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FEM numerical model study of heating in magnetic nanoparticles

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Abstract

Electromagnetic heating of nanoparticles is complicated by the extremely short thermal relaxation time constants and difficulty of coupling sufficient power into the particles to achieve desired temperatures. Magnetic field heating by the hysteresis loop mechanism at frequencies between about 100 and 300 kHz has proven to be an effective mechanism in magnetic nanoparticles. Experiments at 2.45 GHz show that Fe₃O₄ magnetite nanoparticle dispersions in the range of 10¹² to 10¹³ NP/mL also heat substantially at this frequency.

An FEM numerical model study was undertaken to estimate the order of magnitude of volume power density, Q_{gen} (W m⁻³) required to achieve significant heating in evenly dispersed and aggregated clusters of nanoparticles. The FEM models were computed using Comsol Multiphysics; consequently the models were confined to continuum formulations and did not include film nano-dimension heat transfer effects at the nanoparticle surface. As an example, the models indicate that for a single 36 nm diameter particle at an equivalent dispersion of 10¹³ NP/mL located within one control volume (1.0×10^{-19} m³) of a capillary vessel a power density in the neighborhood of 10¹⁷ (W m⁻³) is required to achieve a steady state particle temperature of 52 °C — the total power coupled to the particle is 2.44 μW. As a uniformly distributed particle cluster moves farther from the capillary the required power density decreases markedly. Finally, the tendency for particles *in vivo* to cluster together at separation distances much less than those of the uniform distribution further reduces the required power density.

Keywords

FEM numerical models; Nanoparticle heating; Ferromagnetic nanoparticles

1. Introduction

Hyperthermia therapy seeks to destroy tumors through mild heating to temperatures between 43 and 45 °C in order to trigger apoptosis^(1, 2) and/or necroptosis (i.e. programmed cell death). Necrosis will also occur due to disruption in the microvasculature⁽³⁾ and other mechanisms — depending on treatment duration and temperature realized. The absolute temperature must be sufficient within the tumor and surrounding normal tissue must be maximally spared.

Conventional electromagnetic heating at ISM frequencies as used for diathermy treatments — at radio frequencies (RF) of 13.56 and 27.12 MHz, and microwave (MW) frequencies of 915 MHz and 2.45 GHz — is not well suited to the tumor hyperthermia problem because relatively large volumes of tissue are heated non-specifically. Practical RF and MW hyperthermia applicators are either focused phased-arrays, arrays of surface patches or interstitial electrodes or antennas. However, the required planning and control issues substantially complicate clinical treatment since the tissue structures in which tumors are

often found typically have little-to-no contrast in electromagnetic properties making them difficult to heat specifically.

Nanoparticles are under investigation as a means to provide local enhancement of electromagnetic properties, and make localized heating of the tumor less engineering-intensive. Gold nanoparticles have been studied at 13.56 MHz⁽⁴⁾ — where the heating mechanism is primarily localized refraction in the electric field — and under laser radiation at wavelengths near 800 nm, where the absorption mechanism relies primarily on E-field resonance.⁽⁵⁾ To date the bulk of the investigations in magnetic nanoparticle heating have focused on hysteresis loop heating between 100 and 300 kHz, which is an attractive approach since the only power absorbing structures that respond at these frequencies are the nanoparticles themselves — tissues do not heat measurably in magnetic fields at these frequencies. However, Rabin⁽⁶⁾ points out the difficulty of achieving the required minimum 6 °C rise from 37 to 43 °C when depending on the nanoparticles alone for heating. Their small size results in thermal time constants on the order of 50 ms or less, and their extremely low practical volume fraction limits total coupled power: a practical dispersion of 50 nm diameter particles to 10¹² particles per cm³ is a volume fraction of only $6.54 \times 10^{-3} \%$.

Preliminary investigations⁽⁷⁾ show that at 27 MHz the magnetic nanoparticles act only to very slightly enhance the effective electrical conductivity, and thus do not appear to be useful or attractive at RF. It is also possible that much lower field strengths and simpler applicators may prove practical at microwave (MW) frequencies. If that proves out, normal dielectric and resistive heating will occur in the tissue and the nanoparticles will only be responsible for an incremental increase in local temperature, rather than the entire heating ΔT . Also, relatively simple electromagnetic sources can be used to provide tumor-specific heating, and the temperature-monitoring problem is similarly simplified.

