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Position determine system for lymph node relating breast cancer using a high-T_c SQUID

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Abstract

The performance of a lymph-node detection system used with a high-T_c superconducting quantum interference device was investigated. Ultra-small iron oxide particles containing 360 pg in weight of iron could be detected at a distance of 1 mm using Helmholtz coils. When a pair of angled field coils, which were of a more practical design, were used this value was increased to 2.8 ng. This value is still large enough to apply the technique for sentinel-node biopsy and lymphatic mapping. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: SQUID; Biopsy; Detection; Lymph node

1. Introduction

We have recently proposed the application of a high-T_c superconducting quantum interference device (SQUID) to the newly developed surgical technique of sentinel lymph-node biopsy. Axillary lymph-node dissection is an important procedure in the surgical treatment of breast cancer. However, in the early diagnosis stage, the number of dissections in which axillary nodes are free of disease is apt to be increased. These treatments lead to some problems such as a lymph edema and a sensory neuropathy in the patient. The sentinel-node biopsy is a kind of test to investigate whether the sentinel node, which initially receives malignant cells from a breast carcinoma is disease-free or not. If the sentinel node is free of disease, you can leave the rest of the lymph nodes because of no concern for progression. This biopsy is based on the hypothesis that if the first lymph node (sentinel node) is free of disease, the second and the rest of the nodes must be negative. Two methods which detect the sentinel node have been developed and reported to date [1–3]. One is a kind of radio guide, which uses a gamma detector and a radio isotope such as technetium labeled sulfur colloid. After injecting the isotope into a breast lesion, the sentinel lymph node will be identified by the gamma detector. Then the sentinel node is excised and examined. In this method the sentinel lymph node is successfully identified with 94.4% accuracy [1]. Though the predictability of this method is

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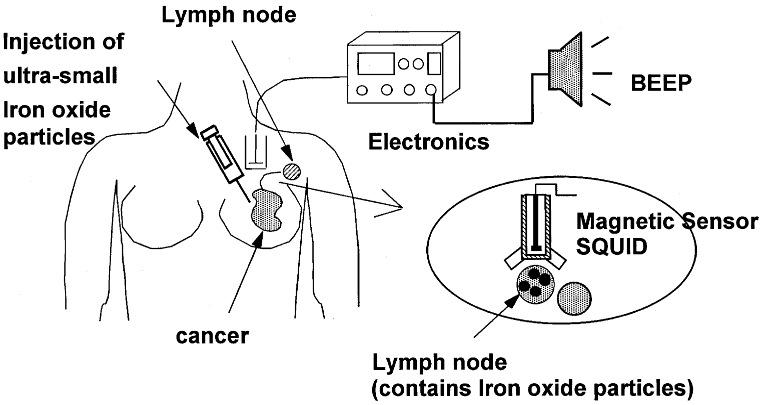

Fig. 1. The system diagram of the sentinel-node biopsy using high-T_c SQUID, which we are proposing. The particles would be injected into the breast; and the high-T_c SQUID is used as a sensing detector for the particles. This method has an advantage of no radiation exposure.

extremely high, radiation exposure is inevitable for medical staff. The other method uses a blue dye; a surgeon identifies the sentinel lymph node with his naked eye. With this method the predictability is still 70% accurate [2].

Therefore we propose a localization system combined with a high sensitivity SQUID magnetometer and ultra-small iron oxide particles. The system we are proposing is shown in Fig. 1. The particles would be injected into the breast; and the high-T_c SQUID is used as a sensing detector for the particles. This method has some advantages: no radiation exposure and an accurate identification because of the visible color of the particles themselves. For this application, the SQUID magnetic sensor should identify the location of the small quantity of particles under the sensor. Although a SQUID biosusceptometry system has been reported [4], it is very difficult to detect the location because of the small quantity. Detection methods of small magnetic particles with a SQUID immunoassay, which can be also applied to our detection system, have been proposed in several groups [5–7]. Even if the particles are made of iron oxide, if their size becomes too small, they show superparamagnetic properties. Therefore, some magnetic field should be applied to the particles for detection because they have almost no permanent magnetic dipole at room temperature. Koetitz et al. applied a pulse field to the particles and then measured the field decay from the particles in the range of ms. Empuku et al. measured the field from the particles under a DC magnetic field. For the work described here, we measured the field from the particles under an AC magnetic field.

We have already reported the results of preliminary study using particles dispersed liquid in a tube [8].

In this paper, we describe the results of the more practical system design and the performances.

2. Instrumentation

The schematic diagram of the system is shown in Fig. 2. The SQUID is made of $YBa_2Cu_3O_{7-y}$ thin film. The junctions utilized in the SQUID are of the step-edge type. The washer size of the SQUID is about 2.5×2.5 mm^2 and the effective area is 0.11 mm^2. The SQUID was operated in a flux-locked loop. The magnetic flux noise in the white noise region was about 30 $\mu\phi_0/\mathrm{Hz}^{1/2}$.

