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Theoretical Predictions for Spatially-Focused Heating of Magnetic Nanoparticles Guided by Magnetic Particle Imaging Field Gradients

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Abstract

Magnetic nanoparticles in alternating magnetic fields (AMFs) transfer some of the field's energy to their surroundings in the form of heat, a property that has attracted significant attention for use in cancer treatment through hyperthermia and in developing magnetic drug carriers that can be actuated to release their cargo externally using magnetic fields. To date, most work in this field has focused on the use of AMFs that actuate heat release by nanoparticles over large regions, without the ability to select specific nanoparticle-loaded regions for heating while leaving other nanoparticle-loaded regions unaffected. In parallel, magnetic particle imaging (MPI) has emerged as a promising approach to image the distribution of magnetic nanoparticle tracers *in vivo*, with sub-millimeter spatial resolution. The underlying principle in MPI is the application of a selection magnetic field gradient, which defines a small region of low bias field, superimposed with an AMF (of lower frequency and amplitude than those normally used to actuate heating by the nanoparticles) to obtain a signal which is proportional to the concentration of particles in the region of low bias field. Here we extend previous models for estimating the energy dissipation rates of magnetic nanoparticles in uniform AMFs to provide theoretical predictions of how the selection magnetic field gradient used in MPI can be used to selectively actuate heating by magnetic nanoparticles in the low bias field region of the selection magnetic field gradient. Theoretical predictions are given for the spatial decay in energy dissipation rate under magnetic field gradients representative of those that can be achieved with current MPI technology. These results underscore the potential of combining MPI and higher amplitude/frequency actuation AMFs to achieve selective magnetic fluid hyperthermia (MFH) guided by MPI.

Keywords

magnetic fluid hyperthermia; magnetic particle imaging; magnetic relaxation; specific absorption rate; bias field; ferrohydrodynamics

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1. Introduction

Magnetic nanoparticles have great potential in the treatment of cancer through magnetic fluid hyperthermia (MFH) [1–3] and targeted drug release [4, 5]. MFH is based on the concept of nanoscale heat dissipation due to rotation of the magnetic nanoparticle's dipoles upon application of an alternating magnetic field (herein referred to as the “actuation AMF”) of frequencies typically in the range of 100–500 kHz and amplitudes typically in the range of 10–30 kA/m. However, pre-clinical studies have shown that application of this actuating AMF to an entire animal (in what could be called whole-body MFH) leads to collateral damage to healthy cells due to non-specific accumulation of magnetic nanoparticles in organs such as the liver.[6] Similarly, although it has not been shown experimentally, one would expect that non-specific accumulation of nanoparticles engineered for magnetically-actuated drug release followed by whole body AMF application would lead to undesirable toxicity in organs such as the liver, where nanoparticles typically accumulate. These limitations motivate the development of approaches and technology that enable spatially selective actuation of the region to be heated by magnetic nanoparticles. Ideally, such an approach should enable dynamic actuation of tissue regions deep within the body, with spatial resolution in the order of millimeters so as to enable treatment of small tumor lesions, which can be in the millimeter to sub-millimeter size range [7, 8].

In order to minimize damage to non-targeted organs, techniques to achieve spatial heating control through the use of static field gradients have been developed [9–12]. Although these approaches are a step in the right direction, they do not enable dynamic selection of the heated region without significant changes in the way they are applied. Hence a significant amount of work still needs to be done in order to achieve clinical application of this approach.

To achieve localized heating, one alternative would be the use of an emerging biomedical imaging technology called magnetic particle imaging (MPI), [13, 14] which utilizes magnetic nanoparticles as tracers. This technology has shown great potential for use in real time imaging of nanoparticle biodistribution [15], angiography [16], and stem cell tracking [17]. MPI utilizes a static field gradient (herein called the “selection field gradient”) to generate a field free region (FFR) in the field of view. Upon application of a superimposed alternating magnetic field (herein referred to as the excitation field), a signal is recorded in a set of receive coils due to the change in rate of magnetization of the magnetic nanoparticles. This signal is highest in the FFR, since particles outside the FFR are in a state of saturation due to the bias field introduced by the selection field gradient. The typical excitation field frequencies and amplitudes used in MPI are in the order of 25 kHz and 40 mT [18], too low in frequency to actuate significant heating by the magnetic nanoparticles. However, one can envision using the same principles used to scan the field of view when constructing an MPI image to constraining the region where heating is actuated by higher frequency fields. This becomes particularly attractive when one can combine the use of MPI excitation fields to image the *in vivo* distribution of magnetic nanoparticles and subsequently actuate heating solely in tumor regions through the use of higher frequency actuation AMFs. This potential has been recognized by others, [19–21] but there is currently a lack of models to predict the spatial selectivity that can be achieved using MPI selection field gradients.

