Magnetic techniques for diagnosis and treatment of breast cancer

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In the treatment of cancer, it is important to identify the lymph nodes involved in metastasis. By administering magnetic nanoparticles to the lymphatic system and detecting accumulation in downstream lymph nodes with a magnetic sensor, lymph nodes involved in metastasis can be identified non-invasively and objectively. To realize this new technique, we developed a handheld device consisting of a permanent magnet and a Hall sensor[1)]. Previous researches on magnetic sensors were mainly based on the approach of detecting small amounts of magnetic nanoparticles using SQUIDs. Those devices were not very suitable for clinical use because the devices reacted to other surrounding magnetic materials due to their high sensitivities. We devised a new mechanism for strongly magnetizing nanoparticles with a permanent magnet and detecting the magnetic field with a small Hall sensor, and developed a prototype handheld device for detecting magnetic nanoparticles. With this mechanism, the influence of external devices was sufficiently reduced and clinical application was realized. Since the power consumption was smaller than that of existing devices, the entire drive circuit can be stored in the grip, making it a compact device. We also reported a technique for quantifying the accumulation of magnetic nanoparticles administered to living organisms by non-invasive imaging using MRI. Animal experiments showed the dose and time dependence of the accumulation. We ensured the safety of the developed magnetic probe by complying with the standards for electrical safety and risk management of medical devices, and proceeded with clinical research. In particular, a multicenter clinical trial was conducted on 200 breast cancer patients, and the new method using magnetic sensors and magnetic nanoparticles is non-inferior in terms of identification rate to the standard RI method[2)]. In addition, in order to expand the application, clinical trials were conducted in 20 and 4 cases of oral cancer and uterine cancer, respectively, and successful results were obtained such as the ability to identify sentinel lymph nodes in all cases. Furthermore, we also developed a prototype device equipped with a diamond quantum magnetic sensor[3)]. Due to the high sensitivity, the sensor could be operated with weak magnetic fields generated from a coil.

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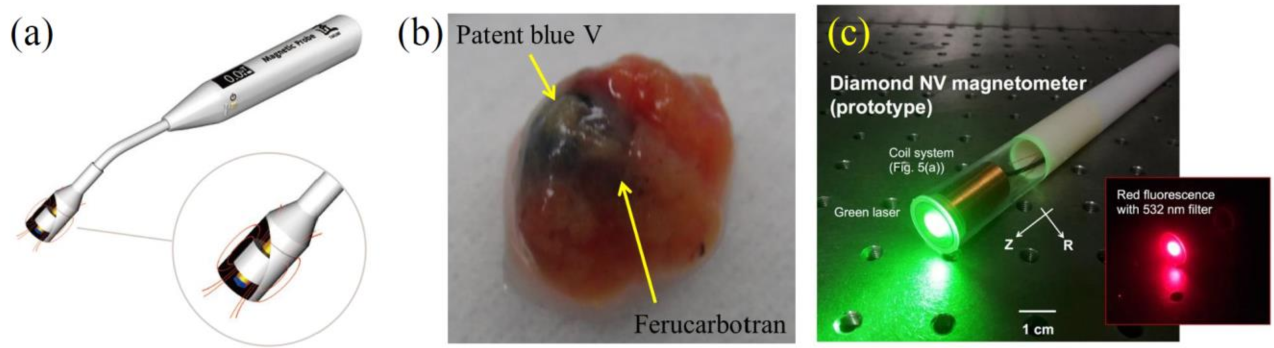

Fig. 1. (a) Handheld magnetic probe for sentinel lymph node biopsy. (b) Extracted lymph node containing magnetic nanoparticles and blue dye. (c) Magnetic probe equipped with a diamond quantum sensor.

Highly sensitive diamond quantum magnetometer with large sensor volume

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Nitrogen-vacancy (NV) centers in diamond are promising solid-state quantum magnetometer working at room temperature. The quantum magnetometer is a magnetometer that measures the magnetic field by using the energy change of qubits[1]. By constructing an appropriate measurement system, it is possible to achieve highly sensitive sensing with measurement noise reduced to the quantum limit. Thanks to the property of the diamond that is a wide bandgap semiconductor, the quantum coherence of the qubits maintains under a wide range of temperatures and pressures, including under room temperature and atmospheric pressure. This characteristic enables us to use the sensor for various applications including operating in vivo and in extreme environments.

