S. Ley*, M. Helbig, and J. Sachs

Preliminary investigations of magnetic modulated nanoparticles for microwave breast cancer detection

Abstract: This paper investigates the potential of magnetic modulated iron oxide nanoparticles in terms of a contrast enhancement for Ultra-wideband (UWB) breast imaging. The work is motivated by the low dielectric contrast between tumor and normal glandular/fibroconnective tissue. The influence of an external polarizing magnetic field on pure and coated magnetite nanoparticles is investigated in this contribution. Measurements were conducted using M-sequence UWB technology and an oil-gelatin phantom. It is shown that a coating, which is necessary for clinical use, results in a lower signal response, and thus leads to a lower detectability of magnetic modulated nanoparticles.

Keywords: UWB; magnetic nanoparticles; magnetic modulation; M-sequence radar technology; breast cancer detection; tissue mimicking phantom

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1 Introduction

Ultra-wideband (UWB) imaging of breast tumors is a potential alternative breast imaging modality. Several studies have shown the potential of this approach for both experimental measurements with breast phantoms and clinical trails [1–5]. The increased permittivity of malignant tissue, caused by the increased water content in the neoplastic tissue, is exploited to detect tumors by means of electromagnetic waves in the microwave range. The UWB imaging exploits non-ionizing radiation and provides a higher patient comfort compared to the X-ray mammography and in comparison to MRI it is a cost-efficient alternative. However, the dielectric contrast between malignant and fibroglandular breast tissue is around 10 percent in the microwave range [6]. This becomes difficult for breast cancer detection especially of young women, because the portion of glandular tissue is high compared to elder women. For this reason several groups investigated the potential of metallic nanoparticles to enhance the contrast between malignant and normal glandular/fibroconnective tissue. A contrast can be induced by a pure permittivity enhancement in terms of a differential measurement between native and contrast enhanced state [7, 8]. In clinical routine this becomes difficult due to the long enrichment time of the nanoparticles into the tumor, because the influence of the slight differences of the breast position between both measurements might be higher than the response caused by the nanoparticles. Bellizzi et al. [9, 10] investigated the behavior of magnetic nanoparticles (MNP) in presence of an external polarizing magnetic field (PMF) for different magnetic field intensities. Their results are promising concerning of introducing a new contrast enhancing approach for breast cancer detection. On condition that a sufficient amount of MNP accumulates within the tumor, the external PMF influences only the scattering behavior of the malignant tissue, whereby the nonmagnetic surrounding tissue will be unaffected.

In this work the influence of an external PMF on MNP (magnetite) is investigated by means of M-sequence UWB technology. An ON/OFF modulation of the PMF is presented to investigate the differences between pure magnetite nanoparticles and magnetite nanoparticles with a biocompatible aminodextran coating.

2 Material and methods

2.1 M-sequence technology

Measurements were performed applying the M-sequence sensor technology, which was developed at Technische Universität Ilmenau. This correlation measurement approach uses a binary pseudo-noise code (M-sequence) to stimulate the medium under test. The M-sequence is generated by a binary high-speed shift register which is pushed by a stable microwave oscillator. The signal energy of the sounding wave is distributed over the stimulus time,

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which enables a low signal magnitude. Due to the low voltage exposure of the medium under test the technology is suitable for medical applications, e.g. for breast cancer detection. Furthermore, the M-sequence technology can be applied to realize flexible and robust (low jitter and drift) UWB sensor systems as described e.g. in [11].

