Simulation of novel permanent magnet array for cell-based therapeutic agent fixation

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Abstract

In this paper, a multiscale simulation approach is presented to optimize the design of permanent magnet array for the fixation of therapeutic agents to the target lesion. Here, we assumed MNPs embedded micro-scaffold for cell loading as the therapeutic agent. In principle, the maximized pulling or pushing magnetic force are required to fix the micro-scaffold to the lesion and those magnetic forces can be generated by assembling the permanent magnets with the different direction of the magnetization. For the preliminary study, we focused on the simulation and we successfully optimized the appropriate permanent magnet array to generate the maximized pulling and pushing magnetic force at the injection points of micro-scaffolds. In future work, on the basis of simulation results, optimized magnet array will be fabricated and assessed for the fixation of micro-scaffolds for cartilage regeneration considering the required depth of targeting and direction of magnetic force on *in vitro* and *in vivo* models.
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1 Introduction

Cell-based therapies are emerging and promising treatment. Stem cell based therapies are, especially, promising treatment for cartilage and spinal cord regeneration [1]: Knee osteoarthritis or spinal cord cannot regenerate naturally so that the therapeutic agent consisting of stem cell can be efficient therapies for those patients [2].

Recently, several studies have been intensively focused on the active targeting of magnetic nanoparticles (MNPs) embedded therapeutic agent using the magnetic actuator to improve the efficiency of the stem cell based therapies [2, 3]: To enhance curative effect and to advance recovery period, the actively controlled micro-scaffold consisting of biocompatible, biodegradable materials, and magnetic nanoparticles (MNPs) were used to enhance the targeting ability [2]. Moreover, there were studies using magnetic properties for improving the proliferation of cell and chondrogenic differentiation of SPIO-labelled MSCs (m-MSCs) [3].

However, not only the active targeting but the following fixation of the therapeutic agents to the target lesions is also important for enhancing the therapeutic performance and effectively targeting the broad range of human diseases [4] because the cell adhesion to the extracellular matrix (ECM) is essential for the cell-cell communication, proliferation, and differentiation.

To fix the cell-based agents to the injured lesion, the pushing and pulling force should be controlled and the external electromagnetic actuation systems can be one of the useful tool. However, there are several disadvantages such as the power consumption and large equipment size. [5, 6]

In this paper, we suggest the simple and versatile permanent magnet arrays based on Halbach array [7-9] to generate the pulling and pushing force for fixing the cell-based agents. And for the preliminary study, we focused on the simulation to optimize the design of the permanent magnet array.

2 Materials and Methods

2.1 Theory

The magnetic force on a single superparamagnetic particle, ***F***, given by

$$\mathbf{F} = \nabla(\mu \cdot \mathbf{B}) = V\nabla(\mathbf{M} \cdot \mathbf{B}) \quad (1)$$

where $\mu = \mathbf{M}(\mathbf{B})V$, $\mathbf{M}$, V , and $\mathbf{B}$ is a moment of the single superparamagnetic particle, magnetization of particles, the volume of particle, and the magnetic

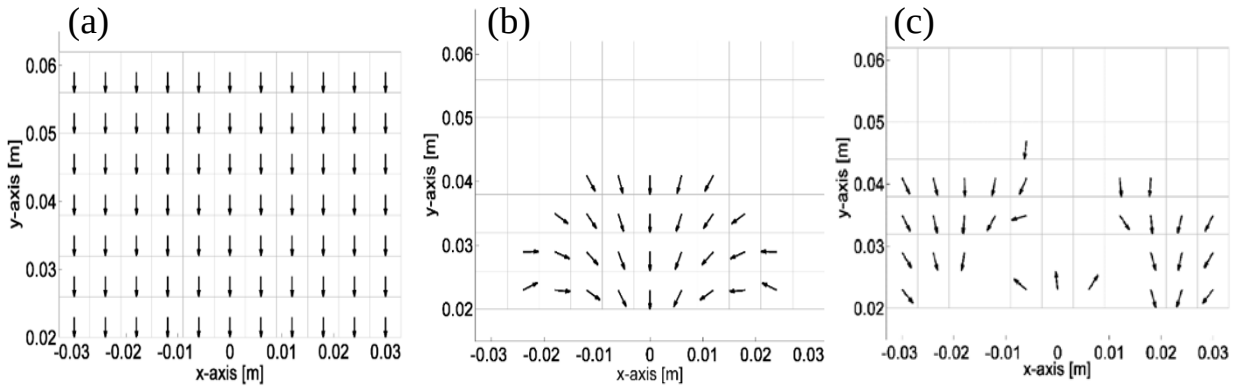

Figure 1. The results of the optimized array of magnets by MATLAB. (a) random number of the magnet (*n*) in 2D plane. (b) Magnitizaion direction for pulling force and value at CP is 1.6975×10^{-16} N. (c) Maginetization direction for pushing force and force at CP is 3.8262×10^{-16} N

