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Quantitative Imaging of the Iron-Oxide Nanoparticle-Concentration for Magnetic Drug Targeting Employing Inverse Magnetomotive Ultrasound

Abstract: Magnetomotive Ultrasound is an imaging technique that is capable to detect tissue, which is perfused by magnetic nanoparticles. However, this modality is restricted to qualitative imaging only. Therefore, we present an extended Magnetomotive Ultrasound algorithm, which allows the quantitative determination of the spatial distribution of magnetic nanoparticle density in tissue. The algorithm is based on an iterative adjustment of simulated data to measurements. Experiments with tissue-mimicking phantoms reveal that the presented method leads to the spatial particle concentration in the correct order of magnitude.

Keywords: Magnetic Drug Targeting, Magnetomotive Ultrasound, Iron-Oxide Nanoparticles, Ultrasonic Imaging, Iterative Method.

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1 Magnetic Drug Targeting

Magnetic nanoparticles offer several possibilities in medical diagnosis as well as in therapy. One of these medical applications is Magnetic Drug Targeting (MDT), a cancer therapy technique, which enables local chemotherapeutic treatment. In comparison to traditional chemotherapy, MDT allows the reduction of the overall dosage of

chemotherapeutic drugs, resulting in reduced side effects. It is worth mentioning that at the same time, an increased local dosage of the chemotherapeutic agent in the tumor area can be achieved [1]. For this purpose, chemotherapeutic drugs are bound to magnetic nanoparticles and are applied intra-arterially in the vicinity of the tumor. Due to their magnetic properties, the particles and, thereby, the medical agent can be accumulated in the tumor area by means of an external static magnetic field. In the currently most extensive preclinical animal study for MDT, a high efficiency could be shown [2].

The success of the MDT treatment requires a well-defined concentration of medical agent in the tumorous area and thus, an appropriate monitoring of the nanoparticles. A potential visualization mode for that purpose is Magnetic Particle Imaging (MPI). For this new imaging technique, superparamagnetic nanoparticles are used as contrast agents [3]. However, MPI demands relatively large technical equipment, is very cost intensive and is not yet suitable for clinical use. In contrast, ultrasound is a widespread and less expensive imaging technology. Actually, an ultrasound based imaging technique that is capable to detect magnetic nanoparticles in tissue has been established. This sonographic imaging modality is known as Magnetomotive Ultrasound (MMUS) [4].

2 Magnetomotive Ultrasound

2.1 Conventional MMUS

The size of nanoparticles is challenging ultrasound-based detection, as they are not depictable directly due to their weak acoustic backscattering. Though, MMUS can be exploited to detect tissue, perfused by magnetic nanoparticles. This mode is based on nanoparticle movement excitations by means of an external time variable magnetic field. The resulting particle movement is transmitted to the surrounding tissue, and the moving tissue can be observed

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sonographically. Tissue movements that match the variation of the magnetic field can be seen as an indicator for the presence of magnetic particles. The aim of MMUS is to detect these tissue movements. Various MMUS algorithms have been presented to detect particle-perfused tissue [5, 6]. Unfortunately, so far no MMUS algorithm has been capable to visualize the nanoparticle density distribution quantitatively.

2.2 Inverse MMUS

The quantitative determination of the particle concentration via Magnetomotive Ultrasound denotes an inverse problem, which describes the process of deducing the input of a technical system, based on the observable output. In case of MMUS, the tissue motion corresponds to the observable output, while the nanoparticle distribution, together with the alternating magnetic field, corresponds to the input. As the presented mode is an extended MMUS mode to solve this inverse problem, it is subsequently called Inverse Magnetomotive Ultrasound.