The cryostat was specially designed for a SQUID microscope. The SQUID was located inside a vacuum and separated by a 50 μm thick quartz window. A more detailed description can be found elsewhere [9]. Two coils (Helmholtz type) were mounted just above the SQUID microscope [10,11]. A fine polytetrafluoroethylene tube with

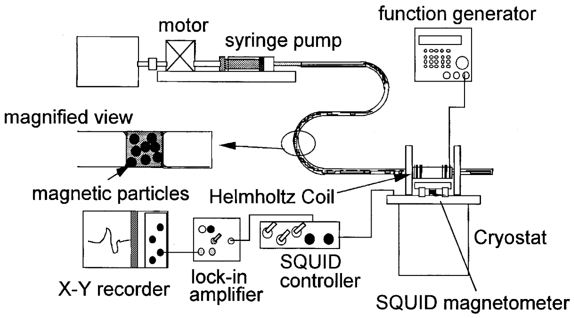

Fig. 2. Schematic diagram of the system for the feasibility test. A pair of coils were mounted just above the SQUID cryostat. External AC magnetic field was applied by the coils. A motor driven syringe pump was employed to push the magnetic particle sample inside a thin tube. The modulated signal associated with the particle motion was demodulated by the lock-in amplifier.

an inner dimension of 0.85–0.95 mm diameter, which conveys small particles, was threaded into the coils. A motor driven syringe pump was employed to convey the particles by pushing air inside the tube. A sinusoidal AC current with a frequency of 5–100 Hz was directed to the coils; the magnetic field generated from the coil was modulated by the frequency. The modulated signal associated with the particle motion was then demodulated by the lock-in amplifier. The lock-in amplifier consists of a phase sensitive detector, a phase shifter and a low-pass filter [12,13]. The roll off frequency of the filter, which sets the bandwidth was 3 Hz. Since the roll off gives you sensitivity to noise only within 3 Hz of the desired signal, the signal/noise ratio is improved. However, you cannot sweep the particles faster than 3 Hz. The phase shifter was adjusted to give the maximum output signal.

The use of the lock-in amplifier is a crucial point to obtain a good resolution in the system. In this scheme, as with signal averaging, the effect of the modulation is to center the signal at the modulation frequency, rather than at DC, in order to get away from $1/f$ noise, which occurs usually in the range from DC to 1 Hz. The SQUID position was carefully adjusted before measurement, so that the SQUID output signal without particles became zero.

3. Magnetic particles

After adjusting the SQUID, the system was ready to measure magnetic field from the particles. We used ultra-small particles from Meito Sangyo Co., Ltd. Similar particles are used as a magnetic resonance imaging contrast agent. The core of the particle is iron oxide Fe_3O_4 (magnetite) which is coated with an alkali-treated dextran. The average core diameter was 11 nm, which was measured from the X-ray diffraction pattern using Scherrer's equation [14]. The averaged diameter of the coated particles was 100 nm. The particles had superparamagnetic properties. The particles were supplied in the form of an aqueous magnetic fluid. The original fluid contained 5.9 mg/ml of iron. If we suppose 5.2 g/cm^3 as the specific gravity of the core, we can estimate the weight of the monoparticle as 3.6×10^{-18} g and the total number of particles in the original solution as 1.5×10^{16} ml^{-1}. The original fluid was diluted with distilled water to have the desired concentrations. Then the fluid was swept in the fine tube with the scan speed of 0.33–1.1 mm/s under an AC magnetic field of 9×10^{-5} to 7×10^{-4} T (peak-to-peak value).

4. Results and discussion

We performed all of the measurements in a magnetically shielded room with a shielding factor of −50 dB at 0.1 Hz. Fig. 3 shows the typical

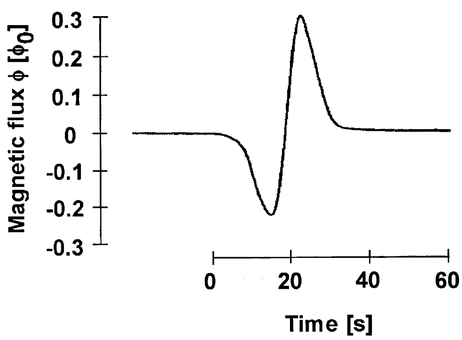

Fig. 3. Typical output signal from the lock-in amplifier. Each positive and negative peak was observed when each edge of the fluid specimen passed over the center of the SQUID.

output signal of the lock-in amplifier [8]. In a fluid length of about 8 mm in the tube, the weight of iron was found to be about 65 μg. In this measurement the distance from the SQUID to the specimen was 10 mm. Each positive and negative peak was observed when each edge of the fluid specimen passed over the center of the SQUID. We define each difference of the negative and positive peaks as the SQUID signal hereafter.

We investigated the detectable weights of the iron. The SQUID signal was proportional to the weight of the iron in the fluid. At a distance of 40 mm, the minimum detectable weight was 1.6 μg. When the distance was decreased to 1 mm, this decreased to 360 pg [8].