flux density, respectively. **B** can be expressed as $\mathbf{B} = \mu_0 \boldsymbol{H}$, wherein μ_0 and $\boldsymbol{H}$ is vacuum permeability and the applied magnetic field inside the particle, respectively.

Each dipole field of the permanent magnet can be expressed as below:

$$\mathbf{B}_i(\mathbf{r}') = \frac{\mu_0}{4\pi}\left(\frac{3\mathbf{r}'(\mu_i \cdot \mathbf{r}')}{r'^5} - \frac{\mu_i}{r'^3}\right) \quad (2)$$

where, μ_i $\mathbf{r}'$ is the point moment and the position vector of the point moment, respectively. The normalized magnetic force owing to a configuration of magnets on the superparamagnetic was calculated at a centre point (CP) on region of interest (ROI). The magnetic force can be normalized as below:

$$\frac{F}{M_s V} = \frac{M}{M_s}\nabla(B) \quad (3)$$

here, the unit is $\mathrm{T} \cdot m^{-1}$ and M_s is the saturation magnetization of the particle. The force is equivalent to the gradient when $M = M_s$. In this simulation, we assumed that the diameter is 1 μm and M_s is 4.7×10^{-5} $A \cdot m^{-1}$ at room temperature.

2.2 Optimization

To optimize the arrays of the permanent magnets (number of magnets and direction of magnetization), univariate search method (one of the direct methods) was applied: the number of the magnets that we interest (V_m), the size of magnet, the vertical distance from CP to surface of the magnet array (L), the initial direction of the magnetization at each of magnets, the degree-varying of the magnetization (M_{ang}) and the position range of the magnets in 3-dimensionals (3D) plane were considered. We set the direction of the force as positive when the MNPs move toward the array of magnets (pulling force).

First, the random number of magnets (n) are placed in ROI, arbitrarily. Then, V_m are set and pulling or pushing force in CP is selected. Note that n should be equal or more than V_m. The initial value of the magnetic force in CP and the direction of the magnetization of each magnet was then calculated. Next, the degree-varying of the magnetization (M_{ang}) on first magnet (n = 1) is given and the magnetic force in CP is recalculated, subsequently. To find the maximum value of the magnetic force in CP, the aforementioned process is repeated to n-th magnet. During this repeating process, the least influenced magnet to CP is eliminated to satisfy the V_m.

In this optimization, we used MATLAB R2014a (MathWorks, Inc., USA) and assumed that the magnet is 6 mm cube L is 20 mm, and M_{ang} is 1˚.

3 Result & Discussion

3.1 Optimization in 2D

Figure 1 shows the optimized arrays of magnets in 2D plane for the pushing and pulling force. Figure 1(a) shows the random number of the magnet (n) in the 2D plane and figure 1(b) and 1(c) show the pulling and pushing force in CP when V_m was set as 30, respectively. Here, the magnetic force for pulling and pushing in CP was 1.6975×10^{-16} N and 3.8262×10^{-17} N, respectively.

Figure 2 indicates the particle trajectories in the ROI under the optimized array of magnets. Here, we imported the optimized results from MATLAB (figure 1) into COMSOL Multiphysics 5.0 (COMSOL, Inc, Burlington, MA, USA) and released MNPs (1 μm diameter) in the CP. Then simulated the MNPs trajectories depending on the magnetic force from the array of magnets. The colour areas in imaginary

