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In Vivo Study on Magnetomotive Ultrasound Imaging in the Framework of Nanoparticle based Magnetic Drug Targeting

Abstract: Various medical procedures make use of magnetic nanoparticles, such as Magnetic Drug Targeting (MDT), which boosts the demand for imaging modalities that are capable of in vivo visualizing this kind of particles. Magnetomotive Ultrasound is an imaging technique that can detect tissue, which is perfused by magnetic nanoparticles. In this contribution, we investigate the suitability of Magnetomotive Ultrasound to serve as a monitoring system during MDT. With the conducted measurements, it was possible for the first time to observe in vivo the accumulation of iron-oxide nanoparticles during a Magnetic Drug Targeting cancer treatment applied to a small animal (rabbit).

Keywords: Magnetic Drug Targeting, Magnetomotive Ultrasound, iron-oxide nanoparticles, ultrasonic imaging.

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1 Introduction

Magnetic nanoparticles enable novel medical treatment modalities, such as Magnetic Drug Targeting (MDT), a cancer treatment procedure that allows local chemotherapeutic intervention. Contrary to traditional chemotherapeutic treatment, MDT is attended by decreasing the overall dose of drugs, which leads to reduced side effects. It is worth mentioning that at the same time, an increased dosage of chemotherapeutic drugs in the tumor area can be achieved [1]. For this purpose, chemotherapeutic drugs stick to magnetic nanoparticles, which are applied intra-arterially close to the tumor. An external magnetic field can enrich the particle density (and, therefore, also the drug concentration) in the tumor area. A high efficiency of MDT in cancer therapy has been proven in animal studies [2]. Therefore,

MDT seems to be a suitable and promising alternative to conventional chemotherapy.

To control the particle concentration in the cancerous tissue, an imaging system to visualize the particle accumulation is essential. Indeed, there are imaging modalities that are capable of detecting magnetic nanoparticles in tissue, which are already in clinical use, such as MRI (Magnetic Resonance Imaging). MRI is a well-known technique and serves as a standard imaging procedure in hospitals [3]. There are also imaging techniques under development that can visualize tissue, contaminated with magnetic nanoparticles, such as MPI (Magnetic Particle Imaging). MPI exploits superparamagnetic nanoparticles as contrast agents [4]. Unfortunately, both modalities have in common that they require large technical equipment and are cost-intensive. However, the most significant drawback is that simultaneous MDT and imaging with the mentioned procedures is not possible, as these procedures require the patient to take place inside a cramped scanner device. But due to lack of space, the necessary equipment for MDT cannot be placed inside this scanner device. Consequently, these imaging modalities are not suitable to serve as a monitoring system during MDT treatment.

In contrast, it is indeed possible to perform ultrasonic imaging of the target tissue while MDT. Moreover, ultrasound is a widely used and a comparatively low-cost imaging technique. Besides, it is portable and offers several diagnostic options. However, the size of nanoparticles poses a massive challenge for ultrasound-based detection, as the particles are not depictable directly due to their weak acoustic backscattering.

Figure 1: Magnetic flux density field of the electromagnet, used in this contribution. The arrows mark the direction of the flux density gradient.

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Nevertheless, Oh et al. [5] have demonstrated that ultrasound imaging techniques can be exploited to detect nanoparticle laden tissue. This sonographic detection of magnetic nanoparticles is known as Magnetomotive Ultrasound (MMUS). MMUS rests on nanoparticle movement excitations, employing an external time-variable magnetic field. This particle movement leads to tissue motion, which can be observed sonographically and which serves as an indicator for the presence of magnetic nanoparticles. Consequently, MMUS is indeed an imaging modality that can be employed to display the distribution of the drug carriers during an MDT treatment.