There are several models available to describe the energy dissipation rate of magnetic nanoparticles in uniform AMFs. Rosensweig [22] provided perhaps the first such model, accelerating research in the field by providing valuable insight into how energy dissipation, quantified by the so-called specific absorption rate (SAR), depends on the properties of the magnetic nanoparticles and the amplitude and frequency of the AMF. Other theoretical models have been developed to describe the effect of a strong DC bias field on nanoparticle magnetization [23–26] and used to evaluate the effect of bias field on energy dissipation rates of nanoparticles. Recently, Murase et al. [20] developed an empirical model to calculate SAR in a static field based on Rosensweig's model. However, the models by Rosensweig [22] and Murase et al. [20] are only valid in the small field amplitude limit and do not take into account the dependence of relaxation time on amplitude of the magnetic field, which becomes relevant for the field amplitudes and frequencies typically used to image in MPI and to actuate heating of magnetic nanoparticle.[27] Recently, Soto-Aquino and Rinaldi [28] applied the ferrohydrodynamics equations, used to describe the behavior of magnetic nanoparticle suspensions known as ferrofluids, to obtain theoretical predictions of the effect of field-dependent relaxation time on the SAR of magnetic nanoparticles under conditions typically used in magnetic fluid hyperthermia (MFH). Here, we extend the work of Soto-Aquino and Rinaldi [28] to the situation of MNP's in a selection magnetic field gradient representative of conditions achievable with current MPI technology and under AMFs representative of the “excitation” and “actuation” field/frequency ranges to obtain theoretical predictions of the spatial focusing of SAR using selection magnetic field gradients representative of those used in MPI.

2. Theory

On the application of an AMF to single domain magnetic nanoparticles they dissipate heat due to relaxation losses. This heat dissipation occurs either due to internal rotation of the magnetic dipole (Néel relaxation) or due to physical rotation of the particles (Brownian relaxation) [22, 29, 30]. Regardless of the mechanism, thermodynamic arguments show that the average rate of energy dissipation per cycle of period $2p$ is given by [22, 28]

$$\langle Q \rangle = -\frac{1}{2p} \int_0^{2p} M \frac{dH}{dt} dt, \quad (1)$$

where M is the magnetization of the suspension of particles and H is the instantaneous magnetic field amplitude. In the analysis of Rosensweig [22], and Soto-Aquino and Rinaldi [28], the instantaneous magnetic field was simply given by a sinusoidal function. However, in the case considered here the instantaneous field will depend on the position of the particles relative to the so-called field-free region (FFR, the location where the bias of the selection magnetic field gradient is zero) and will consist of a bias field H_b and a superimposed sinusoidal magnetic field H_{ex} , as illustrated in Fig. 1.

$$H(t) = H_b + H_{ex}(t), \quad (2)$$

where H_b is assumed to be independent of time (but a function of position relative to the FFR) and the excitation field is assumed to be given by $H_{ex} \cos(\omega t)$. Now, we realize that in MPI the selection magnetic field gradient is non-linear and spatially 3-dimensional, but locally, close to the FFR, one can approximate this as a linear field gradient in order to obtain the simple 1-D model used here to estimate the spatial dependence of heating rate that can be obtained using current MPI technology. Other underlying assumptions in the analysis are that the particles do not interact magnetically and that the effects of magnetophoresis due to the magnetic field gradient are negligible.

