Detection and Estimation of Low-Concentration Magnetic Fluid inside Body by a Needle-Type GMR Sensor

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Due to its biocompatibility, magnetic fluid or nanoparticles have been used inside the body to deliver medicines or to act as self heating agents to kill cancerous tumors. The estimation of magnetic fluid inside tumors is critical in hyperthermia therapy. This paper reports a unique needle-type GMR sensor fabricated for the purpose of confirming the presence and location, and estimating low-concentration magnetic fluid inside the body, in a minimally invasive way. Theoretical analysis is presented for detecting and estimating magnetic fluid *in vivo*. Experiments are performed initially to detect magnetic fluid in trays with embedded cavities followed by detecting and estimating magnetic fluid inside pieces of agar. The results show that the needle-type GMR sensor has good potential to be used in clinical applications such as hyperthermia therapy in cancer treatment.

Index Terms—**Demagnetizing factor, giant magnetoresistance, hyperthermia, magnetic nanoparticles, permeability.**

I. Introduction

SIGNIFICANT advancements in the field of nano-biomagnetism have shown that magnetic nanoparticles can be exploited to play an important and crucial role in health care and biomedical applications [1]. Dextran Magnetite (DM) or magnetic fluid is a complex of the polysaccharide Dextran and magnetite particles. Even though polysaccharides such as Dextran can be structurally weak and be dissolved in highly acidic surroundings, they are biocompatible and offer a range of functionalization options inside the body [2].

Localized or deeply seated cancer tumors exposed to temperatures around 42.5 °C for a prolonged period of time are partly or fully destroyed, while normal healthy cells can tolerate higher temperatures [3]. Tumor cells take up nine times more magnetic fluid than normal cells and heat dissipation in the former is much slower due to an abnormal blood supply to it [4]. Magnetic fluid is injected into the site of the tumor and ac magnetic fields heat up the tumor in hyperthermia therapy [5]. Hysteresis loss of relatively high permeable magnetic fluid in the tumor, causes cell death or apoptosis. Induced heat capacity is directly proportional to magnetic fluid weight density [6], [7]. Hence, precise estimation of the weight density of magnetic fluid is critical in the success of hyperthermia therapy. Once injected into the body magnetic fluid spreads inside tissue providing obstacles to effective treatment. Coupling magnetic fluid to tumor specific ligands such as antibodies, slow infiltration and repeated multi-site injections are some of the methods used to increase the retention of magnetic fluid in tumors. To provide adequate heat to kill the tumor without affecting surrounding healthy cells, the weight density of magnetic fluid needs to be confirmed before and after treatment (to check remaining density).

A unique and simple needle type GMR sensor that can be inserted into the body in a minimally invasive way was fabricated for detecting and estimating magnetic fluid weight density. Detecting and estimating low-concentration magnetic fluid weight density by the needle-type GMR sensor is based on the difference of magnetic flux density inside and outside a magnetic fluid filled area in the body.

II. Estimation of Weight Density of Magnetic Nanoparticles Inside Body

A. Relationship Between Relative Permeability and Weight Density of Magnetic Nanoparticles

The magnetic nanoparticles are assumed to be uniformly distributed in the fluid and cylindrical in shape, where the height equals the diameter. Furthermore, the respective relative permeabilities of nanoparticles and liquid are assumed to be infinite and one. The permeance of an equivalent magnetic path through magnetic nanoparticles and air is estimated and hence, used to obtain the equivalent permeance of a unit volume. The relative permeability is then derived from the equivalent permeance of a unit volume [7]. Considering magnetic fluid as a bulk, the relative permeability, μ^*, is

$$\mu^* = 1 + 4D_v \approx 1 + 4D_w/\gamma_f \quad (D_w \ll 1) \tag{1}$$

where $\gamma_f = 4.58$ (W-35 sample—Taiho company) is the specific gravity. The magnetic fluid volume density, D_v is measured as a percentage, while the weight density is the amount of milligrams of Ferrite particles in 1 milliliter water (mgFe/ml). Equation (1) shows that the relative permeability is proportional to D_v and D_w but independent of shape or size of magnetic nanoparticles.