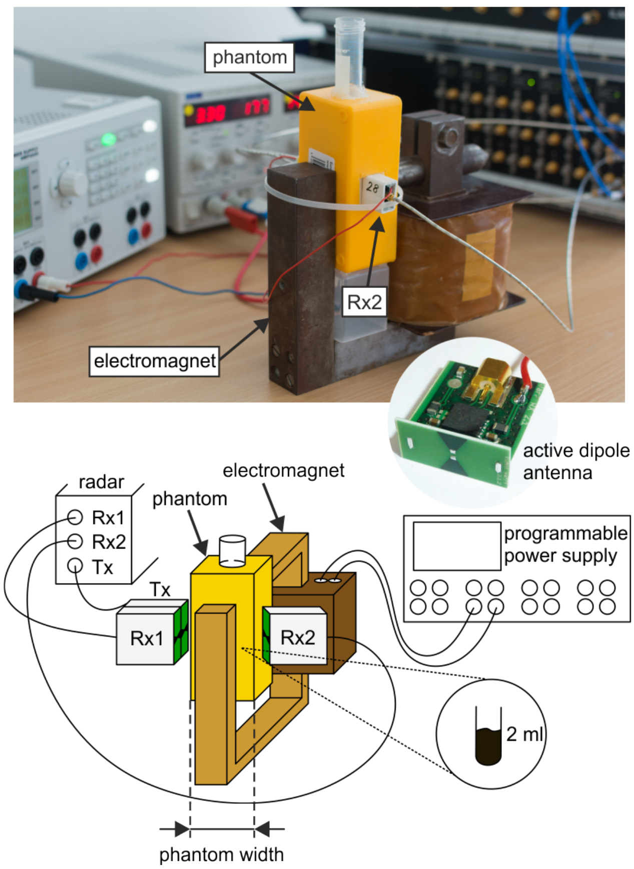

Figure 1: Experimental measurement setup for contrast investigations. The oil-gelatin phantom is placed inside the air gap of the electromagnet. Small active dipole antennas and M-sequence radar are applied for measurements. A programmable power supply is used to modulate the magnetic field intensity.

2.2 Measurement setup

To investigate the influence between pure and coated MNP, PMF modulations combined with UWB measurements are applied. Fig. 1 shows the corresponding measurement setup. Uncoated magnetite nanoparticles (WHKS 1S12, Liquids Research Ltd., Bangor, UK) and magnetite nanoparticles with an aminodextran coating (DFF 107 (in-house production), Biomedical Engineering Group, TU Ilmenau, Germany) are investigated. Both have a particle size of 10 nm. The MNP were diluted with distilled water and filled in a test glass which was positioned inside of a 5 cm wide oil-gelatin phantom [12]. The total volume of the solution inside the test glass was constantly 2 ml. Only the mixture ratio between ferrofluid solution and distilled water was varied to realize different magnetite masses. The phantom was placed inside the air gap of an electromagnet. The maximum magnetic field intensity of the electromagnet at the center of the air gap was 60 kA·m^{-1}. The magnetic field intensities were determined by measuring the absolute magnetic flux density using a Gauss Meter (Model 7030 Gauss/Tesla Meter, F.W. Bell, Milwauki, USA). The probe was placed at the center of the air gap which corresponds to the position of the MNP.

2.3 Signal preprocessing

Reflection and transmission measurements were performed by applying M-sequence technology and small active dipole antennas (see Figure 1) which are also used in the current breast imaging demonstrator [4]. Figure 2 shows the measured raw data $x(t, T)$ of the radar, where t is the propagation time and T corresponds to the observation time and the number of measurements, respectively. Considering $x(t, T)$ the response caused by the MNP is covered by the antenna crosstalk. Therefore, a signal preprocessing is applied by a drift correction:

$$x_{DE}(t, T) = x(t, T) - D(t, T), \tag{1}$$

where $x_{DE}(t, T)$ is the drift corrected radar signal. The system drift ($D(t, T)$) caused e. g. by weak temperature variations is estimated assuming a linear model as described by Helbig et al. [8]. In a further step the radar response $y(t, T)$, as depicted in Figure 2, is computed by

$$y(t, T) = x_{DE}(t, T) - \overline{x}_{DE}(t, T_{OFF}), \tag{2}$$

where $\overline{x}_{DE}(t, T_{OFF})$ is the mean value of the drift corrected radar signal over the time period without the presence of an external PMF and represents an estimation of the deterministic components of the radar response $x(t, T)$.

