The 12th International Conference on Ubiquitous Robots and Ambient Intelligence (URAI 2015)
October 28~30, 2015 / KINTEX, Goyang city, Korea

An Electromagnetic Steering System for Magnetic Nanoparticle Drug Delivery

Ton Duc Do[1], Yeongil Noh[1], Myeong Ok Kim[2], and Jungwon Yoon[1]
[1] School of Mechanical and Aerospace Engineering, Gyeongsang National University, Jinju 660-701, Korea
(Tel : +82-55-772-1678; E-mail: jwyoon@gnu.ac.kr)
[2] Department of Biology and Applied of Life Science, Gyeongsang National University, Jinju, 660-701, Korea
(Tel : +82-55-772-0000; E-mail: mokim@gnu.ac.kr)

Abstract - Targeted delivery of pharmaceutical agents to the brain using magnetic nanoparticles (MNPs) is an efficient technique to transport molecules to disease locations. MNPs can cross the blood–brain barrier (BBB) and can be concentrated at a specific location in the brain using non-invasive electromagnetic forces. The proposed EMA consists of two coil-core system. The cores are added in the center of each coil to concentrate the flux in the region of interest. The EMA can enhance the gradient field 10 times compared to only coil system and generate the maximum magnetic field of 160 mT and 5.6 T/m. A 12-kW direct-current power supply was used to generate sufficient magnetic forces on the MNPs by regulating the input currents of the coils. Effective guidance of MNPs is demonstrated via simulations and experiments using 800-nm-diameter MNPs in a Y-shaped channel. The developed EMA system has high potentials to increase BBB crossing of MNPs for efficient drug targeting to brain regions.

Keyword: Drug delivery, electromagnetic actuator, magnetic drug targeting, magnetic nanoparticles (MNPs).

1. Introduction

Magnetic drugs are pharmaceutical agents combined with magnetic particles, and have applications in targeting disease locations using externally applied magnetic fields. This technique has advantages including avoiding surgery and reducing side effects, and can in principle achieve a high targeting efficiency. Nanometer-scale magnetic particles, or magnetic nanoparticles (MNPs) can be biocompatible, soluble, and metabolically stable [1]. In particular, MNPs are suitable for delivering drugs to specific locations within the brain, and can cross the blood brain barrier (BBB) [2], [3]. However, because the magnetic force is proportional to the cube of the diameter of magnetic particles, the magnetic force on nanoparticles is weak, making it challenging to steer MNPs magnetically.

In recent years, actuator systems have been proposed for steering magnetic particles or microrobot in blood vessels [4]–[9]. Actuator systems using permanent magnets [4], [5] are not effective, however, especially for steering particles deep inside the body, and electromagnetic actuators have been shown to be more suitable for targeting particles deep inside bodies [6]–[9]. Abbott et. al. [6] and Han et. al. [7] proposed using electromagnetic actuators for guiding micron-sized particles. Jeon et. al. [8] and Choi et. al. [9] also designed an intricate actuator system with sets of Helmholtz and Maxwell coils. However, it should be noted that, to date, the steered particles had diameters of a few to tens of microns [6-10]. In [11], the authors developed an actuator system for manipulating a robot, which contains drugs inside and releases the drug at the targeted position. However, the size of the robot is about a few millimeters and it is not feasible for navigating MNPs in blood vessels of a brain.

Here we describe an electromagnetic steering system for controlling MNPs in fluidic environments. The proposed EMA consists of two coil-core system. The cores are added in the center of each coil to concentrate the flux in the region of interest. This actuator system can generate a magnetic field gradient of 5.6 T/m. We experimentally demonstrate that the electromagnetic system can be used to steer 800-nm-diameter MNPs to the correct outlet of a Y-shaped fluidic channel.

2. Nanoparticle Steering Method

The motion of the MNP in a viscous fluid is governed by the following forces: hydrodynamic drag F_d, the magnetic force F_m, the apparent weight of the MNP W_a, the contact force F_c, van der Waals forces F_{vdw}, electrostatic forces F_{el}, and forces due to steric interaction F_s. The Newton-Euler equation can be expressed as

$$m\dot{v} = F_d + F_m + W_a + F_c + F_{vdw} + F_{el} + F_s \tag{1}$$

where $\ddot{v}$ is the velocity of the MNPs. Arcese *et al.* described mathematical models of each of these forces in detail [12]. Compared with the magnitudes of the drag and magnetic forces, the remaining five are several orders of magnitude weaker and therefore can be neglected [13].

