Low-Invasive Detection of Magnetic Particles inside Human Body

Sotoshi Yamada, Chinthaka. P. Gooneratne, Makiko Kakikawa
Institute of Nature and Environmental Engineering, Kanazawa University

ABSTRACT

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. We proposes a unique GMR needle probe 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 weight density *in vivo*. Experiments are performed initially to detect magnetic fluid in trays with embedded cavities followed by detecting and estimating magnetic fluid inside agar cavities simulating various-size tumor by the GMR needle probe. A methodology and experimental results are also presented for analyzing magnetic fluid distribution in cavities. The results show that the GMR needle probe sensor has a high potential to be used in clinical applications such as hyperthermia therapy, a kind of cancer treatment.

INTRODUCTION

Magnetic fluid based hyperthermia has the potential to be an effective, non-invasive cancer therapy with negligible side effects[1]. Magnetic fluid is injected into the affected area and an external ac magnetic flux density is added to exploit the self heating properties of the particles. Temperatures in excess of 42 °C destroy tumors(apoptosis). Currently one of the main problems associated with magnetic fluid hyperthermia is that the magnetic fluid spreads inside tissue after injected, reducing its content density. Specific heat capacity is directly proportional to magnetic fluid content density. Inaccurate estimation of magnetic fluid content density gives thermal under-dosage in the target region which often leads to recurrent tumor growth. Hence, it can be stated that the quality of magnetic fluid hyperthermia treatment is proportional to the accuracy of estimating magnetic fluid content density *in vivo*[2]. The purpose of this research is to develop a method and appropriate tools to estimate magnetic fluid content density *in vivo*. The key feature of this research is the fabricated novel giant magnetoresistance (GMR) needle probe. The GMR needle probe is designed in such a way so that it can be inserted *in vivo* in a minimally-invasive way to detect and estimate magnetic fluid content density.

NEEDLE-TYPE GMR PROBE AND METOD OF ESTIMATING MAGNETIC WEIGHT DENSITY

Giant Magnetoresistance Needle Probe

The fabricated GMR needle probe as shown in Fig. 1 is unique in the sense that it can be applied inside the body in a low-invasive way. The needle is fabricated from a compound of Aluminium Oxide and Titanium Carbide (Al_2O_3/TiC) and has a diameter of 250 μm and length of 20 mm, where 15 mm is available to be inserted inside the body. The novel idea of the GMR needle probe is the GMR sensing area (75 μm × 9 μm × 4 elements) present at the tip of the needle[3]. The Wheatstone bridge structure design of the GMR needle probe allows it to 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 sensors further up near the connecting 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. The small signal characteristics of the GMR needle probe at 100 Hz are shown in Fig. 2. The sensitivity of the sensor is approximately 13 μV/μT.

Method of Estimating Magnetic Fluid Weight Density inside Body

Relationship Between Relative Permeability and Weight Density of Magnetic Fluid

The magnetic nano-particles 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 nano-particles and liquid are assumed to be infinite and one. The permeance of an equivalent magnetic path through magnetic nano-particles 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. Considering magnetic fluid as a bulk, the relative permeability μ^*, is, [4]

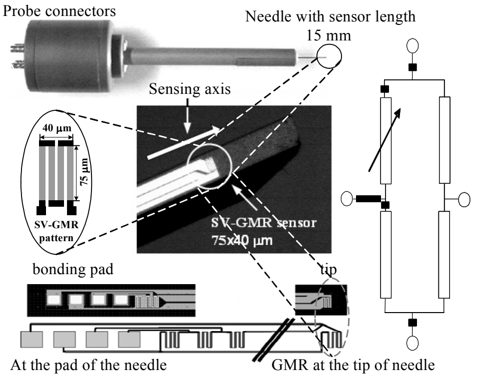


Figure 1： Fabricated GMR sensor.