3 Results

Reflection and transmission measurements with an ON/OFF modulated PMF were conducted. Figure 2 (bottom) shows the modulated response caused by the MNP during the presence of an external PMF (60 kA·m^{-1}), whereby 6 mg magnetite were inside of the phantom. The

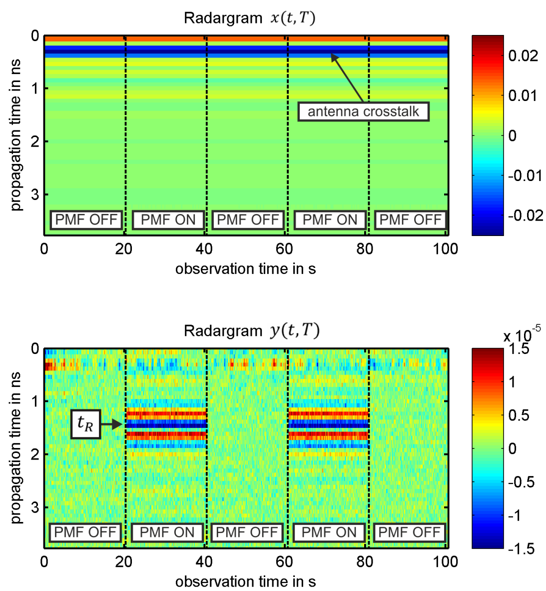

Figure 2: Measured raw data of the ON/OFF modulated reflection measurement (top). Radar response after signal preprocessing (bottom). The magnetic field intensity during the presence of the PMF was 60 kA·m^{-1}, whereby 6 mg magnetite were inside of the phantom.

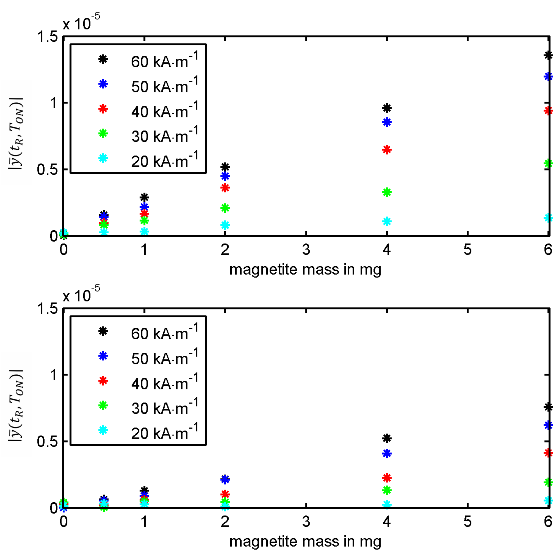

Figure 3: Magnetite mass dependent response of the ON/OFF modulated reflection measurements for different magnetic field intensities in the presence of an external PMF for pure MNP (top) and coated MNP (bottom).

magnitude of the mean value at the propagation time t_R (see Figure 2 bottom) during the presence of the external PMF (T_{ON}) is investigated for different magnetite masses and magnetic field intensities. Figure 3 and Figure 4 show the dependencies for the MNP with and without a particle coating for the reflection and transmission measurement, respectively. Results show a nearly linear dependence between the modulated radar response and the magnetite mass for both pure and coated magnetite nanoparticles. Furthermore, the response increases with the magnetic field intensity. However, the magnitude of the mean value during the presence of an external PMF distinguishes nearly by the factor two between pure and coated MNP.

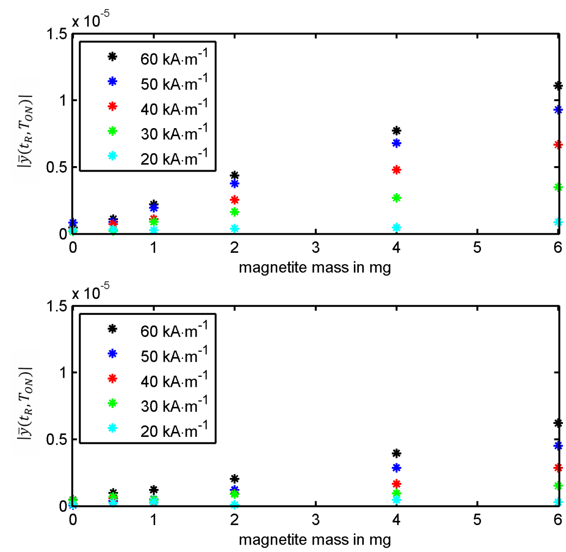

Figure 4: Magnetite mass dependent response of the ON/OFF modulated transmission measurements for different magnetic field intensities in the presence of an external PMF for pure MNP (top) and coated MNP (bottom).

