Application of High Tc SQUID Magnetometer for Sentinel-Lymph Node Biopsy

Saburo Tanaka, Atsushi Hirata, Yusuke Saito, Takahiro Mizoguchi, Yasuhiro Tamaki, Isao Sakita and Morito Monden

Abstract— **The basic performance of a nanoparticle detection system for lymph node used with a high-Tc superconducting quantum interference device (SQUID) was investigated. Ultra-small iron oxide particles of 360 pg could be detected with spacing of 1 mm between the SQUID magnetometer and the particles. When the space was widened to 40 mm, the detectable weight of the particles was increased and was 1.6 μg**

Index Terms—**SQUID, Biopsy, Detection, Lymph Node**

I. Introduction

We propose the application of a high-T_c superconducting quantum interference device (SQUID) for a sentinel node biopsy, which is a newly developed surgical technology. 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. The procedure is shown in Fig. 1. In this method the sentinel lymph-node is successfully identified with 94.4% accuracy [1]. Though the predictability of this method is 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 superconducting quantum interference device (SQUID) magnetometer and ultra-small iron oxide particles. The particles are 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 at a distance of several centimeters. Although a SQUID biosusceptometry system has been reported [4], it is very difficult to detect the location because of the small quantity. Detection of small magnetic particles with a SQUID immunoassay, which can be also applied to our detection system, have been proposed in several groups [5], [6]. 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.

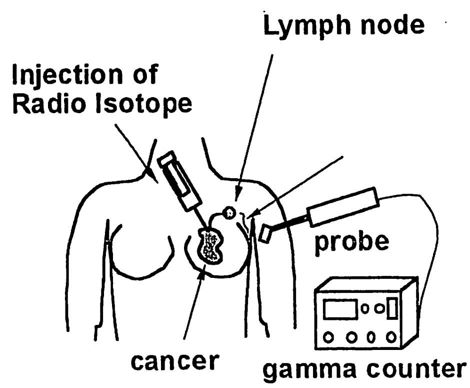

Fig. 1. Procedure of conventional Sentinel Node biopsy.

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In this paper, we describe the design and performance of our basic system in terms of the detectable quantity of ultra-small particles.

II. Experimental

The schematic diagram of the system is shown in Fig. 2. The SQUID is made of $Y_1Ba_2Cu_3O_{7-y}$ thin film, which was fabricated at Sumitomo Electric Industry and modified at our university [7]. The junctions utilized in the SQUID are of the step-edge type. The washer size of the SQUID is about 2.5 x 2.5 mm^2 and the effective area is 0.11 mm^2. The SQUID was operated in a flux-locked loop with a flux modulation frequency of 100 kHz. The magnetic flux noise in the white noise region was about 30 $\mu\phi_0/Hz^{1/2}$.

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 [8]. Two coils (Helmholtz type) were mounted just above the SQUID microscope [9], [10].

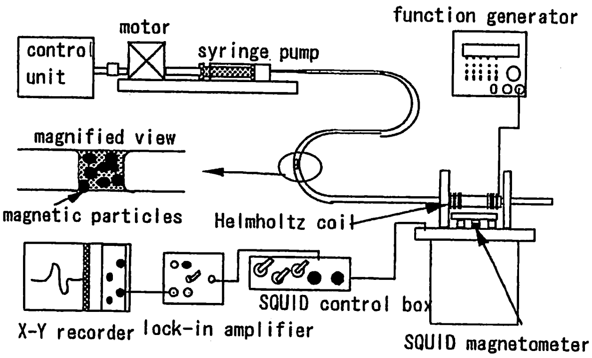

Fig. 2. Schematic diagram of the system. Two identical 1000 turn wound coils (Helmholtz type) were mounted just above the SQUID microscope. A magnetic field generated from the coils was modulated by a 100Hz signal. A motor driven syringe pump was employed to convey the magnetic particles by pushing air inside the tube. The modulated signal associated with the particle motion was demodulated by the lock-in-amplifier.

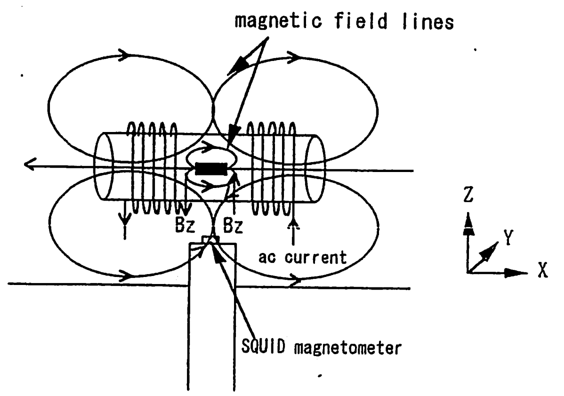

Fig. 3. Detail of the sensing region in the system. Z-axis components of the magnetic field lines at the center of the coils canceled each other. The fluid was swept in the fine tube with a scan speed of 0.2 to 1 mm/s under the AC magnetic field of $9x10^{-5}$ to $7x10^{-4}$ T (peak to peak value). Then the magnetic fields associated with the fluid were measured.

