Improved sensitivity and limit-of-detection using a receive-only coil in magnetic particle imaging

Hendrik Paysen, James Wells, Olaf Kosch, Uwe Steinhoff, Lutz Trahms, Tobias Schaeffter and Frank Wiekhorst

Physikalisch-Technische Bundesanstalt, Abbestrasse 2-12, 10587 Berlin, Germany
Bruker BioSpin MRI GmbH, Rudolf-Plank-Str. 23, 76276 Ettlingen, Germany
E-mail: hendrik.paysen@ptb.de

Keywords: magnetic particle imaging, magnetic nanoparticles, MPI, MNP, gradiometer

Abstract
Magnetic particle imaging (MPI) is an imaging modality capable of quantitatively determining the 3D distribution of a magnetic nanoparticle (MNP) ensemble. In this work, we present a method for reducing the MNP limit of detection by employing a new receive-only coil (Rx-coil) for signal acquisition. The new signal detector is designed to improve the sensitivity and thus quality of reconstructed images. We present characterization measurements conducted with the prototype Rx-coil installed in a preclinical MPI scanner. The gradiometric design of the Rx-coil attenuates the unwanted signal contributions arising from the excitation field, leading to a 17 dB lower background level compared to the conventional dual-purpose coil (TxRx-coil), which is crucial for detecting low amounts of MNP. Network analyzer measurements of the frequency-dependent coil sensitivity, as well as spectral analysis of recorded MPI data demonstrate an overall increase of the coil sensitivity of about +12 dB for the Rx-coil. Comparisons of the sensitivity distributions revealed no significant degradations in terms of homogeneity for the Rx-coil compared to the TxRx-coil in an imaging volume of $6 \times 3 \times 3$ cm$^3$. Finally, the limit of detection was determined experimentally for each coil type using a serial dilution of MNPs, resulting in values of 133 ng of iron for the conventional TxRx-coil and 20 ng for the new Rx-coil, using an acquisition time of 2 s. A linear relationship between the reconstructed signal intensities and the iron mass in the samples was observed with coefficients of determination ($R^2$) of above 99% in the range of the limit of detection to $3 \times 10^3$ ng(Fe). These results open the way for improved image quality and faster acquisition time in pre-clinical MPI scanners.

1. Introduction

Magnetic particle imaging (MPI) is a new tomographic imaging modality, currently applied in pre-clinical investigations (Gleich and Weizenecker 2005). The technique exploits the response of magnetic nanoparticles (MNP) to an oscillating magnetic excitation field, in the presence of static magnetic gradient fields used for spatial encoding. At present, a 3D-map of the MNP distribution can be reconstructed with a temporal resolution of several tens of milliseconds, and a spatial resolution in the millimeter range (Weizenecker et al 2009). The amount of magnetic particles in each voxel can be determined, making this a quantitative imaging technique. Previous studies have demonstrated the capabilities of MPI in vascular mapping, perfusion imaging, monitoring of drug delivery and cell tracking (Maruyama et al 2016, Sedlacik et al 2016, Dieckhoff et al 2017, Franke et al 2017, Le et al 2017). Improvements in the detection and quantification of small amounts of magnetic tracers will accelerate the development of MPI applications. The sensitivity of an MPI measurement is influenced by many factors including scanner geometry, the type of MNP tracer, imaging parameters, reconstruction scheme and hardware components.