Using the applied field given in Eq.(2), Eq. (1) reduces to

$$\langle Q \rangle = \frac{H_{ex} \omega^{2p}}{2p} \int_0^{\tau} M \sin(\omega t) dt. \quad (3)$$

To reduce the number of variables in the calculation of the integral, we non-dimensionalize the magnetization with respect to the saturation magnetization (M_s), whereas frequency and time are non-dimensionalized with respect to the relaxation time (τ) :

$$\tilde{M} = M/M_s; \tilde{\omega} = \omega\tau; \tilde{t} = t/\tau. \quad (4)$$

Substituting in the energy dissipation equation, Eq. (3) can be written as

$$\langle Q \rangle = \frac{H_{ex} \omega \phi M_d^{2\tilde{p}}}{2\tilde{p}} \int_0^{\tilde{\tau}} \tilde{M} \sin(\tilde{\omega} \tilde{t}) d\tilde{t}, \quad (5)$$

where $\tilde{p} = \pi/\omega\tau$. To obtain the time dependent magnetization for the calculation of the energy dissipation rate, we solve the phenomenological magnetization equation derived by Martsenyuk, Raikher, and Shliomis (hereafter referred to as the MRSh equation)[27]. This equation takes into account the effect of field strength on the relaxation time and is valid at moderate to high field amplitudes and frequencies [31, 32], that is, conditions where the magnetic response of the nanoparticles is no longer linear with the applied magnetic field and for particles relaxing by the Brownian mechanism. In our earlier work [33], we have used the MRSh equation to model the properties of magnetic nanoparticles in a magnetic particle spectrometer and have obtained good agreement with experiments. The MRSh equation is

$$\frac{d\mathbf{M}}{dt} = \boldsymbol{\Omega} \times \mathbf{M} - \frac{\mathbf{H} [\mathbf{H} \cdot (\mathbf{M} - \mathbf{M}_0)]}{\tau_{\parallel} H^2} - \frac{\mathbf{H} \times (\mathbf{M} \times \mathbf{H})}{\tau_{\perp} H^2}, \quad (6)$$

where $\tau_{\parallel} = \frac{d \ln(L(\alpha))}{d \ln \alpha} \tau_B$, $\tau_{\perp} = \frac{2L(\alpha)}{\alpha - \ln \alpha} \tau_B$. Here, τ_B is the particle relaxation time at zero field, which for definiteness we take to be the Brownian relaxation time in our model. The Brownian relaxation time is dependent on the viscosity η of the suspending fluid, the magnetic core diameter D , and the thickness β of the coating of the nanoparticles,

$$\tau_B = \frac{\pi \eta (D + 2\beta)^3}{2k_B T}. \quad (7)$$

For the conditions of no flow and collinear fields, Eq. (6) can be written in non-dimensional form as

$$\frac{d\tilde{M}}{d\tilde{t}} = -\left[1 - \frac{\alpha}{\alpha_e}\right] \tilde{M}, \quad (8)$$

where $\alpha = \frac{\mu_0 m H}{k_B T}$ and $\alpha_e = \frac{\mu_0 m H_e}{k_B T}$. Here α is the Langevin parameter, m the magnetic moment, and H_e is the so-called effective field [27]. This differential equation is solved numerically using MATLAB and the calculated dimensionless magnetization is used in Eq. (5) to obtain the average energy dissipation rate. According to the MFH literature [22], this energy dissipation rate is often represented as specific absorption rate (SAR), which is the energy dissipated per unit mass of magnetic particles. The relationship between SAR and average volumetric energy dissipation rate is

$$SAR = \frac{\langle Q \rangle}{\phi \rho}, \quad (9)$$

where ϕ is the particle volume fraction and ρ is the density of the particles. Calculations of SAR at a given bias field can be related to predictions at a given location relative to the FFR by using the field gradient G

$$d_{FFR} = \frac{H_b}{G}, \quad (10)$$

where d_{FFR} is the distance from the FFR.

Simulations for a suspension of non-interacting magnetic nanoparticles in water (0.001 Pa.s) with a core diameter of 20 nm and having a shell thickness of 2 nm were carried out for frequencies in the MPI range [18] (1–25 kHz) and for frequencies typically employed in MFH [34] (100–500 kHz). The bias field used for this study was 50 mT and the excitation field strength was varied from 10–40 mT. SAR values were obtained for different selection field gradients between 1–6 T/m. The distribution of SAR as a function of bias field and distance from the FFR was calculated.