The present investigation employs FEM numerical models to study the effect of nanoparticle volumetric dispersions and the range of power densities required to achieve effective heating in tissues.

1.1 Electromagnetic heating

Electromagnetic heating, Q_{gen} (W m^{-3}), is described by the Poynting Power Theorem in point form below:

$$Q_{\text{gen}} = \text{Re} \{ -\nabla \cdot \mathbf{S} \} = (\sigma + \omega \varepsilon'') |\mathbf{E}|^2 + \omega \mu'' |\mathbf{H}|^2 \quad (1)$$

where: $\mathbf{S}$ = the Poynting Vector = $\mathbf{E} \times \mathbf{H}^*$ (W m^{-2}), σ = electrical conductivity (S m^{-1}), ω = angular frequency (s^{-1}), ε'' = imaginary permittivity (F m^{-1}), $\mathbf{E}$ = electric field strength ($\text{V}_{\text{rms}} \text{ m}^{-1}$), μ'' = imaginary permeability (H m^{-1}), and $\mathbf{H}$ = magnetic field strength ($\text{A}_{\text{rms}} \text{ m}^{-1}$). Dispersed nanoparticles can heat significantly by any of the three mechanisms: Joule heating (σ), dielectric heating (ε'') or magnetic heating (μ'').

The electromagnetic heating term, Q_{gen} , drives the transient bioheat equation:

$$\rho_t c_t \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) + Q_{\text{gen}} + Q_{\text{met}} + w \rho_t c_b (T_a - T) \quad (2)$$

where: ρ_t = tissue density (kg m^{-3}), c_t = tissue specific heat ($\text{J kg}^{-1} \text{ K}^{-1}$), k = tissue thermal conductivity ($\text{W m}^{-1} \text{ K}^{-1}$), T = temperature (K), Q_{met} = metabolic heat (W m^{-3}), w = perfusion (s^{-1}), c_b = blood specific heat, and T_a = effective arterial temperature. As a

practical matter metabolic heat is essentially negligible over hyperthermia time scales, but perfusion heat is quite important: it determines the power required for steady state treatment and proximity to capillaries is a critical determinant of required power densities owing primarily to the extremely small dimensions of the problem.

1.2 Electric field heating mechanisms

Experimental and numerical modeling results⁽⁷⁾ confirm that at ISM radio frequencies, 13.56 and 27.12 MHz, the electric field heating mechanism dominates observed heating mechanisms. At these frequencies the ferrimagnetic nanoparticles acted to slightly enhance the dielectric properties of the hydrated polyacrylamide (PA) hydrogel phantom material (90% water by weight) used in that study, as reflected in Table 1.

1.3 Magnetic field heating mechanisms

Tissue heats in an RF magnetic field by induction heating: the time-varying magnetic field induces an electric field (i.e. eddy currents) according to Faraday's Law of Induction, Eq. (3) in integral and point form:

$$\oint_C \mathbf{E} \cdot d\mathbf{L} = -j\omega \left[\iint_S \mathbf{B} \cdot d\mathbf{S} \right] \text{ and } \nabla \times \mathbf{E} = -j\omega \mathbf{B} \quad (3)$$

where: $\mathbf{B}$ = the applied external magnetic flux density (T). The induced electric field actually does the heating. Tissues are generally devoid of magnetically active material.

Magnetic oxides, such as iron oxide, are biocompatible and significantly lossy in a magnetic field. There are three physical mechanisms for direct absorption from magnetic fields: Neel relaxation (due to losses in magnetic dipole reorientation), hysteresis loop heating (domain wall displacements in multi-domain materials), and viscous dissipation due to motion of the particles in a time-varying magnetic field. Hematite and magnetite nanoparticles have been studied and applied to achieve specific heating of tumors at hysteresis loop frequencies — usually between about 100 and 300 kHz.

In hysteresis loop heating the effective magnetic heating term is $\omega \mu'' |\mathbf{H}|^2 \simeq \omega B_R H_C$, where B_R = the “remanance” — i.e. the residual magnetic flux density when $H = 0$ — and H_C = the “coercivity” — i.e. the applied opposing magnetic field required to drive the residual magnetic flux density to 0 (see Fig. 1). The attractive feature of this mechanism is that tissues do not heat measurably, even in the extreme magnetic field strengths required: the range of 10^5 (A m⁻¹) is typically required *in vivo* to achieve effective heating. The coil currents necessary to achieve these field strengths mean that if fluid cooling is not employed in the coils convective heat transfer from the coil often heats the subject more than the nanoparticles.