A fine polytetrafluoroethylene tube with an inner dimension of 0.85-0.95 mm dia., 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 100Hz 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 is home-made and consists of a phase sensitive detector, a phase shifter and a low-pass filter [11], [12]. The rolloff frequency of the filter, which sets the bandwidth was 3 Hz. Since the rolloff gives you sensitivity to noise only within 3 Hz of the desired signal, the signal/noise ratio is improved. However, you can not 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 100 Hz, rather than at DC, in order to get away from 1/f noise, which occurs usually in the range from DC to 1 Hz. Fig. 3 shows details of the sensing region. The two identical 1000-turn coils were spread apart a distance of 50 mm. The z-component of the magnetic field at the center of the coils canceled each other. The SQUID position was carefully adjusted before measurement, so that the SQUID output signal without particles became zero.

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 (MRI) contrast agent. The coré of the particle is iron oxide Fe_3O_4 (magnetite) which is coated with an alkali-treated dextran. The average core diameter was 11nm, which was measured from the X-ray diffraction pattern using Scherrer's equation [13]. 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 mono-particle as $3.6x10^{-18}$g and the total number of particles in the original solution as $1.5x10^{16}$/ml. 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/sec under an AC magnetic field of $9x10^{-5}$ to $7x10^{-4}$ T (peak to peak value).

III. Result and Discussions

We performed all of the measurements in a magnetically shielded room with a shielding factor of –50 dB at 0.1 Hz. Fig. 4 shows the typical output signal of the lock-in-amplifier. The fluid length of about 8 mm in the tube, which corresponds to the weight of iron in the fluid, was measured as 65 μg. In this measurement the distance from the SQUID to the specimen was 10mm. Each positive and negative peak was observed when each edge of the fluid specimen passed over the center of the SQUID. This means that the particles were homogeneously distributed in the solution and that all of the particles behaved as one large dipole, whose length was 8mm in our experiment. We define each difference of the negative and positive peaks as the SQUID signal hereafter.

Measurements of magnetic fields from fluids with different distances from the SQUID to the specimen were performed. All of the conditions except for the concentration were the same as in the previous experiment. Fig. 5 shows the results. Following the theory of classical electodynamics [14], a field at a point from a dipole decreases as $1/r^3$, when $r \gg \ell$, where r is the distance from the point to the dipole and ℓ is the length of the dipole. However, we found that the fields were inversely proportional to the distance in power for separation r>20 mm. For this investigation, the theoretical calculation was performed. The calculation results are shown in Fig.6. The spatial variation of the applied field from the Helmholtz coil was included in this simulation. The $1/r^3$ relation is indicated as a broken line for the reference. At the distance of 10 to 40 mm, the calculation shows that the magnetic flux depends on the distance as a $1/r^n$ (n<3). Therefore this tendency can be explained by the spatial variation of the applied field.

We next investigated the detectable weights of the iron at the minimum distance of 1 mm and 40mm. In this experiment with the distance r = 1 mm, specimens with the length of 1mm were used. As shown in Fig. 7, the SQUID signal was proportional to the weight of the iron in the fluid. At the distance of 40 mm, the detectable minimum weight of the iron was 1.6 μg.

If 10mg 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 of 1.6 μg is large enough to be used in mapping of a sentinel lymph node. At a distance of 1 mm,

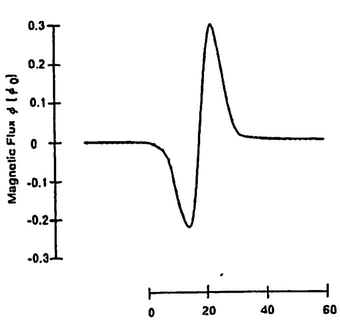

Fig. 4. Typical output signal of the lock- in-amplifier. The fluid length of about 8mm in the tube corresponds to weight of iron in the fluid of 65 μg. The distance from the SQUID to the specimen was 10 mm.

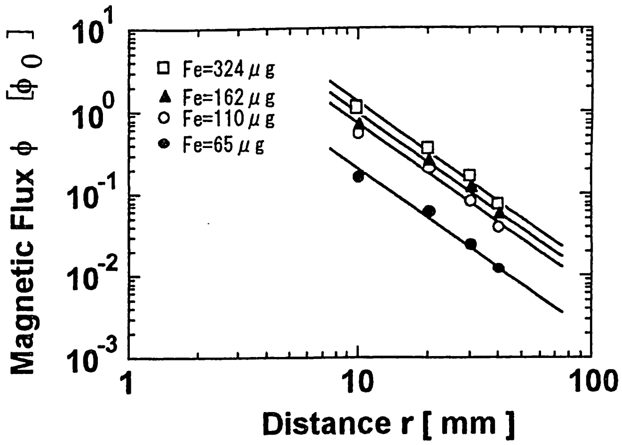

Fig. 5. Magnetic signal intensity vs. distance from the SQUID to the specimen. The fields were inversely proportional to a power of the distance.