Particularly the fundamental geometry and design of the detection coils used for MPI are important due to the small signals produced by MNPs, and the concurrent presence of much larger-amplitude excitation fields. Many existing MPI scanners have implemented dual-purpose coils for both the generation of excitation fields,
and simultaneous signal acquisition (three individual coils positioned in orthogonal directions in space) (Franke et al. 2016). This approach allows for a compact, space-saving coil set-up. The disadvantage of the dual-purpose coils is the simultaneous presence of the large currents used to generate the excitation fields, and the very small current (more than six orders of magnitude lower) generated by the particles’ magnetization response. The extraction of an undistorted MPI signal is thus challenging. Although notch filters are used in the receive path to suppress the excitation frequency, excitation currents cannot be fully suppressed. In addition, higher harmonics of the excitation currents are generated by non-linear components in the transmission- and receive-chains, making the identification of the MNP signals even harder. Since the current induced by the particles is several orders of magnitude smaller than the excitation field current, even small imperfections of the sinusoidal excitation currents can lead to strong distortions in the measurement data, causing a decrease in sensitivity and the signal-to-noise ratio (SNR). To circumvent these obstacles, separate-receive-only coils can be used (Karp and Duret 1980, Roemer et al. 1990, Schulz et al. 2015). These coils can be designed as geometric gradiometers, effectively attenuating the signal components generated internally by the system’s excitation fields, as well as other externally produced magnetic distortions. There are already some reports using this kind of coils in MPI technology before. Goodwill et al presented an MPI setup based on the x-space reconstruction approach using gradiometric receive coils (Goodwill and Konkle 2012, Goodwill et al. 2012). The traveling wave setup introduced by Vogel et al was also designed with dedicated receive coils (Vogel et al. 2014). In this work we will focus completely on the harmonic space MPI based on a reconstruction approach utilizing a measured system function presented by Gleich and Weizenecker (Weizenecker et al. 2009) using a commercial preclinical MPI scanner from Bruker. However, since the basic physical principle of the signal generation and acquisition of different MPI systems is the same, the presented advantages can be translated into improvements for other MPI setups as well. Graeser et al demonstrated the theoretical improvements gained by gradiometric coils and presented experimental results showing big advantages compared to the use of dual-purpose coils (Graeser et al. 2013, 2017). In this work, we present the characterization of a new receive-only coil prototype, designed and optimized for our preclinical MPI scanner (Bruker BioSpin, Germany). Similar as described in Graeser et al. (2017), a smaller coil diameter was chosen to increase the overall sensitivity based on the closer proximity to the samples. However, in the prototype presented here a second order gradiometric design consisting of two different coil diameters for the pick-up and the cancelation coil were chosen (Tumanski 2007). This allows for a larger homogenous sensitivity area compared to the case of coils of similar diameter, which is especially important for imaging of larger volumes. Furthermore, the inductance and the capacity of the prototype were chosen to be compatible with the in-built receive hardware components of our commercial MPI scanner. This enables the acquisition of the full frequency range between 0 to 1.25 MHz. The signal detection performance of the prototype coil is compared to that of the scanner’s original dual-purpose coil.

2. Materials and methods

The following sections describe in detail the measurement protocols used for stage of the study. First, measurements were performed to analyze the fundamental properties of both the dual-purpose coil (TxRx-coil) and the new receive-only coil (Rx-coil). The frequency-dependent sensitivity for detection of magnetic flux changes induced by oscillating magnetic moments was acquired for each coil topology using a calibration coil placed at different positions. The intrinsic noise and background signals of both coil topologies was then characterized by comparing raw spectral data obtained from empty scanner measurements. Additionally, an evaluation of SNRs was used to estimate limits-of-detections (LODs) from a spectral perspective. Finally, individual system functions (SF) were acquired with each coil system, and used for image reconstructions based on raw measurement data of the respective coil system. By repeating these measurements with a serial dilution of MNPs, we determined experimentally the LODs in terms of MNP mass per voxel after image reconstruction was performed.

2.1. MPI system hardware

All MPI measurements were performed using a preclinical MPI system (Bruker MPI 25/20 FF) installed at Charité University Hospital Berlin (figure 1). This system is based on the movement of a field-free-point (FFP) through the whole imaging volume, and employs the system function (SF) approach for image reconstruction (Rahmer et al. 2009, 2012). A selection gradient field of 2.5 T/m/µ₀ in the z-direction (1.25 T/m/µ₀ in x- and y-directions, coordinate system shown in figure 2(c), x-axis parallel to scanner bore) is used to generate the FFP and was chosen for all measurements presented in this work. By moving the FFP through the FOV, a spatially encoded signal of the whole imaging volume can be detected. This movement of the FFP on a closed 3D Lissajous-trajectory is accomplished by applying three orthogonal drive-fields oscillating at slightly different excitation frequencies (2.5 MHz divided by 102/96/99 in x-/y-/z-direction) with amplitudes of 12 mT/µ₀. Thus, in case of an 3D acquisition scheme one total Lissajous-trajectory is completed after a period of 21.5 ms, allowing the reconstruction of a full 3D dataset.
2.2. MPI receive coil hardware

