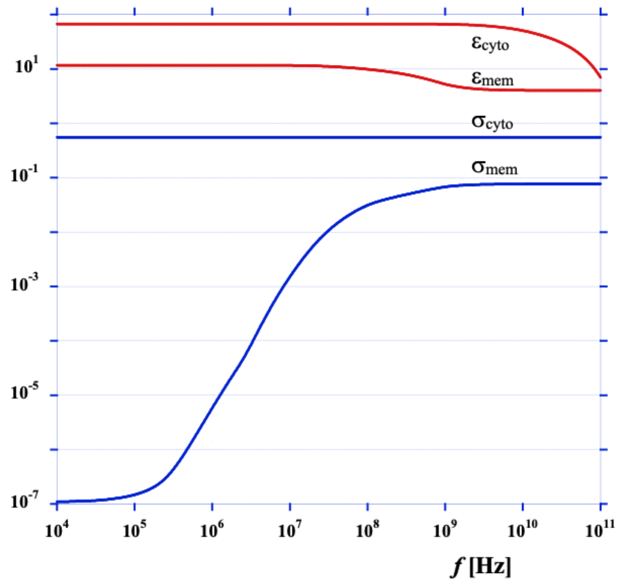


Fig. 2 – Frequency-dependent electric properties of cell parts (Deby models) [1].

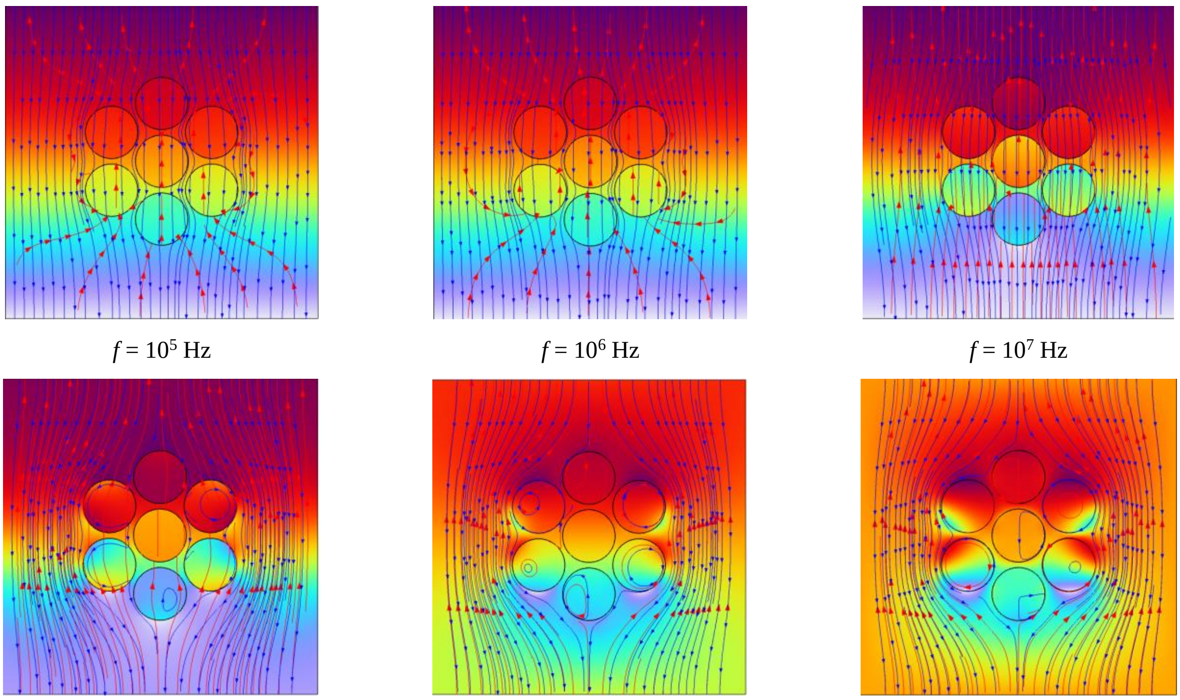
Table 1

Electric properties of cell components (Debye model) [1]