2 Simultaneous MDT Treatment and MMUS Imaging

The cost-efficiency of medical devices increases the potential to be adapted in clinical routines. Hence, with a view to clinical applications, it is reasonable that the magnet used for MDT (to accumulate the particles) shall also be employed for MMUS imaging to generate the alternating magnetic field. However, this request raises two problems:

- The target of an MDT magnet design is to create a static magnetic field (for local particle accumulation). In the case of a high-frequency coil current (for particle movement excitation), the effective magnetic field suffers from eddy current losses. The MMUS procedure is, therefore, limited to low field frequencies. In the low frequency range, however, there are also other movements such as respiratory movements. These other tissue movements possibly impede the detection of particle-induced tissue motions.
- Due to the arrangement of the electromagnet and the ultrasonic transducer, both components perceive the target tissue under different directions, which can complicate signal processing or which may even disable the detection of the particle-induced tissue movements via MMUS.

We may overcome the first-mentioned issue by using coded magnetic excitation signals. In doing so, the particle-induced tissue movement provides a much more pronounced recognition value [6]. This makes it much easier to identify the target movement and to distinguish it from breathing movements, heartbeat movements, or motions caused by muscle contraction.

Figure 2: In vivo measurement setup to investigate clinical MMUS imaging in the framework of Magnetic Drug Targeting (a) and two-dimensional geometrical arrangement of ultrasonic transducer and electromagnet to apply simultaneous MDT treatment and MMUS imaging (b).

The latter issue requires consideration of the geometrical conditions. Therefore, we must note that the qualitative particle distribution (which MMUS shall determine) is related to the tissue displacement that occurs towards the positive magnetic field gradient, as the magnetic force $\mathbf{F}$ is proportional to the gradient of the absolute magnetic flux density $\mathbf{B}$

$$\mathbf{F} \propto \nabla |\mathbf{B}| . \quad (1)$$

Fig. 1 shows the magnetic flux density field around the pole tip of the electromagnet that is used to perform the measurements in this contribution (see Fig. 2a). Moreover, Fig. 1 shows the direction of the flux density gradient. As can be seen, the direction of the field gradient is locally dependent, and so is the direction of the tissue shift.

However, the sonography measurement only provides the tissue displacement $\mathbf{u}_{\parallel}$ in the axial direction of the ultrasonic transducer (see Fig. 2b). Therefore, the measured tissue displacement $\mathbf{u}_{\parallel}$ must be converted to the actual tissue displacement $\mathbf{u}$ to provide the qualitative mapping of the nanoparticle distribution.

For reasons of simplification, in Fig. 2b, the scenario is illustrated via a two-dimensional setup, although the actual configuration is, of course, three-dimensional. According to Fig. 2b, the actual tissue displacement $\mathbf{u}$ can be composed of the vector $\mathbf{u}_{\parallel}$ that points into the direction of the ultrasonic transducer and the vector $\mathbf{u}_{\perp}$ that points perpendicular to it. The component $\mathbf{u}_{\perp}$ cannot be determined via MMUS. Therefore, we compute the relevant tissue displacement $\mathbf{u}$ exploiting the trigonometric identity

$$|\mathbf{u}| = \frac{|\mathbf{u}_{\parallel}|}{\cos(\alpha)} . \quad (2)$$

Although the angle α is locally dependent, it is known for any location within the image plane. Under consideration of the trigonometric identity (2), the determination of the relevant tissue displacement $\mathbf{u}$ will be only possible if the ultrasonic transducer is not arranged perpendicular to the tissue displacement. Fig. 3 shows a schematic image of the target tissue within the image plane of the ultrasonic transducer as well as the locally dependent angle between the image plane and the direction to which the local magnetic force points. At an angle of 90° , the actual tissue displacement cannot be determined, resulting in a blind spot.