Then we measured the frequency dependence of the output signal. The sample consisted of iron particles of 2.4 μg and distilled water of 4.4 μl. The modulation frequency of the Helmholtz coil was changed from 5 to 100 Hz. The results are shown in Fig. 4 (solid circles). The signal from the lock-in amplifier decreased with the increase of frequency in the region of more than 10 Hz. The results suggested that the alignment of the dipole moments or the rotation of the particles is not synchronized with the frequency. Therefore we immersed a piece of cotton with the liquid sample. The content of the iron and the volume of the liquid were as same as the former experiment. In this sample, the rotation of the particles should be restricted by existence of the cotton though it was not perfect. The frequency dependence was measured using this sample. The results were shown in Fig. 4 (open circles). The signal was one order smaller than that of the liquid sample in all the frequency; this is because of the restriction of the particle's rotation. Although further experiments are needed to clarify this phenomenon [7], not only the alignment of the dipole moments but also the physical rotation of the particles is contributed to the polarization. Therefore the lower frequency should be chosen in the system.

We prepared a special pair of external field coils to investigate the practical sensitivity of the system. In an actual system, it is difficult to use the straight wound Helmholtz configuration shown in Fig. 2. Therefore a pair of 1000 turn wound coils were set with angle of 90° as shown in Fig. 5. The tube with a liquid sample was located under the coil and the signal from the sample was measured by the SQUID under the coils. An AC magnetic field of 2.6×10^{-4} T was applied to the sample. The position of the SQUID was carefully adjusted so that the SQUID output signal without samples become zero. As shown in Fig. 6, magnetic flux signal was proportional to the weight of the iron in the fluid. Particles of 2.8 ng in weight of iron would be detected with a spacing of 1 mm. This

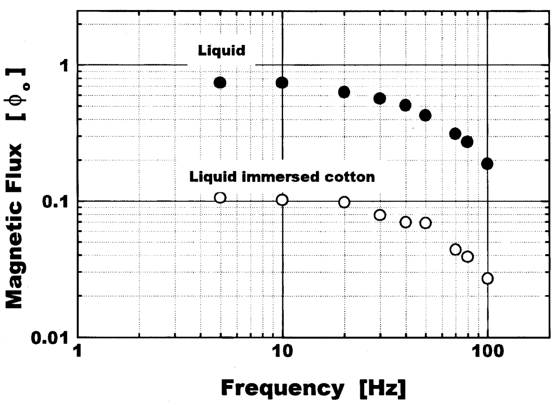

Fig. 4. Frequency dependence of the output signal. The modulation frequency of the Helmholtz coil was changed from 5 to 100 Hz. Closed circles show the results from liquid sample. Open circles show the results from liquid with a piece of cotton.

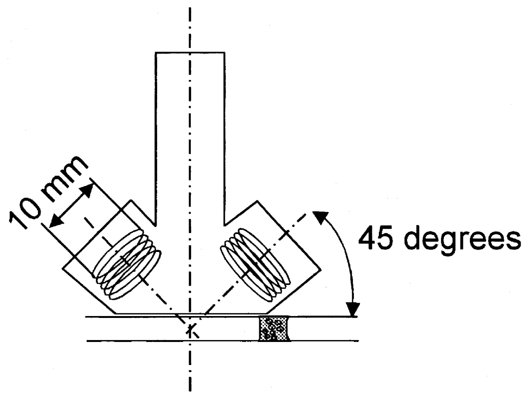

Fig. 5. Schematic drawing of the practical coil design. A pair of 1000 turn wound coils was set with angle of 90°. Tube with a fluid sample was located under the coil and the signal from the sample was measured by the SQUID under the tube.

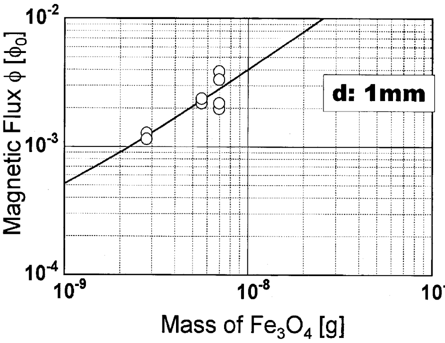

Fig. 6. Magnetic flux vs. mass of iron contained in the sample. Magnetic flux signal was proportional to the weight of the iron in the fluid. Particles of 2.8 ng in weight of iron would be detected with a spacing of 1 mm.

minimum value is about factor of 8 larger than that of weight measured in straight Helmholtz coil configuration.

If 10 mg of Fe is injected into a human body, about 5% of the amount will be concentrated in the lymph node; i.e. Fe of 500 μg will exist at the lymph node. Therefore the detectable value is large enough to be used in mapping of a sentinel lymph node.

5. Conclusion

We have demonstrated the possibility of realization of a nanoparticle detection system used with a high-T_c SQUID, which is useful for sentinel lymph-node biopsies. The ultra-small iron oxide particles of 360 pg in weight of iron could be detected with a spacing of 1 mm. When a pair of angled field coils was used, the value was increased and was 2.8 ng. This value is large enough to apply the technology for sentinel-node biopsy and lymphatic mapping. The signal from the particles was dependent on the frequency of the magnetic field. This result suggested that the polarization is due to not only the alignment of the dipole moments but also the physical rotation of the particles.

Acknowledgements

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