The TxRx-coil, originally designed for the x-axis of the MPI scanner, consists of a single solenoid coil with a diameter of 160 mm (25 turns of copper HF Litz-wire), which is used for both the particle excitation and signal acquisition. The MNP generated signal is separated by using an additional coil, acting as a voltage divider, and is connected to the band-stop-filter (BSF) and the low-noise-amplifier (LNA). Thereby, the receive path is directly connected to the transmit path (whole transmit-receive-chain depicted in figure 2(a)). This configuration involves the risk of a direct feed-through of distortions occurring in the excitation signal to the signal reception process. Non-linear behavior of hardware components in the transmission chain leads to imperfections of the drive field, which are detected at higher harmonics of the excitation frequencies, and can not be differentiated from the MNP signal. The gradiometric design of the prototype Rx-coil is intended to suppress the induced currents in a broad frequency range arising from the excitation field, this includes higher harmonics generated by nonlinearities in the transmission chain, which are not filtered out completely by the band-pass-filter (BPF). In the case of a perfectly matched gradiometer, there would be no signal resulting from a homogeneous excitation field, and only the magnetic field of the MNP would generate an induced signal.

The prototype Rx-coil disconnects the transmit- and receive chains (figure 2(b)). The gradiometer design used for the Rx-coil consists of a pick-up coil \((R = 36 \text{ mm}, 2 \times 13 \text{ turns of copper HF Litz-wire})\) connected in series with a cancelation coil \((R = 52 \text{ mm}, 2 \times 6 \text{ turns of copper HF litz-wire with reverse winding direction})\), as displayed in figure 2(c)). By variation of the distance between the two cancelation coil parts, the mutual inductance with the drive field coil (in x-direction) can be minimized. Thus, the electromagnetic
coupling between these receive coils and possible distortions during the signal acquisition are minimized. In the current prototype, only one of the two cancelation coil parts can be moved. For our prototype we have chosen a larger radius for the cancelation coil to minimize the unwanted detection of the particle signal. This way a larger homogenous sensitivity distribution can be achieved while the homogenous excitation field is still suppressed. The Rx-coil is positioned along the x-axis of the scanner, leading to a smaller accessible bore diameter of about 65 mm (compared to 120 mm without Rx-coil), this is sufficient for studies of phantoms and small rodents. Using the estimation for the sensitivity at the center position of a LNA-noise dominated solenoid coil given in Graeser et al (2017), a factor of about 10 dB is to be expected based on the smaller radius of the Rx-coil compared to the TxRx-coil. The Rx-coil was designed to be compatible with the already existing scanner hardware for signal processing. To perform MPI measurements, the Rx-coil was connected to one independent receive channel, containing similar hardware elements as used for the TxRx-coil-receive chain. Unlike the TxRx-coil, the Rx-coil is directly connected to the BSF without using a voltage divider.

Field simulations (finite element analysis, Ansys Maxwell, Ansys Inc., Canonsburg Pennsylvania) of the prototype coil, including a simplified model of the MPI scanner, were performed to investigate the spatial distribution of the magnetic field amplitude, which also describes the spatial sensitivity profile according to the law of reciprocity (Hoult and Richards 1976). The shielding of the scanner was modeled as solid copper, taking eddy current effects in adjacent structures for an excitation frequency of 25 kHz into account. However, ideal coils were assumed for the TxRx-coil and the Rx-coil, neglecting eddy current effects within the coils.

2.3. Coil characterization measurements
A network analyzer (NWA) (Agilent E5061B ENA, Santa Clara, USA) was used to characterize the receive sensitivities of the two coil types. These results were thereafter compared with those obtained from the simulations. A known reference signal was generated by means of a small coil (3-axes TxRx test coil, Bruker BioSpin, Germany) connected to the function generator output of the NWA, and positioned at the center of the scanner’s FOV. The induced voltage within each receive coil type, when directly coupled to the NWA, was recorded for frequencies between 10 kHz and 2 MHz.

Additionally, the spatial dependence of each coil’s sensitivity was determined by placing the reference coil at various positions along the scanner’s x- and y-axis. At each position, the induced voltage in each coil type was measured.