Besides the local tissue shift $\mathbf{u}$, we have to consider the local magnetic field gradient $\nabla|\mathbf{B}|$ to obtain a measure for describing the qualitative representation of the particle density distribution. As, according to (1), the magnetic force is proportional to the magnetic field gradient, we specify a quantity d

$$d = \frac{|\mathbf{u}|}{\nabla|\mathbf{B}|} , \quad (3)$$

which can be seen as a measure to represent the particle distribution. However, d does not provide a technically reasonable interpretation. That is the reason why we utilize in this contribution the normalized parameter d_{norm}

$$d_{\text{norm}} = \frac{d}{\max(d)} , \quad (4)$$

to assess the local particle density.

In the following, the simultaneous applicability of MDT and MMUS with a single electromagnet will be investigated by means of in vivo measurements.

Figure 3: Schematic representation of the target tissue in the image plane of the ultrasonic transducer (a) and angle between image plane and the magnetic force direction (b).

3 Measurements and Results

We have performed in vivo MMUS measurements in the framework of an MDT animal study. Therefore, a tumor was implanted subcutaneously into the left hind limb of a rabbit. Within the framework of the experiments, we apply drug-laden iron-oxide nanoparticles intra-arterially, and we enrich the particles in the tumor tissue employing an electromagnet, which has been designed for MDT applications (see [7]).

The Section of Experimental Oncology and Nanomedicine (SEON) of the University Hospital Erlangen, Germany, has produced the superparamagnetic nanoparticles used in this contribution. The particles consist of 5 - 15 nm diameter iron-oxide cores, surrounded by lauric acid layers. The outer layers serve as linkages to the medical drug as well as biocompatible coating, as the naked iron-oxide nanoparticles exhibit intrinsic toxicity and are not stable in blood [8].

During the enrichment process, we observed the target tissue sonographically, utilizing the medical ultrasonic system *Ultrasonix Touch*. A linear array (Ultrasonix 4DL-14-5/38) was applied as ultrasonic transducer to collect the rf-data. Fig. 2a shows the main components of the measurement setup (electromagnet and ultrasonic transducer). Moreover, the measurement setup includes a signal generator to shape the excitation signal waveform and a power amplifier to induce the coil current.

The magnetic excitation signal is chosen to be a 4-bit Barker code (the fundamental frequency is 1 Hz) to distinguish particle-induced tissue motions from other tissue movements. The recorded rf-data were evaluated according to the presented MMUS principle. Fig. 4 shows the qualitative particle distribution at different time steps throughout the whole particle accumulation process. The particles are administered at a low rate over a long period to avoid a shock reaction of the animal. Hence, the accumulation process takes 45 minutes.

Figure 4: B-mode image of the tumor in the left hind limb of a rabbit and MMUS evaluation of the collected rf-data at different time steps, while the applied iron-oxide nanoparticles are accumulated in the target area using an MDT magnet.

MMUS. Furthermore, the possibilities of real-time imaging will be investigated.

4 Conclusion

This study demonstrates a suitable setup to perform MMUS imaging simultaneously to MDT treatment. In particular, we could show that MMUS imaging is possible despite the angular offset between electromagnet and ultrasonic transducer. With the measurements carried out in this thesis, the enrichment of the target tissue with nanoparticles during MDT could be observed for the first time. The presented imaging procedure can be performed with the equipment already used for MDT and a standard medical ultrasonic device. Thus, MMUS seems to be a promising modality for mapping the particle distribution (i. e., drug distribution) in MDT applications.

However, we can identify two artifacts when considering the results:

- Tissue oscillations can also be noted in the tumor's neighboring tissue (especially at timestep 35 min). Since these movements disappear thereafter, we think that these tissue motions may be caused by particles that are still circulating in the bloodstream system.
- Throughout the whole enrichment process, the area close to the ultrasonic transducer is detected as particle-free. In this area, the tissue oscillates approximately perpendicular to the image plane of the ultrasonic transducer, resulting in a blind spot. In order to avoid such a blind spot, a second measurement would have to be carried out, viewing this blind spot from a different angle.

In future contributions, we will focus on the potential of three-dimensional imaging of the particle distribution using

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