

Micromanipulation of Biological Systems with Microelectromagnets

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Abstract—Micromanipulation of biological systems with microelectromagnets, a ring trap, and a matrix, was demonstrated. A ring trap is a circular conducting wire topped with an insulating layer, whereas a matrix consists of two arrays of wires, aligned perpendicular to each other, that are separated and covered with insulating layers. Microelectromagnets can create strong and local magnetic field profiles on micrometer length scales, controlling the motion of magnetic particles and biological systems in a fluid at room temperature. Magnetic beads, yeast cells bound to magnetic beads, and magnetotactic bacteria were trapped with a ring trap; they were continuously moved and assembled with a matrix. With versatile manipulation capabilities, microelectromagnets can be a new tool for biological and medical applications.

Index Terms—Biological cells, biological control systems, bio-magnets, electromagnets.

I. INTRODUCTION

WITH the advanced synthesis of micrometer-size magnetic beads that can be attached to biological cells and biomolecules, there is a growing interest in the manipulation of biological systems using these particles [1]. Magnetic beads consist of a large number superparamagnetic nanomagnets enclosed in a polymer matrix. The surface of the beads can be functionalized to make a highly specific binding to a target biological system, allowing fast and selective manipulation of target samples in a fluid by applying an external magnetic field. With the biocompatibility of the magnetic field, magnetic manipulation is an easy and noninvasive method for scientific research and clinical practice [2].

Here, we present microelectromagnets as a novel magnetic manipulation tool for biological experiments. Microelectromagnets consist of multiple layers of lithographically patterned conducting wires that are covered with insulating layers [3]. Microelectromagnets can create versatile magnetic field profiles on microscopic length scales to control the motion of magnetic beads in a fluid at room temperature. Two types of device (a ring trap and a microelectromagnet matrix) were fabricated and tested. To demonstrate the manipulation capability of microelectromagnets, three different samples (magnetic beads, yeast cells bound to magnetic beads, and magnetotactic bacteria [4]) were prepared and manipulated: Ring traps were used to trap

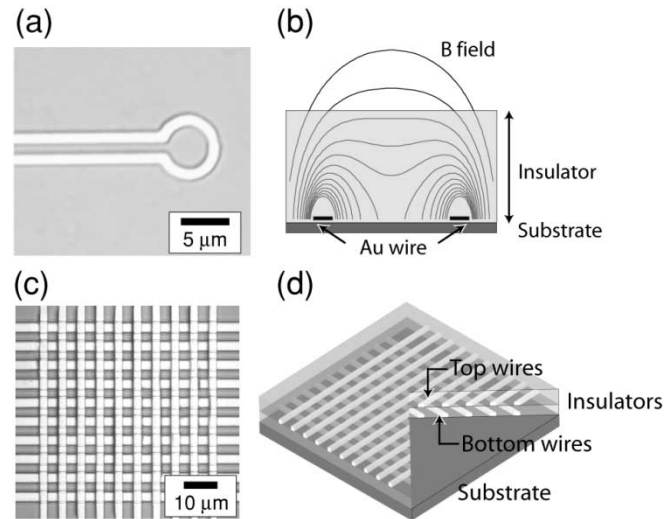


Fig. 1. (a) Micrograph of a ring trap with a diameter of $5 \mu\text{m}$. (b) Schematic cross section of the ring trap with contours of the magnetic field magnitude. The insulating layer should be thick enough to generate the maximum in the magnetic field magnitude at the center of the ring. (c) Micrograph of a microelectromagnet matrix (10×10 wires) with the wire pitch of $8 \mu\text{m}$. (d) Schematic diagram of a matrix. The matrix has two sets of conducting wires and two insulating layers.

the target samples, and microelectromagnet matrices were used to trap, move, and assemble single or multiple samples.

II. DEVICE FABRICATION AND EXPERIMENTAL SETUP

A microelectromagnet has two types of layers: a layer of conducting wires and an insulating layer. Conducting wires are patterned by either photolithography or electron beam lithography, followed by metal (Cr/Au) deposition and liftoff. A resist with good planarization properties was spun on top of the conducting wires to form an insulating layer. Insulating layers prevent electrical shorting between wires and provide a surface for sample manipulation. Figs. 1(a) and (c) show micrographs of a ring trap and a microelectromagnet matrix that were fabricated on silicon/silicon dioxide substrates. A ring trap is a simple circular wire covered with an insulating layer. The thickness of the insulating layer was controlled, as shown in Fig. 1(b), generate the maximum in the magnetic field magnitude formed at the center of the ring. As illustrated in Fig. 1(d), a matrix has a multilayered structure: An array of conducting wires was patterned and covered with an insulating layer, upon which another array of wires was patterned and covered with an additional insulating layer.