2.4. System function acquisition
A system function (SF) was measured for use in reconstructions of measurements of serial dilution of MNPs. All image reconstructions reported here were made using the same SF. This SF was measured using a reference sample of 1 µl Ferucarbotran (FCT, c(Fe) = 0.935 mol l⁻¹, Meito Sangyo, Japan) within a (nearly) cubic 1 mm³ container. The spectra of FCT have been demonstrated to exhibit linear scaling at high concentrations (Löwa et al 2016). The container was robotically positioned at 32 × 32 × 16 individual, equidistant positions in a FOV of 22 × 22 × 11 mm³. For each position, 100 measurement repetitions were acquired and averaged. Note, data acquisition at each point was performed using the TxRx-coil and Rx-coil simultaneously. Empty scanner measurements were acquired intermittently throughout the SF acquisition. These were used to subtract (long-lasting) background contributions from the signals, and to calculate the SNR for all frequency components.

2.5. Serial dilution measurements
A serial dilution of FCT was used to determine the LODs for each coil-type. For this purpose, 14 samples containing 1 µl of FCT at decreasing iron concentrations ranging from c(Fe) = 73.6 mmol l⁻¹ down to 9.3 µmol l⁻¹ (total iron mass ranging from m(Fe) = 4.1 µg to m(Fe) = 500 pg) filled into sample tubes (MicroAmp Fast Reaction Tubes, 0.1 ml Appl. Biosystems, USA) were used. The iron content of all samples was verified by measurements with a magnetic particle spectrometer (MPS-3 Bruker BioSpin, Germany), which was calibrated using a reference sample with a known quantity of MNP (Snyder and Heinen 2011).

The small volume of 1 µl was used to minimize the effects of the encoding scheme (FFP or field-free-line) and the gradient strength, as was proposed in Graeser et al (2017). This also lead to small imperfections in the sample preparation process, since the volume could not be positioned perfectly at the bottom of the sample tube. The droplets stick to the left or the right side of the tube, resulting in potential positioning uncertainty of 1–2 mm. Additional measurements containing no MNP at all were acquired for comparison.

For low iron masses image artefacts will distort the reconstructed images, which might be misinterpreted as the actual sample. Therefore, each sample was measured at three defined locations (A = (0,0,0) mm, B = (5,5,0) mm, C = (–5, –5, 0) mm) within the FOV (centered at (0, 0, 0) mm) to check if the reconstructed distribution is moving accordingly. The total acquisition time was approx. 2 s for all presented measurements (100 averaged 3D measurement repetitions). Before each acquisition, background measurements of the empty scanner were collected for the subtraction of long-term background contributions to the signal. To minimize statistical
uncertainties and to check the reproducibility of the reconstruction, 27 individual measurements were acquired for each sample and each position. These datasets were used separately for image reconstructions, allowing the calculation of a standard deviation of the reconstructed MNP amount.

To test the quantitative information in the reconstructions, the intensities of the reconstructed images at the sample positions were summed. A volume of interest was chosen within each image at the theoretic sample positions. To minimize the influence of image blurring caused by the regularization, only voxel intensities above a threshold 0.5 of the maximum intensity were included in the calculation. For each sample, the mean value and the standard deviation were calculated based on the 27 individual reconstructions. The results were then compared to the actual iron mass of the sample.

2.6. Image reconstruction
Image reconstructions were performed using the Kaczmarz-algorithm with Tikhonov regularization implemented in Matlab (MathWorks, Natick USA) (Knopp et al 2010). The data of each coil type were used separately for reconstructions to provide a comparison of the image reconstruction capabilities of each. Selection of the frequency components used in the reconstruction process was done by stipulating a minimum SNR threshold based on the SNR calculated for all frequency components in the SF. The biggest distortions induced by the excitation fields are detected for frequencies below 80 kHz, thus all components below were neglected. All reconstructions were calculated with a single Kaczmarz iteration. The SNR threshold and the regularization parameter were chosen by visual inspection, with the focus on optimizing the reconstruction of those samples containing the smallest iron masses. A SNR threshold of 150 and a relative regularization parameter of $200 \cdot \lambda_0$ yielded the best results for both coils (Weizenecker et al 2007). A total number of 24 and 139 frequency components were used in the reconstruction for the TxRx-coil and the Rx-coil, respectively. Although samples with higher iron quantities could be reconstructed with less regularization and a smaller SNR threshold, the same parameters were used for all reconstructions for a comparison of the image quality, and to ensure no influence of the reconstruction parameters on the intensity values.

