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Magnetic nanoparticle imaging using multiple electron paramagnetic resonance activation sequences

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Magnetic nanoparticles play an important role in several biomedical applications such as hyperthermia, drug targeting, and disease detection. To realize an effective working of these applications, the spatial distribution of the particles needs to be accurately known, in a non-invasive way. Electron Paramagnetic Resonance (EPR) is a promising and sensitive measurement technique for recovering these distributions. In the conventional approach, EPR is applied with a homogeneous magnetic field. In this paper, we employ different heterogeneous magnetic fields that allow to stabilize the solution of the associated inverse problem and to obtain localized spatial information. A comparison is made between the two approaches and our novel adaptation shows an average increase in reconstruction quality by 5% and is 12 times more robust towards noise. Furthermore, our approach allows to speed up the EPR measurements while still obtaining reconstructions with an improved accuracy and noise robustness compared to homogeneous EPR.

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I. INTRODUCTION

Many biomedical applications make use of magnetic nanoparticles (MNP) because they can be detected non-invasively and can reach virtually every region in the body.1−3 By applying a time-varying magnetic field, the particles can produce heat in order to destroy malignant tissue, i.e., hyperthermia.4,5 To generate the correct temperatures, accurate knowledge of the spatial MNP distribution is of critical importance. Other MNP-based applications such as drug targeting5,6 and detection7,8 also require this knowledge. In this paper, Electron Paramagnetic Resonance (EPR) is employed for recovering the MNP distribution. In an EPR experiment, the MNP sample is placed in a homogeneous magnetic field and an incident wave excites the unpaired electrons of the MNP.9 Their magnetic moments are flipped under a certain angle depending on the homogeneous magnetic field, the frequency of the wave, and the properties of the MNP. In magnetic resonance imaging (MRI), a similar principle is studied, but then using the magnetic moments of nuclei, instead of electrons. Common frequencies for the incident electromagnetic wave in EPR are around 9 GHz, but these frequencies do not allow in vivo visualization of the MNP distribution. Recently, an EPR setup was developed which allows sensitive and direct detection of magnetic nanoparticles.10,11 This setup employs radio frequency electromagnetic waves that can penetrate the human body, making this technique suitable for biomedical applications. A drawback of this method is that only the total MNP amount in the sample can be obtained while no spatial information is recovered. A forward model was devised for this setup so the 1D spatial MNP distribution could be acquired by solving an inverse problem.12 This required movement of the sample through a homogeneous magnetic field, generated by a Helmholtz coil. For every position, a measurement was needed. 2D and 3D reconstructions of the MNP distributions can be achieved by extending the previous model with movements in 2D and 3D, respectively. The Helmholtz coil pair that previously generated the homogeneous magnetic field in the EPR setup is replaced by a coil array of 16 smaller coils that are able to produce different heterogeneous field distributions between the coils. The number of EPR measurements is this way increased so to stabilize the inverse solution. In a first step, each coil is activated sequentially resulting thus in 16 distinct EPR measurements. This proposed imaging method is numerically compared to the conventional approach with homogeneous magnetic field. The activation of the coils and measurement procedure are optimized so to obtain the best reconstruction results using a minimal number of measurements, allowing a speed up of the EPR imaging technique.

II. METHODS

A. EPR principle and setup

EPR is a sensitive tool for determining the MNP amount in a sample. When the sample is placed in a magnetic field, B, the magnetic moments of the particles align themselves with the direction of the magnetic field. If additionally an electromagnetic wave is incident on the sample, the magnetic moments form an angle with B. The incident wave is generated by the excitation coil. The MNP magnetization perpendicular to B is measured by a sensing coil. This measurement is proportional to the MNP amount in the sample. In Sec. II B, we explain how a spatial MNP distribution can be related to these EPR measurements.

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A detailed description of the EPR principle and setup can be found in Ref. 12.

B. Homogeneous EPR

This section explains how a typical EPR measurement is performed and how the MNP distribution, denoted by the vector $c$ with $N$ elements, is recovered. These $N$ elements correspond with the MNP amount in $N$ voxels of the sample. Fig. 1(a) shows the homogeneous EPR setup with the Helmholtz coil for generating the homogeneous magnetic field $B$ (typically $\approx 10$ mT). One complete EPR measurement is subdivided into $M$ smaller measurements$^{12}$

$$S_{EPR} = [s_1, \ldots, s_m, \ldots, s_M]. \quad (1)$$

Each element $s_m$ corresponds to a measurement of the MNP sample at position $m$ in the magnetic field. Positions are changed by rotation and translation of the sample through the magnetic field. An EPR measurement can also be represented by a forward model$^{12}$