The manipulation process was observed with a bright field microscope or an epifluorescent laser microscope, equipped

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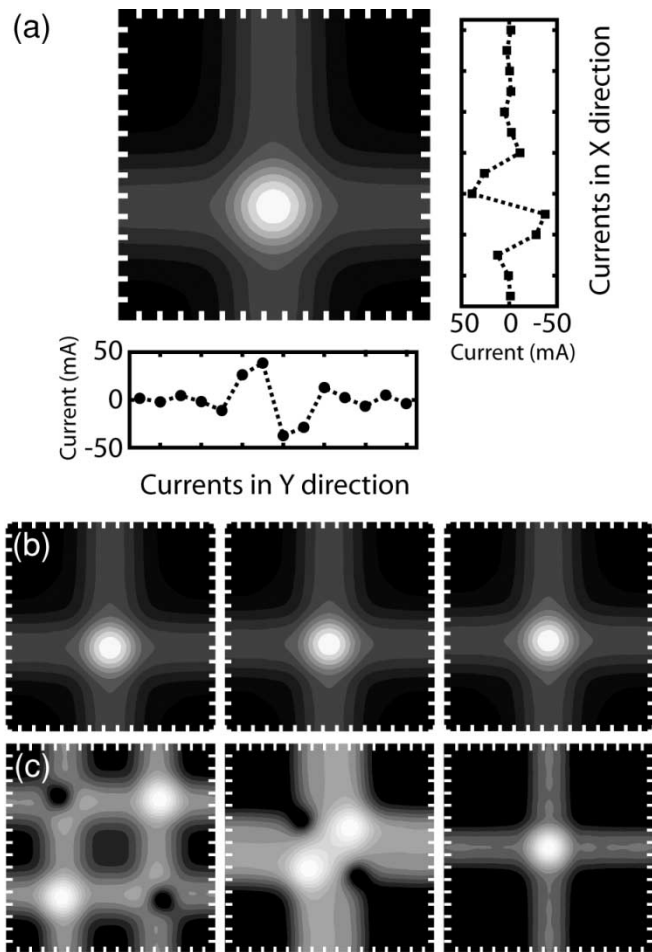


Fig. 2. Magnetic field profiles calculated for a matrix with 14 wires in each conducting layer. The wire pitch and the total thickness of the insulating layer were set to 1 and 1.2 μm , respectively. White ticks indicate wire positions. (a) Single peak in the magnetic field magnitude with current distribution in wires. Currents were adjusted to produce a Gaussian shape peak with $B = 10$ mT. (b) The single peak was moved continuously with increments less than the wire pitch. (c) Two separate peaks were moved diagonally to converge at one position.

with a CCD camera. A computer-controlled power supply with 20 separate output channels was constructed to supply currents to microelectromagnets. To prevent the thermal break down from Joule heating, the microelectromagnets were mounted on a copper stage cooled by a thermoelectric cooler. With the active cooling, current densities up to 5×10^7 A/cm² were achieved, producing magnetic field magnitudes up to $B \sim 0.1$ T.

III. RESULTS AND DISCUSSION

A. Versatile Magnetic Field Generation With a Microelectromagnet Matrix

By controlling the current in each wire, a microelectromagnet matrix can create versatile magnetic field patterns to trap, continuously move, and assemble magnetic objects suspended in a fluid. As an example, Fig. 2 shows calculated magnetic field patterns on the surface of a model matrix: 14 wires in each conducting layer (a 14×14 matrix) with the wire pitch $w = 1$ μm and the total insulating layer thickness 1.2 μm . In Fig. 2(a), a single peak with $B = 10$ mT in the magnetic field magnitude

