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Understanding mNP Hyperthermia for cancer treatment at the cellular scale

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Abstract

The use of magnetic nanoparticles (mNP's) to induce local hyperthermia has been emerging in recent years as a promising cancer therapy, in both a stand-alone and combination treatment setting. Studies have shown that cancer cells associate with, internalize, and aggregate mNP's more preferentially than normal cells. Once the mNP's are delivered inside the cells, a low frequency (30 kHz–300 kHz) alternating electromagnetic field is used to activate the mNP's. The nanoparticles absorb the applied field and provide localized heat generation at nano-micron scales. It has been shown experimentally that mNP's exhibit collective behavior when in close proximity. Although most prevailing mNP heating models assume there is no magnetic interaction between particles, our data suggests that magnetic interaction effects due to mNP aggregation are often significant; In the case of multi-crystal core particles, interaction is guaranteed. To understand the physical phenomena responsible for this effect, we modeled electromagnetic coupling between mNP's in detail. The computational results are validated using data from the literature as well as measurements obtained in our lab. The computational model presented here is based on a method of moments technique and is used to calculate magnetic field distributions on the nanometer scale, both inside and outside the mNP.

Keywords

Magnetic nanoparticle; hyperthermia; cancer therapy; magnetic interaction; interparticle interaction; collective behavior; method of auxiliary sources; multi-scale modeling

1. INTRODUCTION

Cancer is the second most prevalent cause of death in America, closely following heart disease¹. The standard of care treatment for most cancers involves some combination of surgical excision, chemotherapy and radiation therapy. Even with these three primary treatment techniques, there is still a one in four probability of dying from cancer in one's lifetime². Clinical hyperthermia has proven to be an effective cancer treatment, especially in an adjuvant setting along with radiation and chemotherapy, but has not yet become a

standard of care³⁻⁸. It has been shown that most cancers have similar thermal tolerance as compared to surrounding normal tissues⁹. This inherent similarity necessitates the localized application of the heat source to the target tumor region, to prevent heating of normal tissue. Magnetic nanoparticles (mNP's) provide a promising solution to the problem of providing highly localized heat deposition. Particles which are designed to have higher delivery and uptake in tumor tissues, as compared to surrounding normal tissues, provide a cellular level mechanism of specificity of heat source localization¹⁰⁻¹².

Models for magnetic nanoparticle heating under relevant conditions for clinical hyperthermia applications have been improved in recent years to account for the many variables which influence mNP heating efficiency^{13, 14}. Modifications have been made to account for multiple heating mechanisms and to expand the fields strength, frequency, and particle size range over which these models are applicable¹⁵. One assumption that has yet to be adequately addressed is that of nanoparticles which are magnetically non-interacting in nature. This is a valid assumption under conditions where magnetic objects are well dispersed with respect to the size of the object. This is a key limitation of the model for the application to mNP hyperthermia, as there is a tendency for mNP's to form aggregates either extracellularly, or in endosomes as a result of active particle uptake into cells¹⁶. The use of multiple crystal core mNP's, which are inherently interacting without regard to particle aggregation, are also being investigated for use in mNP hyperthermia¹⁶⁻¹⁸. In the present paper a method of auxiliary sources (MAS) model is employed to explore the basis of magnetic interaction at the nanoscale. The Jiles-Atherton model of ferromagnetic hysteresis¹⁹ is then expanded upon to incorporate magnetic interaction on the macroscale. The model is then compared against experimental findings.

2. BACKGROUND

There are three different magnetic loss mechanisms which result in heat generation within mNP's: Neel relaxation, Brownian relaxation, and magnetic hysteresis. The first two are single domain mechanisms, while hysteresis is traditionally considered the dominant loss mechanism for particles with multiple magnetic domains within a single magnetic core.

2.1 Hysteresis heating

Within bulk ferromagnetic material, magnetic domains are defined as sub-regions within the material for which the atomic scale magnetic dipoles are aligned in a single direction. The region of transition between two adjacent domains is referred to as a domain wall. Hysteresis heating occurs when, under an applied magnetic field, the domain walls shift and the domains themselves grow and shrink. This is a lossy process and thus energy is transferred to the environment as heat. There are many approaches to modeling magnetic hysteresis, though there is no one universal model. Refer to Bertotti, *Hysteresis in magnetism*²⁰ for an in depth discussion of magnetic hysteresis.