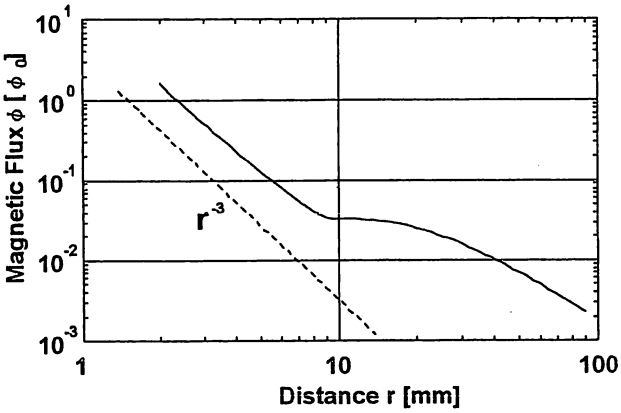

Fig. 6. Theoretical calculation of the dependence of detected magnetic flux on distance. Broken line indicates $1/r^3$ properties. At the distance of 10 to 40 mm, the dependence of the magnetic flux on the distance shows $1/r^n$ (n<3).

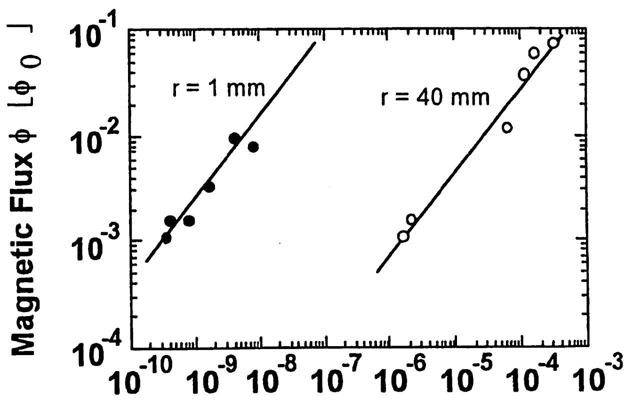

Fig. 7. Magnetic signal intensity vs. weight of Fe in particle. The SQUID signal was proportional to the weight of the iron in the fluid. The iron weight of 360 pg and 1.6 μg could be detected at the distances of 1 mm and 40 mm, respectively.

the signal from less than 340 pg was comparable with the level of the noise. And 360 pg of Fe could be detected in this system. This value is larger than the noise limit of the SQUID. If you lower the system mechanical noise, this result could be improved.

In the actual biopsy, the particles are not concentrated in a length of 1mm like the above experiment. Accordingly, we measured the effect of the sample length. Several samples with different length, but constant 40.3 ng of iron, were prepared. The distance between the SQUID and the samples was 1 mm. Fig 8 shows the results. When the sample length became larger, the signal increased. Although this phenomenon may be due to the spatial variation of the magnetic field from the Helmholtz coil, it means that the diluted particles can be detected in this range.

IV. 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 1mm. When the spacing was widened up to 40 mm, the detectable weight of the particles was increased and was 1.6μg. The resolutions are good enough to apply the technology for Sentinel-node biopsy and lymphatic mapping. The use of the lock-in-amplifier is a crucial point to obtain a good resolution in the system.

Our technique has not been applied to actual biopsy yet. Real magnetic environment may not be so good because of presence of interfering signal arising from some iron particles concentrated in the liver or other organs. The next step is to develop a small sensor head for the application and to demonstrate that it works in a partially shielded ambient field with the use of experimental animals

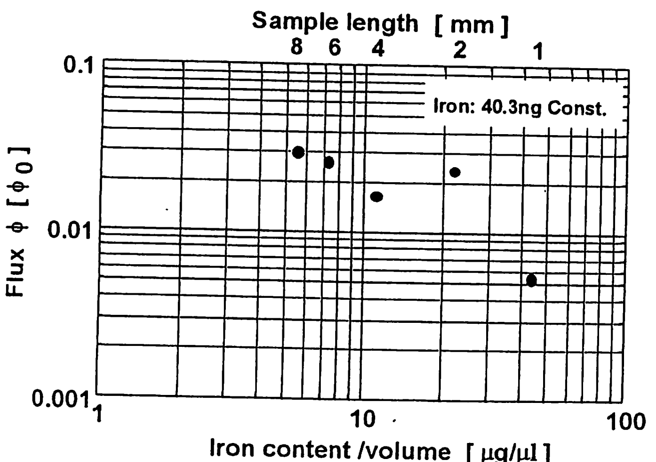

Fig.8 Sample volume dependence of the signal. Several samples with different length, which contains the same weight of the iron particles, 40.3ng were prepared. The distance between the SQUID and the samples was 1 mm. When the sample length became larger, the signal increased.

to investigate the interference. The technology presented in this paper is not limited to the biopsy application but can be applied to immunoassay applications.

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