3. Results
3.1. Coil sensitivities
The frequency-dependent sensitivities for detection of magnetic flux changes were analyzed for both coils using a NWA. Figure 3(a) displays the power transfer ($S_{21}$) from the reference coil, located at the center of the FOV, to the Rx-coil (blue) and the TxRx-coil (red), respectively. Both coils show similar qualitative behavior over the whole frequency range. The region below 80 kHz is mainly influenced by the BSF of the receive chain, which lead to a strong attenuation of about 120 dB for frequencies around 25 kHz. Above 80 kHz the sensitivities increase until a maximum is reached around 600 kHz. The frequency where this maximum occurs is determined by the resonance frequency of the LNA and is slightly different for the TxRx-coil and the Rx-coil due to different inductances.

Calculating the difference between the curves reveals the sensitivity increase gained by the Rx-coil (figure 3(b)). Neglecting the strong deviations caused by the BSF below 80 kHz and the variation caused by the slightly different positions of the resonance peaks around 600 kHz, a nearly constant sensitivity increase of about +12 dB is achieved by the Rx-coil. One reason for the higher sensitivity is the closer proximity of the Rx-coil to the reference coil (due to the smaller diameter of the Rx-coil compared to the TxRx-coil). Furthermore, the Rx-coil is directly connected to the BSF, without using a voltage divider, which minimizes additional losses of the measurement signal.

Figure 4(a) displays simulated sensitivity ($\rho_\lambda$) values for the Rx-coil in a central z-slice. The simulations reveal a homogenous region in the center of the coil. This was achieved by a radial gradiometric coil design, i.e. in which the coil diameters of the inner pick-up and the outer cancelation coil differ. To quantify the homogeneity of the coil sensitivity, a volume of interest was defined by a 6 cm $\times$ 3 cm $\times$ 3 cm cuboid around the center position, which represents an MPI relevant region. The relative deviation between the maximum and minimum sensitivity in this volume was determined to be 15% for the Rx-coil and 14% for the TxRx-coil.

Figures 4(b) and (c) show the comparison of the simulation results with measured sensitivities along the central x- and y-axis to validate the simulations. The maximum values of the measured data were normalized to the maximum values of the simulation, to compare the spatial dependence. For both coil types, the measured sensitivities are in close agreement with the simulated data, with relative deviations below 1%.

3.2. Spectral analysis
The raw MPI measurement data for both coils were analyzed in the frequency domain. Figures 5(a) and (b) display the signal amplitudes acquired from an empty scanner. A total acquisition time of 2 s for each dataset was used, which represents 100 averaged measurement repetitions. The strongest signal components can be
found for integer multiples of the x-direction excitation field frequency. This is mainly caused by unwanted higher harmonics of the excitation field, due to non-linear distortions within the transmit-(receive) chain. The gradiometric design of the Rx-coil provides broadband suppression of spatially homogeneous signals. As a result, spurious harmonics and external distortions are suppressed, resulting in a much lower overall background signal level of the empty scanner compared to the TxRx-coil (figure 5(b)). The pure harmonics of the excitation frequency in the x-direction are attenuated by factors up to 54 dB. However, some parts of the excitation fields generated in y- and z-direction are still detected due to non-symmetric decoupling with the x-receive coils.

Averaging all frequency components over the whole frequency range to determine an average background level showed a background level approximately 17 dB lower for the Rx-coil compared to the TxRx-coil. Since noise is a determining factor in the lowest resolvable signal, a decrease of the noise level improves the system’s sensitivity for detecting samples containing small amounts of MNP.

The improved sensitivity, discussed in the previous section, combined with less background signal, leads to improved SNRs in SF measurements using the Rx-coil rather than the TxRx-coil (figures 5(c) and (d)). High SNRs can be found for frequencies close to the pure harmonics of the excitation field, as it was described in Rahmer et al (2009, 2012). Below 80 kHz distortions caused by the signal excitation lead to a strong attenuation of the calculated SNRs in case of the TxRx-coil. For the Rx-coil, these distortions are filtered out, and the SNRs in this region are clearly higher (factors up to 54 dB). For other frequency ranges, a nearly constant SNR-increase of approximately 10 dB was determined. This agrees with the NWA measurement results, which showed a sensitivity increase of 12 dB.

Assuming a linear scaling of the SNR with the iron mass of the sample, one can calculate a rough estimation for the lowest detectable iron mass for each coil. For this purpose, the iron content used in the SF acquisition (52 µg) is divided by the highest SNRs. This procedure results in iron masses of approximately 80 ng for the TxRx-coil and 6 ng for the Rx-coil. However, it is important to note that this procedure yields only an initial estimation of the LODs. A more reliable determination will be made in the following section based on serial dilution measurements.