2.2 Relaxation based heating

A particle whose magnetic core is only large enough to support one domain is classified as a single domain particle. Assuming uniaxial anisotropy, each particle has two antiparallel

stable magnetic states, defined by the crystal's easy axis. Under an applied AMF these particles will absorb energy from the field in two ways. Brownian relaxation is a mechanism by which a particle physically rotates to align its core's net magnetic moment with the applied field. Energy is lost to the environment via friction between the particle hydrodynamic surface and the surrounding media. Néel relaxation is a mechanism by which the net magnetization of the particle core may spontaneously reverse direction along the easy axis when it overcomes the energy barrier between states; off axis net magnetization is possible but is energetically unfavorable. The spontaneous change between the two states is also a lossy process, converting electromagnetic energy into thermal energy. These relaxation mechanisms are competitive, with the dominant mechanism being the one with the shorter time constant (Eq. 1–4, Fig. 1)¹⁴.

$$\tau_B = \frac{3\eta V_H}{kT} \quad (1)$$

where, k is the Boltzmann constant, η is the viscosity coefficient of the matrix fluid, and T is the absolute temperature in Kelvin

$$\tau_N = \frac{\sqrt{\pi}}{2} \tau_0 \frac{e^\Gamma}{\Gamma^{3/2}} \quad (2)$$

$$\Gamma = \frac{\gamma V_M}{kT} \quad (3)$$

where γ is the anisotropy constant, accounting for both shape and magnetocrystalline anisotropy, V_M is the volume of the magnetic core, k is the Boltzmann constant, T is the temperature, and $\tau_0 = 10^{-9}$.

$$\frac{1}{\tau} = \frac{1}{\tau_B} + \frac{1}{\tau_N} \quad (4)$$

The effect of size distribution on particle heating was developed by Rosensweig for strictly superparamagnetic mNP's using a relaxation theory approach¹⁴. The validity limits of this heating model have been thoroughly defined²¹. In essence, the model is limited to small particle sizes and applied field strengths, and does not cover the entire range which is of interest for applications in mNP hyperthermia. Hergt developed a more complete phenomenological model of mNP heating by first determining a relationship between particle size and coercivity, then relating coercivity to the specific absorption rate (SAR). The contribution of Rayleigh losses were also included to account for the effect of domain wall pinning. The resulting mNP heating model (Fig. 2) accounts for the effect of field strength and particle size, spanning from superparamagnetic to multidomain ferromagnetic particles.

This model is much more applicable to the range of conditions relevant to mNP hyperthermia, however, it still relies on the non-interacting mNP assumption of the earlier models.

3. PARTICLE INTERACTION

3.1 Method of auxiliary sources

The computational model for simulating particle interaction is based on the Method of Auxiliary Sources (MAS). The MAS has been shown to be a robust, accurate numerical technique for evaluating electromagnetic wave propagation and scattering problems. In our other work, this model has been coupled to a bioheat equation in order to model macroscale temperature distributions during treatment in an effort to develop a patient specific treatment planning model for mNP hyperthermia. For this application, the MAS model is used to explore the mechanism of magnetic nanoparticle interaction on the nanoscale. In this method, boundaries between regions of differing electromagnetic properties are defined and discretized as points on the surface. Inner and outer fictitious surfaces which conform to the real surface's features are defined for each object by assigning an inner and outer pair of points on either side of the interface for every collocation point on the actual surface. Each pair is designated as a dipole source with unknown magnitude and direction. These auxiliary sources are solved for directly as a boundary value problem, where the change in the electric and magnetic field components across the interface are governed by,

$$[\hat{n} \times \mathbf{E}_{\beta-1}^{total}] = [\hat{n} \times \mathbf{E}_{\beta}^{total}], \beta=1, 2 \quad (5)$$

$$[\hat{n} \times \mathbf{H}_{\beta-1}^{total}] = [\hat{n} \times \mathbf{H}_{\beta}^{total}], \beta=1, 2 \quad (6)$$

Which simply state that the tangential field components must be continuous across the surface. β denotes regions of different electrical properties, $\hat{n}$ is the unit normal vector of the surface between regions. The result is a finite linear combination of analytical solutions to Maxwell's Equations. The region to be modeled is then discretized and the field at each point in space is calculated as contributions from the individual sources using the Green's function (Eq. 7, 8). The field outside of an object is calculated as the contributions of the sources on the inner surface and the field within the object is likewise calculated using the sources on the external surface.

$$\mathbf{H}(\mathbf{r}) = \frac{1}{4\pi\mu_{\alpha}} \sum_{i=1} \left(\mathbf{I} + \frac{\nabla\nabla}{k_{\alpha}^2} \right) \frac{e^{-jk_{\alpha}R}}{R} \mathbf{p}_i \quad (7)$$

$$\mathbf{E}(\mathbf{r}) = \frac{1}{4\pi\mu_{\alpha}} \sum_{i=1} \nabla \times \left(\frac{e^{-jk_{\alpha}R}}{R} \mathbf{p}_i \right) \quad (8)$$

where I is the identity tensor, P is the dipole moment vector tangential to the auxiliary surface. k_a is the wave number in medium $a=1,2$, where $k_a = \sqrt{\mu_a * \epsilon_{alpha}}$, μ_a is the permeability and ϵ_a is the complex susceptibility.