At microwave frequencies we expect some direct coupling of γ -Fe₂O₃ nanoparticles to the magnetic field: Brosseau *et al.* report the electromagnetic properties of ZnO/Fe₂O₃ nanoparticle and micro-particle (micron-sized) composites; the data in Table 2 are at 2.45 GHz. Note that the size of the particle makes a huge difference in the effective properties of the composite. Particles smaller than about 100 nm are not large enough to show well-developed magnetic domain structures,⁽⁸⁾ and thus respond to higher frequencies much differently than either bulk material or larger particles (above, say, 1 μ m in diameter). The data in Table 2 are at a volume fraction of 25% nanoparticles, a much higher volume fraction than can practically be obtained in tissues. The ZnO/Fe₂O₃ nanoparticle composites

in their study have a μ'' relaxation maximum at about 1.5 GHz, which should be observable in lower volume fractions as well. The relaxation maximum is due entirely to the Fe_2O_3 nanoparticles, and will be present in tissue suspensions as well.

Using Table 2 data for $\gamma\text{-Fe}_2\text{O}_3$ nanoparticles, the electric field heating product at 2.45 GHz, $\omega\epsilon'' = 0.095 \text{ (S m}^{-1}\text{)}$, is much smaller than that of a water-based phantom carrier material (or tissue), $\omega\epsilon'' \simeq 2 \text{ (S m}^{-1}\text{)}$. The magnetic field heating product at 2.45 GHz at this high volume fraction is quite large by comparison: $\omega\mu'' = 13.5 \times 10^3$. Consequently, for typical tissue properties, we would expect a characteristic impedance in the range of $\eta \simeq 47\text{--}6^\circ \text{ (}\Omega\text{)}$; so that $|\mathbf{H}|^2 \simeq 0.453 \times 10^{-3} |\mathbf{E}|^2$. This means that (at the higher 25% volume fraction) the overall contribution from magnetic field heating is estimated to be $6\times$ that from electric field heating.

1.4 Experimental confirmation

Confirming experimental evidence for the hypothesis at 2.45 GHz was presented in a recent paper⁽⁹⁾ and is summarized in Fig. 2. In the experiment Fe_3O_4 magetite nanoparticles were injected into excised porcine *longissimus dorsi* muscle at an effective final concentration of around 10^{12} Np/mL and illuminated from a standard microwave diathermy corner director (Burdick Inc., Milton WI, Model MW/225) at an applied power of 130 W. Ultrasound phase data were decoded to estimate the temperature fields shown in Fig. 2, as described in recent papers.⁽¹⁰⁻¹²⁾ A maximum differential temperature 20°C higher than surrounding normal tissue was achieved after 50 seconds of heating at this frequency within the nanoparticle inclusion zone.

2. Fem Numerical Models

Comsol Finite Element Method (FEM) numerical models were used to study the volume power densities required to achieve practical heating results in a variety of nanoparticle dispersions (Comsol, Inc. Burlington, MA). The 3-D bioheat equation mode geometry consisted of spherical particles suspended in cartesian volumes with and without dextran coatings at equivalent volume dispersions in the neighborhood of 10^{13} Np/mL . The electromagnetic coupling was not modeled; rather, a constant volume power density was applied in the particles, and occasionally added to the surrounding tissue constituents. Two representative model geometries are shown in Fig. 3 for reference purposes. The x- and y-dimensions of $0.464 \mu\text{m}$ correspond to a particle volume dispersion of 10^{13} Np/mL . The bottom face of the model space was treated as a constant temperature surface at 37°C to simulate the location of a capillary vessel — note that a capillary vessel of around $8 \mu\text{m}$ effective outer diameter and $1 \mu\text{m}$ wall thickness is huge compared to the dimensions of the model space, justifying the use of a flat bottom face and a constant temperature boundary. All other faces were zero-flux, and represent planes of symmetry. The result is that a mirror image of the geometry shown exists above the solid part, placing another capillary at the top virtual boundary (gray features in Fig. 1a). Similar symmetry applies in the multiple particle models, but has been omitted from Fig. 1b for clarity. The model series inspects the effect of the distance between the lowest nanoparticle and the capillary wall, as well as the effect of particle size and clustering.