It can be seen from the electron microscopy image in Fig. 1 that magnetic nanoparticles have a cluster structure. It was then assumed that it is also uniformly distributed as shown in the spherical cluster of the model. Since there is space between the particles the space factor of spherical magnetite was considered. Equation (1) is then written as

$$\mu^* = 1 + 4D_w/h_s\gamma_f \quad (D_w \ll 1) \tag{2}$$

where $\gamma_f' = h_s\gamma_f$ (space factor of spherical magnetite, $h_s = 0.523$). In Fig. 1, the calculated results were obtained by (2) while the experimental results were obtained by measuring the relative permeability of various magnetic fluid weight densities using a vibrating sample magnetometer (VSM). It can be seen

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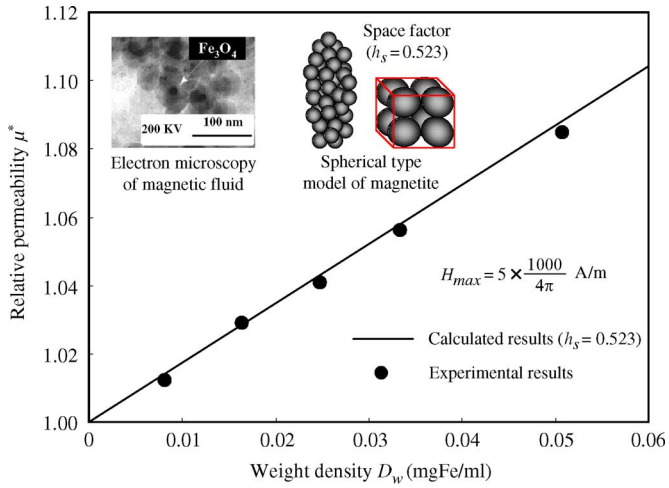

Fig. 1. Relative permeability as a function of weight density ($H_0 = 100$ A/m), assuming space factor h_s, of 0.523.

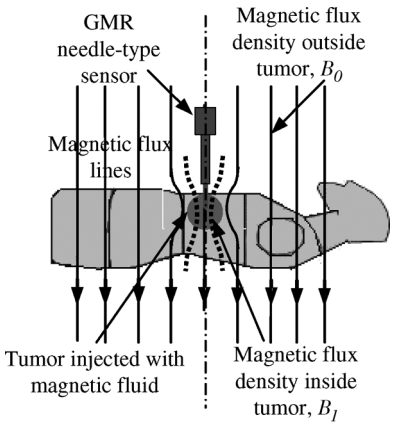

Fig. 2. Magnetic fluid filled tumor under a uniform magnetic flux density.

from the results that the relative permeability is linearly proportional to the magnetic fluid weight density.

B. Content Density Estimation by Measuring Magnetic Flux Density Inside and Outside a Magnetic Fluid Filled Body

Fig. 2 shows a uniform magnetic flux density B_0, produced by a Helmholtz tri-coil, applied to a body with a tumor that is injected with magnetic fluid. Magnetic flux lines will converge at the fluid filled tumor and the magnetic flux density at the center of the tumor B_1 can be expressed as

$$B_1 = \mu^* B_0 / \{1 + N(\mu^* - 1)\} \quad (\mu^* \approx 1) \tag{3}$$

where N is the demagnetizing factor of the cavity [7]. By substituting (2) into (3), the difference between the magnetic flux density inside the magnetic fluid tumor (B_1) and the applied magnetic flux density B_0, can be expressed as

$$\begin{aligned} \delta &= (B_1 - B_0)/B_0 \times 100 \\ &\approx 4(1-N)D_w/(h_s\gamma_f) \times 100(\%) \quad (D_w \ll 1). \end{aligned} \tag{4}$$

Equation (4) shows that the magnetic fluid weight density can be effectively calculated from the difference between B_1 and B_0.

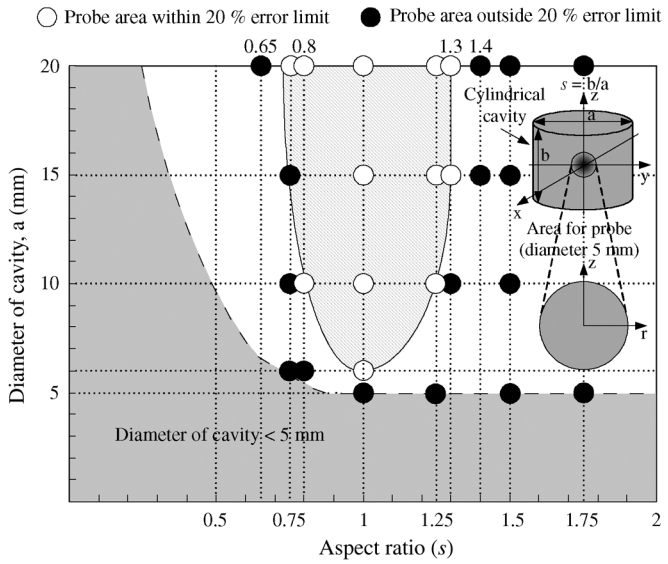

Fig. 3. Condition for cavity for 20% error inside 5-mm spherical area.