3.2 Interacting spheres

Using the MAS method^{22–24}, several simulations were performed to explore various variables which influence the magnetic behavior of nanoscopic magnetic objects. The total field within, and external to, a 100nm and 20nm Fe_3O_4 sphere was individually modeled for the case where the net magnetization of each particle is parallel to the applied field (Fig. 3a). The field within a magnetic sphere is shown to be the sum of the applied field and the magnetization of the object which is induced by the applied field. The key feature to note is that there is a region nearby the magnetic object for which the field strength is greater than the applied field, and decays rapidly with distance from the object. We will call this the interaction region. The length scale of this interaction region is proportional to the radius of the sphere. This result is the mechanistic basis of contrast enhancing agents for MRI. The water molecules in the interaction region nearby gadolinium or iron oxide contrast agents experience a different local magnetic field, thus changing their Larmor frequency, resulting in quicker dephasing of the spins, and thus greater contrast due to altered relaxation times.

Just as the interaction region influences the unpaired spins of water protons, it also influences adjacent magnetic objects. Two 100nm magnetic spheres were modeled with varying distances between them (Fig. 3b). The results show that there is a strong inter-object distance dependence on the field strength experienced by the each magnetic object. The effect is not simply a superposition of the two object's field interaction regions, but is actually a synergistic effect. The rationale for this can be thought of in an iterative sense. As a magnetic object experiences a higher total field due to the presence of a nearby magnetic object, it becomes more magnetized, increasing the field strength within its interaction region, then repeat. This phenomenon will be referred to as magnetic interaction, or simply interaction for the sake of brevity.

The next simulation takes into account various quantities of magnetic spheres arranged in an equidistant linear configuration (Fig. 4a). The results show that, beyond the requisite two objects, the interaction effect is not greatly influenced by magnetic objects outside of its interaction region, which are interacting with its neighbors. The case of five magnetic spheres arranged in a linear equidistant configuration was repeated for varying sphere sizes and inter-object distances (Fig. 4b). These results show that interaction increases inversely with inter-object distance and that for equal inter-object distances, the effect is greater for larger magnetic objects.

The resulting magnetic flux density for interacting 80nm magnetic spheres, whose net magnetization is parallel to the applied field, is illustrated in Figure 5. The simulated interobject distance was 10nm.

The interaction of these magnetic objects has obvious implications for nearby mNP's, as in the case of mNP's packed into an endosome *in vivo* (Fig. 6a). The effect of interparticle distance on heating efficiency of mNP aggregates has been shown experimentally²⁵. In

addition to interparticle magnetic interaction, we would like to extend this concept to multicrystal core mNP's which are being used by many groups for mNP hyperthermia experiments^{16–18}. The TEM image shown in Fig. 6 is a BNF-starch® nanoparticle (MicroMod, Partikeltechnologie, GmbH, Rostock, Germany). This particle construct has a 60nm nominal magnetic core diameter, which consist of closely aggregated 12nm Fe₃O₄ sub crystals. It is coated in either dextran or hydroxyethyl starch with 100nm nominal hydrodynamic radius. These particles are intrinsically interacting in nature^{25, 26}. Adjacent subcrystals are interacting due to the small distance between subcrystals in relation to the subcrystal size.

The consideration of interaction can be brought to the micron scale by considering particles which have been endocytosed. Under TEM imaging (Fig. 6b), these endosomes have been observed to cause particles to be densely aggregated, enforcing interparticle distances of approximately two coating thicknesses. There are often multiple micron scale endosomes within a single cell, thus, if the inter-endosomal spacing is on the order of the diameter of the endosome, magnetic interaction between endosomes on the micron length scale may exist. This will be the focus of future work.