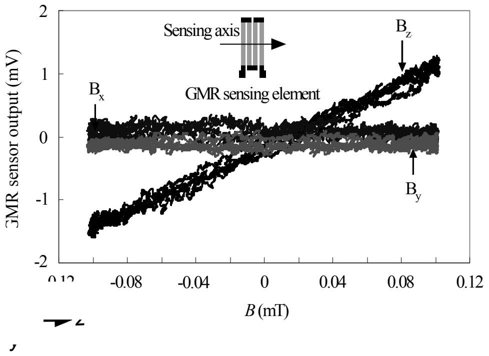


Figure 2: Small signal ac characteristics at 100

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

where γ_f = 4.58 (W-35 sample – Taiho company) is the specific gravity. The magnetic fluid volume density, D_v , is a volume ratio of ferrite particles, while the weight density is the amount of ferrite particles in 1 milliliter water (gFe/ml). Eq. (1) shows that the relative permeability is proportional to D_v and D_w but independent of shape or size of magnetic nano-particles.

It can be seen from the electron microscopy image in Fig. 3 that magnetic nano-particles 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,

$$\mu^* = 1 + 4D_w / \gamma'_f \tag{2}$$

where $\gamma'_f = h_s \gamma_f$ (space factor of spherical magnetite, h_s = 0.523). In Fig. 3, the calculated results were obtained by Eq. (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 from the results that the relative permeability is linearly proportional to the magnetic fluid weight density.

Weight Density Estimation by Measuring Magnetic Fields inside and outside a Magnetic fluid Filled Body

Figure 4 shows a uniform magnetic flux density B_0, applied to 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

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

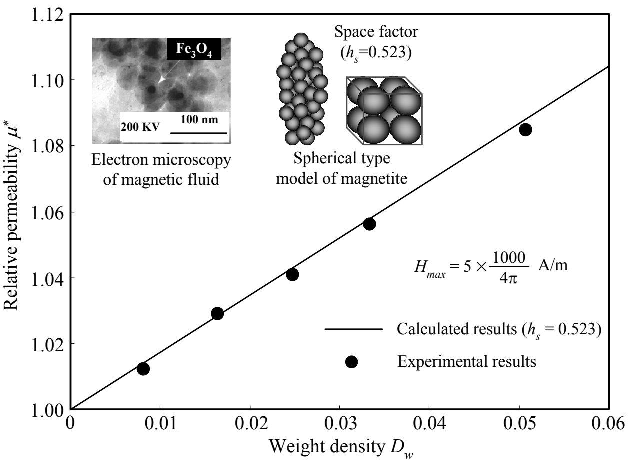
where N is the demagnetizing factor of the cavity. By substituting Eq. (2) into Eq. (3), the difference between magnetic flux density inside the magnetic fluid filled tumor (B_1) and applied magnetic flux density (B_0) can be expressed as [3]

$$\begin{aligned}\delta &= (B_1 - B_0)/B_0 = (\mu^* - 1)(1 - N)/\mu^* \approx (\mu^* - 1)(1 - N) \qquad (\mu^* \approx> 1)\\ &= 4(1 - N)D_w / \gamma'_f \end{aligned} \tag{4}$$

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

Evaluation of Error due to Variatioal Shape of Magnetic Fluid Filled Area

Magnetic nano-particles are considered to be uniformly distributed in a spherical or ellipsoidal cavity. However, when magnetic fluid is injected into the tumor during the medical procedure, fluid may be concentrated near the injected part. Thus, the exact shape and the size of the area are 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.



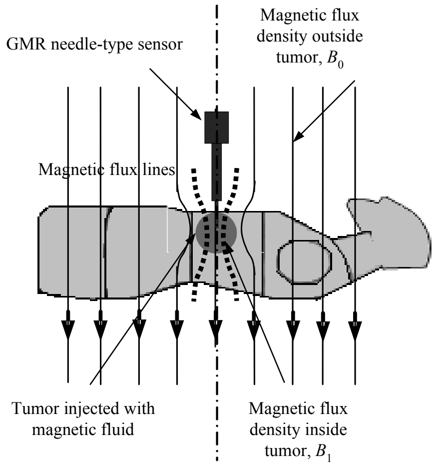


Figure 3: Relative permeability as a function of weight density (H_0 = 100 A/m), assuming space factor h_s, of 0.523

Figure 4: Magnetic fluid filled tumor under a uniform magnetic flux density.