3. Results

We start by considering the predicted effect of bias field on the magnitude of SAR as a function of AMF frequency at fixed AMF amplitude. Fig. 2 shows a representative plot for the effect of bias field on SAR values at frequencies relevant for MPI and MFH and an excitation field amplitude of 30 mT (~24 kA/m). The predictions suggest the possibility of controlling the SAR values through the application of a bias field gradient. As expected [22], the magnitudes of SAR for frequencies used in MPI are much lower than those for frequencies used in MFH. It should be noted in Fig. 2a that although the SAR is low, it is comparable to SAR values commonly used in the MFH literature for *in vitro* [35, 36] and *in vivo* experiments [37–39]. However, during an MPI scan, the FFR has a short residence time [40] (in the order of milliseconds) in any given region, and hence the total amount of energy deposited in a particular region, which will correspond to the product of SAR and the residence time in that region, will be much lower. Thus, for these reasons the effects of magnetic nanoparticle heating during an MPI scan are expected to be negligible. In contrast, with the same range of bias fields, heating under frequencies typical of MFH is much greater. Furthermore, once a region of interest (say nanoparticles accumulated in a tumor) has been identified through an MPI scan, the residence time in the targeted region can be extended to achieve a desired dose of thermal energy effective for treatment.

In order to further understand the results of Fig. 2, we consider the dynamic hysteresis loops illustrated in Fig. 3. Fig. 3a shows results representative of the magnetization response of particles to frequencies used in MPI. At zero bias field, we observe that the area in the loop for an excitation frequency of 25 kHz is large compared to other frequencies. As the amount of heat generated is given by the product of the frequency and the area of the hysteresis loop, we see in Fig. 2 that the increase in frequency results in higher SAR values. The calculated area of the dynamic hysteresis loops is plotted in Fig. S1 which is included in the Supporting Information file. It can also be seen that increasing frequency leads to opening of the hysteresis loop. At high frequencies the particles fail to respond instantaneously to the applied field as their relaxation time is almost equal to the period $1/\omega$ of the alternating field. This leads to a delay in their magnetization response, and ultimately leads to the opening of the dynamic hysteresis loop. Referring to Figures S2, S3 and S4 in the Supporting Information file, we see that there is a considerable lag between the magnetization curve and the applied field. This delay increases as frequency increases. The magnetization versus time plot in Figures S2 and S3a shows a sinusoidal dimensionless magnetization curve. Although the frequency of oscillation is high and there is a delay in the particle response relative to the magnetic field due to relaxation, we observed that the particles reach values close to saturation (unity). However, in the case of MFH frequencies, as shown in Fig. 3b, for zero

bias field the increase in frequency leads to the dynamic hysteresis loop to become more compact and the loop area to decrease. This can be attributed to the particle relaxation time being larger than the period of the AMF, and thus a reduced response of particles to a rapidly changing alternating field. This is further illustrated in Figures S3b and S4 in the Supporting Information file. In this case, the particles fail to keep up with the change in the field, resulting in reduced magnetization magnitude as shown in the time response plot in Fig. S4b, where the magnetization magnitude changes from +0.5 to -0.5 for 500 kHz. However, as the energy dissipation rate is proportional to the frequency times the area of loop, the high frequency compensates for the decrease in area to give higher SAR values than those predicted for MPI frequencies.

Now, as the bias field increases to 25 mT, the dynamic hysteresis loops appear asymmetric due to the asymmetric shape of the magnetization curve. The asymmetric shape of the magnetization curve arises because of competing torques acting on the particles when the direction of the alternating field is opposite to the bias field, slowing down particle alignment, and due to speeding up of the alignment process because of additive torques acting on the particles when the bias and alternating fields are in the same direction. This asymmetry leads to a decrease in the area of the loop. In this case, for the same frequency, we see that the area in the loop decreases as compared to the area in the case of zero bias field, resulting in reduced SAR. This explains the drop in SAR values in Fig. 2. for increasing bias fields. The decrease is much faster in the case of MFH frequencies because at these frequencies the dynamic hysteresis loops have a much-reduced area, compared to that at imaging frequencies for the same bias field. Again referring to the figures in the Supporting Information file, it is evident that at all times there is a torque aligning the particles, but the magnitude of that torque oscillates quickly. Hence, particles simply change from one state close to saturation to another state close to saturation. This explains the partial saturation of the particles and the change of magnetization magnitude over a short range.

