Three Dimensional Motion Control System of Ferromagnetic Particles for Magnetically Targeted Drug Delivery Systems

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Fumihito Mishima, Shin-ichi Takeda, Yoshinobu Izumi, and Shigehiro Nishijima

***Abstract*—The development of a 3-dimensional (3-D) navigation system of ferromagnetic particles in a flow system was performed. In order to improve the practice of using externally-applied magnetic fields for targeting the magnetic particles to a circumscribed body region, we tested the feasibility of a novel 3-D navigation system, made by applying a strong external (magnetic) field through a GdBaCuO bulk superconductor. A 3-D theoretical model is proposed and used in order to evaluate the efficiency of the navigation/retention of magnetic particles in the flow system. Furthermore, an experimental model system was made and the efficiency of a prototype system was examined. Comparisons of experimental and the corresponding calculation results were made to examine the theoretical model system.**

***Index Terms*—Bulk superconductor, drug delivery system, ferromagnetic particle, magnetic targeting.**

I. Introduction

THE concept of magnetically targeted drug delivery systems (MT-DDS) shows considerable potential for a wide variety of medical applications that include, among others, cancer therapy, blood detoxification, anti-ischemic therapeutics, and drugs to prevent programmed cell death. However, there are several problems associated with the use of external magnets in magnetic drug targeting [1]. One limitation results from the negative influence that high blood flow velocities in large arteries or veins may have on the accumulation of medicative magnetic micro/nano-particles at the target site. Another problem is the depth of the target site. Sites which are more than 2 cm deep in the human body are difficult to target because the strength of the magnetic field decreases abruptly with distance. Unfortunately, the use of larger magnets to extend the magnetic field to inner parts of the body may not resolve the problem since low magnetic field gradients tend to result. The magnetic force is strongly dependent on the gradient of the magnetic field and thus the ability to retain magnetic micro/nano-particles by larger magnets becomes reduced. It is for this very reason that we propose the application of an external superconducting magnet.

So far, we have developed an integrated system based on ferromagnetic, nonvirus vector attached to a nano-sized maghemite particle as a tool of targeted but noninvasive delivery of drugs for gene therapy within the human vasculature. Indeed, we found that a magnetically assisted gene transfection system has considerable potential for a gene therapy [2]. Drug targeting is achieved through venous injection of drug-loaded magnetic, biocompatible micro/nano-particles which freely circulate throughout the body but are magnetically trapped and concentrated at the local site under magnetic field (targeted delivery). Our system offers the following advantages over the use of other externally-applied magnetic field systems: 1) enabling relatively high local magnetic gradients deep within the human body; 2) permitting multiple, targeted drug delivery and hence treatment modalities utilizing convenient systemic drug injections (i.e., repeated targeted drug delivery in cancer therapy).

Theoretical studies have proven the efficiency of this novel magnetically targeted drug delivery system where the strong magnet can collect magnetic micro/nano-particles from arterial/venous blood flow [2]. In the present paper, an in vitro flow model system was developed to validate the theoretical model and evaluate the efficiency of a bulk superconducting magnet to accumulate ferromagnetic particles (2 μm diameter) inside blood flow.

II. Calculation Method

A 2-D schematic of the controlling particle system used for modeling the magnetically targeting of magnetic particles in the flow system is shown in Fig. 1. The particle feels a viscous drag force when it begins to move. Simultaneously, the magnetic force acts floating ferromagnetic particles.

The parameters used for calculating the particle trajectory are summarized in Table I. The black and white color in the flow system represents a measure of the flow velocity. The flow velocity is high at the center, and low near the inner surfaces of the flow system. The velocity distribution of the flow system was calculated using ANSYS 9.0 (Fig. 2).

The trajectory of the magnetic particles is calculated according to the following model.