To steer particles to a desired site through the vascular system, a closed-loop control approach is desirable, and there have been a number of reports of such systems for micron-sized particles [6], [7], [14], [15]. In theory, it is possible for such an approach to achieve good performance with only a small tracking error; however, this places exacting demands on the control components and requires real-time high-quality imaging, as well as magnetic/electromagnetic actuators with strong magnetic fields that can overcome the drag force due to the flow of blood. Unfortunately, the utility of this approach for nanoparticles appears to be limited. Cherry et al. [16] suggested that targeted drug delivery via steering MNPs using electromagnets is not suitable for use of small arteries because it is difficult to control particles smaller than 20 μm in diameter. However, by changing the control method and designing a suitable magnetic actuation system, electromagnets can be used for targeted drug delivery in the brain.

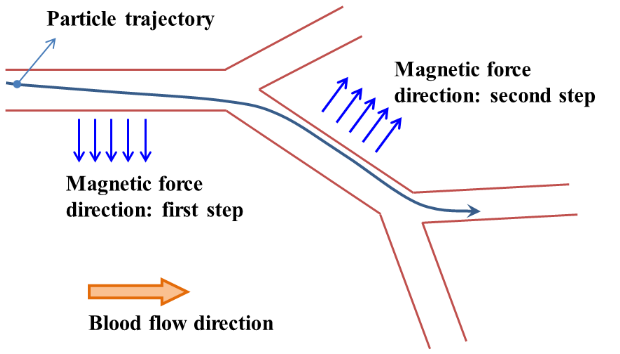

Fig. 1. The principle of the magnetic guidance approach.

Unlike with a closed-loop control approach, in which the magnetic/electromagnetic actuators are used as a propulsion system, here the actuator is used only to steer the direction of the nanoparticles; i.e., the blood flow propels the particles and the magnetic force is perpendicular to the flow inside the vessel to guide the particles to the correct branch by controlling the direction of the magnetic force at each bifurcation. Compared with the closed-loop control approaches discussed above, this method requires a weaker magnetic force because the drag force exerted on a particle perpendicular to the blood flow is considerably less than the drag force in the flow direction. Fig. 1 shows the principle of our approach.

2. Electromagnetic Actuator System

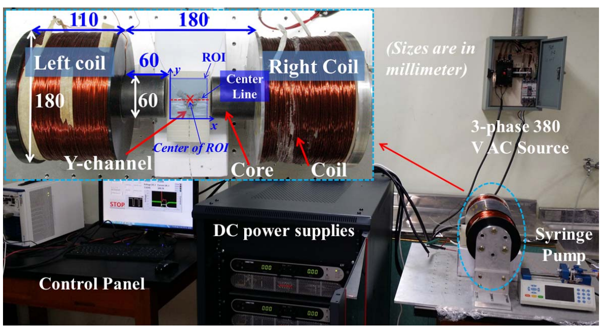

Fig. 2. Experimental setup of the proposed electromagnetic actuator.

Fig. 2 illustrates the experimental setup of the electromagnetic actuator system and its geometry. The geometric parameters were optimized via extensive simulation studies, which have been reported previously [17]. The proposed electromagnetic actuator consists of two Cooper coils and, in each coil, a core is added to increase the magnetic field density. Each coil had 7000 turns with diameter of d = 1.0 mm, and the cores were formed of a soft magnetic cobalt–iron alloy (Vacoflux 50).