Such an inverse problem can be solved employing iterative methods [7], which aim at the iterative adjustment of simulated data to measurements [8]. Therefore, additional conversant information that is idle in conventional MMUS is utilized, like the properties of the magnetic field and of the nanoparticles. Knowing the magnetic flux density as well as the material properties and the size of the nanoparticles allows to calculate the local magnetic force exerting on a single particle. By means of an initial guess, concerning the nanoparticle distribution, and by means of approximated mechanical tissue parameters, like Young's modulus, the resulting tissue movement is computed which can be compared to the measured tissue motion that results from the conventional MMUS mode. Consequently, a common Magnetomotive Ultrasound measurement still has to be performed. However, the actual choice of the MMUS algorithm is largely irrelevant for the Inverse MMUS evaluation. In addition to the common MMUS algorithm, multiple simulation steps have to be performed. The magnetic field has to be analysed initially which can be done by employing a Finite Element Method (FEM) simulation. Afterwards, the magnetic force F_m exerting on a single nanoparticle can be calculated via $F_m = \nabla(m \cdot B)$ [9], with the magnetic dipole moment m of the particle and the magnetic flux density B . Thereafter, another FEM simulation enables to calculate the tissue shift resulting from an assumed particle distribution. This particle distribution can be iteratively adjusted, so that the deviation between simulated and measured tissue movement gets minimized. In this way, the

particle distribution and thereby the local particle concentration can be estimated. The procedure is illustrated in Figure 1.

Figure 1: Basic steps of Inverse Magnetomotive Ultrasound

3 Measurement Setup

An electromagnet is used to induce magnetically evoked particle motion within a tissue mimicking phantom and a linear array ultrasonic transducer (Ultrasonix L9-4/38 Linear) is used to sonographically observe the tissue. The measurement setup is designed in such a way that the electromagnet and the ultrasonic transducer point to the tissue mimicking phantom from opposite directions (see Figure 2).

Figure 2: Measurement setup to sonographically investigate magnetically evoked tissue movements.

It is known that agarose [10] and polyvinyl alcohol [11], which is used in our work, are suitable to be utilized as tissue mimicking material in medical ultrasound applications. The phantom contains both particle-free and particle-loaded tissue. In the latter one, the nanoparticles are randomly distributed, whereat the mean density is 2.5×10^{14} particles per ml. It should be mentioned that Figure 2 shows a section through the phantom.

Figure 3: B-mode image of the tissue mimicking phantom with the particle-loaded area marked by a dashed line (left), common MMUS evaluation of the rf-data (center) and evaluation according to the Inverse Magnetomotive Ultrasound algorithm (right).

The electromagnet is driven by a 1 Hz alternating electric current. This rather low frequency is chosen to reduce eddy-current losses in the iron core and thus, to generate a strong magnetic force on the nanoparticles. The resulting tissue movements are observed sonographically by collecting a sequence of ultrasound data. The rf-data are captured using the system Ultrasonix Touch working at a framerate of 50 Hz.

4 Results and Outlook

Figure 3 (left) depicts the B-mode image based on the collected rf-data of the tissue mimicking phantom. Neither the nanoparticle concentration can be determined by considering the B-mode data, nor the particle-free tissue can be distinguished from the particle-loaded tissue. For that matter, Magnetomotive Ultrasound has to be performed. Thus, the data were initially post-processed employing a common MMUS algorithm, which tracks the magnetically evoked tissue motion. As the magnetic excitation is sinusoidally oscillating, the tissue movement is an oscillating movement, too. The amplitude of the corresponding oscillation within the tissue is displayed in the center image of Figure 3. Considering this amplitude enables to detect the particle-loaded tissue. However, with the aid of Inverse MMUS, even the local particle concentration can be estimated. Figure 3 (right) shows also the result of the Inverse MMUS evaluation.

The particle-loaded area of the tissue mimicking phantom exhibits a production-related particle concentration of 2.5×10^{14} particles per ml. The Inverse MMUS result lies slightly beneath this value, however, the correct order of magnitude could be determined.

The deviation can be caused by the fact that only approximated material data of the Young's modulus and the shear modulus of the phantom material were used for the FEM simulations. In addition, various simplifications, on which the FEM simulations are based on, 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 this deviation more accurately. The influence of uncertainties concerning the material parameters will be investigated as well as the influence that goes along with the choice of the FEM setup. We will also conduct measurements on real biological tissue perfused by magnetic nanoparticles.

Author Statement

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