3.3. Limits of detection

Having analyzed the coil performance and sensitivity gain of the Rx-coil, we next determined the MPI imaging capability in a phantom study. The images of the serial dilution reconstructed separately from the TxRx-coil and Rx-coil data are shown in figure 6, for the three different spatial positions. Displayed are maximum intensity projections along the z-axis. The brightness is scaled to the maximum intensity for each image individually.

The different positions A, B and C can be reconstructed precisely at the true locations (marked with a red cross) for a wide range of iron contents. The high regularization in the reconstructions leads to blurred images compared to the real MNP distribution. This blurring appears to be more pronounced for the TxRx-coil images, where fewer frequency components were used in the reconstruction, leading to a loss of spatial information (Rahmer et al 2009, 2012). Small deviations from the nominal sample position could be caused by the sample preparation of the 1 µl volume (as described in section 2.5).

The lowest iron amount that could be resolved at all three positions, contains 133 ng of iron for the TxRx-coil and 20 ng for the Rx-coil, which is close to the previous estimation made on the SNR values. Measurements
containing lower iron masses are disturbed by noise, and their reconstructions contain image artefacts. Above the LODs, no distinct image quality differences can be observed between samples containing high or low amount of MNP, when using the same reconstruction parameters.

Finally, we analyzed the quantification capability of the reconstructed images for both coil types. The MPI signal intensities extracted from the reconstructions are shown in figure 7 as a function of the iron content of the samples. Displayed are the mean values of the 27 individual reconstructions, with the standard deviations as error bars for each sample. Both coil types show a linear dependency of the MPI signal with iron content above the LODs. A linear regression was performed for all cases, including all data above the LOD, with coefficients of determination ($R^2$) above 0.99, indicating a clear linear relationship. The quantitative values gained by both coils agree nicely for all sample positions above the LOD with relative standard deviations ranging between 4 to 33% for the TxRx-coil and 2%–29% for the Rx-coil. The relative standard deviations for both coils are below 7% for iron masses 10-times above the LODs.

4. Discussion

We have presented a detailed comparison of the TxRx- and the Rx-coil, showing big improvements gained by the prototype coil. The results of the NWA measurements, the spectral analysis and the reconstructed phantom images were in good agreement and were used to quantify the improvements of the Rx-coil.
In Graeser et al (2017) a similar scanner with a prototype gradiometric receive coil was used, which reported a LOD of 5 ng. The presented measurements were acquired with almost the same measurement parameters as used for our studies. The drive field amplitude and the acquisition time were the same, only the gradient strength of 2/1/1 T/m was slightly lower. The gradiometric receive coil used in Graeser et al (2017) was designed with a diameter of 40 mm. Assuming a linear scaling of the LOD with the sensitivity, and using the sensitivity scaling, derived in Graeser et al (2017), we project that reducing the size of our own coil (72 mm) to match that used in Graeser et al (2017) would result in a detection limit of 8 ng. Additionally, the used MNP type (LS-008) show an
about 3-fold higher MPI performance compared to the commercial Ferucarbotran (Ferguson et al 2015), which was used for our measurements. Using the same type of MNP would decrease our LOD even further.

A major difference between the Rx-coil presented here and previously presented gradiometric Rx-coils (Schulz et al 2015, Graeser et al 2017) is the use of different geometries of the pick-up and the cancelation coil. An ideal gradiometer would cancel the excitation field completely, without removing parts of the signal generated by the MNP. However, even for a simple magnetic dipole source this is not feasible due to the magnetic field distributions (Wiekhorst et al 2008). A parasitic inductance from the cancelation coil removes parts of the MNP signal, lowering the overall sensitivity of the scanner compared to a simple magnetometer (without cancelation coils). Using the same diameter for the pick-up and the cancelation coil would lead to big sensitivity losses or ‘blind spots’, where the sensitivity reaches zero. This pitfall can be overcome by using a radial gradiometer, with a larger coil diameter for the cancelation coil (Zimmerman 1977). This method results in smaller losses of the MNP signals, and a more homogenous sensitivity distribution. This feature is especially important for future MPI applications, where larger FOVs of several centimeters will be measured, for example by employing the focus field approach (Knopp et al 2015).

