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DEVELOPMENT OF MAGNETIC NANOPARTICLES TOMOGRAPHY IN NUCLEAR AND MEDICAL ELECTRONICS DIVISION

Przemysław Wróblewski, Waldemar Smolik
Warsaw University of Technology, Institute of Radioelectronic and Multimedia Technology, Nuclear and Medical Electronics Division

Abstract. *In this article summary of all accomplishments of Nuclear and Medical Electronics Division in the field of Magnetic Nanoparticles Imaging. Magnetic Nanoparticles Imaging is a new tomographic and molecular imaging method that employs superparamagnetic nanoparticles as the tracer. This article includes the most importuned definition regarding this technique, its most interesting features, as well as report about research conducted in the Division in prospect to advance this imaging method in Poland.*

Keywords: nanoparticles, superparamagnetic materials, tomography, molecular imaging

ROZWÓJ TOMOGRAFII NANOCZĄSTECZEK MAGNETYCZNYCH W ZAKŁADZIE ELEKTRONIKI JĄDROWEJ I MEDYCZNEJ

Streszczenie*. Artykuł ten podsumowuje dotychczasowe osiągnięcia Zakładu Elektroniki Jądrowej i Medycznej w dziedzinie obrazowania nanocząsteczek magnetycznych. Obrazowanie nanocząsteczek magnetycznych jest to nowa metoda obrazowania molekularnego i tomograficznego wykorzystująca jako znacznik nanocząsteczki superparamagnetyczne. W treści artykułu zawarto najważniejsze definicje dotyczące tego zagadnienia. Obecny stan rozwoju tej techniki oraz jej najbardziej interesujące właściwości, jak również opis prac badawczych podjętych przez Zespół w celu rozwoju tej metody obrazowania w Polsce.*

Słowa kluczowe: nanocząsteczki, materiały superparamagnetyczne, tomografia, obrazowanie molekularne

Introduction

Magnetic Particle Imaging (MPI) is novel imaging diagnostic technique. This new molecular imaging method was developed by researchers from Philips Research Laboratories: Bernhard Gleich and Jürgen Weizenecker. In 2005 the first results of their works on imaging using magnetic nanoparticles were published in Nature. Since that publication some research institutes commenced investigations on this imaging technique. Currently the leading scientific centers in this field are University of Lubeck (Thorsten M. Buzug) and University of Berkley, California (Patrick W. Goodwill). Division has ambition to became such a pioneer in Poland.

The increased attention regarding this modality is result of unique features characterizing MPI. First of all, initial research results reviled its high sensitivity, comparable in this regard with the best available molecular imaging techniques such as SPECT or PET, combined with high spatial and time resolution, rivaling Magnetic Resonance Imaging. Secondly, MPI is a method simple to implement. However, not as easily scalable. Although the third and most importuned reason is variety of possible applications of MPI. Some of which are quite unique. Magnetic nanoparticles, which are used as a marker in this technique, can fused with bio-molecules to label specific of organic substances or tissues. Which in turn allows study of biological and physiological through observation of time and spatial changes of markers density in the subject. MPI can be applied to function imaging of kidneys or liver, examination of blood flow in the coronary arteries, in diagnostic of pulmonary diseases as well as localization of cancers or implanted stem cells. Potentially, if used along with magnetic hyperthermia, the same nanoparticles or even the same equipment can be applied for both diagnostic and therapy of malignant diseases. MPI scanner can be design as typical tomographic scanner similar in appearance to CT scanner or one-sided scanner of similar uses as mini-gamma camera. At last, this technique can be used to research properties of superparamagnetic nanoparticle itself [1].

Table 1. Comparison of parameters of chosen molecular imaging modalities.

