Detecting Ferrite Nanobeads for Sentinel Lymph Node Mapping with a Highly Sensitive Hall Differential Magnetic Field Sensor

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Abstract. We fabricated a novel type of Hall differential magnetic field sensor for anti-cancer sentinel lymph node (SLN) mapping using ferrofluid as a marker. A pair of Hall devices are mounted on both end surfaces of a ferrite core (10 mm $\phi \times 32$ mm) of an electromagnetic coil which generates an AC exciting magnetic field at 2.5 kHz. The signals are retrieved by a digital phase sensitive detection circuit. Mapping a ferrofluid (Resovist$^\text{R}$) sample of 100$\mu$g in Fe atomic amount (comparable to that accumulated in human SLNs) was attained when the sample was placed within 6 mm distance from the sensor head. The detectable distance is limited primarily due to the magnetic induction effect of the metal XYZ stage which held the sample.

1. Introduction

Distant metastasis of cancer is caused by cancer cells which are isolated from primary tumors and drifted along with blood flow and lymph flow. Cancer cells drifting along with lymph flow are trapped inside lymph nodes, where lymph cells attack to kill them. If the cancer cells survive, metastasis occurs at the lymph nodes.

As such the concept of “sentinel lymph node” (SLN) was established: SLN is the first lymph node that filters the fluid draining away from the primary tumor. If the SLN is not metastasized, cancer is not spread to down stream lymph nodes. This phenomenon has been exploited in “SLN mapping and biopsy”, or “SLN navigation surgery”. Tracers are injected as a marker from near the primary tumor and the SLN is identified by detecting the marker that has migrated along the lymph channel. The SLN is then resected for pathological examination of the staging of the metastasis. If the SLN is not metastasized, resection of down stream lymph nodes can be avoided, and the patient’s quality of life is much improved.

SLN navigation surgery has become a standard treatment for breast cancer and melanoma at present, and it is gaining popularity for other kinds of cancers [1].

In conventional SLN mapping a radioisotope and a pigment are used at the same time as the marker. The isotope is detected by a $\gamma$-ray probe and pigment is used for secondary eye observation. However, they have drawbacks: the pigment can be allergy provoking, and the radio-isotopes are strictly...
regulated by law and small-scale medical agencies can not afford to use them. To solve the problems researchers tried to replace the marker with ferrite nanobeads and detect them with magnetic field sensors, as shown in Fig.1. They first used magnetoresistance (MR) devices for the sensing and clinical tests were performed [2, 3]. Then, sensors utilizing SQUIDs were developed to improve the sensitivity [4, 5]. However, SQUIDs are expensive and complicated to use.

To address these issues we invented sentinel lymph node mapping by exploiting the magneto-acoustic effect [6,7]. The magnetic beads trapped and accumulated in the SLN were excited by an AC magnetic field to generate acoustic waves, which were detected by a microphone. This gave sensitivity high enough for SLN mapping.

However, we found problems with the acoustic detection. In actual SLN surgery, conclusive identification of SLN is made by directly touching the γ-ray probe head to the lymph nodes in open wound or to the resected lymph nodes put on a back table. This is impossible by using the microphone probe, because the direct contact causes acoustic impedance mismatch; impedance matching is obtained when the lymph nodes are embedded in continuous media such as living body.

Therefore we developed a novel type of Hall differential magnetic field sensor [8]. In this paper we will describe the principle of our novel sensor, report their performance evaluated from our preliminary experiments, and discuss the outlook for the new sensor.

2. Principle and experimental

Figure 2 shows our new sensor, which is molded in a gun type case. The sensor head has a pair of Hall devices (Honeywell SS495A) mounted on both end surfaces of a ferrite cylindrical core (10 mm φ ×32 mm) of an electromagnet coil. This enables differential detection of near field signals from the magnetic beads, and magnetic (far) fields of environmental noise and earth magnetism are cancelled. The ferrite core concentrates magnetic fluxes generated by the exciting coil and by the magnetic beads. These features enhance the sensitivity of the sensor.