However, the radial geometry design requires precise positioning of the two coil parts, which need to be parallel to the excitation field lines. In the presented work, the strongest distortions were detected for frequencies of 80 kHz and below, mainly caused by coupling with the $y$- and $z$-excitation fields. This could be attributed to a small tilt of one of the coil parts, or by coupling of the excitation fields with parts of the coil or the connection lines. A reduction of the influence of the $y$- and $z$-drive fields would be highly beneficial, since the strongest MPI signals are expected in this frequency range, which are not currently included in the image reconstruction process. Inclusion of the sub 80 kHz frequency range could be achieved by implementing better shielding on the connection lines between the Rx-coil and LNA, or by tilting the coils with respect to the $y$-and $z$-drive field coils. For this purpose, the next iterations of the Rx-coil will be designed with two moveable cancelation coil parts, for easier and improved coil handling and fixation to improve the decoupling and the homogeneity over the whole volume of interest.

5. Conclusion

We have successfully characterized a prototype Rx-coil and implemented it within a preclinical MPI system. Using this prototype for MPI signal detection, two main improvements were achieved compared to the standard TxRx-coil. First, an increase in sensitivity of approximately 12 dB over the whole MPI relevant frequency range was validated by NWA measurements using a small reference coil to generate a signal. The sensitivity gain was attributed to the smaller coil diameter used for the Rx-coil, chosen to optimize the setup for rodent studies and a direct connection of the Rx-coil to the BSF and the LNA without using a voltage divider. This improvement in sensitivity is especially important for signal acquisition in the higher frequency domain, which are crucial for a well spatially-resolved MPI image (Rahmer et al 2009, 2012).
Second, the influence of external and internal background components on the measured signal were strongly attenuated by the use of a gradiometric design consisting of an inner pick-up and an outer cancelation coil. MPI measurements of an empty scanner showed less signal contributions generated by the excitation fields in the pure harmonic frequency components. The overall background signal, determined by MPI measurements of an empty scanner, decreased by a factor of about 17 dB. For pure harmonics of the x-direction excitation frequency, this attenuation is even stronger, with factors of up to 54 dB possible.

The combination of a higher coil sensitivity and a lower background signal level led to an increase of the SNRs calculated from the SF. In particular, the SNRs for the frequency range around 80 kHz and below were improved by factors up to 54 dB, because of the attenuation of the background signals. For higher frequencies, the SNRs were increased by a factor of about 10 dB, mainly influenced by the overall higher sensitivity of the Rx-coil. As a result, detection of samples containing as little as 20 ng of iron can be realized using the prototype coil, with an acquisition time of 2 s. This represents a significant improvement on the original receive coil, where the lowest detectable iron mass was 133 ng. The expected linear correlation between the MPI signal and the iron mass of the samples was observed for all reconstructions above the LODs with coefficients of determinations of $R^2 \geq 0.99$.

We have shown the higher amplitude signals resulting from the improved sensitivity can be translated into real improvements in spatial resolution, temporal resolution and/or limits of detection in MPI image reconstruction. Therefore, the Rx-coil approach presented here offers promising improvements for the MPI technology in advanced biomedical applications, where small amounts of MNP have to be detected and quantified.

Possible improvements of the coil design were pointed out and will be incorporated in a commercial Rx-coil design to circumvent the pitfalls of non-symmetric decoupling and fixation as well as coil handling.

**Acknowledgments**

This project was supported by the DFG research grants ‘AMPI: Magnetic particle imaging: Development and evaluation of novel methodology for the assessment of the aorta in vivo in a small animal model of aortic aneurysms’ SHA 1506/2-1, ‘quantMPI: Establishment of quantitative magnetic particle imaging (MPI) application oriented phantoms for preclinical investigations’ 1 FKZ TR 408/9-1, by the European Commission FP7 project ‘NanoMag’, grant agreement no. 604448 and by the EMPIR program co-financed by the Participating States and from the European Union’s Horizon 2020 research and innovation program, grant no. 16NRM04.

