The use of magnetic nanoparticles in thermal therapy monitoring and screening: Localization and imaging (invited)

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Magnetic nanoparticles have many diagnostic and therapeutic applications. A method termed magnetic spectroscopy of nanoparticle Brownian motion (MSB) was developed to interrogate *in vivo* the microscopic environment surrounding magnetic nanoparticles. We can monitor several effects that are important in thermal therapy and screening including temperature measurement and the bound state distribution. Here we report on simulations of nanoparticle localization. Measuring the spatial distribution of nanoparticles would allow us to identify ovarian cancer much earlier when it is still curable or monitor thermal therapies more accurately. We demonstrate that with well-designed equipment superior signal to noise ratio (SNR) can be achieved using only two harmonics rather than using all the harmonics containing signal. Alternatively, smaller magnetic field amplitudes can be used to achieve the same SNR. The SNR is improved using fewer harmonics because the noise is limited. © 2012 American Institute of Physics. [doi:10.1063/1.3675994]

INTRODUCTION

Magnetic nanoparticles have many applications in medicine. One of the more intriguing is the diagnosis and treatment of cancer. Diagnosis generally depends on imaging the distribution of nanoparticles targeted for cancer. Magnetic nanoparticles can also be used to treat cancer by activating them with an alternating magnetic field. The cytotoxic mechanism is not well understood so the best therapeutic schemes are not known but it is clear that the nanoparticle distribution needs to be known to understand the initiation and completion of the therapy. The microscopic distribution of nanoparticles within the microenvironment will probably be central for initiating therapy; how many nanoparticles are in the vascular space, interstitial space, cancer cell surface bound and in vesicles within the cancer cells? The temperature achieved will also probably be central to completing the therapy; to what temperatures have the cancer cells been exposed? Magnetic nanoparticles have the capability to provide the nanoparticle temperature^{1,2} and bound fraction³ using a method termed magnetic spectroscopy of nanoparticle Brownian motion (MSB).

The macroscopic spatial distribution of the magnetic nanoparticles is also important for both diagnosis and therapy. Often only minimal localization is sufficient. For example, ovarian cancer screening only requires the nanoparticle uptake by the two ovaries so a two-point localization scheme is sufficient. However, the same trends and trade-offs should apply for all spatial resolutions.

Expense and sensitivity are the two critical features for new screening examinations. To implement a screening method widely, a method must be relatively inexpensive, robust and sensitive. MRI can be used to detect magnetic nanoparticles but only at relatively high concentrations and is quite

expensive. Both characteristics detract from its appeal as a screening modality. Detecting magnetic nanoparticles using the magnetization induced by the nanoparticles in an alternating magnetic field provides the sensitivity required and can be measured remotely, which allows *in vivo* application. The sensitivity has been estimated from magnetic particle imaging (MPI)⁴ work to be sensitive to nanogram quantities.^{5,6}

In this paper, different methods of localizing the magnetic nanoparticles using the magnetization induced by an alternating magnetic field are compared using simulations. The specific application modeled is two point localization that would be useful for screening examinations. The original MPI method measures the magnetization in the frequency domain⁷ and use as many of the harmonics as possible excepting the first harmonic because it is difficult to measure in practice. An alternative⁸ uses all harmonics but in the time domain. We have proposed two different methods⁹⁻¹² that employ a more limited number of harmonics; one that uses only 4 or 5 harmonics and another that mimics a wavelet basis uses only one or two harmonics.

The simulations allow the sensitivity and size of the required fields to be compared. These two features characterize two critical features for application as a screening modality. The size of the fields that are required has a strong influence on the expense of the apparatus and sensitivity has a strong influence on how early the cancer can be detected.

MATERIALS AND METHODS

Simulations were made using a Langevin^{2,13,14} model for the mNP magnetization, that is, relatively short relaxation times were assumed:

$$M = M_S \left[\coth \left(\frac{M_S V H_0}{kT} \right) + \left(\frac{M_S V H_0}{kT} \right)^{-1} \right], \quad (1)$$

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where M is the magnetization, M_S is the nanoparticle saturation magnetization, V is the volume of the nanoparticle's magnetic core, H_0 is the applied magnetic field, k is the Boltzmann constant and T is the absolute temperature. The numerical singularity around zero was removed using a spline interpolation between the value at zero, found analytically using l'Hospital's rule, and the larger values which are numerically stable.