One of the important steps towards the practical use of the diamond quantum magnetometer is to improve the sensitivity. Because the sensitivity of the diamond quantum magnetometer increases as the number of NV centers increases[2], a large sensor volume is required to achieve high sensitivity. We have developed a technology of the diamond quantum magnetometer to achieve high sensitivity by improving the control and readout of the qubit with a large sensor volume, such as enhancing a microwave and an effective photoexcitation method[3]. In parallel to these improvements, we are also improving the quality of the diamond quantum magnetometer such as the density and coherence time of the NV center. Our institute has a technology of electron irradiation with high temperature and ion implantation. We constructed an evaluation system suitable for the material evaluation of the diamond quantum magnetometer, and are researching the relationship between NV center generation efficiency and coherence time by the electron beam irradiation.

Another important point towards the practical use of the diamond quantum magnetometer is noise rejection from the signal. The diamond quantum magnetometer potentially achieves highly sensitive magnetic field sensing without any magnetic shield because the Zeeman shift of the qubit even occurs under a strong magnetic field. To realize this, we constructed a gradiometer system that cancels environmental magnetic field noise for DC magnetic field sensing, and a dynamical decoupling system that works as a noise rejection filter for AC magnetic field sensing.

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Development of a compact ultra-low field MRI system

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Magnetic resonance imaging (MRI) around geomagnetic field strength, also referred to as ultra-low field MRI (ULF-MRI), has been expected to be the new application of Biomagnetics. Comparing to conventional MRIs that use a much stronger magnetic field, the benefits of the ULF-MRI include the low cost of the system, more open geometry, decreased susceptibility to artifacts, increased relaxation time contrast, and being combined with biomagnetic "functional" measurements, e.g., magnetoencephalography (MEG).

Existing studies have mainly dealt with developing ULF-MRI systems for human body or head. In contrast, the author's group has conducted extensive studies on measuring biomagnetic signal from small-animals, known as small-animal MEG systems. Therefore, we have been developing a compact ULF-MRI system for small-animals.

Our compact ULF-MRI system consists of a set of five pairs of coils: for a polarizing field, a measurement field, and three dimensional gradient fields[1)]. These coil sets were designed and fabricated to be the desktop size for installation inside a magnetically shielded box. The coil pairs for measurement and gradient fields were optimized by using a target field method, and sufficient area of homogeneity has been obtained for ultra-low field MRI measurements.

In our research, two types of magnetic sensors have been tested to detect the magnetic resonance signal. The first sensor is a superconducting quantum interference device (SQUID) sensor that has extremely high sensitivity in the ultra-low magnetic fields and is commonly used for ULF-MRI measurements. We demonstrated ULF-MRI measurements of water phantoms and a rat head at 33 μT using the SQUID sensor[2)].

However, there are some difficulties with using SQUIDs because of their fragility against larger magnetic fields such as a polarization pulse and necessity of cooling with a cryogen, like liquid nitrogen or helium. We also developed a novel detection unit composed of an induction coil that has been used to detect magnetic resonance signal in a higher magnetic field so far. The induction coil does not need a cryogen and is more robust and easier to handle than SQUIDs. We demonstrated ULF-MRI measurement[3)] and T_1 relaxation time measurement of water and aqueous solutions at 70 μT, as shown in Figs. 1 and 2. The results show the potential of using induction coil detection to realize a compact ULF-MRI system.

In the presentation, we would like to discuss these two detection techniques for ULF-MRI applications.

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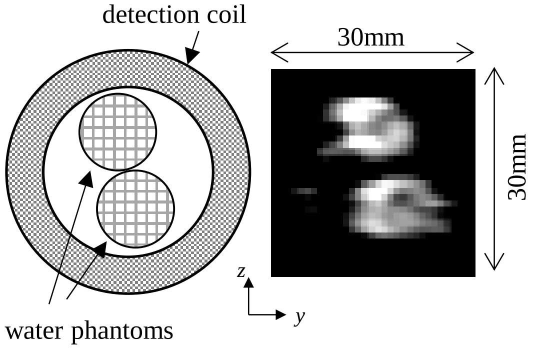

Fig. 1 Magnetic resonance image of water phantoms taken by the detection coil at 70 μT.

