Developing magnetorelaxometry imaging for human applications

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Keywords: magnetic nanoparticles, magnetorelaxometry imaging, glioblastoma tumor, head phantom

Abstract

Objective. Magnetic nanoparticles (MNPs) are a promising tool in biomedical applications such as cancer therapy and diagnosis, where localization and quantification of MNP distributions are often mandatory. This can be obtained by magnetorelaxometry imaging (MRXI). Approach. In this work, the capability of MRXI for quantitative imaging of MNP inside larger volumes such as a human head is investigated. We developed a human head phantom simulating a glioblastoma multiforme (GBM) tumor containing MNP for magnetic hyperthermia treatment. The sensitivity of our MRXI setup for detection of MNP concentrations in the range of 3–19 mg cm\(^{-3}\) was studied. Main result. The results show the high capability of MRXI to detect MNPs in a human head sized volume. Superficial sources with a concentration larger than 12 mg cm\(^{-3}\) could be reconstructed with a resolution of about 1 cm\(^{-3}\). Significance. The reconstruction of the MNP distribution, mimicking a GBM tumor of 7 cm\(^{3}\) volume with clinically relevant iron concentration, demonstrates the in vivo feasibility of MRXI in humans.

1. Introduction

Magnetic nanoparticles (MNPs) have shown excellent potential for biomedical applications. Due to manipulation by magnetic gradient fields, these MNPs can be used as nanocarriers to transport a therapeutic agent to specific sites in the body known as magnetic drug targeting (Ghosh et al 2020). Furthermore, they can act as local heat generators inside tissue to harm malignant cells in magnetic hyperthermia (Mahmoudi et al 2018). However, it is crucial for these therapy applications to localize and quantify MNP distributions inside a body before, during and after cancer treatment. There are several techniques, such as magnetorelaxometry imaging (MRXI) (Liebl et al 2014), magnetic particle imaging (MPI) (Gleich and Weizenecker 2005, Paysen et al 2019) and AC biosusceptometry (ACB) (Quini et al 2017), that are capable to provide this information.

In recent years, our group has been working on MRXI and MPI for preclinical rabbit and rat sized models, respectively (Liebl et al 2015, Hildebrand et al 2020). Both techniques can be applied for functional imaging, however, they have some advantages and limitations. For example, MPI has high spatial and temporal resolution due to the application of high magnetic field gradients, but this system requires selected MNPs and the time-consuming acquisition of a calibration function. In contrast, MRXI does not need selected MNPs; it can deploy MNPs with large core sizes that are commonly used for therapy applications such as hyperthermia. In addition, in MRXI a moderate magnetic excitation field around mT is applied and this imaging modality offers a large field of view. None of these imaging modalities has so far been established for quantitative imaging of MNPs in humans in clinical environment. For upscaling MPI, one needs to construct a scanner with larger size to fit the head or the torso (Gräser et al 2019). This requires considerable technical effort, in particular, for the gradient generating field coils. However, for upscaling MRXI to human head size, the required magnetic fields for proper spatial encoding of the field of view are considerably smaller and thus also present a lower technical obstacle.

Therefore, in this work we aim to extend our MRXI setup, which was originally developed for in vitro investigations of animal models, for human applications.
MRX is based on the measurement of the decaying net magnetic moment from an MNP ensemble. More specifically, the MNP are first magnetized by an external magnetic field aligning their magnetic moments with the field direction. Then, after switching off the external field, the magnetic flux density $B$ produced by decaying net magnetic moment can be measured by sensitive magnetometers such as superconducting quantum interference devices (SQUIDs) (Richter et al., 2010, Wiekhorst et al., 2012) or optically pumped magnetometers (OPMs) (Baffa et al., 2019, Jaufenthaler et al., 2020). MRX can be obtained by combination of distinct multichannel MRX measurement with inhomogeneous magnetic fields and solving an ill-posed inverse problem.

Generally, increasing the detection volume for human size in MRX will lead to a loss of sensitivity as the MNPs are further away from the sensor system/ coil setup. Therefore, it is necessary to develop novel imaging infrastructures and measurement procedures to increase the sensitivity of the system and monitor MNPs in specific human body regions (e.g. brain, prostate, breast, etc.). In this work, we investigate the capability of MRX for quantitative imaging of MNP distributions inside the human head. As a first experimental model for MRX in humans we deploy a head phantom simulating a glioblastoma multiforme (GBM) tumor. This is the most aggressive form of cancers originating within the brain which can be treated by magnetic hyperthermia therapy (Thiesen and Jordan, 2008, Maier-Hauff et al., 2011). The reconstruction of MNP distribution mimicking GBM in the head phantom will be shown.