$$F_{he}(c) = F_{ho} \cdot c. \quad (2)$$

$F_{ho}$ is the $M \times N$ system matrix of the EPR setup constructed from $R_{ho}$, the homogeneous response function. $R_{ho}(m)$ equals $s_m$ (Eq. (1)) but has the limitation that the sample can only contain one voxel ($N = 1$), i.e., the sample is not spatially extended. Typical iron amounts for these samples are around $1 \mu$mol. The MNPs employed are Resovist$^\text{TM}$ (Schering AG, Berlin, Germany) particles, frequently used as MRI contrast agents. $R_{ho}(m)$ expresses the relationship between grid position $m$, the distance to the excitation coil, and the distance to the sensing coil. In practice, a decrease in response is observed for particle positions further away from excitation and sensing coil. Each row $m$ of $F$ represents all the response values for the $c_n$ ($n = 1, \ldots, N$) on grid position $m$ during measurement $S_m$. The unknown spatial MNP distribution is obtained by minimizing the differences between the model solution (Eq. (2)) and the EPR measurement (Eq. (1))

$$c^* = \arg \min_c \| S_{ho}(c) - S_{EPR} \|. \quad (3)$$

Equation (3) can be solved by truncated singular value decomposition (TSVD)$^{12,13}$

$$c^* = F_{ho,k}^{-1} S_{EPR} = (U \Sigma V^T)^{-1} \sum_{j=1}^{k} \frac{1}{\sigma_j} u_j^T v_j. \quad (4)$$

The eigenvalues, $\sigma_j (j = 1, \ldots, L)$, associated with $F_{ho}$ are ordered according to decreasing size. It is of critical importance to select the correct cut-off $k$ of the eigenvalues because these eigenvalues correspond to signal sources which originate from measurement sources (larger eigenvalues) and noise sources (smaller eigenvalues). The noise portion of the measurement signal can be reduced by selecting the right cut-off value. A method for obtaining this $k$ can be found in Ref. 12.

C. Heterogeneous EPR

Fig. 1(b) depicts the heterogeneous EPR setup where the Helmholtz coil is substituted by $K = 16$ smaller coils for generating heterogeneous magnetic fields. Each of these coils consists of 9 winding turns and has a diameter of about 1 cm and is distributed in 2 groups of 8 coils with a spacing of $\approx 1.5$ cm in between, where the unknown MNP sample is placed. 16 coils are chosen, so the total magnetically activated area is of a similar size as when the Helmholtz coil pair was employed and their diameter is sufficiently small to allow a sufficient imaging resolution. The currents flowing through each coil are called activation currents and are denoted by a $K \times 1$ vector $I$. In this case, the response function is extended to incorporate responses for different magnetic field amplitudes, $R_{he}(m, B)$. A change in the magnetic field’s amplitude alters the required energy of the radio frequency wave, generating a different measurement value $s_m$. The response values construct the $M \times N$ matrix $F_{he}$ (similar as in Eq. (2))

$$S_{he}(c, I) = F_{he}(I) \cdot c. \quad (5)$$

In a first approach, the coils are activated sequentially, i.e., $K$ EPR measurements are performed and each measurement $k$ ($k = 1, \ldots, K$) has $I_k \neq 0$, while the other activation currents equal zero

$$S_{he}(c, I_k) = F_{he}(I_k) \cdot c \quad k = 1, \ldots, K. \quad (6)$$

Furthermore, it is possible to merge the $K$ measurements together in the forward model

$$S_{he,tot}(c) = F_{he,tot} \cdot c. \quad (7)$$

$F_{he,tot}$ is in this case a $(M K) \times N$ matrix. Reconstructions are done by following Eq. (3), but with the adapted models $S_{he}(c, I_k)$ or $S_{he,tot}(c)$ instead of $S_{ho}(c)$.

III. RESULTS AND DISCUSSION

A. Magnetic field dependent response

We measured the response function for increasing magnetic field amplitudes. Fig. 2 shows the dependence of $R_{he}$ on the magnetic field amplitude $B_c$ for the grid position $m$ where $R_{ho} = 1$. For every grid position, the maximum response is obtained at 10 mT (which corresponds to

![Image](https://example.com/image.png)

FIG. 1. (a) Example of the setup for homogeneous EPR. (b) Example of the EPR setup for heterogeneous EPR.
We assume a similar dependence as in Fig. 2 for other grid positions, with respect to their maximum response value at 10 mT. $B_z$ is used because of the fact that $B_y, B_x \ll B_z$. To have magnetic field amplitudes between 0 and 10 mT, the current in the coils is limited to \( \approx 12 \) A in the sequential activation approach.