The trajectory of the magnetic particles is calculated according to the following model. When the magnetic particle is assumed to be spherical, the energy $-\Delta U$ arising from magnetic force is represented by the following:

$$F_M = -\Delta U = \frac{4}{3}\pi b^3 \mu_0 (\chi_p - \chi_f) H \nabla H. \tag{1}$$

When velocity v_p of the magnetic particle is different from the flow velocity v_f, the particle is dragged by the fluid and the drag force F_D can be expressed using Stokes's law as

$$F_D = 6\pi\eta b(v_f - v_p). \tag{2}$$

Manuscript received September 20, 2005.

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Digital Object Identifier 10.1109/TASC.2005.869666

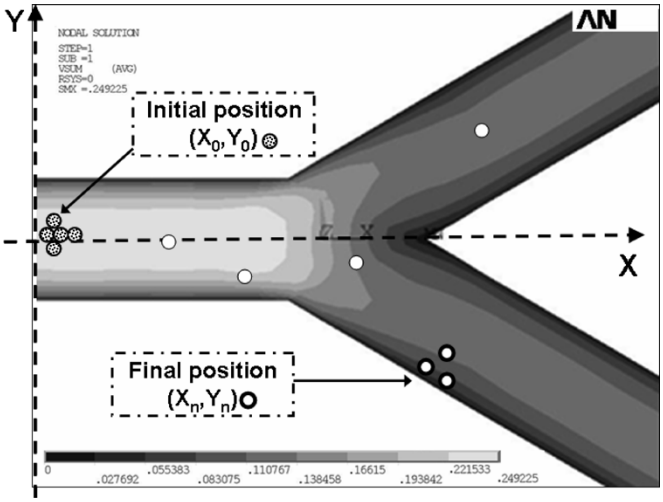

Fig. 1. Schematic of the controlling particle system utilized for modeling the targeting of magnetic particle inside the flow system under the magnetic force. The trajectory of the magnetic particles from the initial position $(\mathrm{X}_0, \mathrm{Y}_0)$ to the final position $(\mathrm{X}_\mathrm{N}, \mathrm{Y}_\mathrm{N})$ under the magnetic field was calculated using ANSYS9.0.

Therefore, the equation to represent the particle motion is

$$F = ma = F_M + F_D. \tag{3}$$

Substituting (1) and (2) into (3)

$$\frac{dv_p}{dt} = \frac{6\pi\eta b}{m}\left(v_p - v_f + \frac{F_M}{6\pi\eta b}\right) \tag{4}$$

and solving, we obtain

$$v_p = v_f + \left(\frac{F_M}{6\pi\eta b} + c_1 e^{\frac{-6\pi\eta b}{m}}\right) \tag{5}$$

where c_1 is a constant of integration. Thus, the displacement, S_p can be written as

$$S_p = \left(v_f + \frac{F_M}{6\pi\eta b}\right)t - \frac{m}{6\pi\eta b}c_1 e^{\frac{-6\pi\eta b}{m}} + c_2. \tag{6}$$

Where c_2 is a constant of integration.

To obtain $c_1$and c_2, we calculate S_p and v_p at two different times (t_N, t_{N+1}) and use v_f and F_M calculated through ANSYS 9.0.

$$c_1 = v_n - v_f - \frac{F_M}{6\pi\eta b} \tag{7}$$

$$c_2 = S_N + \frac{m}{6\pi\eta b}c_1. \tag{8}$$

Substituting (7) and (8) into (5) and (6), we obtained $v_{\mathrm{N}+1}$ and S_{N+1} at $t = t_{N+1}$. When we calculate the integrated constant, v_f and F_M at $t = t_N$ are taken from the analyzed data using ANSYS 9.0 for magnetic field and flow system, respectively.

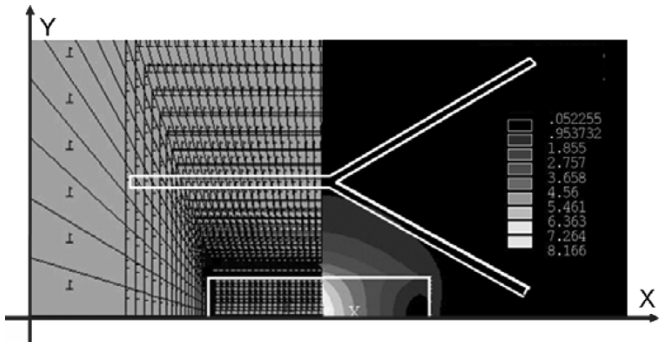

Fig. 2. Calculated magnetic flux density using ANSYS 9.0 induced by the magnet placed outside the flow system. The Y-shape tube is the model flow system, and the right side of the figure shows the strength of the magnetic flux density (white color represents strong and black color weak). The left side shows the mesh sizes of the calculation.