Finally, at a bias field of 50 mT, the particles reach a state of almost complete saturation, causing the hysteresis loops to become flat. The extreme reduction in the loop area leads to a drastic drop in SAR. The magnetization response of particles to a strong bias field as seen in Figures S2 and S3a shows oscillations in a very small range and almost complete saturation. We observe a similar behavior in the case of MFH frequencies and we can make a similar argument as before to explain the decrease in the SAR.

We now look at what can be achieved in terms of predicted SAR values at different frequencies in the FFR to understand the effect of field amplitude. Fig. 4 shows the maximum achievable SAR for different excitation field amplitudes and in a range of frequencies spanning those typically used in MPI and MFH. We observe that the increase in field amplitude results in a sharp increase in the SAR for frequencies beyond 25 kHz, reaching a plateau value at the highest frequencies. SAR values associated with MPI frequencies are much smaller than those corresponding to MFH frequencies. An increase in field amplitude leads to an increase in magnetization magnitude due to an increase in torque applied to the magnetic dipoles, thereby resulting in faster alignment of the dipoles with the AMF. We see a frequency plateau at fixed amplitude, indicating that the product of field

frequency and loop area is roughly constant even as loop area decreases with increasing frequency.

Finally, in order to illustrate the potential of using MPI selection field gradients in achieving selective heating of particles, we varied the strength of the selection field gradient from 1 T/m to 6T/m and calculated the SAR as a function of the distance from the FFR using Eq. (10). Fig. 5 shows the effect of variation in the selection field gradient to achieve spatial control of SAR. By increasing the magnitude of the selection field gradient, the SAR distribution peak becomes narrower and results in localizing the energy dissipation in a specific region. The results of Fig. 5 illustrate the possibility of achieving millimeter-scale focusing of magnetic nanoparticle heating with current MPI selection field gradient technology. Furthermore, tuning of the selection field gradient can aid in minimizing damage to areas surrounding the region of treatment without affecting the maximum achievable SAR. Finally, the potential of spatial control of energy dissipation regions while acquiring images of the magnetic nanoparticle distribution in the same instrument makes combination of MPI and focused heating particularly attractive for image guided therapy.

4. Conclusions

Using a theoretical model based on the ferrohydrodynamics equations, this study provides a framework to explore the potential of achieving spatially-focused heating of magnetic nanoparticles through use of MPI selection field gradients. According to the calculations, heating can be spatially-focused at length scales of millimeters to centimeters using currently available MPI selection field gradients. In this work, SAR predictions were based on a phenomenological model of magnetic relaxation, which can accurately account for the effect of field-dependent relaxation on the behavior of magnetic nanoparticles in suspension. As such, we hope this work will serve as stepping stone to developing technology that combines MPI with spatial focusing of magnetic nanoparticle heating, paving the way towards magnetic particle imaging guided heating and drug delivery using magnetic nanoparticle theranostic agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

The selection magnetic field gradient creates a field free region (FFR) where the magnetic dipoles of the nanoparticles may freely rotate in response to an AMF and a saturated region where the magnetic dipoles are aligned with the local bias field and do not respond to the AMF. Thus, heating due to relaxation losses is spatially focused in the FFR.

Fig. 2. Representative plot for the SAR distribution as a function of the bias field at frequencies relevant to a) MPI and b) MFH at an excitation field of 30 mT.

Fig. 3.

Dynamic hysteresis loops for frequencies used in a) MPI and b) MFH. Here, marker shapes are used to differentiate frequencies.

Fig. 4. SAR values for MPI and MFH frequencies under different field amplitudes in the field free region (FFR). Inset: zoom-in of the low frequency range (MPI).

Fig. 5. Effect of selection magnetic field gradient on the spatial distribution of SAR for a frequency of 250 kHz and excitation field amplitude of 30 mT.