Modality	PET	SPECT	MRI	MPI
Time resolution	1 min	1 min	1 s	<0,1 s
Spatial resolution	3 mm	10 mm	1 mm	<1 mm
Sensitivity	Very high 10^{-11} - 10^{-12} mol/L	High 10^{-9} mol/L	Low (Moderate - hyperpolarization) 10^{-3} mol/L (10^{-6} mol/L)	High 10^{-8} mol/L

1. Theory of Magnetic Particles Imaging

In MPI superparamagnetic nanoparticles are used as a tracer. The core of such particles is usually manufactured from super-paramagnetic iron oxide (SPION) (Fig. 1). It is of radius from 10 to 100 nm and coated with biocompatible polymers.

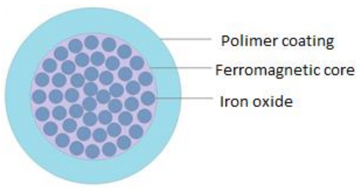

Fig. 1. Cross-section of superparamagnetic iron oxide nanoparticle. Core is made of magnetite or maghemite. Coating consist of biocompatible and biodegradable polymers (for example Dextran) and eventual attached molecules, giving the nanoparticle an affinity for specific substances or tissues

Superparamagnetism is form of magnetism in which ferromagnetic material nanoparticles of sufficiently small size and magnetically isolated from one another can be recognized as separate magnetic domains and randomly flip direction of magnetization vectors under the influence of temperature. In this state nanoparticles behavior can be described by Langevin's theory of paramagnetism and their magnetization curve by equation:

$$M(t) = m_s c_p (\coth(kH_D(t)) - \frac{1}{kH_D(t)}) \tag{1}$$

where c_p – particles concentration, H_D – magnetic field strength, $k = \frac{\mu_0 m_s}{k_B T}$, μ_0 – magnetic permeability of vacuum, k_B – Boltzman's constant, T – temperature, m_s – magnetic momentum of saturation, equal to: $m_s = \frac{1}{6}\pi d_c^3 M_s$, where M_s is saturation magnetization of magnetite and d_c is diameter of nanoparticle. The most imported features of nanoparticles that can be deducted from this equation are nonlinear magnetization curve, high magnetic moment compere to normal paramagnets and fact that in high enough magnetic field nanoparticle undergo saturation.

Thanks to this properties detection of nanoparticles is possible if tracers containing them are placed in changing magnetic field (preferably sinusoidal) and signal from their magnetization is simultaneously acquired by appropriate receiving coil. Unfortunately, in this case one would acquire both signal from magnetization changes and excitation signal, which is stronger by about six orders of magnitude.