2.1 Dispersed particles

The effect of proximity to the capillary vessels was studied with uncoated particles at the nominal uniform distribution, $1 \times 10^{13} \text{ Np/mL}$. The single particle results simulate two particles between capillaries that are $0.928 \mu\text{m}$ apart. In these models extreme volume power densities, $10^{17} \text{ (W m}^{-3}\text{)}$, are required to achieve a measurable temperature rise. The second

series with three particles and three empty control volumes represents capillary separations of 5 μm to 20 μm . Models were executed for particle diameters of 36, 50 and 80 nm.

In all cases steady state was reached within 10 to 20 ms in the particle. The particle diameter strongly influences the steady state temperatures and volume power densities required to achieve them. As would be expected, for the smallest capillary separation distance the temperature difference between the particle and tissue was the greatest, and decreased as the number of particles and separation distance increased. The volume power density required to achieve temperatures in therapeutic ranges decreases markedly as the particle diameter increases, as would be expected. What was not expected was the order of magnitude required: $10^{17} (\text{W m}^{-3}) = 10^8 (\text{W mm}^{-3})$. This volume power density does agree with the corresponding analytical solution for a sphere in an infinite medium, however. These super high power densities do appear to be achieved by practical systems experimentally. Of course, the nano-dimensions of the model dominate all other considerations, and capillary heat transfer is somewhat exaggerated by the extremely small numerical model space.

2.2 Clusters of particles

Recent results indicate that the nanoparticles tend to cluster together *in vivo*.^(20, 21) Dextran coated nanoparticles were modeled as clustered together at the center of the lowest particle-containing control volume in the three-particle model space.

The effect of proximity to the capillary vessel was modeled in 50 nm particles with 25 nm dextran coatings and clustered close together at a power density of $10^{15} (\text{W m}^{-3})$, as in Fig. 5a. In Fig. 5a the capillary vessel is 1.5 μm below the particle cluster and the color scale depicts the 37 to 39 $^{\circ}\text{C}$ range. As the capillary vessel location moves down to 10 μm below the particle cluster the steady state temperatures increase to 54 $^{\circ}\text{C}$, Fig. 5b. The results were unchanged when local tissue heating at $6 \times 10^6 (\text{W m}^{-3})$ was added — that power level approximates to the applied microwave power in the experiment in Fig. 2 (i.e. 130 W in a 17 $\times$ 14 cm “corner director”).

2.3 Particles on a simulated cuboidal cell nuclear surface

A 10 μm cuboidal cell was simulated as a more realistic model space. The simulated cell has an included 4 μm diameter simulated nuclear sphere, which was given the same physical properties as the rest of the cell body (i.e. “tissue” in Table 3), but kept separate to facilitate the superposition of a thermal damage model at a later date. It turned out not to be feasible to implement separate membrane subdomains in this model owing to their extremely thin dimensions — 4 to 7 nm membrane thickness is typical, and models with separate membranes failed to mesh out, presumably due to quantization limitations and small geometric uncertainties. The 3-D model space used is depicted in Fig. 6. Five 50 nm diameter nanoparticles with 25 nm thick dextran coatings were placed on the nuclear surface, as shown (exaggerated relative dimensions). The nanoparticle cluster has an effective “hydraulic diameter” of approximately 86 nm not including the dextran coating. An applied volume power density of $3 \times 10^{16} (\text{W m}^{-3})$ was required to achieve a nanoparticle temperature of 55 $^{\circ}\text{C}$ (Fig. 7). In the figure, the highly localized nature of the heating is apparent, with the elevated temperature zone confined to within a few diameters of the nanoparticles.

3. Discussion

Numerical model predictions of nanoparticle volume power densities required to achieve therapeutic temperatures are astoundingly high, but agree well with analytical calculations based on the classical solution of a sphere in an infinite medium. There is abundant

experimental evidence that magnetic nanoparticles can elevate tissue temperatures to therapeutic levels; however, it is not clear at this point the extent to which their tendency to clump together is critical to overall results. Recent experiments suggest that clumping to effective hydraulic diameters in excess of 200 to 250 nm substantially increases heating in a global temperature sense.⁽²²⁾ Plainly, much of the heating occurs in a highly localized form, and if the nanoparticles cluster onto the surface of a membrane it is entirely likely that their highly localized heating may have far-reaching global effects. More extensive numerical model studies are warranted and necessary to illuminate the underlying phenomena.

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Fig. 1.
Illustration of hysteresis loop heating.

Fig. 2.