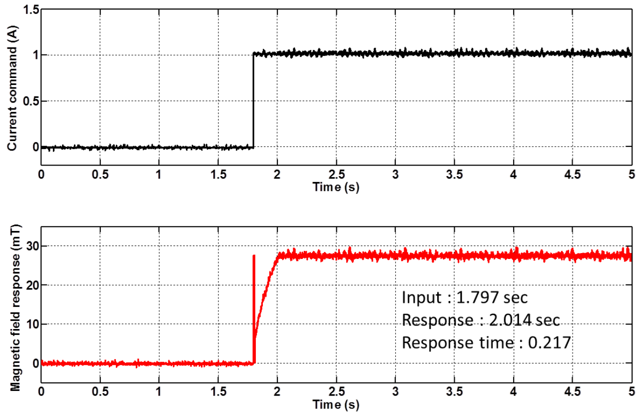

Fig. 3. Response time of the coil-core system.

The magnetic field at the region of interest (ROI) was a 60-mm diameter at the center of the actuation system, and was designed for tests on mice. The magnetic force was controlled by regulating the current in the coil using DC power supplies. A current of up to 17 A could be applied to the coil-core system, which has a resistance 20 Ω, the inductance 0.42 H, and the rated power of DC power supply was 6 kW. Fig. 3 shows the response time of the coil-core system with a DC power supply. The 1A input current command to the DC power supply is set as a step function at 1.797 s. At 2.014 s, the magnetic field response at the center of ROI reaches 28.2 mT. It means the response time of the system is 0.217 s. This response time is mainly affected by the inductance of coil and response time of the DC power supply. Although this response time is quite slow, it is fast enough for particle guidance applications as being presented in the next section. Since the proposed actuator has been designed for steering MNPs with an open-loop method [17], the direction of particle trajectory is only required to be controlled through a non-invasive magnetic force and the nonlinear effects of the core can be slight on the nanoparticle delivery system. Table 1 lists the relationship between the input current and actuator responses (i.e., the magnetic field and magnetic field gradient) at the center of ROI.

Table 1 Relationship between the input current and magnetic field, and the magnetic field gradient using a single-coil-core system at the Center of ROI

Current (A)	1	2	3	4	5	6
B (mT)	28.2	54.1	79.8	106.3	132.6	160.7
∇B (T/m)	0.43	0.92	1.39	1.9	2.4	2.8

4. Nanoparticle Steering

To verify the effectiveness of the proposed electromagnetic guidance system, we discuss experimental results with different magnetic fields. Table 2 lists the specifications of the MNPs and the experimental conditions.

Table 2 . Experimental Conditions for Studies

MNP material	Iron powder (Fe)
MNPs diameter	800 nm
MNPs purity	>99.9%
Flow velocity	13.3 mm/s
Diameter of the Y-shaped channel	1.0 mm
Fluid environment	Water

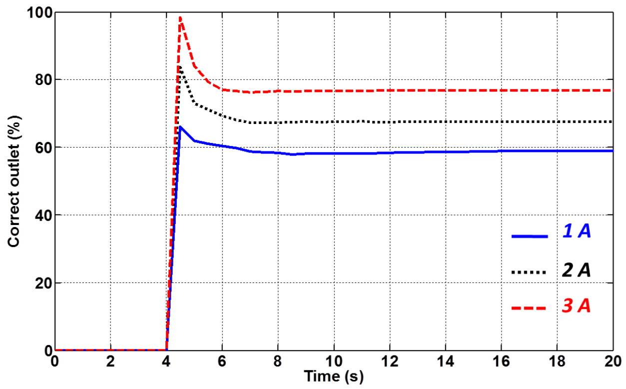

Fig. 4. Simulated results of guidance with different currents.

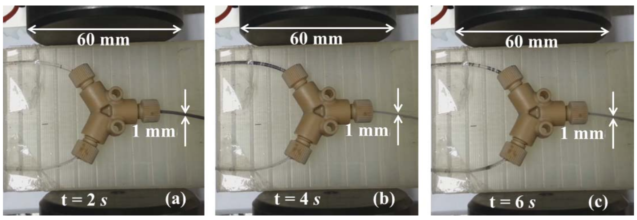

Fig. 5. Snapshots of the locations of MNPs in the channel at various times using the electromagnetic actuator with a current of 3 A.

