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An Enhanced Magnetomotive Ultrasound Algorithm to Quantitatively Estimate the Concentration of Iron-Oxide Nanoparticles in Perfused Tissue for Magnetic Drug Targeting

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***Abstract*—Numerous medical applications make use of magnetic nanoparticles, which boosts the demand for imaging systems that can visualize these particles. Magnetomotive Ultrasound (MMUS) is an ultrasound-based imaging modality that can detect tissue perfused with magnetic nanoparticles. However, MMUS can only provide a qualitative mapping of the particle-loaded tissue. Therefore, we introduce in this contribution an extension of the MMUS algorithm that enables a quantitative representation of the nanoparticle density distribution in tissue. The presented algorithm is based on an iterative comparison between simulated data and measured data. Experiments with tissue-mimicking phantoms reveal that the presented procedure can be used to determine the local nanoparticle concentration in the correct order of magnitude.**

Keywords—Magnetic Drug Targeting, Magnetomotive Ultrasound, iron-oxide nanoparticles, ultrasonic imaging, inverse problem

I. Introduction

Magnetic nanoparticles are widely used in medical applications [1], [2]. One of these applications is Magnetic Drug Targeting (MDT), a therapeutic approach that can be deployed in cancer therapy. MDT offers several advantages compared to conventional chemotherapy. In contrast to the standard chemotherapeutic treatment, MDT goes along with the reduction of the overall dosage of medical drugs, which results in reduced side-effects for the patients. Remarkably, however, an increased dosage of the medical drug can be achieved in the tumorous tissue at the same time [3]. For this purpose, the active ingredient is bound to magnetic nanoparticles. The particles and thereby, the medical drugs are then applied to the bloodstream system. The magnetic properties of the drug-carrying particles enable guiding of the particles inside the patient utilizing a magnetic field, which can be generated by an electromagnet pointing to the target tissue. Thus, a much larger proportion of the administered substance ends up in the target area. In preclinical animal studies for MDT, a high efficiency has been demonstrated. Tietze et al. have shown that a single application of 5 % and 10 %, respectively, of the standard dose of a chemotherapeutic agent led to complete tumor remission in 30 % of the tested animals. Moreover, the tumor growth of another 26 % of the animals was strongly reduced [4]. Hence, Magnetic Drug Targeting seems to be a promising and beneficial alternative to the standard chemotherapeutic procedures.

In order to assess the enrichment of medical substance in the target area during the MDT application, an imaging system is indispensable. Several modes to image magnetic nanoparticles can be employed that are already in clinical use, such as Magnetic Resonance Imaging (MRI) and Micro Computer Tomography (Micro CT), which are utilized as standard imaging techniques in clinics. Moreover, Magnetic Particle Imaging (MPI), which is a visualization technique that is still under development, can detect magnetic nanoparticles. For this new imaging technique, superparamagnetic nanoparticles are used as contrast agents [5]. However, the mentioned imaging modalities have in common that they need sizeable technical equipment and are very cost-intensive. In addition, these imaging procedures require the patient being located inside a cylindrical scanner device. Unfortunately, the electromagnet needed for MDT cannot be positioned inside the scanner due to lack of space. Furthermore, the magnetic field caused by the electromagnet would influence the function of the scanner. Therefore, simultaneous MDT treatment and imaging with the mentioned visualization techniques is not possible.

In contrast, it is possible to sonographically observe the target-area with an ultrasound array during the MDT application. Moreover, ultrasound is a widespread and way less expensive imaging technology. However, the size of nanoparticles, and therefore, the small acoustic backscattering cross-section, is challenging for ultrasound-based detection. Consequently, the nanoparticles are not depictable using standard ultrasound imaging techniques like the B-mode modality. Nevertheless, Oh et al. have demonstrated that ultrasound imaging techniques can be exploited to detect tissue that is perfused by magnetic nanoparticles [6]. This ultrasound-based technique is known as Magnetomotive Ultrasound (MMUS). MMUS requires a nanoparticle movement excitation caused by an external time-variable magnetic field. The particle movement thereupon is transferred to the surrounding

tissue. The resulting tissue movement, in turn, can be observed sonographically because of the acoustic scattering properties of the tissue and can be used as an indicator for the presence of magnetic nanoparticles. This procedure enables an estimation of the spatial distribution of magnetic nanoparticles in the corresponding tissue area.

Meanwhile, various MMUS algorithms have been established [7], [8]. However, so far, no MMUS algorithm has been capable of determining the nanoparticle concentration quantitatively. The presented extension of MMUS to an inverse Magnetomotive Ultrasound approach allows a quantitative estimation of the concentration of nanoparticles in the observed tissue.