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:

$$D_v = \langle D_v \rangle + \Delta D_v \quad , \qquad N' = \langle N \rangle + \Delta N \qquad (5)$$

where $\langle D_v \rangle$, $\langle N \rangle$ are the expected mean values, and ΔD_v and ΔN are errors. Given that 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 = (long axis b)/(diameter a) ≈ 1.4) and N = 0.5 (flat ellipsoidal, s ≈ 0.6). The shape of the mean value $\langle N \rangle$ = 0.375 and corresponding s ≈ 0.864. Taking the aforementioned $\langle N \rangle$ into account and substituting equation (5) into (4) we obtain the following equations,

$$\frac{\Delta D_v}{\langle D_v \rangle} = 0.6 \frac{\Delta N}{\langle N \rangle} \qquad (6) , \qquad \frac{\Delta D_v}{\langle D_v \rangle} = 0.2 \qquad (\text{if } (\Delta N / \langle N \rangle) \text{ is } 1/3) \qquad (7)$$

It can be seen from Eq. (7) that the maximum error is 20 %. In this research, 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. 5.

DETECTION AND ESTIMATION OF MAGNTIC FLUID WEIGHT DENSITY IN VAROUS CAVITIES

Estimation of Magnetic Fluid Weight Density inside Cylindrical Containers

The experimental setup is shown in Fig. 6. The tip of the needle was placed at the center of the Helmholtz-tri-coil, which supplied 0.1 mT magnetic flux density at 100 Hz for all experiments.

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. The GMR needle probe was inserted as shown in Fig. 6. The GMR needle probe was then used to estimate the D_w of the thinned magnetic fluid, by measuring the applied magnetic flux density (B_0 = 100 μT) and the magnetic flux density (B_1) inside thinned magnetic fluid filled cavities simultaneously[3, 4]. The experimental results are shown in Fig. 7. The figure denotes the relationship between D_w and the change ratio of magnetic flux densities. When the cavity is thin and long (N = 0), the relationship shows the upper limit. The demagnetizing factor N for an elliptic body depends on the shape ratio of the cavity s, as shown in the figure. For spherical shaped cavities s = 1 and N= 1/3, and for flat shaped cavites s = 0.5 and N = 0.527. It can be seen from the experimental results that D_w is proportional to change in magnetic flux density and the results fall between theoretical lines for long and flat ellipsoidal cavities.

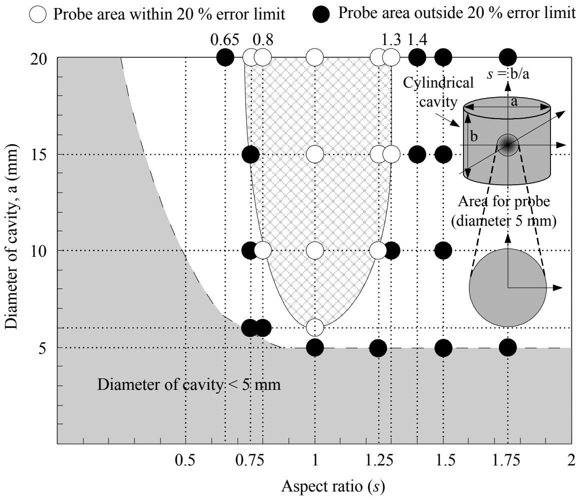


Figure 5: Condition for cavity (20 % error inside 5 mm spherical area).

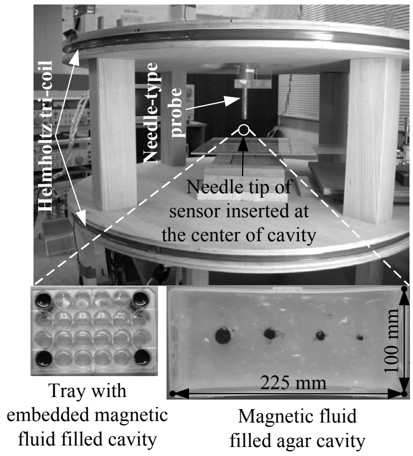


Figure 6: Experimental setup for detecti and estimating magnetic fluid weig density.

Detection of Magnetic Fluid inside Various Cylindrical Agar Cavities

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. The diameters of the agar pieces were chosen to be 4 – 14 mm ($s = 1$, $N = 0.33$). 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 cavity tray as shown in Fig. 6. The change in signal corresponds to the difference between the signal obtained inside the magnetic fluid filled agar and the reference medium (potato starch). It can be seen from Fig. 8 that the GMR needle probe can detect magnetic fluid injected into agar pieces with diameter as low as 4 mm. Figure 8 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 s and N is the same) and that the signal is proportional to the weight density of thinned magnetic fluid. This means that even though the size of the cavity may change (s and N are constant), the signal will only change with D_w, thus verifying Eq. (4). Furthermore, detection of magnetic fluid in samples with diameters as low as 4 mm shows that the GMR needle probe has a potential to be used effectively as a tool for detecting drug coupled magnetic nano-particles, in targeted therapy for tumors.