TABLE I
CALCULATION PARAMETERS

Quantity	Values
Inner radius of simulated blood vessel	2 mm
Velocity in X direction (V_f max)	200 mm/s
Diameter of the ferromagnetic particle	2μm
Magnetic susceptibility of ferromagnetic particles.	0.1
Saturated magnetization of ferromagnetic particles	0.2 T
Viscosity η	0.0028 mPa·s
Mass density of the ferromagnetic particle	5000 kg/m^3

III. CALCULATION RESULT

The calculated particle trajectory is shown in Fig. 3. In Fig. 3(c), the accumulated particles are seen at the right-below wall of the flow system. This result indicates the feasibility of the magnetically targeted drug delivery system. The simulation results also show the efficiency of the accumulation of the magnetic particles at the target site (final position). In the simulation without the magnet (Fig. 3(b)), 53\% of the particles go into upper tube after branch point and the rest (47\%) go into the lower tube. This result shows that the particle accumulation does not occur. On the other hand, in the case of simulation with the magnet (Fig. 3(c)), the number of the accumulated particles in the lower tube after the branch point was 2.7 times higher than that of those going to upper tube. But, 27\% of the number of the particles was captured before branch point thanks to the shape of the induced magnetic field. The obtained results clearly show that the magnetic accumulation in the flow system was possible even in the case where magnet was placed outside the flow system.

IV. EXPERIMENT

A. Magnet

A photograph of the bulk type of superconducting magnet system used in this experiment was shown in Fig. 4. The magnet was a GdBaCuO bulk superconductor (Nippon Steel, Japan) of

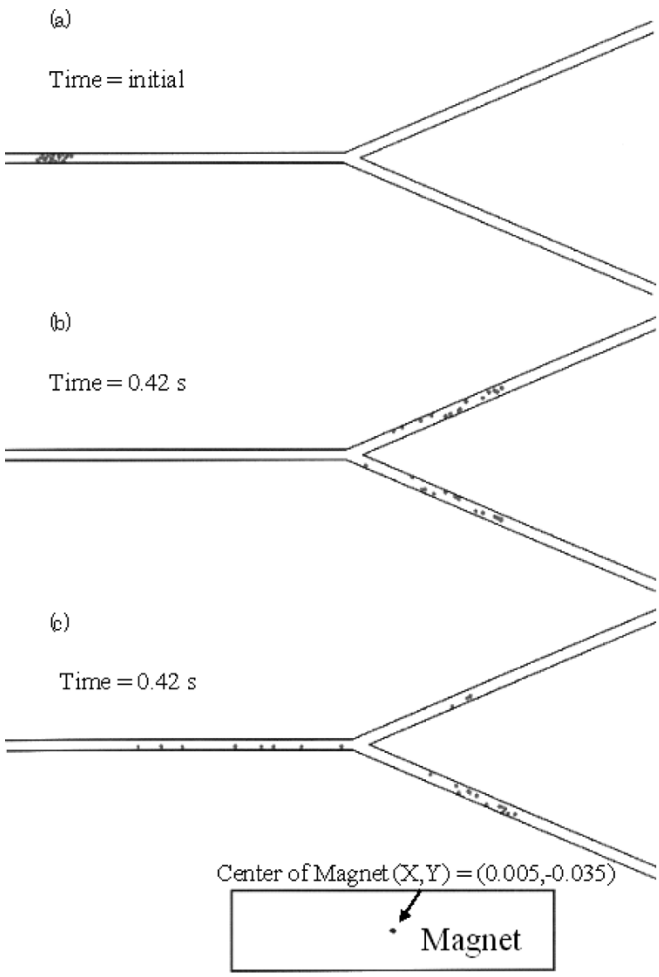

Fig. 3. Calculated particle trajectory under flow system (flow velocity: 200 mm/s). Bold points represent magnetic particles under magnetic field. (a): Initial position ($\mathrm{Time} = 0$ sec), (b) final position without magnet ($\mathrm{Time} = 0.42$ sec), and (c) final position with magnet which was placed in the place under 35 mm from outside the flow system ($\mathrm{Time} = 0.42$ sec).