While the change ratio of B_1 and B_0 is directly proportional to the magnetic fluid weight density, it must be noted that the shape of the tumor has an effect and thus influences differential magnetic flux density.

C. Evaluation of Error Due to Variation of Shape of Magnetic Fluid Filled Area Inside Body

Magnetic nanoparticles are considered to be uniformly distributed in a spherical or ellipsoidal cavity. However, when magnetic fluid is injected into the tumor during a medical procedure fluid may be concentrated near the injected part. Thus, the exact shape and the size of the area is difficult to predict and the density is not uniform. Therefore, the relationship between the shape of the cavity and the accuracy of the estimated value should be considered.

It is assumed that the density of magnetic fluid is uniform with the shape of magnetic fluid filled cavity. Consider the errors of N and D_v as follows:

$$\begin{aligned} D_v &= \langle D_v \rangle + \Delta D_v \\ N' &= \langle N \rangle + \Delta N \end{aligned} \tag{5}$$

where $\langle D_v \rangle$, $\langle N \rangle$ are the expected mean values, and ΔD_v and ΔN are errors. Given that $D_v = D_w/h_s\gamma_f$, (5) is substituted into (4) to obtain (6)

$$\delta = 4\,(1 - \langle N \rangle - \Delta N)\,(\langle D_v \rangle + \Delta D_v) \tag{6}$$

and

$$\frac{\Delta D_v}{\Delta N} = \frac{\langle D_v \rangle}{1 - \langle N \rangle}. \tag{7}$$

Finally, we obtain the following equation:

$$\frac{(\Delta D_v / \langle D_v \rangle)}{(\Delta N / \langle N \rangle)} = \frac{1}{(1/\langle N \rangle) - 1}. \tag{8}$$

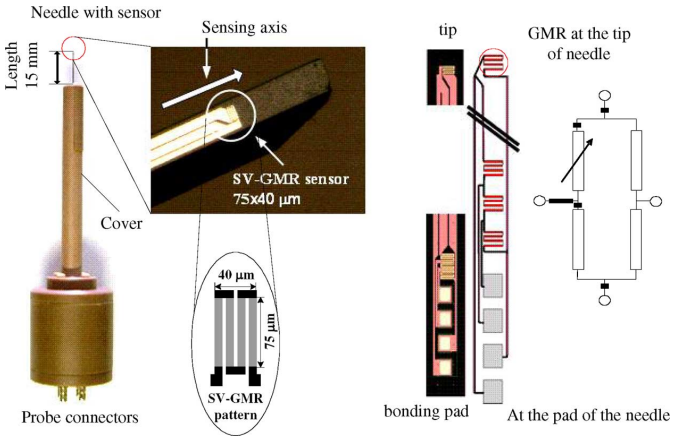

Fig. 4. Fabricated needle-type GMR sensor.

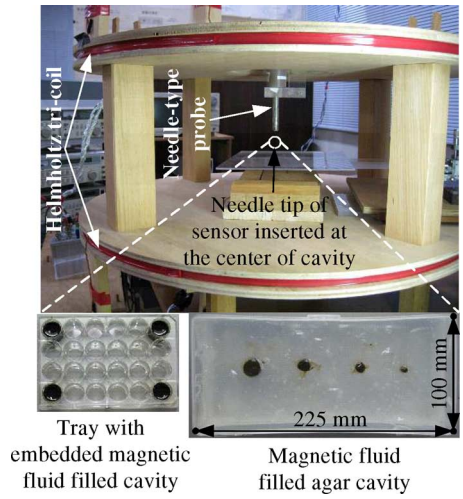

Fig. 5. Experimental setup.