2. Materials and methods

2.1. Materials

In this work, commercial MNPs (EMG 700 Ferrofluid, FerroTec) with 10 nm core size were used. These MNPs have a magnete core ($\text{Fe}_3\text{O}_4$) with an anionic surfactant coating and show magnetic saturation at 35.5 mT. They are commonly applied in basic physical and biomedical research. Since the relaxation of MNPs which are accumulated in tumor is governed by Neel process (Liebl et al., 2015), we immobilized MNPs by TFC Silikon Kautschuk Typ15 (TFC troll factory, Germany).

2.2. Methods

2.2.1. Preparation of MNPs immobilized in silicon

First, we spectrophotometrically determined the iron concentration of $\epsilon(\text{Fe}) = 3.2 \, \text{mol} \, \text{l}^{-1}$ for the original EMG system by phenanthroline assay. For the preparation of immobilized MNPs in silicon, the desired amount of MNPs was gently mixed with silicon for a few minutes to achieve a homogeneous dispersion. Air bubbles were then removed by keeping the mixture under vacuum system for 5 min. Using a mold, MNP phantoms composed of 1 cm$^3$ cubes were prepared at four different nominal iron concentrations of 3.1, 6.2, 12.1 and 19 mg cm$^{-3}$. In addition, empty cube phantoms were prepared to provide an inhomogeneous MNP arrangement mimicking a GBM tumor. The homogeneity of the MNP distribution in the silicon phantom was examined by cutting a single MNP cube into several sub-cubes and measuring their third harmonic amplitude normalized to the mass by magnetic particle spectroscopy (MPS) (Arsalani et al., 2021). A maximum deviation of 5% in the homogeneity was estimated.

2.2.2. Quantitative imaging of MNP distributions

For quantitative reconstruction of MNPs in MRX, multiple excitation coils producing inhomogeneous magnetic fields, have to be incorporated into the forward model which is formulated as (Liebl et al., 2014):

$$
\Delta B_k = \frac{\mu_0}{4\pi} \left( 3(n^T(r - r_k^1))(r - r_k^2)^T \right) \frac{n^T(r - r_k^1)}{|r - r_k^1|^3} - \frac{n^T(r - r_k^2)}{|r - r_k^2|^3} H_{mag,k} \chi(t_{mag}) \Delta \kappa \chi_{MNP,k}
$$

(1)

where $\Delta B_k$ is the magnetic relaxation amplitude that has taken place between the time instants $t_1$ and $t_2$ in voxel $k$ (the sample volume $V$ divided into $k$ voxels) at the voxel center $r_k^i$ detected by a planar sensor at location $r$ and its sensitive direction $n = [n_x, n_y, n_z]$. $H_{mag,k}$ is the magnetizing field assumed to be constant within voxel $k$ and is calculated numerically according to Biot–Savart’s law (Schier et al., 2020). $\chi$ is the constant magnetic susceptibility of the MNPs depending on the experimental magnetizing time $t_{mag}$ and the magnetic field $H_{mag}$.

$\Delta \kappa = \kappa(t_2) - \kappa(t_1)$, where $\kappa(t)$ is the relaxation function with values between one and zero, and $\chi_{MNP,k}$ is the amount of MNPs in voxel $k$. The total relaxation amplitude $\Delta B(r)$ at the sensor location $r$ is obtained by combination of all voxels. Equation (1) can be written compactly:

$$
\Delta B(r) = \sum L_k \chi_{MNP,k}
$$

(2)

where $L_k$ encodes the signal impact of the voxel $k$ on the total measurements of a single sensor as response to an applied magnetic field. The different relaxation amplitudes resulting from $N$ spatially varying magnetic fields...
and $S$ sensors are combined in a vector $\Delta B$ as

$$\Delta B = LX_{\text{MNP}}$$

with $L = [L_1^T, L_2^T, \ldots, L_N^T]^T \in \mathbb{R}^{SN \times K}$ and

$$\Delta B = [B_1^T, B_2^T, \ldots, B_K^T]^T \in \mathbb{R}^{SN},$$

with $K$ representing the number of voxels. The reconstruction of MNP distribution is achieved by solving the inverse problem of the forward model (3). We applied a Tikhonov regularization with non-negativity constraint (Schier et al. 2020):

$$\hat{X}_{\text{MNP}} = \arg \min_{X_{\text{MNP}}} \| LX_{\text{MNP}} - \Delta B_{\text{meas}} \|^2_2 + \alpha \| \Gamma X_{\text{MNP}} \|^2_2,$$

where $\Delta B_{\text{meas}}$ contains the measured relaxation amplitudes, $\alpha \in \mathbb{R}$ is the regularization parameter and $\Gamma$ a weighting matrix which is the identity matrix, for more details see Schier et al. (2020).