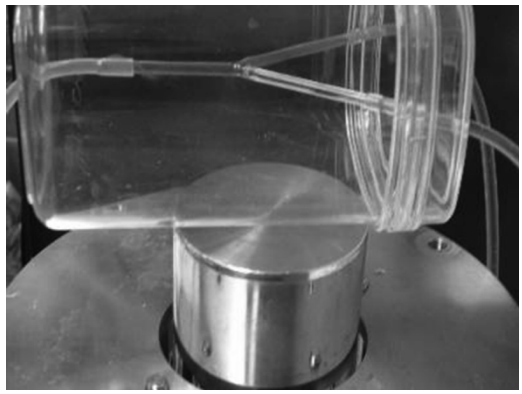

Fig. 4. Photograph of the bulk superconducting magnet.

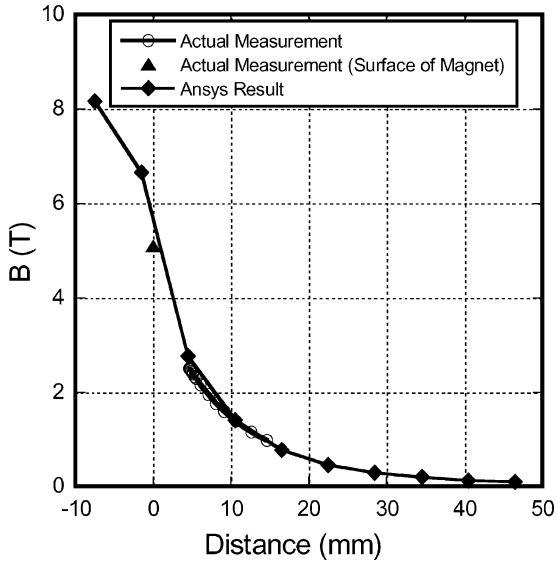

Fig. 5. Calculated and experimentally determined magnetic flux density of a vertical element of the magnet against the distance from the surface of the cover above the bulk magnet.

cylindrical shape (45 mm large and 15 mm thick). Magnetization was performed by the pulse magnetization method (PFM) that can be done with copper wire [3]. The bulk superconductor can generate a strong magnetic field in an open space. Therefore, the magnetic field generated by bulk superconducting magnet is wide range and feasible to MT-DDS. Fig. 5 shows the magnetic flux density of a vertical element of the magnet against the distance from the surface of the cover. The calculated value of magnetic flux density with the distance shows good agreement with the measured values (Fig. 5). This suggests that the result of the magnetic field analysis by the finite element method is correct and can allow us to design the magnetic field and the magnet itself.

B. Experimental Model System

An experimental model system is shown in Fig. 6. The branching tube was placed at the same distance in the case of a rat where the vena cava was assumed to be located at 50 mm from the body surface of a rat. The size of the model system was $90\ \mathrm{mm} \times 90\ \mathrm{mm} \times 95\ \mathrm{mm}$ (H), made of acrylic box. The diameter of the tube was 2 mm and the length was 100 mm.