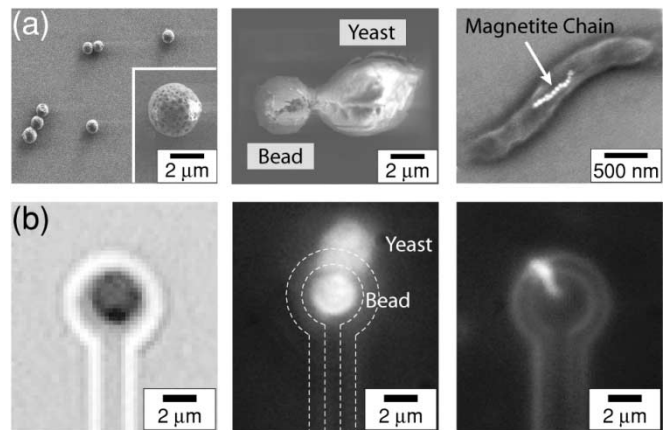


Fig. 3. (a) Scanning electron microscope images of target samples prepared for experiments: magnetic beads, a yeast cell tagged with a magnetic bead, and a magnetotactic bacterium with an intracellular chain of magnetite nanomagnets. (b) Trapping experiments with a ring trap. At the center of the ring, $B = 6$ mT was created, stably trapping target samples in a fluid. Yeast cells and magnetotactic bacteria were stained with fluorescent dyes.

was shown along with current distributions in wires. The currents were determined by the least square fitting to produce a Gaussian shape peak in the field magnitude. By applying the same algorithm, a set of current distributions was obtained to move the single peak with increments less than the wire pitch, as shown in Fig. 2(b). Magnetic objects and magnetically tagged biological objects can be trapped and moved continuously to desired locations using this magnetic field profile. To assemble or sort target samples, a matrix can produce and independently control multiple peaks. As an example, Fig. 2(c) shows how two peaks can be moved diagonally to converge at one position. Depending on the number of target samples to be manipulated, more peaks can be created by adjusting currents in wires.

B. Target Sample Preparations and Experiments with a Ring Trap

For magnetic manipulation with microelectromagnets, three different target samples were prepared, as shown in Fig. 3(a): magnetic beads, yeast cells bound to magnetic beads, and magnetotactic bacteria.

Magnetic beads are a spherical polymer matrix embedded with a large number of superparamagnetic nanoparticles. These beads are widely used in biological experiments because they can be linked to target biological systems with high selectivity. In addition, due to their paramagnetic nature, magnetic beads do not exhibit remnant magnetic moments, facilitating magnetic manipulation of target samples with an external magnetic field. For the experiment shown here, magnetic beads with the diameter $d \approx 2.1$ μm and the saturation magnetic moment $m \approx 1 \times 10^{-14}$ A \cdot m² were purchased [5] and diluted in distilled water.

The magnetic bead bound yeast sample was prepared to demonstrate a general approach to the micromanipulation of nonmagnetic biological systems using microelectromagnets. Magnetic beads $d \approx 2.8$ μm , $m \approx 1 \times 10^{-14}$ A \cdot m² and covered with a polyurethane layer, were purchased [6]. The beads were further coated with Concanavalin: a lectin that can recognize sugar molecules expressed on the cell wall and

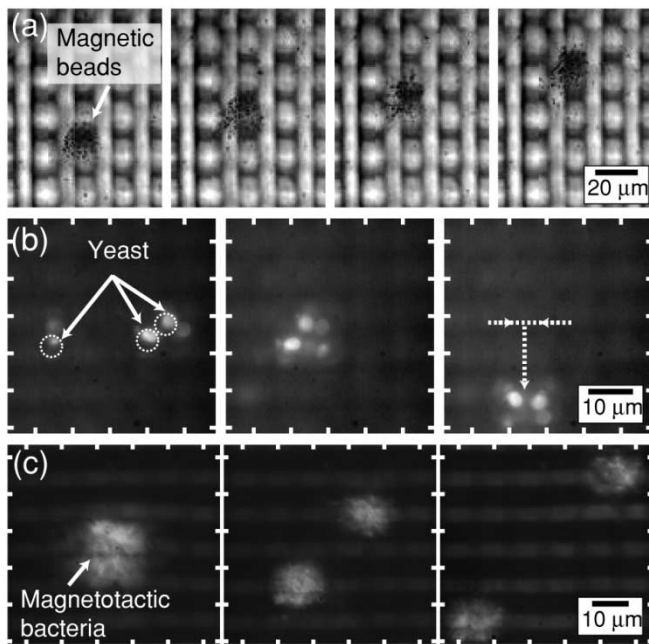


Fig. 4. (a) Continuous movements of a group of magnetic beads. A matrix with seven wires in each layer (a 7×7 matrix) was used. A single peak in the magnetic field magnitude was created and moved with steps less than the wire pitch, continuously transporting the trapped beads on the surface of the device. (b) Yeast cell manipulation with a 10×10 matrix. Two groups of yeast cells bound to magnetic beads were separately trapped and brought together to form a single group. White ticks indicate wire positions. (c) A group of magnetotactic bacteria was trapped using a 10×10 matrix and split into two groups that were moved away diagonally. White ticks indicate wire positions.

make specific binding to them [7]. The Con-A coated beads were mixed with baker's yeast (*Saccharomyces cerevisiae*) and incubated for bead-cell binding.