II. Inverse Magnetomotive Ultrasound

Inverse Magnetomotive Ultrasound (IMMUS) is an extension of the MMUS procedure and is intended to enable the quantitative determination of the local concentration of magnetic nanoparticles in biological tissue. However, this denotes an inverse problem, as the input of the system has to be deduced from the observable output. Precisely, the distribution of magnetic nanoparticles has to be determined by evaluating the observable tissue movements. The solution to such an inverse problem can be found in different ways. On the one hand, direct inverse approaches can be applied [9]; on the other hand, indirect inverse approaches based on an iterative application of a suitable forward solver can be deployed [10]. IMMUS belongs to the latter ones.

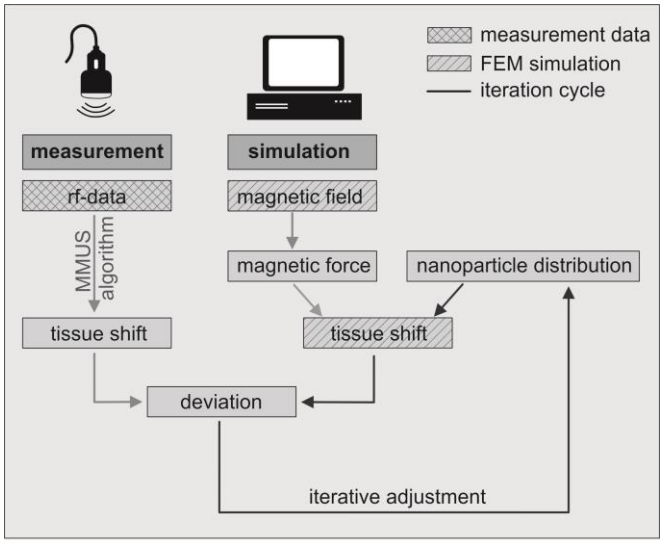

Fig. 1. Basic steps of Inverse Magnetomotive Ultrasound.

The basic idea is an iterative adjustment of simulated data to measurement data [11]. Specifically, the computed tissue displacement field has to be adjusted to the measured displacement field. For this purpose, in comparison to classical MMUS, additional information gets used in IMMUS that is idle in conventional MMUS, namely the material properties of the nanoparticles and the surrounding tissue as well as the properties of the electromagnet, which generates the time-variable magnetic field. The knowledge of this information enables to calculate the magnetic quantities within the tissue, which can be done efficiently by a finite element method (FEM) calculation. In addition, the local magnetic force acting on the particles can be computed. Assuming that the nanoparticles behave like magnetic dipoles, this magnetic force can be approximated. Finally, one can calculate the tissue displacement field by means of an assumed particle distribution. Again, this can be realized via FEM computation. The computed displacement field can then be compared to the measured displacement field that results from the conventional MMUS process. Thus, a standard MMUS algorithm still has to be performed. However, the actual choice of the MMUS algorithm is highly irrelevant. The assumed particle distribution can be adjusted until the deviation to the measured data is sufficiently small. The basic steps of the IMMUS procedure are illustrated in Figure 1.

III. Measurement Setup

The measurements have been performed on tissue-mimicking phantoms, made out of polyvinyl alcohol, which is known as suitable mimicking material in medical ultrasound applications.

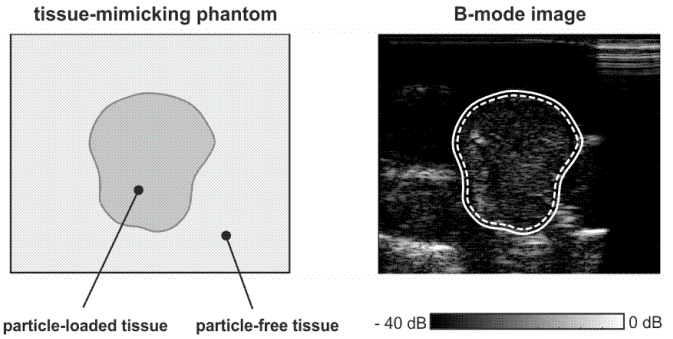

Fig. 2. Schematic depiction of the tissue mimicking phantom (left) and B-mode image of the tissue mimicking phantom (right). In the B-mode image, the particle-loaded tissue is marked by a dashed line.

