

Electroporation-Enhanced Ferrite Nanoparticle Delivery and Apoptosis via MH: Effects of Electric Pulses and AMF on Viability

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This study investigates electroporation to enhance nanoparticle delivery into cancer cells, combined with magnetic hyperthermia (MH) to induce apoptosis. Optimizing electroporation (EP) pulses increases membrane pore size, reducing cancer cell activity while minimizing normal cell damage. Alternating magnetic fields (AMF) generate a magnetothermal effect from internalized nanoparticles (NPs), triggering apoptosis. Finite element simulations optimize electroporation and MH for enhanced therapeutic efficacy.

EP simulations assessed pulse effects on membrane pore size and potential difference, while MH simulations analyzed NP heating under varying concentrations and fields. Results show that optimized EP enhances NP delivery and MH performance.

Index Terms—Electroporation; Nanoparticles; alternating magnetic fields; Magnetic hyperthermia; Finite element method.

I. INTRODUCTION

In recent years, nanotechnology-based cancer therapies, particularly magnetic hyperthermia (MH), target tumor cells via nanoparticle-induced heating under alternating magnetic fields (AMF). However, challenges in delivery and efficacy persist. Electroporation enhances nanoparticle delivery and reduces cell viability through electric pulses, offering a synergistic cancer treatment approach.

Recent studies have explored these synergies. Runsheng Wang et al^[1] synthesized $Zn_{0.5}Fe_{2.5}O_4/SiO_2$, demonstrating their uptake and MH potential as tumor-targeting agents. Sayma Vizcarra-Ramos et al^[2] combined electrochemotherapy and electromagnetic hyperthermia to boost prostate cancer cell cytotoxicity. However, comprehensive investigations into EP-facilitated nanoparticle uptake and its interplay with MH-induced apoptosis still require further in-depth research.

This study combines EP-enhanced membrane permeability with MH, using finite element simulations to model nanoparticles (NPs) uptake and thermal efficiency.

II. ELECTRIC PERFORATION SIMULATION MODEL

A. Mathematical model of electroporation

Cell components are modeled as isotropic, linear media with defined conductivity and permittivity. A spherical cell (10 μm radius) in culture medium with 2 mm electrode spacing forms the electroporation simulation model. This study adopts the classical electroporation model^[3], using the simplified Smoluchowski equation to describe the formation of hydrophilic pores in the cell membrane under an electric field.

The pore density and radius of the membrane vary with time:

$$\frac{dN(t)}{dt} = \alpha e^{(\Delta\psi/U_{EP})^2} \left(1 - \frac{N(t)}{N_0} e^{-q(\Delta\psi(t)/U_{EP})^2}\right), \Delta\psi = \psi_i(t) - \psi_o(t) \quad (1)$$

$$\frac{dr_j}{dt} = \frac{D}{kT} \left(\frac{(\Delta\psi)^2 \cdot F_{max}}{1 + r_h / (r_j + r_t)} - 2\pi\gamma + 2\pi\delta_{eff} \cdot r_j + \frac{4\beta \cdot r_j^4}{r_j^5} \right) \quad (2)$$

Here, D is the diffusion coefficient, k is the Boltzmann constant. F_{max} is the maximum electric force at 1V. r_h and r_t are constants for advection velocity. γ is the edge force of hydrophilic pores, β is the spatial repulsion energy of phospholipids, r_j is the minimum radius of hydrophilic pores, δ_{eff} is the membrane tension coefficient.