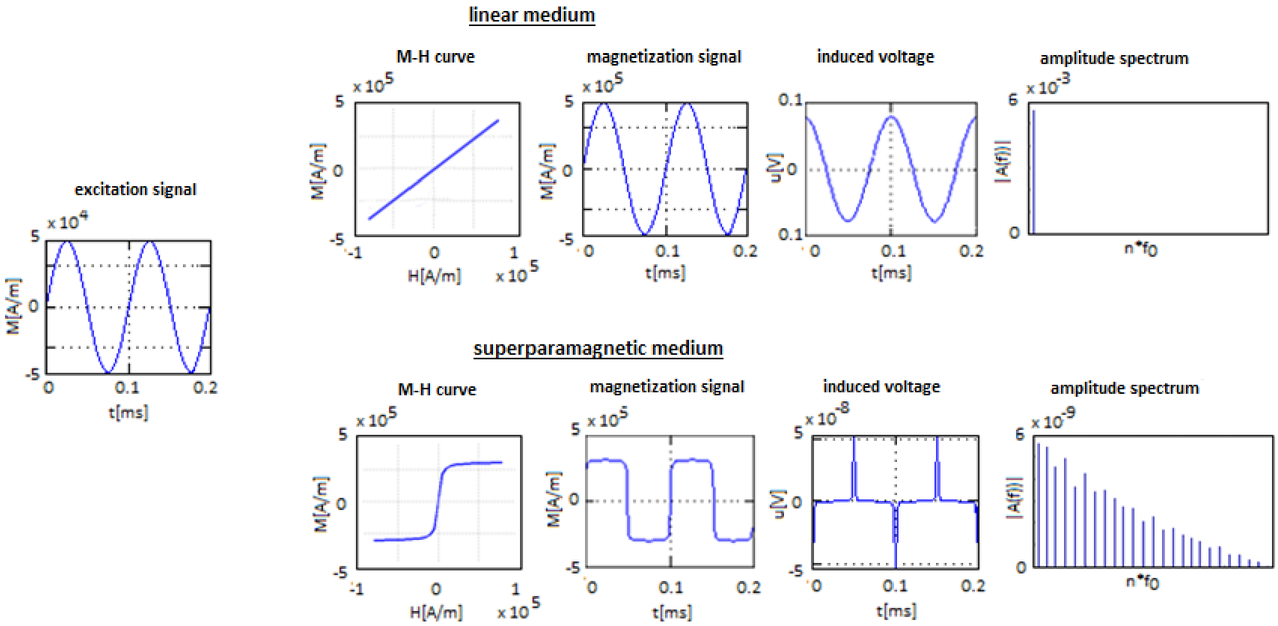

Fig. 2. Magnetization signals, signals induced in receiving coil and their amplitude spectra for medium excited with sinusoidal signal depending on the magnetization curve: linear medium (top) and nonlinear medium - superparamagnetic nanoparticles (bottom)

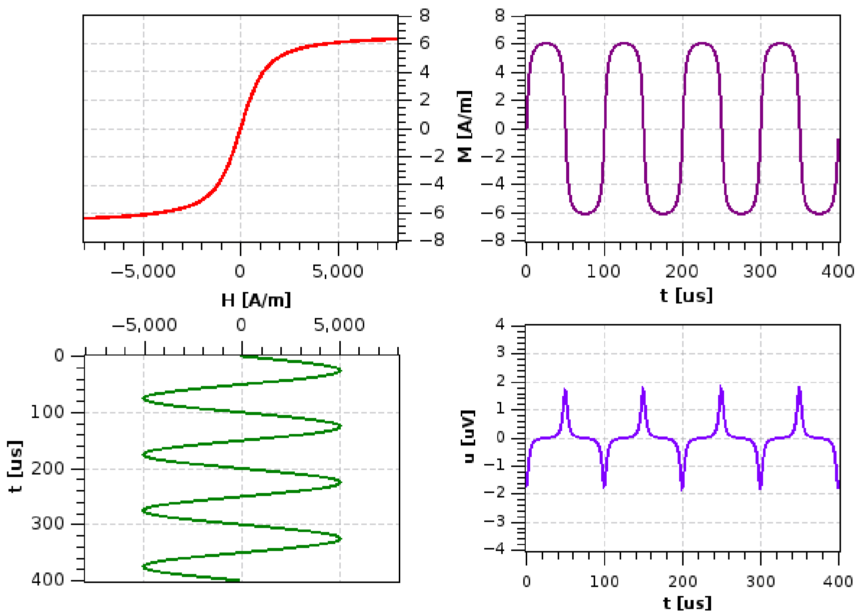

Fig. 3. Dependence of magnetization signal induced in receiving coils on nonlinear magnetization curve (M-H curve). Excitation signal (bottom left), magnetization curve (top left), superparamagnetic nanoparticels magnetization (top right), voltage signal induced in receiving coil (bottom left)

If nanoparticles magnetization curve was liner, separation of this signal would be impossible (Fig. 2). However, as the magnetization curve is nonlinear signal from nanoparticles contains harmonics of excitation frequency (Fig. 3). It is possible than to separate those high frequencies by filtering out excitation frequency (broadband method) or by measurement of each harmonic separately (narrowband method). Through analysis of this harmonics signals for example particles concentration can be estimated.