Estimation of Low-Concentration Magnetic Fluid Weight Density

Since the GMR needle probe was used to successfully detect magnetic fluid inside cylindrical agar pieces of different sizes, experiments were performed to accurately estimate D_w inside cylindrical agar pieces. Experiments are performed with the GMR needle sensor to estimate D_w in 18 mm diameter agar cavities ($s = 1$, $N = 0.33$) since, to provide adequate heat to kill the tumor without affecting surrounding healthy cells, D_w needs to be confirmed before and after treatment (to check remaining density)[5, 6]. The GMR needle was inserted at the center of the 18 mm agar cavities and, B_1 and B_0 were measured simultaneously due to the bridge circuit design of the GMR needle probe. It can be seen from Fig. 9 that D_w 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 could be successfully estimated.

ESTIMATION OF VERY LOW-CONCENTRATION MAGNETIC FLUID WEIGHT DENSITY

Since, for very low weight densities the percentage change in magnetic flux density is in the order of 1/10,000 and distribution analysis requires super uniformity, it is imperative that the applied magnetic flux density is at least 1/10th more uniform in the experimental area. A Lee-Whiting coil was designed and fabricated to produce a uniform magnetic flux density (fluctuation ≤ 0.001 %, 0.1 m along the axial and radial direction from the midpoint). The experimental setup is shown in Fig. 10.

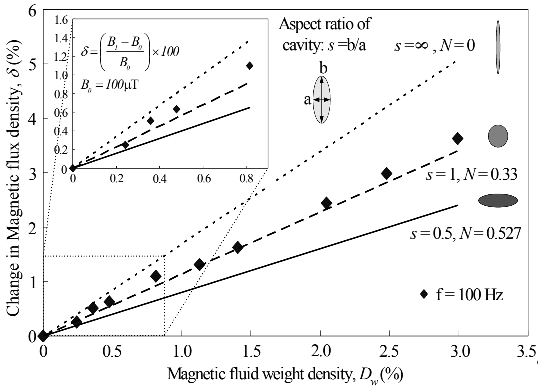


Figure 7: Estimation of magnetic fluid weight density in tray with embedded cavities.

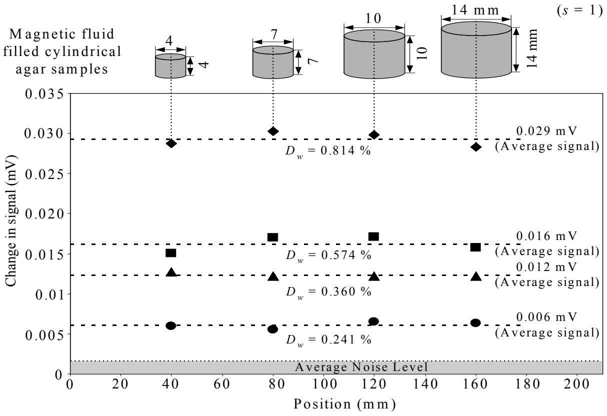


Figure 8: Detection of magnetic fluid inside agar cavities.

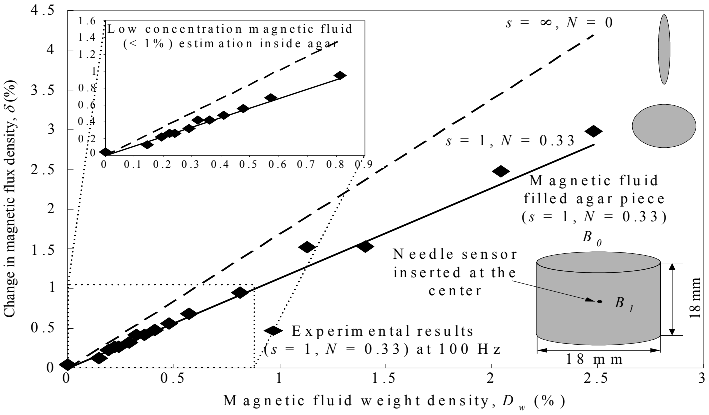


Figure 9: Estimation of low-concentration magnetic fluid weight density.