Under an electric field, the transmembrane current density is:

$$J(t) = \frac{(\psi_i - \psi_o)}{d_{men}} \sigma_{men}(t) + \frac{\epsilon_0 \epsilon_{men}}{d_{men}} \frac{\partial(\psi_i - \psi_o)}{\partial t} \quad (3)$$

$$\sigma_{men}(t) = \sigma_{men0} + N(t) \sigma_p \pi r_j^2 A / d \quad (4)$$

$$A = \frac{e^{V_m} - 1}{e^{V_m} (\omega_0 e^{e\phi_0 - nV_m} - nV_m) / (\omega_0 - nV_m) - (\omega_0 e^{e\phi_0 + nV_m} + nV_m) / (\omega_0 + nV_m)} \quad (5)$$

$$V_m = (\psi_i - \psi_o)(F / RT) \quad (6)$$

In the equation: σ_{men0} represents the conductivity of the intact cell membrane, d_{men} is the membrane thickness, σ_p denotes the pore conductivity, F , R and T are the Faraday constant, gas constant, and absolute temperature, respectively.

B. Simulation details

A current field applies electrical pulses, using contact impedance conductivity for the cell membrane and a coefficient-based boundary differential equation to solve for A , $N(t)$ and $r(j)$. Simulation values are based on literature^[4].

III. MAGNETIC THERMAL SIMULATION MODEL

A. Magnetocaloric calculation model

In the MH model, a magnetic coil replaces electrode needles. NPs are treated as part of the cytoplasm, with an equivalent heat source approach representing the intracellular region, simplifying the model significantly.

This study focuses on the heat - generation mechanism of superparamagnetic nanoparticles (NPs) in an alternating magnetic field (AMF). NPs heat via relaxation (Brownian & Néel relaxations), with power dissipation as^[5] described.

$$P = \pi \mu_0 \chi_0 H_0^2 f \frac{2\pi f \tau}{1 + (2\pi f \tau)^2} \quad (7)$$

$$\chi_0 = \frac{3\chi_i}{\xi(\coth \xi - 1/\xi)}, \chi_i = \frac{\mu_0 \phi M_d^2 V_M}{3k_B T}, \xi = \frac{\mu_0 M_d H_0 V_M}{k_B T} \quad (8)$$

Where μ_0 is the vacuum permeability, χ_0 is the equilibrium magnetic susceptibility, τ is the effective relaxation time. H_0 and f are the amplitude and frequency of the applied AMF. The volume fraction of magnetic NPs is ϕ , M_d is the domain magnetization, k_B is the Boltzmann constant, T is the absolute temperature, V_M is the particle volume. τ consists of the Brownian and Néel relaxation times (τ_N, τ_B).

$$\frac{1}{\tau} = \frac{1}{\tau_N} + \frac{1}{\tau_B}, \tau_N = \frac{\sqrt{\pi}}{2} \tau_0 \frac{\exp(\Gamma)}{\sqrt{\Gamma}}, \tau_B = \frac{3\eta V}{k_B T}, \Gamma = \frac{KV_M}{k_B T} \quad (9)$$

K is the anisotropy constant, τ_0 is the time constant (10^9 s),

η is the viscosity of the carrier fluid, V is the particle's hydrodynamic volume. The heat generation from NPs is equated to that from the cytoplasm:

$$Q = P \cdot \phi, \phi = V_M \cdot N / V_{cell} \quad (10)$$

N represents the number of NPs internalized by cells:

$$N = c / (k_F \rho V_M) \quad (11)$$

Where c is the iron content per cell, k_F is the mass fraction of iron in the NPs, and ρ is the NP density.

B. Simulation details

Electroporation-induced nanoparticle uptake increases concentration. This study compares magnetothermal effects of varying NP concentrations to assess its impact on MH, using an AMF ($H = 14 \text{ kA/m}$, $f = 430 \text{ kHz}$) with biothermal effects and literature^[5]-based heat source calculations.

IV. SIMULATION RESULTS

A. Simulation of different waveform electroporation

Due to the impact of different waveforms on pore density and radius in electroporation, this study investigates square wave pulses (100V amplitude), symmetrical square wave pulses, and sine wave pulses, as shown in Fig.1 and Fig.2.