**References**

Dieckhoff J et al 2017 In vivo liver visualizations with magnetic particle imaging based on the calibration measurement approach Phys. Med. Biol. 62 3470–82

Ferguson R M et al 2015 Magnetic particle imaging with tailored iron oxide nanoparticle tracers IEEE Trans. Med. Imaging 34 1077–84

Franke J et al 2016 System characterization of a highly integrated preclinical hybrid MPI-MRI scanner IEEE Trans. Med. Imaging 35 1993–2004

Franke J, Lacroix R, Lehr H and Heinen U 2017 MPI Flow Analysis Toolbox exploiting pulsed tracer information – an aneurysm phantom proof IJMPI 31–5

Gleich B and Weizenecker J 2005 Tomographic imaging using the nonlinear response of magnetic particles Nature 435 1214–7

Goodwill P W and Konkle J 2012 Projection X-space magnetic particle imaging pattern IEEE Trans. Med. Imaging 31 1076–85

Goodwill P W, Lu K, Zheng B and Conolly S M 2012 An x-space magnetic particle imaging scanner Rev. Sci. Instrum. 83 33708

Graeser M et al 2017 Towards picogram detection of superparamagnetic iron-oxide particles using a gradiometric receive coil Sci. Rep. 7 1–13

Graeser M, Knopp T, Grüttner M, Sattel T F and Buzug T M 2013 Analog receive signal processing for magnetic particle imaging Med. Phys. 40 042303

Hoult D and Richards R 1976 The signal-to-noise ratio of the nuclear magnetic resonance experiment J. Magn. Reson. 24 71–85

Karp P and Duret D 1980 Unidirectional magnetic gradiometers J. Appl. Phys. 51 1267–72

Knopp T et al 2010 Weighted iterative reconstruction for magnetic particle imaging Phys. Med. Biol. 55 1577–89

Knopp T, Them K, Kaul M and Gdaniec N 2015 Joint reconstruction of non-overlapping magnetic particle imaging focus-field data Phys. Med. Biol. 60 L15

Le T-A, Zhang X, Hoshiar A K and Yoon J 2017 Real-time two-dimensional magnetic particle imaging for electromagnetic navigation in targeted drug delivery Sensors 17 2050

Löwa N, Radon F, Kosch O and Wiekhorst F 2016 Concentration dependent MPI tracer performance Int. J. Magn. Part. Imaging 25

Maruyama S M K, Shimada K, Emmeij K and Murase K 2016 Development of magnetic nanocarriers based on thermosensitive liposomes and their visualization using magnetic particle imaging Int. J. Nanomed. Nanosurg. 2

Rahmer J, Weizenecker J, Gleich B and Borger J 2009 Signal encoding in magnetic particle imaging: properties of the system function BMJ Med. Imaging 9 4

Rahmer J, Weizenecker J, Gleich B and Borgert J 2012 Analysis of a (3D) system function measured for magnetic particle imaging IEEE Trans. Med. Imaging 31 1289–99

Roemer P B, Edelstein W A, Hayes C E, Souza S P and Mueller O M 1990 The NMR phased array Magn. Reson. Med. 16 192–225

Schulz V, Straub M, Mahlke M, Hubertus S, Lammers T and Kessling F 2015 A field cancelation signal extraction method for magnetic particle imaging IEEE Trans. Magn. 51 6501804

Sedlacek J et al 2016 Magnetic particle imaging for high temporal resolution assessment of aneurysm hemodynamics PLoS One 11 e0160097

Snyder S R and Heinen U 2011 Characterization of magnetic nanoparticles for therapy and diagnostics Bruker BioSpin Appl. Notes 11 1–4
Tumanski S 2007 Induction coil sensors—a review Meas. Sci. Technol. 18 R31–46
Vogel P, Ruckert M A, Klauer P, Kußmann W H, Jakob P M and Behr V C 2014 Traveling wave magnetic particle imaging IEEE Trans. Med. Imaging 33 400–7
Weizenecker J et al 2009 Three-dimensional real-time in vivo magnetic particle imaging Phys. Med. Biol. 54 1–10
Weizenecker J, Borge R and Gleich B 2007 A simulation study on the resolution and sensitivity of magnetic particle imaging Phys. Med. Biol. 52 6363–74
Wiekhorst F, Steinhoff U, Haberkorn W, Lindner G, Bär M and Trahms L 2008 Localization of a magnetic nanoparticle spot from features of the magnetic field pattern and comparison to a magnetic dipole fit 4th European Conference of the International Federation for Medical and Biological Engineering (IFMBE Proceedings vol 22) pp 2347–51
Zimmerman J E 1977 SQUID instruments and shielding for low-level magnetic measurements J. Appl. Phys. 48 702–10