4 Discussion and conclusion

The preliminary investigations indicate the possibility to detect low permeability changes of pure and coated MNP induced by a PMF by means of *in vitro* measurements using M-sequence UWB technology. Results display that a coating of MNP influences the measured radar response. Hong et al. [13] show that a dextran-coating of magnetite reduces the magnetic susceptibility of MNP, and thus might be a reason for the lower response. This also leads to a lower detectability of the coated MNP, but such a coating is necessary because pure magnetite nanoparticles are prohibited for clinical use. An additional functionalization of the coated MNP is necessary to enable selective targeting of cancerous cells. The influence of such a functionalization has to be included in future work. Furthermore, the presented contrast enhancing approach has to be combined with the current measurement setup for breast imaging [4].

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Author's Statement
Conflict of interest: Authors state no conflict of interest. Material and Methods: Informed consent: Informed consent has been obtained from all individuals included in this study. Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

References

[1] Fear EC, Hagness SC, Meaney PM et .al. Enhancing breast tumor detection with near-field imaging, IEEE Microwave Magazine, vol. 3, no. 1, pp. 48-56, 2012.
[2] Klemm M, Craddock IJ, Leendertz J et al. Clinical Trials of a UWB Imaging Radar for Breast Cancer, Proc. European Conference on Antennas and Propagation (EuCAP) 2010, Barcelona, Spain, pp. 1-4, 2010.
[3] Bourqui J, Sill JM, Fear EC. A Prototype System for Measuring Microwave Frequency Reflections from the Breast, International Journal of Biomedical Imaging, vol. 2012, pp. 1-12, 2012.
[4] Helbig M, Dahlke K, Hilger I, Kmec M, Sachs J. Design and Test of an Imaging System for UWB Breast Cancer Detection, Frequenz, vol. 66, pp. 387-394, 2012.
[5] Conceição RC, Medeiros H, O'Halloran, et al. Initial Classification of Breast Tumour Phantoms Using a UWB Radar Prototype, Special Session "Microwave and Multimodal Imaging Techniques in Medical Applications" - ICEAA 2013, Turin, Italy, 2013
[6] Lazebnik M, Popovic D, McCartney L et al. A large-scale study of the ultrawideband microwave dielectric properties of normal, benign and malignant breast tissues obtained from cancer surgeries, Physics in Medicine and Biology, vol. 52, pp. 6093-6115, 2007.
[7] Klemm M, Leendertz J, Gibbins D et al. Towards contrast enhanced breast imaging using ultra-wideband microwave radar system, Proc. of the IEEE Radio and Wireless Symposium (RWS) 2010, pp. 516-519, 2010.
[8] Helbig M, Sachs J, Tansi F, Hilger I. Experimental feasibility study of contrast agent enhanced UWB breast imaging by means of M-sequence sensor systems, Proc. European Conference on Antennas and Propagation (EuCAP) 2014, The Hague, Netherlands, pp. 311-315, 2014.
[9] Bellizzi G, Bucci OM, Catapano I. Microwave Cancer Imaging Exploiting Magnetic Nanoparticles as Contrast Agent, IEEE Transactions on Biomedical Engineering, vol. 58, no. 9, pp. 2528-2536, 2011.
[10] Bellizzi G, Bucci OM. A Novel Measurement Technique for the Broadband Characterization of Diluted Water Ferrofluids for Biomedical Applications, IEEE Transactions on Biomedical Engineering, vol. 49, no. 6, pp. 2903-2912, 2013.
[11] Sachs J. Handbook of Ultra-Wideband Short-Range Sensing: Theory, Sensors, Applications, Wiley-VCH, Berlin, 2012.
[12] Lazebnik M, Madsen EL, Frank GF, Hagness SC. Tissue-mimicking phantom materials for narrowband and ultrawideband microwave applications, Physics in Medicine and Biology, vol. 50, no. 18, pp. 4245-4258, 2005.
[13] Hong RY, Li JH, Qu JM, Chen LL, Li HZ. Preparation and characterization of magnetite/dextran nanocomposite used as a precursor of magnetic fluid. Chemical Engineering Journal, vol. 150, pp. 572-580, 2009.