4. MODIFIED MODEL FOR MNP HEATING

Though it is insightful to model mNP's at the nanoscale, increasing the number of particles toward the scale of millions or billions with inhomogeneous size, spatial, and orientational distributions – which is true for realistic experimental conditions – is limited by finite computational resources and time. It is thus prudent to carry over the insight from the nanoscale model into a macroscopic statistical approach. We use a modified Langevin function as described in the Jiles-Atherton model of magnetic hysteresis¹⁹, and have accounted for particle size distribution (Fig. 7a) as well as adding in a magnetic interaction term. The mNP's being modeled are the previously mentioned Micromod BNF-starch® nanoparticles which consist of 12nm average diameter subcrystals packed together to form a 60nm average diameter aggregate core. The energy per unit volume was defined as

$$E = -\mu_0 \mathbf{m} \cdot (\mathbf{H} + \alpha \mathbf{M}) = -\mu_0 \mathbf{m} \cdot \mathbf{H}_e$$

where μ_0 is the permeability of free space, $\mathbf{m}$ is the net magnetic moment of a single crystal, $\mathbf{H}$ is the applied field, $\alpha \mathbf{M}$ is the net magnetization of the other crystals in the core which is scaled by the interaction strength factor. $\mathbf{H}_e$ is the effective field experienced by the crystal which includes the contribution of the applied field as well as the field due to the presence of neighboring subcrystals. The magnetization is described as

$$M(H_e) \approx M_s \left[\coth \left(\frac{\mu_0 H_e M_s V_m}{k_B T} \right) - 1 / \left(\frac{\mu_0 H_e M_s V_m}{k_B T} \right) \right]$$

where M_s is the saturation magnetization of a single crystal, k_B is the Boltzmann constant, V_m is the crystal volume and T is temperature. Before incorporating the effect of magnetic

interaction between particles, the model could not account for the coercivity of the BNF particles as seen in the experimentally obtained quasi-static hysteresis loop data (Fig. 7b). Fitting the magnetic interaction term to the data resulted in good agreement between the modeled hysteresis loop data (Fig. 8).

The SAR (Specific Absorption Rate, analogous to SLP) of the particles was modeled based on the Langevin function with interaction model. The modeled curve was found to be in agreement with experimental results within our group and in the literature²⁷ for the same particles (Fig. 9). Note that the collection of data using different AMF frequencies between groups were accounted for by assuming a linear dependence of SAR on frequency which is reasonable for such a small range of frequency.

5. CONCLUSIONS

In this paper we explore the basis of this magnetic interaction by modeling the particles on the nanoscale using a method of auxiliary sources model. The relationship between interparticle distance, magnetic core size, and number of particles is illustrated, and the consideration of magnetic interaction is expanded to the case of multicrystal core mNP's. A multiscale approach is taken to account for the crystal size distribution which is observed experimentally via TEM imaging. The Langevin function which describes superparamagnetic magnetization curves is modified to account for magnetic interaction, resulting in a hysteresis loop area, which, when fitted to experimental data, results in an accurate prediction of experimentally obtained bulk scale SAR.

Acknowledgments

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Figure 1.

The theoretical relationship between total relaxation time for a Fe_3O_4 magnetic nanoparticle and particle size is shown above. The mechanism which dominates single crystal non interacting mNP heating is the mechanism with the shortest relaxation time constant. The Néel relaxation time constant is dependent on core diameter. The Brownian relaxation time constant is dependent on hydrodynamic diameter.

Figure 2.
Relation of particle diameter and field strength plotted using Hergt model of mNP heating¹⁵.

Figure 3.

(a) The size dependence of the length scale of interaction for magnetic spheres. (b) The inter-object distance dependence of the length scale and strength of interaction of adjacent magnetic spheres.

Figure 4.

(a) The strength of interaction effects in varying quantities of a linear array of equidistant spherical magnetic objects. (b) The distance and size dependence of magnetic interaction for five linearly arranged magnetic spheres.

Figure 5. The magnitude of the (a) z-directed B field and (b) x-directed b field for two 80nm Fe_3O_4 spheres in a 400A/m applied field.

Figure 6.

(a) A TEM image of the multicrystal core of a BNF nanoparticle. Note the close proximity of the individual crystals within the core. (b) A TEM image of BNF nanoparticles being endocytosed by breast cancer cells after 3 hours of incubation *in vivo*.

Figure 7.

(a) Measured crystal size distribution with continuous distribution fitted for model. (b) Model without interaction (red circles) vs. measured quasistatic hysteresis loop (blue solid).

Figure 8.
Model with interaction (red) vs. measured quasistatic hysteresis loop (blue).

Figure 9.

The model of mNP heating is found to be in good agreement with experimentally collected SAR data for BNF particles²⁷.