Localization of the tracer can be achieved by application of gradient magnetic field, which cause nearly all nanoparticles to undergo saturation thus preventing them from contributing in signal generation, except those in small volume near the zero magnetization field strength, called field free point (FFP). In such circumstances magnetization signal induced in receiving coil originates only from particles in FFP [3]. To scan whole imaged volume FFP can be moved. There are two known procedures of scanning using this method of localization – frequency mixing method (excitation frequency much higher than movement of FFP) and driving field method (high frequency movement of FFP used as exciting field) [2]. Time resolution of imaging is highly dependent on applied scanning process.

2. Research conducted in Division

In Nuclear And Medical Electronics Division research on model of tomographic scanner for nanoparticles imaging are being carried out since 2011. In the wake previous studies, conducted under statutory works, one dimensional nanoparticles scanner was created. Presently system for nanoparticles spectroscopy is being developed. Furthermore, numerical calculation MATLAB toolbox is being written that will allow simulation of MPI measurement system, generation of simulated measurement result of such systems and reconstruction of MPI images from both artificial and real data.

2.1. Magnetic Nanoparticles Scanner

MPI scanner developed in Nuclear And Medical Electronics Division allows one dimensional imaging of nanoparticles concentration [4] (Fig. 4 and 5). It is designed for research of small objects. Current acquisition system employs narrowband detection method using lock-in amplifier and mix frequency method for field free point displacement. Particles are excited with signal of 10 kHz frequency and 8 mT of amplitude. Gradient coils generate field of about 1 T/m strength. Field of view of the scanner has about 30 mm diameter. Using this setup first real measurements were conducted [7] (Fig. 7). The phantoms with the chambers for water solution of nanoparticles with 0.5 mol/L concentration (Fig. 6) were used in the experiments. The phantoms were made using 3D printing technology.

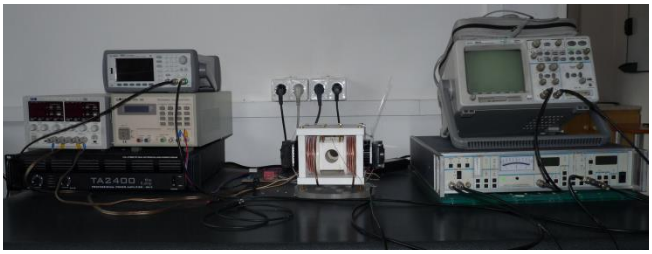

Fig. 4. Measurement setup for one dimensional MPI scanner. On the left side, equipment used for generation of excitation signal and gradient field (function generator, power supply, audio power amplifier). In the middle, MPI scanner gentry containing coils and cooling system. On the right side, equipment used in acquisition setup (lock-in amplifier and oscilloscope)