Assuming the tumor has a spherical structure $(N = 1/3)$ we assume the injected area can vary between $N = 0.25$ (long ellipsoidal, aspect ratio $s = (\text{long axis b})/(\text{diameter a}) \approx 1.4$) and $N = 0.5$ (flat ellipsoidal, $s \approx 0.6$). The shape of the mean value $\langle N \rangle = 0.375$ and corresponding $s \approx 0.864$. Taking the mean value into account, (8) is written as

$$\frac{\Delta D_v}{\langle D_v \rangle} = 0.6 \frac{\Delta N}{\langle N \rangle} \tag{9}$$

$$\frac{\Delta D_v}{\langle D_v \rangle} = 0.2 \quad (\text{if } (\Delta N/\langle N \rangle) \text{ is } 1/3). \tag{10}$$

It can be seen from (10) that the maximum error is 20%. In this paper, experiments are performed with cylindrical cavities so the magnetic flux density is not uniform inside the cavity. Therefore, the position of the sensor is important. Even though the sensor needle is inserted at the center of the cavity it is assumed that there could be some positioning error within a spherical area of 5-mm diameter. Then by numerical analysis we obtain conditions for the shape and diameter of the cavity which is within the 20% error limit (N at any point in the spherical area should be between 0.25 and 0.5) as shown in Fig. 3.

III. Experimental Setup and Analysis

A. Fabricated GMR Sensor and Experimental Setup

The fabricated needle-type GMR sensor as shown in Fig. 4 is unique in the sense that it can be applied inside the body in a minimally invasive way. The needle is fabricated from a compound of Aluminium Oxide and Titanium Carbide (Al_2O_3/TiC) and has a diameter of 310 μm and length 20 mm, where 15 mm is available to be inserted inside the body. The novel idea of the needle-type GMR sensor is the GMR sensing area $(75 \times 40\ \mu\text{m})$ present at the tip of the needle. The bridge structure of the sensor allows it measure the magnetic flux density inside and outside a magnetic fluid filled tumor simultaneously, since one GMR sensor is at the tip (which is inserted into magnetic fluid) and the other three further up near the bonding pads (which is exposed to the applied flux density). These distinctive characteristics allow the potential use of the needle sensor in a variety of clinical applications.

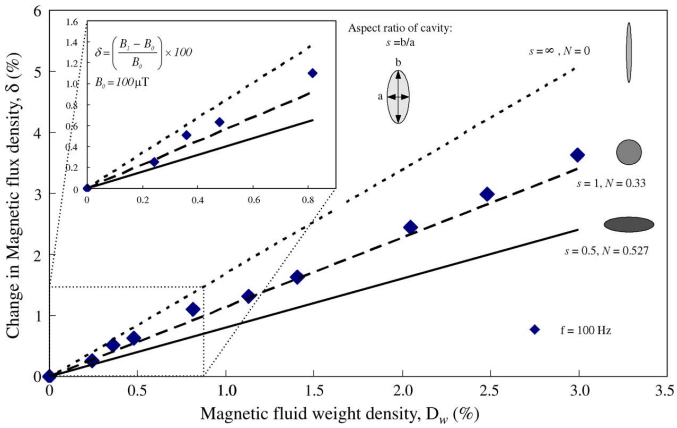

Fig. 6. Estimation of magnetic fluid weight density in tray with embedded cavities.

Fig. 5 shows the experimental setup where the tip of the needle is placed at the center of the Helmholtz tri-coil (a variant of [8]), which supplies 100 μT magnetic flux density at 100 Hz for all experiments performed. For small signal characterization at 1 kHz the sensitivity of the sensor is 12.5 μV/T.

B. Experimental Results

1) Estimation of Low-Concentration Magnetic Fluid in a Tray With Embedded Cavities: Magnetic fluid weight densities used for clinical applications are typically less than 2.8% and would decrease even more when injected inside the body, due to spreading inside tissue. Hence, magnetic fluid of original weight density 40% was thinned by mixing with distilled water. Plastic trays with embedded cavities $(s = 0.625)$ were filled with thinned fluid of various densities. Then, the GMR needle sensor was inserted as shown in Fig. 5 to estimate the weight density of the thinned magnetic fluid, by measuring the applied flux density ($B_0 = 100\ \mu$T) and the magnetic flux density inside (B_1) thinned magnetic fluid filled cavities. By applying the results to (4), the change in magnetic flux density was obtained for all the cavities with different thinned magnetic fluid weight densities. It can be seen from Fig. 6 that the magnetic fluid weight density is proportional to the change in magnetic