Magnetotactic bacteria [4], which synthesize intracellular chains of nanomagnets to guide their motions, were chosen as a target sample because their smaller magnetic moment poses interesting challenges: stable manipulation of nanomagnets in a fluid. *Magnetospirillum magnetotacticum* (MS-1), which have a single chain of intracellular magnetite (Fe_3O_4) nanoparticles [8] were used for the experiments reported here. The diameter and the magnetic moment of an individual nanomagnet in MS-1 are ≈ 50 nm and $\approx 6 \times 10^{-17}$ A \cdot m², respectively. Each MS-1 bacterium has ~ 15 nanomagnets, which gives the total magnetic moment of a single bacterium $\approx 1 \times 10^{-15}$ A \cdot m².

Fig. 3(b) shows the trapping operation of the target samples with a ring trap. Solution containing target samples was introduced into a fluidic chamber placed on top of the trap. Trapping magnetic field with $B = 6$ mT was created at the center of the ring by applying the current $I = 50$ mA. During the experiment, the device was cooled down by a thermoelectric cooler attached on the back. Biological samples (yeast and magnetotactic bacteria) were stained with fluorescent dyes for better imaging and observed with fluorescent microscope. With strong and local magnetic field produced by the ring trap, a single magnetic bead and a single yeast cell bound to a magnetic bead were stably

trapped. A viable magnetotactic bacterium could also be trapped and remained inside the trap with magnetic field on. These operations demonstrate the stable and noninvasive micromanipulation capability of microelectromagnets.

C. Micromanipulation Experiments with Microelectromagnet Matrices

Using the microelectromagnet matrices, more versatile manipulation of target samples was performed. Fig. 4(a) shows the operation of a 7×7 matrix with the wire pitch $w = 7$ μ m to trap and continuously move a group of magnetic beads in a fluid. A single peak in the magnetic field magnitude was generated and then moved with increments less than the wire pitch, leading to the continuous transport of trapped magnetic beads. To improve the control on the motion of target samples, a matrix can be modified to have more wires and decreased wire pitches. In Fig. 4(b) and 4(c), 10×10 matrices with $w = 8$ and $w = 10$ μ m, respectively, were used to control multiple samples simultaneously. In Fig. 4(b) two groups of yeast samples (two yeast cells bound to two beads and a single cell attached to a bead) were trapped separately and brought together to form a single group, whereas in Fig. 4(c), a single group of magnetotactic bacteria was split into two groups that were moved away diagonally.

These operations show how the microelectromagnet matrix can be a powerful tool for biological applications. By using a matrix, biological systems can be stably trapped in a fluid and precisely moved to desired locations where further experiments can be performed. Moreover, the motion of multiple samples can be controlled simultaneously without any modification in the structure of the device. Different biological objects that are trapped separately, for example, can be brought together to force interactions or moved away for sorting. Because each wire in a matrix can have a different current, a matrix can create optimized magnetic field patterns to meet specific experimental needs, enabling new class of biological experiments on micrometer length scales.

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REFERENCES

- [1] U. Häfeli, *Scientific and Clinical Applications of Magnetic Carriers*. New York: Plenum, 1997.
- [2] C. Haber and D. Wirtz, "Magnetic tweezers for DNA micromanipulation," *Rev. Sci. Instrum.*, vol. 71, p. 4561, 2000.
- [3] C. S. Lee, H. Lee, and R. M. Westervelt, "Microelectromagnets for the control of magnetic nanoparticles," *Appl. Phys. Lett.*, vol. 79, p. 3308, 2001.
- [4] R. Blakemore, "Magnetotactic bacteria," *Science*, vol. 190, p. 377, 1975.
- [5] Estapor (ME01N), Bangs Labs, Inc., Fishers, IN.
- [6] Dynabeads (M-280), Dynal Biotech, Oslo, Norway.
- [7] N. Sharon and H. Lis, "Lectins-cell-agglutinating and sugar-specific proteins," *Science*, vol. 177, p. 949, 1972.
- [8] D. L. Balkwill, D. Maratea, and R. P. Blakemore, "Ultrastructure of a magnetotactic spirillum," *J. Bacteriol.*, vol. 141, pp. 1399–1408, 1980.