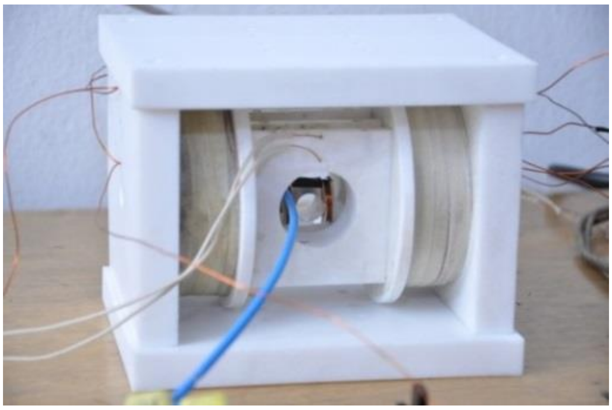

Fig. 5. MPI scanner gentry. View of gradient coils and receiving coil

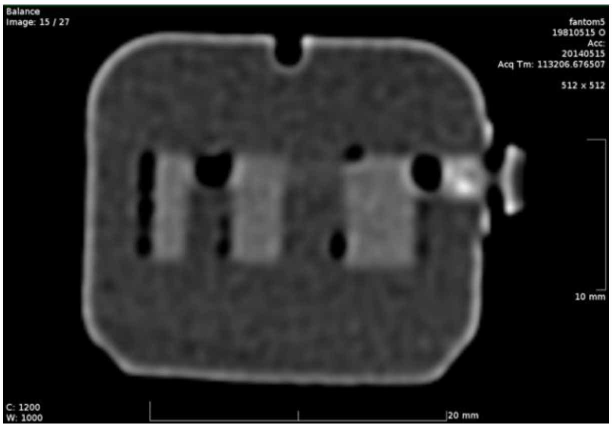

Fig. 6. CT image of phantom with three chambers filled with ferrofluid. Phantom was printed in 3D printing technology and use for MPI scanner research

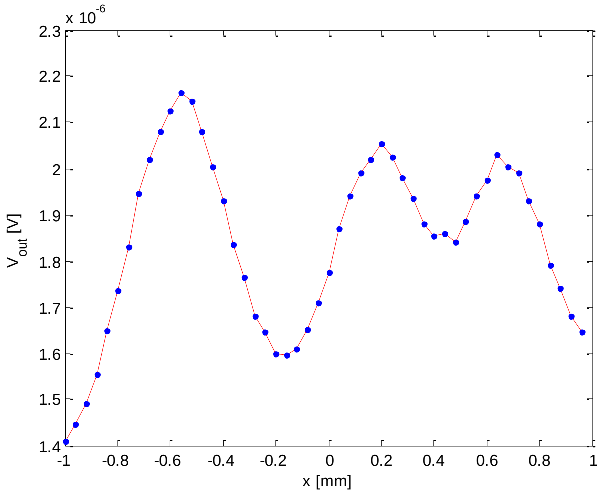

Fig. 7. Measurement along X axis of scanner of magnetic response of 60 nm nanoparticles dispersed in water in three chamber phantom. "Zero" position corresponds to center of the FOV of the scanner. Amplitude of 5rd harmonic measured by lock-in amplifier is proportional to concentration of nanoparticles

2.2. Magnetic Nanoparticles Spectroscopy

Magnetic Particles Spectroscopy (MPS) allows measurement of harmonic spectra of magnetization signal of magnetic nanoparticles. It is used for research of properties of nanoparticles, for example particle diameter or magnetization curve estimation. Magnetic particles spectrometer may can be considered a zero dimensional MPI scanner. To acquire the spectra of magnetization signal harmonics only detection of magnetization signal is necessary. In this case gradient coils are irrelevant. Signal from whole volume is acquired and afterwards amplitude and phase of each harmonic is measured or calculated by Discreet Fourier Transform from signal. Set of amplitudes and phase angles of all harmonics in function of frequency is called magnetic particle spectrum and is unique for specific nanoparticles batch. First trial measurements of amplitude and phase angle spectra of nanoparticles using modified MPI scanner model (Fig. 8) were conducted in Division (Fig. 9 and 10). Development of new magnetic particles spectroscope is planned in the near future.

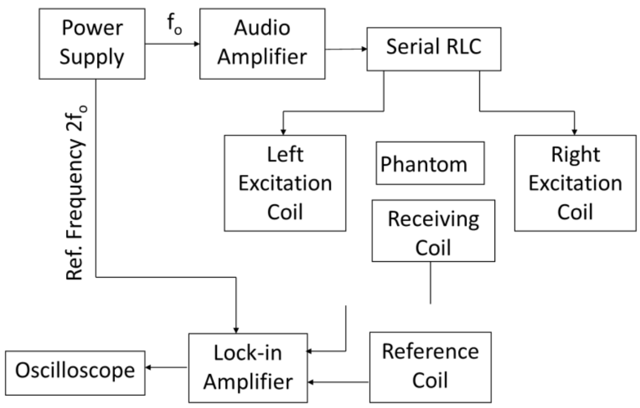

Fig. 8. Scheme of MPS setup, using narrowband detection method. It is in fact MPI scanner setup without driving and gradient coils. In this configuration signal is acquired from whole volume