2.2.3. MRXI setup and measurements for human applications

The MRXI setup was developed for quantitative imaging of MNP distribution inside large volumes such as a human head with a $16 \times 20 \times 25$ cm$^3$ volume (see figure 1(a) for the experimental setup and figure 1(b) for a schematic representation). Here, we used the sensor system consisting of 304 low-Tc SQUIDs, arranged in 4 horizontal layers with a diameter of 25 cm inside a liquid Helium Dewar vessel. The SQUIDs are oriented along five directions to allow spatial mapping of the magnetic induction vector (Schnabel et al. 2004, Coene et al. 2017).

A 3D printed helmet that was derived from an MRI scan is fixed on the surface of the 3D printed head phantom centered below the Dewar. The distribution of MNP cubes with defined ($c(\text{Fe}) = 3.1 \text{ mg cm}^{-3}$) plus 1 cube without MNPs, (arrangement shown in the inset figure 1(a))) were inserted into the top frontal part of the head phantom, mimicking a glioblastoma tumor with 7 cm$^3$ volume. The vertical distance between the top of the MNP cubes and lowest SQUID sensors is about 5.5 cm.

Subsequently, each magnetization coil was fed by the current $I_{\text{mag}} = 0.23 \text{ A}$ for the magnetization time $t_{\text{mag}} = 1 \text{ s}$. Following a delay time of 100 $\mu$s after switching off the magnetization fields, the relaxation signals were recorded for $t_{\text{meas}} = 2 \text{ s}$ with a sampling frequency $f_s = 500 \text{ Hz}$. A complete measurement including the magnetization and relaxation signal measurements of all 49 coils lasted about 152 s, which is still a feasible measurement time for clinical applications. The measurements were repeated for the same cube arrangement but with different $c(\text{Fe}) = 6.2, 12.1, \text{ and } 19 \text{ mg cm}^{-3}$.

The position of the coil configuration relative to the sensor system was estimated by localization measurements. For this purpose, the coils were individually driven by a sinusoidal current at a frequency of
28.8 Hz and an amplitude of 20 μA to generate a magnetic field pattern that was measured with the 304 channel SQUID system. From this, the position and orientation of the sensor system was determined by a quasi-Newton optimization procedure minimizing the root-mean-square deviation between the measured and the simulated localization amplitudes (Schier et al 2022).

3. Results and discussions

To investigate the sensitivity of our MRXI setup with respect to detecting different amounts of MNPs in the head phantom, the relaxation curves of the immobilized MNP with various \( \chi(\text{Fe}) \) were recorded with the same MRX parameters mentioned above. Figure 2(a) shows the relaxation curves of an arrangement without any MNPs (empty) and with 7 cm\(^3\) volume of MNP. The \( \chi(\text{Fe}) \) ranged from 3.1 to 19 mg cm\(^{-3}\), the selected sensor was sensitive in the z-direction and located at the first horizontal layer of the Dewar. According to equation (1) we expect a linear relationship of the relaxation amplitude with MNP amount. It can be seen in figure 2(b) that the relationship is approximately linear, showing the system capability of detecting total MNP amounts down to at least 3.1 mg cm\(^{-3}\) in a human head sized volume.

Reconstructions were performed for an MNP arrangement at different concentrations, mimicking an inhomogeneous glioblastoma tumor with 7 cm\(^3\) volume, treated by hyperthermia. The ground truth and reconstruction of MNP distribution with clinically relevant \( \chi(\text{Fe}) = 6.2, 12.1 \) and 19 mg cm\(^{-3}\) are shown in figures 3(a)–(d), respectively. To measure the performance and the accuracy of the reconstruction results the Pearson correlation coefficient (CC) is employed between ground truth and reconstruction images (Dunn and Clark 1986, Schier et al 2020).