Fe_3O_4 nanoparticle heating in excised porcine *longissimus dorsi* by 2.45 GHz MW illumination up to 50 s of heating at a total power of 130 W ($\sim 5,400 \text{ W m}^{-2}$).⁽¹²⁾

Fig. 3.

Illustration of representative FEM model geometries at a number density of 10^{13} Np/mL — the cubic control volumes are $0.464 \mu\text{m}$ on a side. In this model the central plane of symmetry sets the distance between capillary vessels. a) A single particle in a box models two particles located very close to capillary vessels — the relative thickness of the capillary wall is grossly under-represented in the illustration. b) Three particles are located varying distances from the capillary vessel at $z = -z_{\text{max}}$ with similar symmetry implications. A third geometry (not shown) includes five nanoparticles in the heated section.

Fig. 4.

Uncoated nanoparticle numerical model results for three uniformly distributed particles, particle temperature = T_p . The distance to the capillary is $1.5 \mu\text{m}$. a) 36 nm diameter at $Q_{\text{gen}} = 10^{16}$, $T_p = 52 \text{ }^\circ\text{C}$ (scale 37 to 52 $^\circ\text{C}$) b) 50 nm at $Q_{\text{gen}} = 10^{16}$, $T_p = 72 \text{ }^\circ\text{C}$ (scale to 72 $^\circ\text{C}$), and c) 80 nm at $Q_{\text{gen}} = 10^{15}$, $T_p = 50 \text{ }^\circ\text{C}$ (scale to 50 $^\circ\text{C}$).

Fig. 5.

Dextran coated nanoparticle numerical model results for three clustered 50 nm diameter particles with a 25 nm dextran coating and volume power density $Q_{\text{gen}} = 10^{15} \text{ (W m}^{-3}\text{)}$. a) Particle cluster located 1.5 μm above the capillary vessel, scale 37 to 39 °C. b) As the capillary vessel moves from 1.5 μm to 10 μm away from the cluster the particle and top plane model space temperatures increase from 39 to 54 °C.

Fig. 6. 3-D FEM model space simulating a $10\text{ }\mu\text{m}$ cuboidal cell with $4\text{ }\mu\text{m}$ simulated nucleus. a) As previously, the bottom face is iso-thermal at $37\text{ }^{\circ}\text{C}$ and the other faces are 0-flux . b) Close up view of dextran coated nanoparticle placement (not to scale).

Fig. 7.

3-D FEM model results at an applied volume power density $Q_{\text{gen}} = 3 \times 10^{16} \text{ (W m}^{-3}\text{)}$ and $t = 10$ minutes. a) X-Y plane through the nanoparticles at the level corresponding to $Z = 0$ in Fig. 6b, color scale 37 to 55 °C. The particle temperature is 55 °C b) X-Z plane through the nanoparticles at the surface of the simulated nucleus, color scale 37 to 48 °C.

Table 1

Radio frequency electrical properties of dispersed ferrimagnetic nanoparticles, dispersions given in (particles cm^{-3}).

Material	13.6 MHz		27.1 MHz	
	ϵ'	σ (S/m)	ϵ'	σ (S/m)
Water	80.8	0.089	80.7	0.091
10% PA	78.5	0.235	76.2	0.245
γ -Hematite				
Bulk	17.8	4.85	7.1	4.85
10^{12}	79.2	0.27	79.7	0.283
10^{13}	82.7	0.318	86.2	0.328
Magnetite				
Bulk	224	1.02	186	1.11
10^{12}	82.1	0.298	82.3	0.312
10^{13}	82.2	0.318	80.6	0.328

Table 2

Microwave (2.45 GHz) electrical properties of ZnO / Fe₂O₃ composites at 25% volume fraction Fe₂O₃.⁽⁸⁾

Particle size	ϵ'	ϵ''	μ'	μ''
Micron	6.3	< 0.1	1.05	< 0.05
Nano	5.5	0.7	1.5	0.7

Table 3

Thermal properties used in the FEM numerical models.

Subdomain	k ($\text{W m}^{-1} \text{K}^{-1}$)	ρ (kg m^{-3})	c ($\text{J kg}^{-1} \text{K}^{-1}$)
Tissue ⁽¹³⁾	0.6	1050	3700
Dextran	0.614 ⁽¹⁴⁾	1430 ⁽¹⁵⁾	1260 ⁽¹⁶⁾
Nanoparticles	3.85 ⁽¹⁷⁾	5180 ⁽¹⁸⁾	641.5 ⁽¹⁹⁾