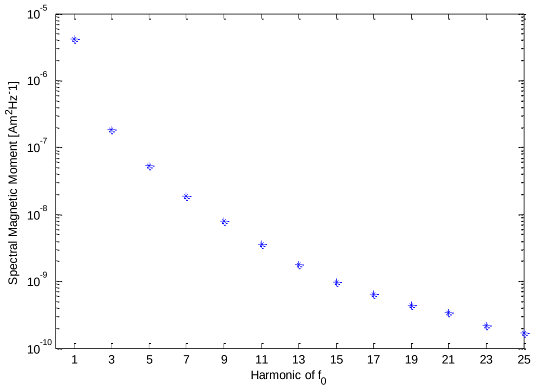

Fig. 9. Magnetic moment spectrum of FeraSpin™ XL nanoparticles at a field strength of 8 mT/µ0

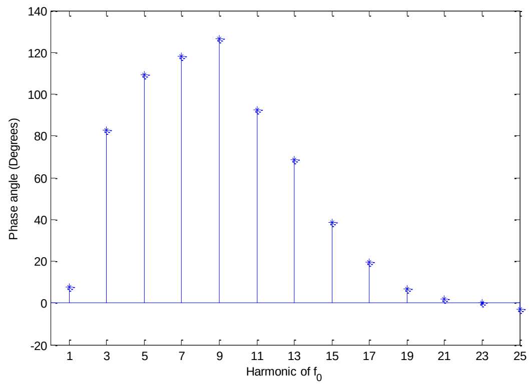

Fig. 10. Phase angle spectrum of FeraSpin™ XL nanoparticles at a field strength of 8 mT/µ0

2.3. Numerical Simulation Toolbox

The last important project connected to MPI developed in Division is work on program for numerical calculations. MPIsim software is written in MATLAB. When completed this toolbox will be ideal scientific help for designing new models of the MPI scanner or coils setups or for verification of results of real measurements. Its first module will allow simulation of magnetic field generated by coils of the scanner [5, 6], including gradient field, driving field and excitation field (Fig. 11 and 12). Second part will be used for simulation of 1D/2D/3D MPI measurements (Fig. 15), which theoretical with allow numerical estimation of system function of analyzed scanner. Last function of the program will be reconstruction of MPI images and particles concentration distribution. Using this toolbox it will also be possible to numerical calculation of magnetic particles spectra (Fig. 13) and estimation of particle magnetization curve, from both simulated and real data (Fig. 14). This feature will allow not only estimation of magnetic parameters of nanoparticles but also may lead to better theory describing superparamagnets behavior.

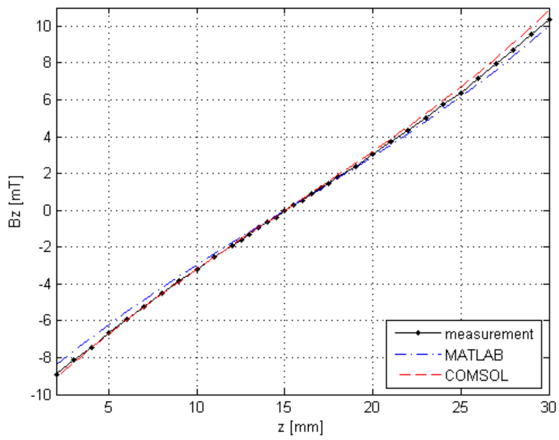

Fig. 11. Comparison of result of simulation and real measurement of Z-component of magnetic induction of field generated by gradient coils of MPI scanner model