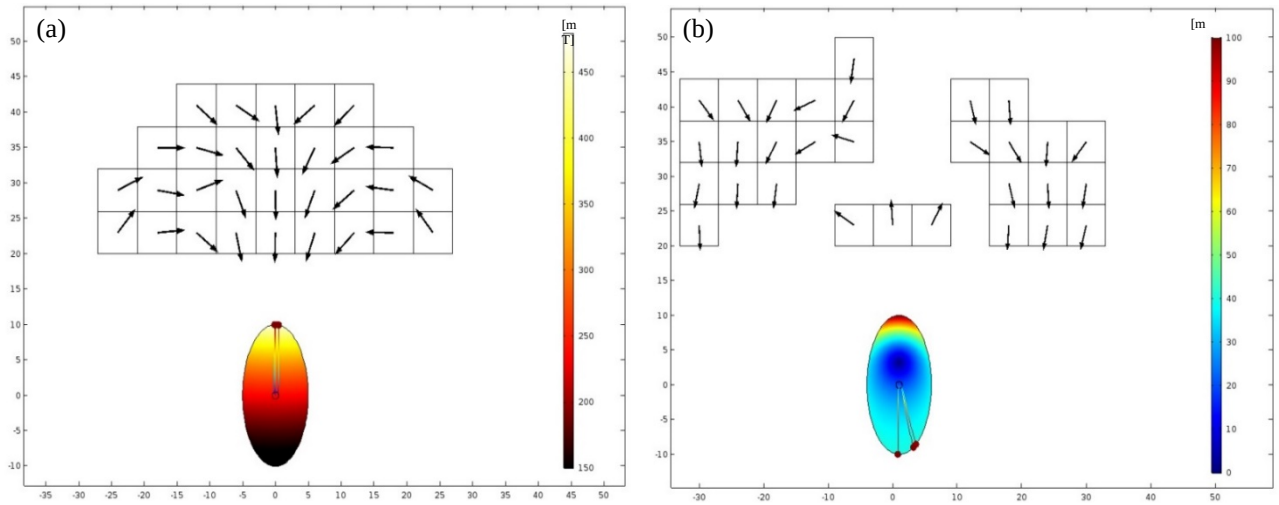

Figure 2. Optimization of permanent magnet arrays in 2D. The x-axis and y-axis are the distance (mm). (a) Pulling force at CP. The magnetic flux density is from 150 to 500 mT. The velocity is 350 m/s, approximately. (b) Pushing force at CP. The magnetic flux density is from 0 to 100 mT. The velocity is 25 m/s, approximately.

boundary of ROI are considered the distribution of the magnet flux density and has units of mT.

It is well know that when the superparamagnet is positioned near the permanent magnet, only one force is generated, *i.e*., pulling force, and it attracts the superparamagnet from low to high magnetic field. However, when the permanent magnets are arranged as we optimized, the position of the field free point (FFP), where the magnitude of the magnetic field becomes near zero, can be adjusted into the ROI. Therefore, not only pulling, but the pushing force also can be generated by controlling the position of FFP.

In figure 2(a), since there is no FFP, the gradient of magnetic fields are only distributed from CP toward the array of magnets. Hence, the MNPs at CP are attracted toward the magnet arrays. In contrast, as shown in figure 2(b), FFP is generated upper position from CP and the gradient of magnetic field is distributed in radial direction in ROI. Therefore, when the MNPs are released at the CP, MNPs are repulsed from the magnet array. Here, V_m is 30 and the velocity of MNPs is 25 m/s.

3.2 Optimization in 3D

The optimization and corresponding simulation were conducted in 3D planes. In 3D simulation, the equations and the optimization method are the same as those of the 2D but *z*-axis is additionally considered. Here, we assume that the magnet is a cube and has 6 mm length and the V_m is 30, and both attraction and repulsion are the same. As shown in Figure 3, we successfully demonstrate the particle motion under the optimized magnet arrays in 3D for pulling (figure 3(a)) and pushing force (figure 3(b)).