Applying a continuous AC current at 2.5 kHz to the exciting coil (which is resonated with capacitors connected in parallel) a 250 Oe rms field is generated on the sensor head as measured by the Hall device on the head. The signals from the magnetic beads are retrieved by a digital phase sensitive detection circuit with a 24 bit A/D conversion resolution. Data acquired over 50 msec were averaged over 400 cycles (sampling time: 20 sec), which improved the S/N ratio by about 26 dB (=20 sec/50 msec).

We evaluated the sensitivity of the sensor by detecting Resovist®, an FDA approved intravenous injection MRI contrast agent of ferrite nanobeads ferrofluid. The ferrofluid was adsorbed on the tip of a cotton swab to make a dot-like sample which was less than 1 mm in size. The sample was roughly 100 μg in Fe atomic amount, a value comparable to that accumulated in human axillary SLNs in SLN surgery.
The cotton swab containing the sample was mounted on an XYZ stage via a plastic bar (ca. 20 cm in length), as shown in Fig.3, in order to minimize the magnetic induction effect of bulk metal of the XYZ stage. This length was chosen to limit signal deterioration due to mechanical vibration. Also the background signal (obtained when the sample was removed), which was mainly caused by the XYZ stage, was subtracted from the raw signal. The background signal was nearly independent of the distance, \(x\), of the sample from sensor head.

![Fig. 3 Experimental setup for mapping a dot-like sample of ferrofluid (Resovist\textsuperscript{R}) on the tip of a cotton swab. The sample is moved by XYZ stage with respect to the sensor head (Hall device).](image)

### 3. Results and discussion

Figure 4(a) shows the output signal plotted in logarithmic scale as a function of \(x\). Here we fixed the lateral position (\(y\) and \(z\)) of the sample to the place where the signal reached maximum, roughly along the coil axis. The maximum detectable distance \(x\) (corresponding to depth of SLN from body surface) with S/N ratio=1 was determined to be 13 mm. The exciting magnetic field decreased to 12 Oe rms at \(x=13\) mm.

Figure 4(b) shows the output signal plotted as a function of \(y\) (a lateral distance), obtained when \(x\) was fixed at values between 4 mm and 10 mm; when \(x\) was smaller than 4 mm we could not retrieve signals which were too strong to fall in the dynamic range of the circuit. When \(x=4\) mm and 6 mm the signal exhibited a nearly symmetrical curve making a peak around the coil axis. Thus our sensor is capable of mapping the Resovist\textsuperscript{R} sample at 6mm depth. For \(x=8\) mm and 10 mm the signal curves did not exhibit a peak and mapping was impossible. This is because the signal is dominated by the magnetic induction effect of the XYZ stage.

![Fig. 4 Signal obtained for ferrofluid (Resovist\textsuperscript{R}) sample: (a) plotted as a function of distance (\(x\)) of sensor head from sample, obtained when lateral position (\(y\) and \(z\)) was fixed around coil axis, and (b) plotted as a function of a lateral distance (\(y\) in relative value), obtained when \(x\) was fixed to various values.](image)
4. Concluding remarks

For the Resovist® sample of an amount comparable to that accumulated in human SLNs, we obtained maximum detectable distance ($x$) of 13 mm when the sample was placed roughly along the coil axis (Fig. 4(a)). Since in actual SLN mapping maximum detectable depth of 10 mm is required, our sensor has a potential for clinical application. However, for mapping the sample in the lateral directions ($y$ and $z$) maximum detectable distance decreased to ca. 6 mm (Fig. 4(b)) due to the magnetic induction from the metal XYZ stage, albeit it being separated from the sensor head by about 20 cm. Therefore in clinical SLN mapping metal materials must be separated from the sensor much longer than 20 cm.

The sensitivity of our new sensor will be improved by introducing the spread-spectrum noise reduction technique [9] to the digital phase sensitive detection circuit. If the signal spectrum is spread from present 20 Hz (corresponding to 50 msec sampling time) to e.g. 200 kHz, the information capacity increases by factor 10,000 ($=200$ kHz/20 Hz) and thus we can improve the S/N ratio by nominally 40 dB ($=(10,000)^{1/2}$) at maximum. We are currently investing our efforts to take advantage of this.

On a final note, our sensor might be easily integrated into an endoscope by separating the sensor head from main circuit and mounting it on the endoscope edge.

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