Title 1	Membrane	Cytoplasm & extracellular fluid
Static electrical conductivity, σ_s [S/m]	$1.1 \cdot 10^{-7}$	0.55
Static dielectric permittivity, ε_s [S/m]	11.7	67
Residual dielectric constant, ε	4	5
Relaxation frequency, f_r [Hz]	$179.85 \cdot 10^{6}$	$17.9 \cdot 10^{9}$

3. **RESULTS**

In a lossy dielectric, the EMF intrinsic (EF - MF) coupling results in conduction ($\mathbf{J}_c = \sigma\mathbf{E}$) and displacement ($\mathbf{J}_d = \partial\mathbf{D}/\partial t$) currents. The cytoplasm conductivity here is higher than the membrane's; $\mathbf{J}_c$ cannot penetrate the membrane at lower frequencies, and its flow is mainly through the external cytoplasm (Fig. 3). At higher frequencies, the solenoidal part of $\mathbf{E} = -\text{grad}\, V - \partial\mathbf{A}/\partial t$ becomes significant (the amplitude of the applied electric field, Fig. 1, is constant), $\mathbf{J}_d$ increases and may flow through the membrane. EP may occur when the transmembrane voltage (the local **E**) exceeds a threshold that may cause the membrane pores to "open", letting the substance flow through it. This simplistic explanation of EP is accompanied here by EMF spectra at some frequency values (medium and high frequencies of the Hertzian spectrum), which evidence the conduction–displacement currents flow.

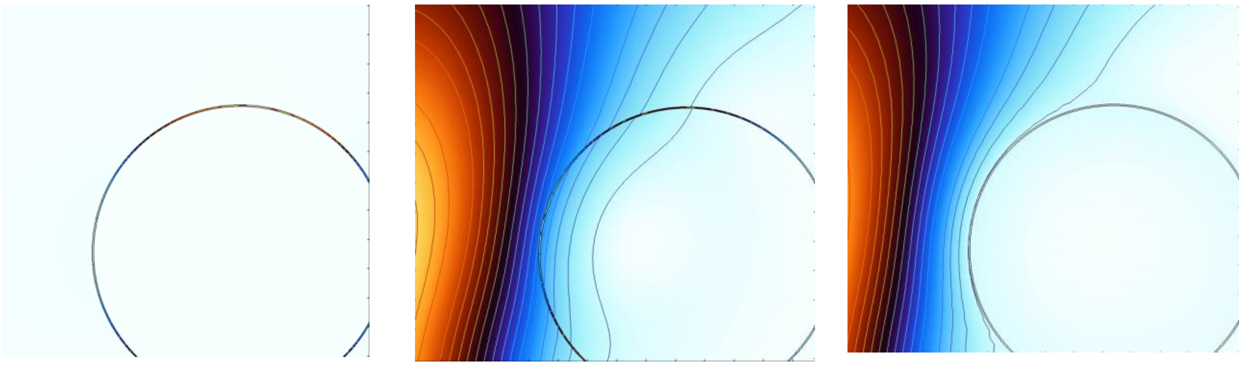


$f = 10^5$ Hz $f = 10^6$ Hz $f = 10^7$ Hz

$f = 10^8$ Hz $f = 10^8$ Hz f = ^{109} Hz

Fig. 3 – EMF spectra and current flow at different frequencies – conduction vs. displacement currents – ~~$\mathbf{J}_d$~~ $\mathbf{J}_c$ black streamlines and arrows; $\mathbf{J}_d$ red streamlines and arrows; *V* surface color map.

The electric power absorbed by the cell membrane, which may be related to EP success, differs at low vs. high frequencies, Fig. 4.



f = 10 kHz … 1 MHz *f* = 10 MHz *f* = 10 GHz

Fig. 4 – Electric power density (j/m^3) distribution. The membrane concentrates it at frequencies up to ~10 mhz.

4. DISCUSSION AND CONCLUSIONS

In this EP numerical experiment, the total electric current comprises the conduction current (which flows through highly conductive or higher-sigma media at any frequency) and the displacement current (which flows through highly polarizable or higher epsilon media at higher frequencies). The conduction current dominates the low-frequency range: it flows outside the cells (does not cross the membrane). The displacement current becomes more critical at higher frequencies. The role interplay between these currents accompanies the EP. Further research is devoted to drawing the limit.

The intrinsically coupled underlying EMFs here source each other. Evolution's constructal nature [2,3] applies to EMFs [4], and it governs their action-reaction morphing into propagation.

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