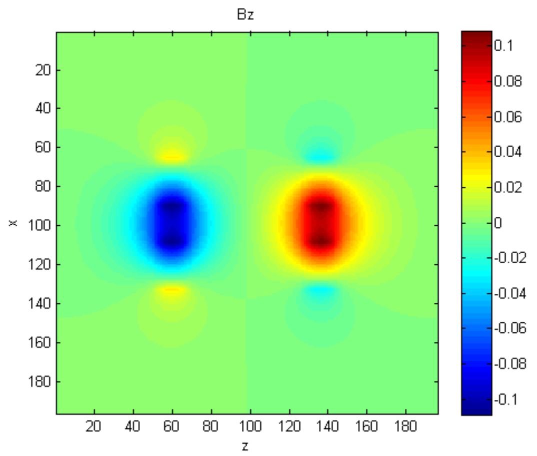

Fig. 12. Distribution of Z-component of magnetic induction of field generated by gradient coils of MPI scanner model. Computed in MPIsim toolbox

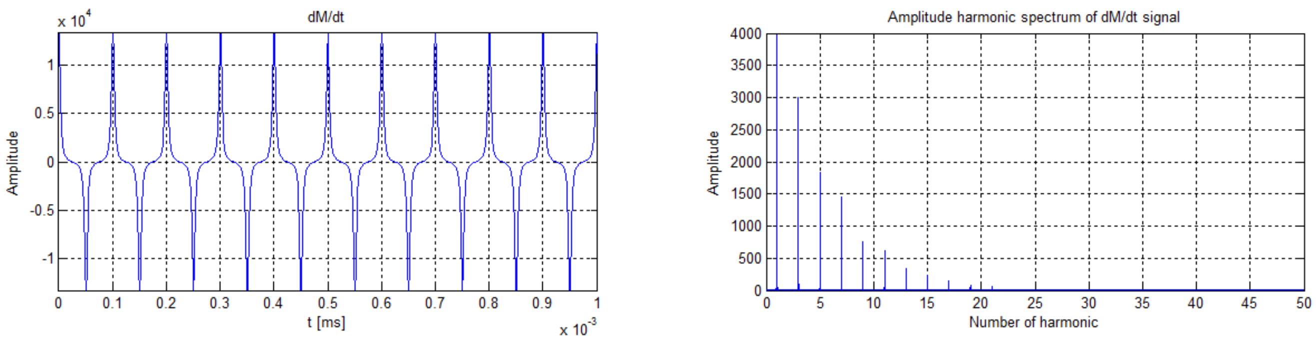

Fig. 13. On the left side, signal induced by changing magnetization of nanoparticles in receiving coil calculated in MPI toolbox. On the right side, amplitude harmonic spectrum of this signal