Cylindrical agar pieces of $d = 18$ mm ($s = 1$) were injected with very low- concentration magnetic fluid ($D_W = 0.03 – 0.2$ %). The GMR needle probe with a sensing area of 75 × 45 µm at the tip of the needle was inserted to the center of magnetic fluid filled agar cavities. The differential magnetic flux density is in the order of nT in the experimental situation. The bridge structure of the GMR needle probe measured the differential magnetic flux density simultaneously. Experimental results shown in Fig. 11 indicate that the change in magnetic flux density is proportional to D_W. However, the current limit of estimation has a good possibility to be influenced by the construction and coiling errors of the Lee-Whiting coil. Shown in Table 1 are the error percentages at 0.02 m in the axial direction if the coils or diameters are altered by ±1/2 mm.

CONCLUSION

This paper describes a novel GMR needle probe that is utilized to detect and estimate magnetic fluid weight density. The unique design of the fabricated GMR needle probe is especially made for application *in vivo* in a low-invasive way. A theoretical basis is obtained for detecting and estimating magnetic fluid weight density *in vivo* based on relationships between relative permeability, weight density of magnetic fluid and magnetic flux density inside and outside a magnetic fluid filled cavity. An experimental setup (including a novel GMR needle probe, Helmholtz tri-coil and Lee-Whiting coil) and procedure with agar injected with magnetic fluid to simulate actual clinical process was developed. Experiments were performed to detect and estimate magnetic fluid weight density inside a variety of mediums simulating tumors, using the GMR needle probe, with the long term objective of estimating *in vivo*, especially in the area of hyperthermia therapy, a form of cancer treatment.

Table 1: Analysis of error percentages due to coiling and construction.

Coil number	+1 mm (%)	-1 mm (%)	+2 mm (%)	-2 mm (%)
1 Distance	0.007	0.007	0.015	0.015
2 Distance	0.008	0.008	0.015	0.015
1 Radius	0.0037	0.0037	0.0075	0.0075
2 Radius	0.006	0.006	0.012	0.012

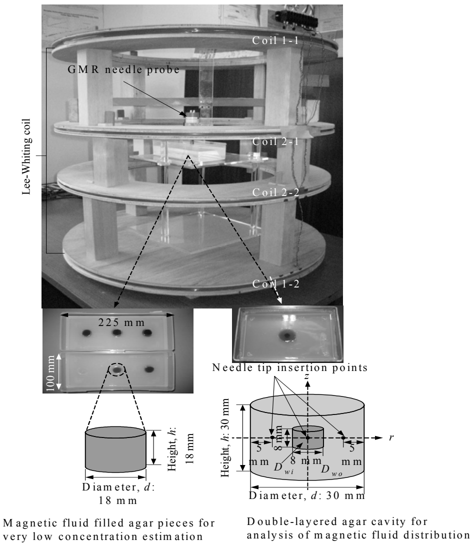


Figure 10: Experimental setup for very low-concentration estimation and distribution analysis of magnetic fluid.

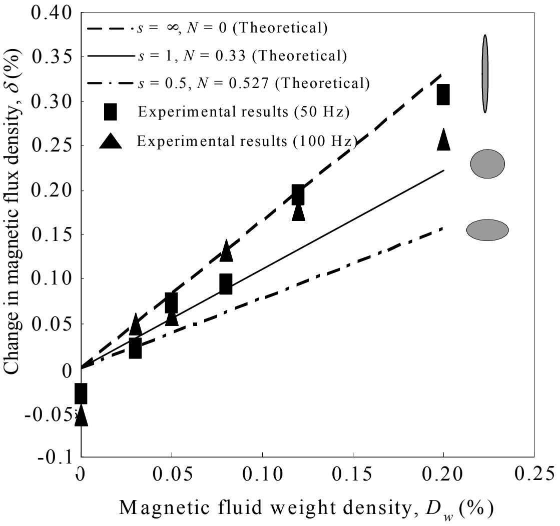


Figure 11: Estimation of very low -concentration magnetic fluid weight density in cylindrical agar cavities.

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