### B. Sequential activation

We numerically generated five random fractal clustered MNP distributions using fractal Brownian motion.\(^{14}\) These distributions are ideally suited for the representation of MNP injection sites and allow to thoroughly test and compare heterogeneous EPR with conventional EPR. For each distribution, a reconstruction is made for increasing noise levels ranging from 1\% to 10\% with respect to the response, $R_{ho}$. These are typical noise levels for the EPR setup.\(^{12}\) The noise is considered to be white Gaussian noise and for each distribution and noise level, 200 noisy reconstructions are performed which are then averaged. The reconstructions are evaluated by calculating a correlation coefficient (CC)\(^{12}\) between the actual MNP distribution $c$ and the reconstructed MNP distribution $c^\ast$. A CC equal to 1 corresponds with a “perfect” reconstruction, while a CC equal to 0 means that there is no correspondence between actual distribution and reconstruction. A first approach was to activate the coils separately and sequentially, see Sec. II C and Eqs. (6) and (7). Figure 3 shows the average reconstruction results and their standard deviation for each separately activated coil (Eq. (6)), all the coils combined in sequential EPR (Eq. (7)) and homogeneous EPR (Eq. (2)). The purple lines represent the single activation of the outer coils (the 4 coils furthest away from the center of the sample, below, and above, 8 in total, see Fig. 1(b)). Because these coils magnetically activate regions where $R_{ho}$ is significantly lower than 1 at 10 mT (further away from excitation and sensing coil) and taken into account the relative decrease from Fig. 2, these regions vary only slightly in response values for changing $B_z$ (a variation of only 1\%–10\%), which is why the reconstruction results deteriorate. The middle coils (black lines) activate regions where a change in amplitude of $B$ sufficiently alters the response values (a variation of 70\%–90\%), adding information to the inverse problem to be solved and resulting in improved reconstructions of the distributions. These variations also reflect in the corresponding eigenvalue distributions which show a slower decrease for the middle coils compared to the outer coils, generally accepted as an increased signal-to-noise ratio.\(^{12}\) Differences between coil lines of equal color result from changes in the maximum response value in the region of activation. Combining all these measurements together (blue line) results in an increase in average reconstruction quality of 5\% and is 12 times more robust towards noise (12 times smaller standard deviation) compared to the conventional homogeneous approach. This result shows that the combination of coils is necessary so as to obtain localized and general information of each part of the sample and this way increases noise robustness and reconstruction quality.

### C. Multiple activations with decreased sample movement

In Sec. III B, we showed the advantage of using heterogeneous instead of homogeneous magnetic fields for EPR-based reconstruction of MNP distributions. However, the proposed method had 16 times more measurements than the conventional method (Eqs. (2) and (7)). We therefore aimed at decreasing the number of measurements by decreasing the measurements associated to position changes of the sample.

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**FIG. 2.** Impact of $B_z$ on the measured response on position $m$.

**FIG. 3.** CC for increasing noise levels for activation of the coils separately (black and purple lines), all the coils combined (blue line) and homogeneous EPR (red line).
This way it is possible to obtain an increased accuracy in less measurements compared to the conventional method. We performed a full rotation of the sample, while limiting translational movement only to the center of the setup (near positions of sensing coil and excitation coil). We only employed the 4 middle coils as the other coils activate this region only slightly. The amount of measurements was this way reduced by ≈15% (or 180 measurements) compared to homogeneous EPR without limited movement, while still obtaining an improved accuracy of 4% and a 2 times improved noise robustness. Fig. 4 depicts a reconstruction of a MNP distribution with sequential EPR and limited movement of the sample (Fig. 4(b)) and with homogeneous EPR and complete movement of the sample (Fig. 4(c)). Homogeneous EPR with limited number of positions of the sample decreases the CC with ≈75%.

IV. CONCLUSION

In this paper, we present an adaptation of the EPR imaging technique by employing a distributed coil array that generates heterogeneous fields instead of the conventional homogeneous magnetic fields. The accuracy of the MNP reconstructions was increased by 5% and had a 12 times increased robustness towards noise. Furthermore, if we decrease the number of measurements, a speedup of the technique by 15% can be achieved by using our adapted approach, while maintaining an increase in reconstruction accuracy of 4% and a 2 times improved noise robustness compared to homogeneous EPR.

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