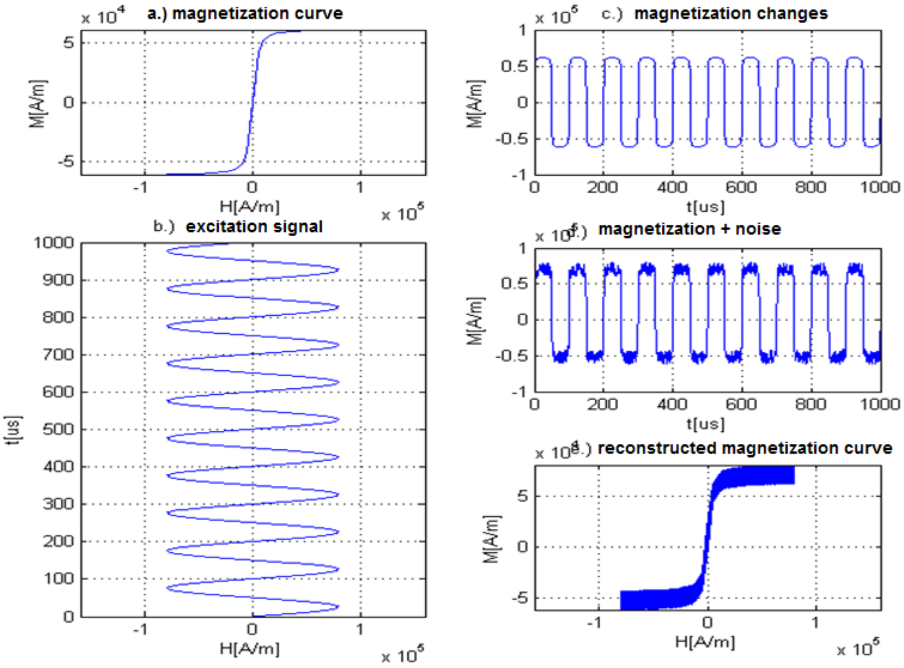

Fig. 14. In left top corner, theoretical Langevin's curve of magnetization. In left bottom corner, excitation signal. On the right side, from top to bottom, clear magnetization signal, magnetization with noise, reconstruction of Langevin's curve from signal with noise. Calculated in MPI toolbox

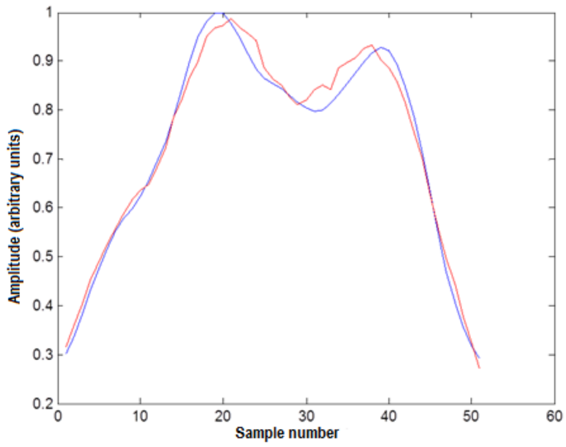

Fig. 15. Comparison of results of real measurement (red) of 3rd harmonic amplitude and result of 1D numerical simulation (blue). Measurement of three chamber phantom filled with nanoparticles of 40 nm diameter dissolved in water

3. Conclusions

Magnetic Particles Imaging is a very promising molecular imaging technique with wide range of potential applications. Its progress will surly contribute to expansion of knowledge in both fields of electronics and medicine. Due to this rezone it became one of the main topics of interest in the Nuclear And Medical Electronics Division. Past results motivate us to continue work in this field. Probable next step will be extension of functionality of current MPI scanner model to 2D or 3D imaging, which in turn will allow further research in this new imaging technique.

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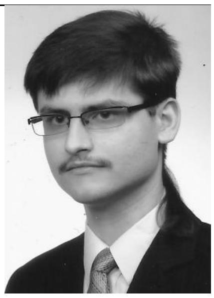
M.Sc. Eng. Przemysław Wróblewski
e-mail: P.Wróblewski@ire.pw.edu.pl



Received the M. Sc. degree in biomedical engineering from Warsaw University of Technology, Warsaw, Poland in 2013. Ph.D. student in the Nuclear and Medical Electronics Division, Institute of Radioelectronics and, Electronics and Information Technology Faculty, Warsaw University of Technology. His field of interest covers Magnetic Particles Imaging and Magnetic Particles Spectroscopy, especially design of scanners and simulations of the magnetic field.

Prof. Waldemar Tomasz Smolik
e-mail: W.Smolik@ire.pw.edu.pl

Waldemar T. Smolik received the M.Sc., the Ph.D. and D.Sc. degree in electronics engineering from Warsaw University of Technology, Warsaw, Poland in 1991, 1997 and 2014, respectively. Since 2014, he is an Associate Professor at the Institute of Radioelectronics and Multimedia Technology, Electronics and Information Technology Faculty, Warsaw University of Technology. He is the head of the Laboratory of Electronics Application in Nuclear Medicine at the Division of Nuclear and Medical Electronics. His main research interests are computer engineering, computed tomography and medical imaging. He has published over 70 scientific papers.

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