The phantom contains tissue which is free from particles as well as tissue which is perfused by magnetic nanoparticles. The concentration of iron-oxide nanoparticles in the particle-loaded tissue amounts 2.5e14 particles per ml. The iron-oxide nanoparticles were manufactured at the Section of Experimental Oncology and Nanomedicine (SEON) of the University Hospital Erlangen, Germany. The iron-oxide cores exhibit a diameter of ≈ 10 nm and are surrounded by layers that serve as linkage to the medical drug. Due to the small size of the iron-oxide cores, the acoustic scattering level of the particles is very low, and therefore, they are not visible directly using B-mode imaging technique. Figure 2 shows a schematic depiction as well as the B-mode image of the tissue-mimicking phantom. An electromagnet is used to apply an alternating magnetic field within the tissue-mimicking phantom. We choosed a low magnetic field frequency of 1 Hz to reduce eddy current losses within the core of the electromagnet. The

magnetically evoked tissue motion is observed sonographically, utilizing the ultrasound system Ultrasonix Touch, working at a framerate of 50 Hz. In doing so, the pole tip of the electromagnet and a linear array (L9-4/38) are positioned on opposite sides of the phantom, facing each other. This arrangement allows to observe tissue motion toward the magnet, since the ultrasonic transducer can detect axial displacements in the image plane. Figure 3 shows the measurement setup.

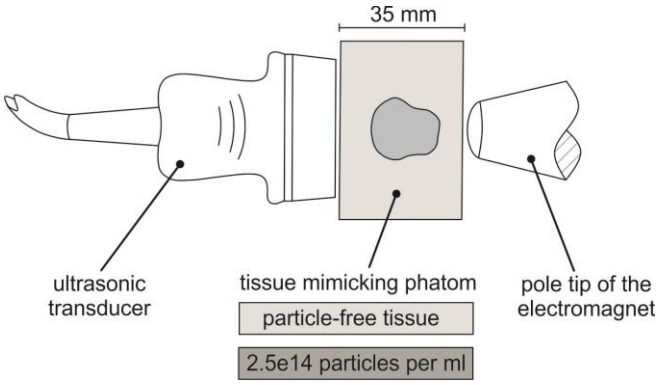

Fig. 3. Measurement setup.

IV. RESULTS

The collected rf-data were post-processed employing a conventional MMUS algorithm, which discovers the magnetically evoked tissue oscillation. Due to the sinusoidal magnetic excitation, the mechanic response of the tissue is sinusoidal as well. MMUS aims to determine the amplitude of the corresponding frequency component of this oscillation. As a matter of course, this oscillation primarily occurs in the particle-loaded area. The evaluation, according to MMUS, is shown in Figure 4. With the aid of Inverse MMUS, we estimated the local particle concentration. Figure 4 also displays the result of the Inverse MMUS evaluation.

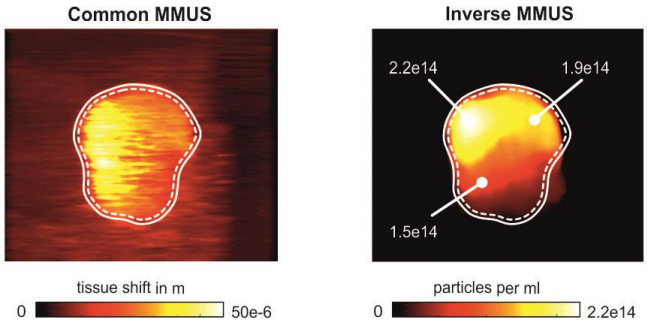

Fig. 4. Evaluation of the rf-data according to a common MMUS algorithm (left) and according to an Inverse MMUS algorithm (right).

V. CONCLUSION AND OUTLOOK

The measurements have shown that IMMUS is indeed capable of estimating the iron oxide nanoparticle concentration in biological tissue or biological tissue-mimicking material, respectively. The Inverse MMUS result lies slightly beneath the actual particle concentration of 2.5e14 particles per ml. However, we could determine the correct order of magnitude. IMMUS is, therefore, a cost-effective visualization technique that can be used to estimate the local concentration of magnetic nanoparticles in tissue and that can be operated simultaneously to a Magnetic Drug Targeting application. The deviation from the target value may be caused by the fact that only approximated material data were available for the FEM simulations. Besides, various simplifications, on which the FEM simulations are based, may be responsible for the deviation. For instance, the simulation setup is modeled as a two-dimensional setup, while the actual setup poses a three-dimensional problem.

In future contributions, we will investigate the arising deviation more accurately. This refers to the influence of uncertainties concerning the material parameters as well as to the influence that goes along with the choice of the FEM setup. In the case of successful investigations, also measurements on real biological tissue perfused by magnetic nanoparticles and supporting measurements in MDT animal studies can be considered.

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