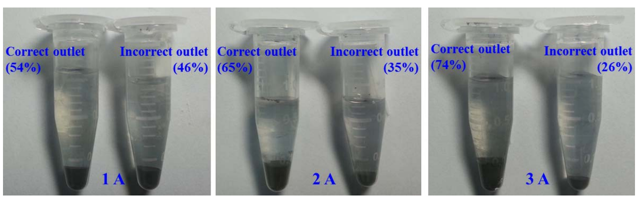

Fig. 6. Experimental results of MNPs guidance using different currents.

The experiments were carried out with a constant magnetic field and only one coil-core was used to generate a unidirectional force. The magnetic field and magnetic field gradient associated with each input current are listed in Table 2. To evaluate the performance of this steering approach, a particle tracking simulation was carried out using the same experimental conditions using Comsol Multiphysics. The particles were released at the center of the channel inlet, and the trajectory was calculated in the presence of a magnetic field and drag forces due to the fluid flow using the particle-tracking module in Comsol Multiphysics. The rates of achieving the correct outlet for the 800-nm MNPs in both the simulations and experiments are lists in Table III. With no magnetic field, the rate of the MNP entering the correct outlet was 50%. We define the performance improvement (Per. Im.) when the magnetic field was used as follows:

$$Per.\,Im.\,(\%) = \frac{percentage\ of\ MNPs\ in\ correct\ outlet - 50}{50} \times 100$$

Table 3 Simulated and measured results of the MNPs guidance experiments.

Current (A)		1	2	3
Simulation	Correct (%)	59	67	77
	Incorrect (%)	41	33	23
Experiment	Correct (%)	54	65	74
	Incorrect (%)	46	35	26
Simulated improvement (%)		18	34	54
Measured improvement (%)		8	30	48

Table 3 lists the performance improvement in both the simulations and experiments. Figs. 4–6 illustrate further details of the simulated and experimental results that are summarized in Table 3. Fig. 4 shows simulated results of guidance with various currents in the coil. Fig. 5 shows snapshots of the location of the MNPs in the channel at different times using the electromagnetic actuator with a current of 3 A. Fig. 6 shows the rate of MNPs exiting via the correct outlet for different input currents. To measure the density of the MNPs, centrifuge tubes were used to store the MNPs mixed with water at the outlets. The MNPs were allowed to settle at the bottom of the tubes (which required approximately 5 min), and the water was removed. The remaining MNPs in the tubes were transferred to microtubes with a scale to measure the quantity of MNPs, as shown in Fig. 6. The measurements were repeated to accurately read the scale on the microtubes.

We can see that almost 100% of the particles go into the correct outlet around 4.3 seconds but after 4.3 seconds, the particles go to both correct and incorrect outlets. This phenomenon can be explained due to laminar flow in a pipe. The velocity becomes fastest at the center and is gradually decreasing to zero at the edges. Therefore, the particles at the center are firstly reaching to the bifurcation region and they can be easily directed to the correct outlet with the magnetic guidance. On the other hand, the particles that are closer to the incorrect outlet and far from the center reach later at the bifurcation region, they have more difficulties to be guided to the correct outlet. That is the reason why there is a maximum rate of particles at the correct outlet around 4.3 seconds. These trends are observed in both the simulation and the experiments (Figs. 5 and 6). As can be seen from Figs. 4–6, good agreement was achieved between the simulations and the experimental results.

5. Conclusion and Future Work

We have described an electromagnetic guidance system for MNPs for applications in targeted drug delivery. The actuator system includes two coil-core systems, and DC power supplies were used to supply electric current to the coils. A soft core was placed at the center of the coil to increase the magnetic field in the region of interest. The experimental results show that the electromagnetic actuator was able to efficiently steer 800-nm-diameter MNPs in a Y-shaped channel.

As part of future work, we plan to experimentally investigate the factors that affect the performance of the MNP guidance system including sticking and aggregations of the MNPs, as well as to test the MNP guidance using experiments on mice. We also have a plan to develop a cooling system in order to mitigate the heating problems in the coils and extend the actuator system to 2D/ 3D.

Acknowledgement

This research was supported by the Pioneer Research Center Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT & Future Planning (2012-0009524).