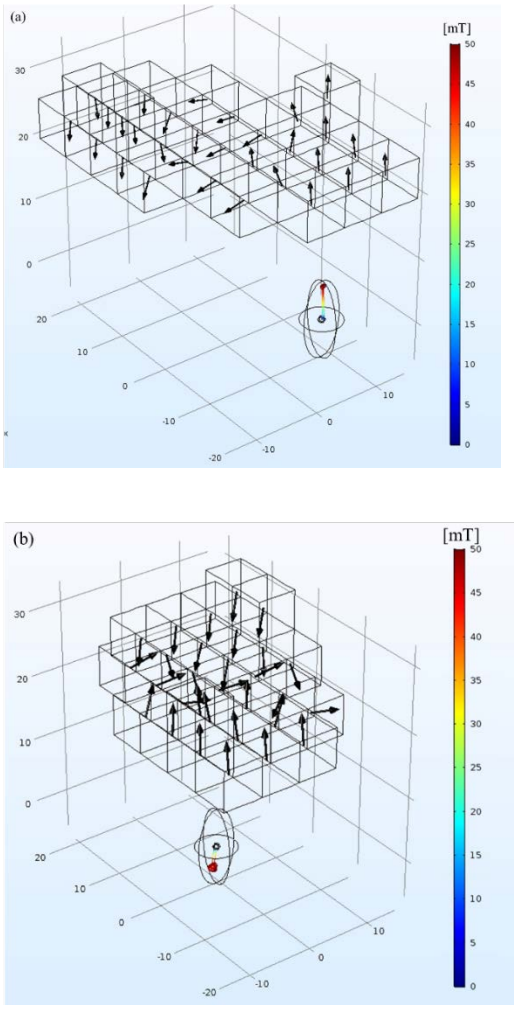

Figure 3. Optimization in 3D. The unit of each grid is mm. The direction and colour legend are the magnetic flux density direction and magnitude, respectively. (a) Pulling force (b) Pushing force.

4 Conclusions

In this paper, we performed the simulation to optimize the design of the permanent magnet array for the fixation of therapeutic agents to the target lesion. By varying the direction of the magnetization and the number of the permanent magnet, we can control the position of FFP in ROI so that can generate the pulling and pushing force. These results show the possibility that after injecting the MNPs embedded therapeutic agents into the body, the agents can be fixed to target lesion by using the optimized magnet array. In future work, on the basis of simulation results, the optimized array of magnets will be fabricated and assessed for the fixation of micro-scaffolds for cartilage regeneration considering the required depth of targeting and direction of magnetic force on *in vitro* and *in vivo* models.

5 Acknowledgement

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6 Reference

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7月6日（星期四）Thursday，July 6, 2017， Room: M3-04

主题/Topic		类人/仿生/足式机器人，微型机器人 Biologically Inspired Robotics, Micro / Nano Robotics
会议室/Room 1		M3-04
Time	Number	Paper Title
09:40-10:00	No.87	用于基于细胞的治疗剂固定的新型永磁体阵列的模拟 Simulation of Novel Permanent Magnet Array for Cell-based Therapeutic Agent Fixation
		Kyungmin Lee
		School of Mechanical Engineering, Chonnam National University, Korea
10:00-10:20	No.84	多功能胶囊内窥镜新型电磁驱动系统：可行性研究 Novel Electromagnetic Actuation System for Multifunctional Capsule Endoscopes: A Feasibility Study
		Manh Cuong Hoang
		School of Mechanical Engineering, Chonnam National University, Gwangju, Korea Medical Microrobot Center, Robot Research Initiative, Chonnam National University, Gwangju, Korea
10:20-10:40	No.85	PLGA-PEG 基磁纳米胶囊，用于对比增强 MR 成像和聚焦超声触发药物递送 PLGA-PEG base magnetic nanocapsule for contrast-enhanced MR imaging and focused ultrasound-triggered drug delivery
		Zhen Jin
		School of Mechanical Engineering, Chonnam National University, Gwangju, Korea
10:40-11:20	Keynote Speech	生物医学微/纳米机器人 Biomedical Micro/Nano Robotics
		Prof. Jong-Oh Park
		IFR Executive Board Member Director, Medical Microrobot Center Director of Robot Research Initiative Professor of Chonnam National University, Korea
11:20-12:00	Keynote Speech	人工智能驱动智能机器人工业走向创新经济 AI Driven Intelligent Robotics Industry towards Innovation Economy
		罗仁权教授 Prof. Ren C. Luo
		Chair Professor & life distinguished professor at National Taiwan University Director of International Center of Excellence on Intelligent Robotics and Automation Research in National Taiwan University Member of EU Industrial Advisory Board, Taiwan Editor-in-Chief, IEEE Transactions on Industrial Informatics (Impact Factor 4.708)
12:00-12:50		午餐 Lunch Break

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