Both MPI methods and the new proposed methods can be described as a combination of a sinusoidal field that is uniform in space and a gradient field that is static in time as diagrammed in Fig. 1. (A) The most common implementations of MPI were modeled by recording all of the harmonics with signal: [1,63], [2,63], [3,63], [4,63]. It uses a large sinusoidal field and a large gradient field. (B) We have proposed using a more limited number of harmonics to localize the nanoparticle distribution: [1,7], [2,7], [3,7], or [4,7]. (C) The "wavelet like" implementation is obtained by recording pairs of harmonics: [1,2] or [2,3] or [3,4]. In this method, the even harmonics act like the wavelets and the odd harmonics act like the scaling functions in the wavelet transform. The shape of the magnetization over space only approximates a wavelet so the inversion is not strictly orthogonal but it is reasonably close. It is difficult to measure the first harmonic because the applied field is at the same frequency and therefore contaminates the magnetization at the first harmonic. Therefore, we also examined the reconstructions without the lower harmonics.

The SNR for each combination of sinusoidal and gradient field was calculated as the product of the size of the magnetization, the inverse condition number of the reconstruction and the inverse of the bandwidth sampled. The signal energy was the energy of the magnetization summed over harmonics. The stability of the reconstruction was estimated as the condition number of the response matrix. The response matrix was the calculated magnetization for each harmonic for the nanoparticles at both positions considered. The field applied to the

FIG. 1. (Color online) Schematic of the apparatus and associated magnetic fields used to image magnetic nanoparticles.

TABLE I. The maximum SNR for different combinations of harmonics.

	Harmonics Employed	Maximum SNR
MPI-like	Harmonics 1 to 63	0.036
	Harmonics 2 to 63	0.035
	Harmonics 3 to 63	0.036
	Harmonics 4 to 63	0.034
Limited harmonics	Harmonics 1 to 7	0.066
	Harmonics 2 to 7	0.071
	Harmonics 3 to 7	0.069
	Harmonics 4 to 7	0.078
Wavelet-like	Harmonics 1 to 2	0.091
	Harmonics 2 to 3	0.105
	Harmonics 3 to 4	0.103
	Harmonics 4 to 5	0.095

two positions was the sum of the static field at a given gradient size and the sinusoidal field that was the same for both positions; i.e., the sinusoidal field was spatially uniform. The noise component of the SNR was assumed to be proportional to the number of harmonics used. The bandwidth around each harmonic is inversely proportional to the number of cycles measured and was assumed to be the same for all methods. For well-designed equipment, the total noise energy is proportional to the bandwidth sampled, which is proportional to the number of harmonics sampled. This formulation assumes optimally designed equipment so the noise is white and proportional to the bandwidth sampled. Structured noise may dominate in experiments with immature equipment but ultimately the energy of the noise will be proportional to the bandwidth unless insuperable equipment problems occur.

RESULTS AND DISCUSSION

The normalized SNR was calculated for each value of the sinusoidal and gradient field amplitudes using different collections of harmonics. The maximum SNR achieved using all the combinations of harmonics are listed in Table I. The

FIG. 2. The optimal SNR for each amplitude of the sinusoidal field for MPI like encoding methods. The MPI like encoding methods are those that use most of the harmonics.

FIG. 3. The optimal SNR for each amplitude of the sinusoidal field for encoding methods using limited number of harmonics.

maximum SNR for each amplitude of the sinusoidal field is shown in Figs. 2 through 4. The different collections of harmonics are grouped into three classifications: Fig. 2 shows the MPI-like encoding. Figure 3 shows the limited harmonics encoding. Figure 4 shows the wavelet-like encoding.

In all cases, the SNR increased with increasing amplitude of the sinusoidal drive field. The gradient field amplitude at which the optimal SNR was achieved increased with increasing sinusoidal amplitude. Although the best SNR always required the largest sinusoidal amplitude, the wavelet-like schemes had shoulders in the optimum curves that allowed almost optimal SNR at much lower sinusoidal and gradient field amplitudes. The limited harmonics encoding also exhibited shoulders but achieved lower SNRs.

FIG. 4. The optimal SNR for each amplitude of the sinusoidal field for wavelet-like encoding methods.

It is not entirely clear how the results will translate into higher spatial resolution applications. There is a good deal of controversy about the differences between imaging methods to which these results should contribute in a limited way. The comparison of SNR values needs to be made for the higher spatial resolution methods as well. We suspect that using fewer harmonics to limit noise will be useful in higher spatial resolutions as well.

CONCLUSIONS

The simulations of the magnetization valid for low frequencies show that two-point localization can be accomplished using a single measurement of the magnetization at multiple harmonic frequencies. Only two-point localization is required for ovarian screening because the concentration of nanoparticles in each ovary is all that is required. Better resolution would certainly provide advantages but two points is all that is required. Sensitivity is necessary so the SNR is essentially determinative of the detection scheme used. The amplitude of the gradients required is also important as it influences cost. For two-point encoding like that required for ovarian cancer detection, the wavelet-like imaging is superior (a) in terms of optimal SNR achieved, and (b) in terms of maximum gradient field required. The factor of three increase in SNR is large. Alternatively, the wavelet-like encoding methods allow significantly lower gradient amplitudes to achieve the same SNR.

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