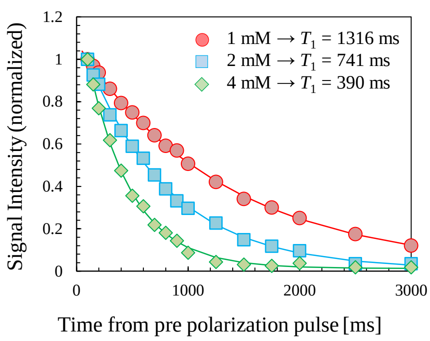

Fig. 2 Measured relaxation curves and calculated relaxation time of $NiCl_2$ aqueous solution phantoms.

Application of EEG/MEG analytical methods to magnetic nanoparticle imaging

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Imagining of magnetic nanoparticles (MNPs) is expected to be a new biomedical technique for imaging of targets, e.g. cancer cells[1]. We previously propose an MNP imaging method that uses multiple magnetic sensors; this method is referred to as "magnetic nanoparticle tomography" (MNT)[2,3]. We used multiple pickup coils, or magnetic sensors, to achieve imaging in accordance with signal processing techniques used in electroencephalography (EEG) and magnetoencephalography (MEG). In this paper, we apply the techniques and compare the imaging performances.

Figure 1 shows the experimental setup. The Resovist MNP sample containing 100 μgFe was arranged in the AC magnetic field generated using an excitation coil. The third harmonic magnetic field from MNPs were detected using 16 pickup coils. To improve the sensitivity, the cancelation circuit for the fundamental magnetic field was employed. Then, the two-dimensional concentration map of the MNP sample was obtained by solving an inverse problem. In this paper, we chosen non-negative least squares (NNLS) method and minimum variance spatial filter (MV-SF). The former one is often used in magnetic particle imaging (MPI) analytical methods[1-3], whereas the latter one is often used in EEG/MEG analytical methods[4].

Figure 2 shows the result of the reconstructed map when the MNP sample was set at $(x, y, z) = (0, 0, -25\ \text{mm})$. As shown in Fig. 2(a), a sharp signal peak is observed in the vicinity of the sample position using NNLS method, however, several artifacts also appear. In contrast, as shown in Fig. 2(b), the signal peak is observed in the vicinity of the position and the artifacts do not appear using MV-SF. The result indicates that EEG/MEG analytical methods such as MV-SF is useful for estimating MNP sample position.

Acknowledgments
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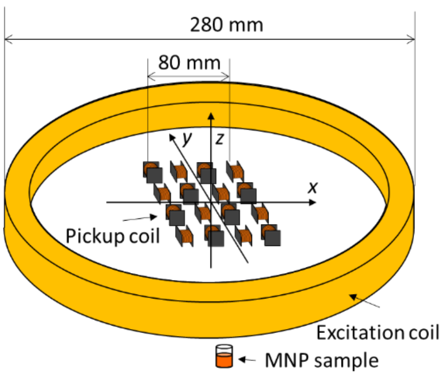

Fig. 1 Overview of the experimental setup.

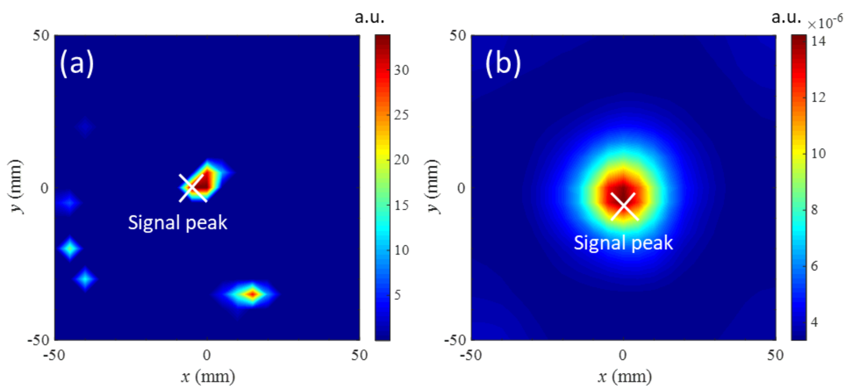

Fig. 2 Result of reconstructed map. (a) NNLS and (b) MV-SF

Development of heating element and techniques for detecting its temperature and position for hyperthermia