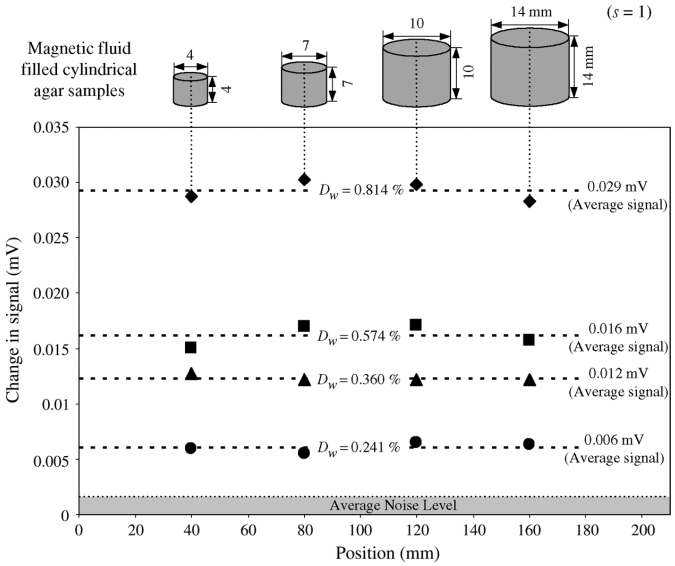

Fig. 7. Detection of magnetic fluid inside agar.

flux density and the results fall between theoretical lines for long and flat ellipsoidal cavities.

2) Detection of Low-Concentration Magnetic Fluid Inside Cylindrical Agar Pieces: To simulate the situation of detecting magnetic fluid inside the body, cylindrical agar pieces (simulating tumors) were injected with thinned magnetic fluid of various densities and immersed in potato starch, which acted as a reference medium. A uniform magnetic flux was applied (100μT) and the needle tip of the sensor was inserted at 10 mm intervals hence, to the middle of agar pieces along the length (225 mm) of the magnetic fluid filled agar cavity tray shown in Fig. 5. The change in signal corresponds to the difference between the signal obtained inside the magnetic fluid filled agar and the reference medium. Fig. 7 shows that for a given weight density of thinned magnetic fluid the change in signal does not vary so much between the four samples (since N and s is the same) and that the signal is proportional to the weight density of thinned magnetic fluid thus, verifying (4).

3) Estimation of Low-Concentration Magnetic Fluid Inside Cylindrical Agar Pieces: The final step involved performing experiments to estimate the weight density of thinned magnetic fluid inside agar pieces. Accurate estimation of magnetic fluid weight density injected inside tumors is very important in hyperthermia therapy. The model used for these experiments contained agar pieces of height and diameter 18 mm $(s = 1)$ injected with magnetic fluid. It can be seen from Fig. 8 that the magnetic fluid weight density is proportional to the change in magnetic flux density and agrees well with theoretical results obtained based on ellipsoidal cavities. Concentrations as low as 0.145% weight density can be successfully estimated.

IV. Conclusion

Hyperthermia treatment for tumors can be performed with a high success rate and minimal error if it is possible to detect and

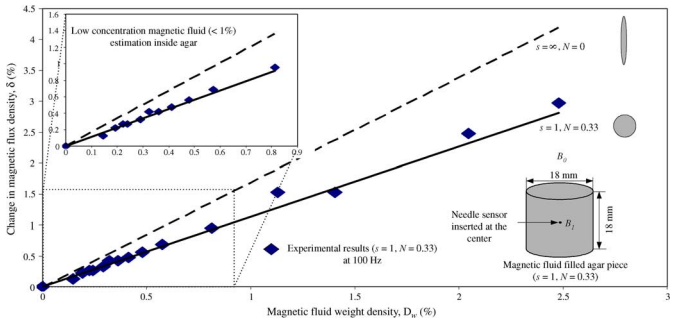

Fig. 8. Estimation of magnetic fluid weight density inside agar.

estimate magnetic fluid weight density inside the body. In this paper, we have shown the theoretical method of detection inside the body supported by experimental analysis. The experimental results show that when the needle-type GMR sensor is inserted inside agar pieces it can detect and estimate low-concentration magnetic fluid. When considering *in vivo* applications in the future it is very important to consider the strength of the needle since the needle breaking inside the body would lead to further complications in an already challenging procedure. The experiments also imply that the sensor is not limited to only hyperthermia application but also has a great potential to be used for other novel, advanced clinical applications.

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