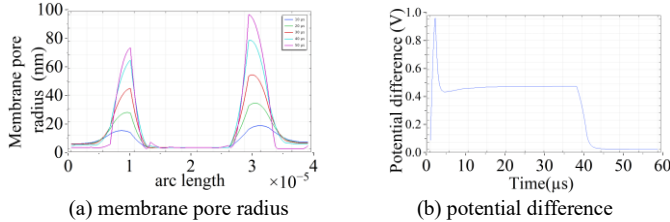
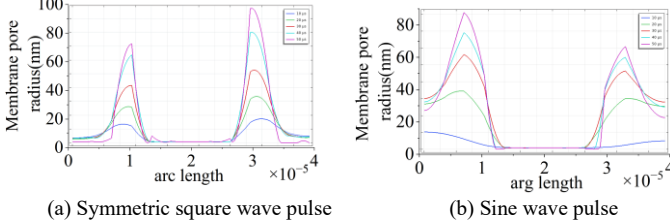


Fig. 1. The pore radius and potential difference under square wave pulses.



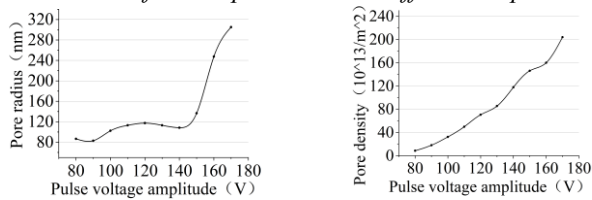
(a) Symmetric square wave pulse

(b) Sine wave pulse

Fig. 2. The pore radius under symmetric square and sine wave pulses.

Figure shows that square wave pulses produce the largest pore radius (102.34 nm), while sine wave pulses yield the smallest but cover a broader range of larger radii.

B. Simulation of electroporation with different amplitudes



(a) Maximum EP radius at 50us

(b) Maximum density of EP holes

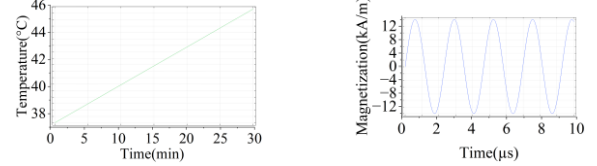
Fig. 3. Pore radius and density under pulses of varying amplitudes.

To avoid potential effects on normal cells due to excessive pulse field strength, this study examines the impact of square wave pulses with varying amplitudes on pore density and radius within a specified range, as shown in Fig.3.

As shown, increasing pulse amplitude uniformly raises pore density. The pore radius increases steadily up to 120 V, then decreases slightly before rising rapidly above 140 V, likely due to EP damage affecting cell viability.

C. Simulation results of magnetocaloric models of nanoparticles with different concentrations

This study examines the MH effect and magnetic field waveform at an iron concentration of 45 pg/cell, in Fig.3.



(a) the MH effect

(b) the magnetic field waveform

Fig. 4. the MH effect and magnetic field at an iron concentration of 45 pg/cell

Fig. 4 shows a significant temperature rise to 45.82 °C at this iron concentration. Fig. 5 shows cell temperature changes after 30 - minute AMF exposure at varying iron concentrations.

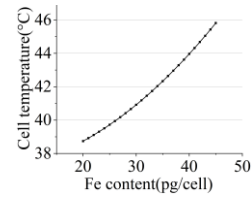


Fig. 5. Cell temperature after 30 minutes under varying NP concentrations.

Increasing intracellular iron concentration enhances the temperature rise in MH, with temperature increasing from 38.74 °C to 45.81 °C as concentration rises from 20 to 45 pg/cell. Thus, electroporation-enhanced NP uptake boosts MH.

V. CONCLUSION

In conclusion, electroporation improves NP delivery and MH efficacy. Optimizing pulse amplitude increases pore density and radius, while higher voltages may damage normal cells, highlighting the need for a balance to ensure effective treatment.

ACKNOWLEDGEMENT

This work was supported by the National Natural Science Foundation of China (52177225).

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