References

[1] M. E. Davis, Z. Chen, D. M. Shin, "Nanoparticle therapeutics: an emerging treatment modality for cancer," Nat. Rev. Drug. Discov., 7 (2008), 771–782.

[2] H. Fischer, R. Gottschlich, A. Seelig, "Blood-Brain Barrier Permeation: Molecular Parameters Governing Passive Diffusion," J. Membran. Bio., 165 (1998), 201–211.

[3] A. BÈduneau, P. Saulnier, J. P. Benoit, "Active targeting of brain tumors using nanocarriers," Biomaterials, 28 (2007), 4947–4967.

[4] C. Alexiou, R. Jurgons, C. Seliger, O. Brunke, H. Iro, and S. Odenbach, "Delivery of superparamagnetic nanoparticles for local chemotherapy after intraarterial infusion and magnetic drug targeting," Anticancer Res,. 27. 4a (2007), 2019–2022.

[5] S. I. Takeda, F. Mishima, S. Fujitomo, Y. Izumi, S. Nishijima, "Development of magnetically targeted drug delivery system using superconducting magnet," J. Magn. Magn. Mater., 311. 1 (2007), 367–371.

[6] J. J. Abbott, O. Ergeneman, M. P. Kummer, A. M. Hirt, and B. J. Nelson, "Modelling magnetic torque and force for controlled manipulation of soft-magnetic bodies," IEEE Trans. Robot., vol. 23. 6 (2007), 1247–1252.

[7] X. Han, Q. Cao, and L. Li, "Design and evaluation of three-dimensional electromagnetic guide system for magnetic drug delivery," IEEE Trans. Appl. Supercond., 22. 3 (2012), 4401404.

[8] S. M. Jeon, G. H. Jang, H. C. Choi, S. H. Park, and J. O. Park, "Magnetic navigation system for the precise helical and translational motions of a microrobot in human blood vessels," J. Appl. Phys., 111. 7 (2012), 07E702.

[9] H. Choi, K. Cha, J. Choi, S. Jeong, S. Jeon, J. O. Park, and S. Park, "3-D locomotive and drilling microrobot using novel stationary EMA system," IEEE/ASME Tran. Mechatronics, 18. 3 (2013), 1221–1225.

[10] Z. Zhang and C. H. Menq, "Design and modelling of a 3-D magnetic actuation for magnetic microbead manipulation," IEEE/ASME Tran. Mechatronics, 16. 3 (2011), 421–430.

[11] S. H. Kim and K. Ishiyama, "Magnetic robot and manipulation for active-locomotion with targeted drug release," IEEE/ASME Tran. Mechatronics ,19. 5 (2014) 1651–1659.

[12] L. Arcese, M. Fruchard, and A. Ferreira, "Endovascular magnetically guided robots: navigation modeling and optimization," IEEE Trans. Biomed. Eng., 59. 4 (2012), 977–87.

[13] M. Dadkhah Tehrani, M. Kim, J. Yoon, "A novel scheme for nanoparticle steering in blood vessels using a functionalized magnetic field," IEEE Trans. Biomed. Eng., 62. 1 (2015), 303–313.

[14] S. Martel, O. Felfoul, J.-B. Mathieu, A. Chanu, S. Tamaz, M. Mohammadi, M. Mankiewicz, and N. Tabatabaei, "MRI-based Medical Nanorobotic Platform for the Control of Magnetic Nanoparticles and Flagellated Bacteria for Target Interventions in Human Capillaries," Int. J. Robot. Res., 28. 9 (2009), 1169–1182.

[15] K. Belharet, D. Folio, and A. Ferreira, "Simulation and planning of a magnetically actuated microrobot navigating in the arteries," IEEE Trans. Biomed. Eng., 60. 4 (2013), 994–1001.

[16] E. M. Cherry, P. G. Maxim, and J. K. Eaton, "Particle size, magnetic field, and blood velocity effects on particle retention in magnetic drug targeting," Med. Phys., 37. 1 (2010), 175.

[17] M. Dadkhah Tehrani, M. Kim, and J. Yoon, "A novel electromagnetic actuation system for magnetic nanoparticle guidance in blood vessels," IEEE Trans. Magn., 50. 7 (2014), 5100412.