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Magnetic hyperthermia is a promising cancer therapy gaining great interest in recent years with less invasive than surgical therapy and fewer side effects compared to chemotherapy. This therapy induces cell death within the therapeutic temperature range of 40–45°C utilizing heat generation from magnetic particles injected into tumor subjected to a high frequency magnetic field. To make this therapy feasible in clinical settings, in addition to the magnetic particles, important elements include techniques for detecting the temperature and position of magnetic particles in determining the effectiveness of therapeutic heating. Among heating elements, nanoparticles have been gaining more attention due to their potential as diagnostic and therapeutic agents. Besides, self-controlled heating elements with low Curie point have been studied due to the fact that they are capable of avoiding overheating and damaging of the surrounding healthy tissue. In previous studies[1-2], we developed thermosensitive magnetic micro/nanoparticles with high heating efficiency for tumor treatment and considerable permeability change around Curie point for temperature and position monitoring by using the nanoparticles to fill the gaps between microsize ferromagnetic implants with low Curie temperature (FILCT) (Fig. 1). Thereafter, by utilizing the permeability of FILCT that varies around its Curie point resulting in the change in the magnetic field around it, we also developed a wireless temperature measurement method to monitor the temperature of treated areas using pickup coils (Fig. 1).

Currently, noninvasive methods for sensing the magnetic particles in vivo are magnetic resonance imaging, positron emission tomography, and magnetic particle imaging. However, they are either costly, complex, time-consuming, requires expertise or a combination of these disadvantages. Taking the advantage of the fact that the induced voltage in pickup coil depends on the position of magnetic particles, we also developed a simple, rapid, low cost and automated localization system using three pickup coils symmetrically installed inside drive coil[3]. To localize the implant, the magnetic field supply and detection unit of drive coil and pickup coils is coarsely scanned over the whole existence possibility area of the implant and then moved to a position close to the implant until there is no difference in pickup voltages (Fig. 1). Using the developed system, the implant could be automatically localized with accuracy below 1 mm. Future studies are needed to extend the detectable distance for deeper tumor by investigating the optimal micro/nanoparticles and pickup coil as well as investigate in vivo how distribution of the implant in affected part affects the accuracy of the proposed method.

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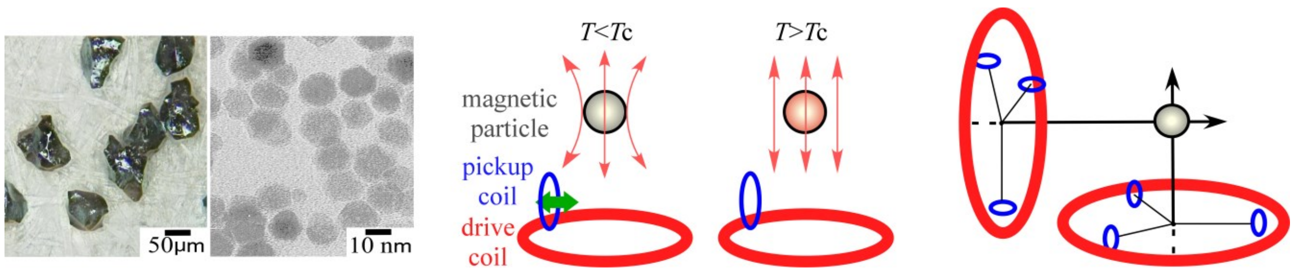

Fig. 1 Heating elements (microsize ferromagnetic implant with low Curie temperature and magnetite nanoparticles) (left), the concepts of wireless temperature measurement method (middle) and localization method (right) for the implant using the voltages induced in pickup coils around its Curie point.