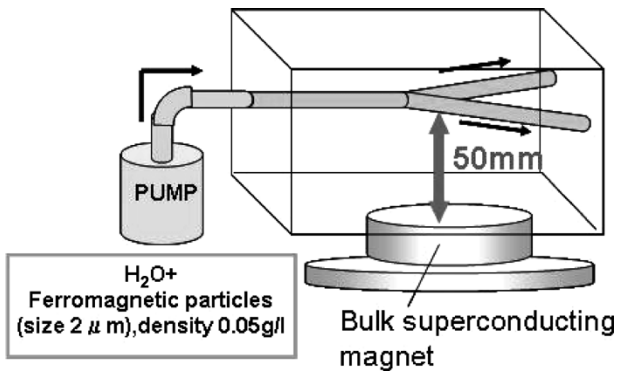

Fig. 6. Schematic of experimental model system for magnetic targeting.

The center of the tube in the flow direction has a branch with an angle of 60 degrees.

Fig. 7 shows the result of the experimentally accumulating test using a glass tube. Ferromagnetic particles flow from the left side (corresponding to the initial position in Fig. 1) and feel the drag force and the magnetic force. It is clearly seen that the ferromagnetic particles are accumulated in a local part of the

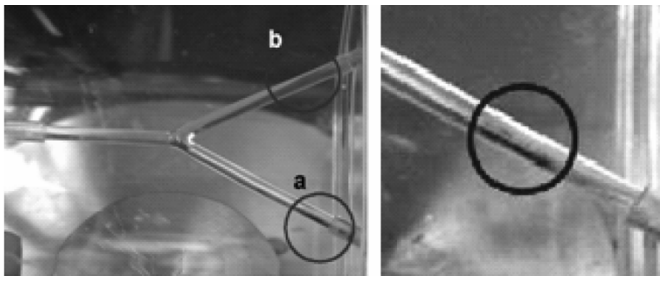

Fig. 7. Results of the experimentally accumulating test using the tube.

glass tube by the magnetic force. These ferromagnetic particles have a diameter of 2 μm and a magnetic susceptibility of 68 emu/g. This experimental result shows that particles are accumulated, as predicted (see Fig. 3(c)) even at a flow velocity of 200 mm/s.

V. Conclusion

This theoretical and experimental study shows the feasibility of a novel magnetically targeted drug delivery system, where a strong magnet can accumulate magnetic micro/nano-particles in the flow system. In the present paper, an *in vitro* flow model system was established to examine the theoretical model and evaluate the efficiency of bulk superconducting magnet to accumulate of ferromagnetic particle, 2 μm diameter, inside flow system using an externally placed magnet at the distance of 35mm from the flow system. *In vitro* flow experiments were used to check the accuracy of the theoretical model of a strong magnet for accumulating magnetic particle under flow system. Comparisons of experimental and corresponding modeling data verified theoretical predictions. A further study using a bulk superconducting magnet confirmed the efficiency of accumulating particles even at flow velocities of 200 mm/s. The obtained results show that the magnetic accumulation in the flow system was possible even in the case where magnet was placed at the distance of 35 mm from the flow system.

Two important findings were obtained from this study. The first is that our 2-D computational approach is sufficient to examine the relatively simple magnetic system, as we see good correlation between model and experiment. Secondly, the capture efficiencies are sufficiently enhanced with the placement of the bulk superconducting magnet to warrant further investigation into the clinical efficacy of this magnetic drug targeting system.

Acknowledgment

F. Mishima would like to thank Prof. H. Fujishiro (Iwate University, Faculty of Engineering) for allowing them to use the bulk superconducting magnet, providing many useful discussions, and supporting this work.

References

[1] M. O. Avilés, A. D. Ebner, H. Chen, A. J. Rosengart, M. D. Kaminski, and J. A. Ritter, "Theoretical analysis of a transdermal ferromagnetic implant for retention of magnetic drug carrier particles," *J. Magn. Magn. Mater.*, vol. 293, no. 1, pp. 605–615, May 2005.

[2] S. Takeda, F. Mishima, B. Terazono, Y. Izumi, and S. Nishijima, submitted in this issue.

[3] K. Yokoyama, M. Kaneyama, T. Oka, H. Fujishiro, and K. Noto, "Temperature measurement of RE123 bulk superconductors on magnetizing process," *Phys. C: Supercond.*, vol. 412–414, pt. 1, pp. 688–694, Oct. 2004.