For the MNP arrangement with \( \chi(\text{Fe}) \) of 6.2, 12.1, and 19 mg cm\(^{-3}\) CCs of 69%, 82%, and 83%, respectively, were determined, where a CC of 100% corresponds to a perfect reconstruction and complete correlation between two images. As expected, the correlation between ground truth and reconstruction improved with increasing \( \chi(\text{Fe}) \) (see figure 3) due to the higher signal \( \Delta B \) (see figure 2). However, an improvement in the reconstructed images could be achieved by increasing the SNR or equivalently \( \Delta B \) which has a direct relationship with \( H_{\text{mag}} \), \( t_{\text{mag}} \) and \( \chi \) (see equation (1)) within a certain parameter range. We could increase the external inhomogeneous magnetizing field beyond 1.7 mT by applying a higher current to the coil setup. However, instrumental limitations of the power supply did not allow this, so that a more powerful but at the same time low-noise current source would be required. An increase in the magnetizing time (\( t_{\text{mag}} > 1 \) s) comes at the cost of a prolonged acquisition time and a compromise must be found. Additionally, a more suitable system of MNPs with higher susceptibility \( \chi \) could be used as another way to improve SNR. It should be noted, there are constraints for the maximum amplitude of the magnetizing field exposed to the 304 channel SQUID system. At present, a maximum field of about 50 μT at the location of the SQUIDs must not be exceeded to avoid reduced performance. An upgraded SQUID system is under construction that will avoid this problem in the future (Storm et al 2016).

We demonstrated the MNP reconstruction for a GBM tumor close to the surface of the head as shown in figures 3(b)–(d). However, the tumor could also be located in a deeper part of the head exhibiting different shapes and sizes. To examine the resolution of our MRXI setup for such cases, another experiment (reconstructed images not shown here) has been performed for a MNP arrangement of 6 cubes
(2\(N_x \times 3N_y \times 1N_z\)) and \(c(\text{Fe}) = 19 \text{ mg cm}^{-3}\). The cubes were located in the frontal head region with a vertical distance of about 4 cm to surface. Between ground truth and reconstruction, a CC of 17% was determined, showing the limitations of the setup for a MNP source located in the deeper part of the head.

This limitation is caused by two reasons: with increasing distance, the magnetization fields become spatially more homogeneous and thus the signals from adjacent voxels are more difficult to separate. Furthermore, the relaxation amplitude detected by a SQUID sensor is reduced at a greater distance \(r\) (roughly proportional to \(r^3\)) and in consequence diminishing the SNR. But to improve the image reconstruction of a MNP source which is in the deeper part of the head, an even higher SNR is needed. This could be provided by increasing the parameters \(H_{\text{mag}}\) and \(t_{\text{mag}}\) as mentioned above. Larger excitation coils with more homogenous field profiles could be more beneficial in this case. Besides providing a higher \(H_{\text{mag}}\) at deeper MNP sources, the combination of multiple larger coils in addition to the small coils, generating higher superficial inhomogeneous fields, could potentially improve the reconstruction making the setup more suitable for clinical applications.

We would also like to discuss briefly the minimum achievable resolution which is expected to be a complex function of MNP concentration and their location within the head. For example, sources closer to the surface with a high concentration should be resolvable with higher resolution compared to deeper lying sources. For our present setup, a resolution for superficial sources of about 1 cm\(^3\) is estimated. A detailed investigation of the achievable resolution incorporating the mentioned source depth and concentration dependency will be addressed in a future work.

4. Conclusions

We established MRXI in a human head sized phantom. The relaxation amplitudes showed an approximately linear relationship with iron concentration as used in glioblastoma treatments, demonstrating the system capability of detecting various amount of MNPs in the human head. The reconstruction of MNP distribution with clinically relevant iron concentrations indicates that in \(vivo\) MRXI in humans would be feasible. Necessary improvements can be achieved by increasing the maximum magnetizing field above the currently used 1.7 mT and by an optimized combination of additional larger coils added to the small coils. These would facilitate the translation of MRXI in pre-clinical studies which will be the subject of future work.
Acknowledgments

Financial support by the German Science Foundation (DFG), project ‘quantMRX’, Grant 428329263, WI 4230/4-1 and Austrian Science Fund (FWF), Grant number I 4357-B, is gratefully acknowledged. Furthermore, we thank Dr Rainer Körber from Physikalisch-Technische Bundesanstalt for technical support.

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