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Agitation of magnetic beads by multi-layered flat coils

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ABSTRACT

The beads were magnetically agitated inside a droplet by changing the external magnetic-field distribution. We used both the multi-layered flat coils and the permanent magnet for keeping enough magnetic force for driving the beads and for forming a non-uniform magnetic-field. The temperature in the well solution was kept below 35 °C at the appropriate agitation drive currents by adding a heat-sink foil between the flat coils. The agitation performance was evaluated by using an enzymatic reaction. The reaction efficiency increased linearly with increasing reaction time and was more than four times higher with agitation than without agitation.

1. Introduction

Various micro-total analysis systems (μ-TAS), in which mechanical and electrical components are integrated on the same chip, have been developed by using micro-electro-mechanical-systems technologies. Such systems are expected to reduce the amount of reagent solutions and analysis time required and to enable the on-site monitoring of chemicals. Generally, most systems need complicated mechanical fluidic devices, such as valves and pumps, for handling solutions, because they use continuous flow as a reaction medium. A system can therefore become large, even if fluid channels and reactors are integrated onto microchips [1–5]. Fabrication processes making the devices and typical mechanical fluidic components developed for μ-TAS application are described in Ref. [6]. To miniaturize the system, different mechanisms based on a droplet solution as a medium have recently been proposed [7–11]. These mechanisms are, in principle, rather simple and can achieve fusion and separation by electrowetting control. However, the method based on the electrowetting droplet handling is difficult to extract the targeted sample from the droplet.

Given these difficulties, we therefore previously proposed a novel type of magnetic bead-droplet handling mechanism for a μ-TAS application [12–14]. The proposed mechanism has the advantages that it does not require complicated fluid-control devices for handling solutions and it can collect and extract the targeted samples effectively from a droplet. Beads are used for sample collection [15–18] in the field of μ-TAS. The use of beads has extended to various applications, including mixing [19,20], micro-channel formation to increase reaction efficiency [21], surface modification [22] and screening at micro-reactor array chips [23]. Gijs's group has recently developed a unique magnetic bead-handling method based on a planar coil. They have also shown that their system can perform two-dimensional manipulation of the beads on chips [24,25]. We used magnetic beads as carriers of a chemical material and handled them in a droplet configuration on the chip. We previously focused on handling magnetic beads [12] and a biochemical reaction unit [13], which is a key component of our μ-TAS. To construct a palm-sized biochemical-analysis system, we also recently developed transportation and agitation mechanisms that apply rotary motion [14].

As described above, droplet handling based on a combination of beads and magnetic force makes it possible to collect and extract targeted samples effectively from a droplet on a palm-sized system and to reduce the amount of reagent. However, the biochemical reaction inside the droplet takes a certain amount of time because there is no physical actuation force inside the droplet available for agitation of the beads in the systems. Generally, agitation is one of the main problems in μ-TAS applications, because the Reynolds number becomes small as system size decreases (meaning that the viscosity of a liquid dominates flow conditions). We therefore developed an agitation device constructed from multi-layered flat coils and a permanent magnet to increase reaction efficiency, and we evaluated its performance by using an enzymatic reaction.

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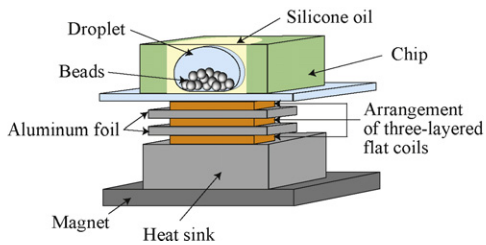

Fig. 1. Schematic view of agitation device.

2. Operation of palm-sized system

2.1. Overview of system

We previously developed a rotary-drive-type biochemical-analysis system using a bead-cluster handling mechanism [14]. It consists of a multi-well chip, two small magnets, another magnet coupled with multi-layered flat coils, a rotary table, and a stepping motor and controller. The two magnets and the flat coils with the magnet are fixed on the rotary table. The two small magnets are used for the transporting the beads, and the magnet with the set of the coils is used for the agitating the beads. The multi-well chip consists of eight wells arranged in a concentric fashion, bent channels, and a glass-bottom plate. A droplet, which contains magnetic beads with samples adhered to their surfaces, is placed in the first well. Various types of reagent and dilution droplets are pipetted into the other wells. A series of reactions is performed by transferring the magnetic beads from one well to the next. The system performs two operations: transportation and agitation. Details of the system are given in Ref. [14].

2.2. Agitation principle

A schematic view of the agitation device is shown in Fig. 1. It consists of three-layered flat coils, a permanent magnet, a heat sink, and two aluminum foils. We used a custom-ordered flat coil produced by Fujikura Ltd., Japan. A photograph and schematic view of the flat coil is shown in Fig. 2. Square-shaped coils were formed on both sides of the polyimide film to increase the number of turns (14 turns). At first, copper foils were attached on both sides of the polyimide base film by pressure bonding. The thicknesses of the polyimide film and copper foil were 25 and 30 μm, respectively. The coil pattern on both sides of the polyimide film was formed by photolithography. The hole for an electrical connection between the both sides of the coil patterns was formed at the center of them by laser. After that, metal deposition was performed to connect the both coil patterns. Finally, the surface of the coil patterns were covered by a polyimide film, with thickness of 30 μm, as an electrical insulation layer. The copper wiring had a width of 100 μm and a height of 30 μm, and the space between the windings was 50 μm. The heat sink was made of aluminum alloy, and its size was 6.5 mm × 6.5 mm × 6.0 mm. A commercially available magnet (a Nd–Fe–B permanent magnet, produced by Niroku Seisakusho Co. Ltd.) with magnetic flux density of 0.07 T and diameter and thickness of 10 and 0.5 mm, respectively, was used in the agitation device.

The agitation of the magnetic beads inside the droplet is performed by controlling the magnetic-field strength by means of the pair of three-layered flat coils and the permanent magnet. The magnetic force acting on the beads is expressed by

$$\vec{F} = \left(\vec{I} \times \nabla\right)\vec{H} \tag{1}$$

where $\vec{F}$, $\vec{I}$ and $\vec{H}$ are magnetic force per unit volume (N/m^3), magnetization of the magnetic material (Wb/m^2), and magnetic-field strength (A/m), respectively. By partially differentiating Eq. (1), the magnetic force per unit volume, F_x (N/m^3), in the horizontal x-direction can be written as [2]

$$F_x = I_x \frac{\partial H_x}{\partial x} + I_y \frac{\partial H_x}{\partial y} + I_z \frac{\partial H_x}{\partial z} \tag{2}$$

As shown in Eq. (2), the magnetic force acting on the beads depends on the bead's magnetization, which increases with increasing magnetic-field strength. We therefore used a permanent magnet having a large enough magnetic-field strength to maintain enough actuation force for handling the beads. The magnetic force also depends on the gradient of the magnetic-field, meaning that the beads move to a position under higher magnetic-field strength. The flat coils were used to form a magnetic-field gradient inside the droplet. Generally, the magnetic-field strength induced by a flat coil is much smaller than that of a permanent magnet, and it increases

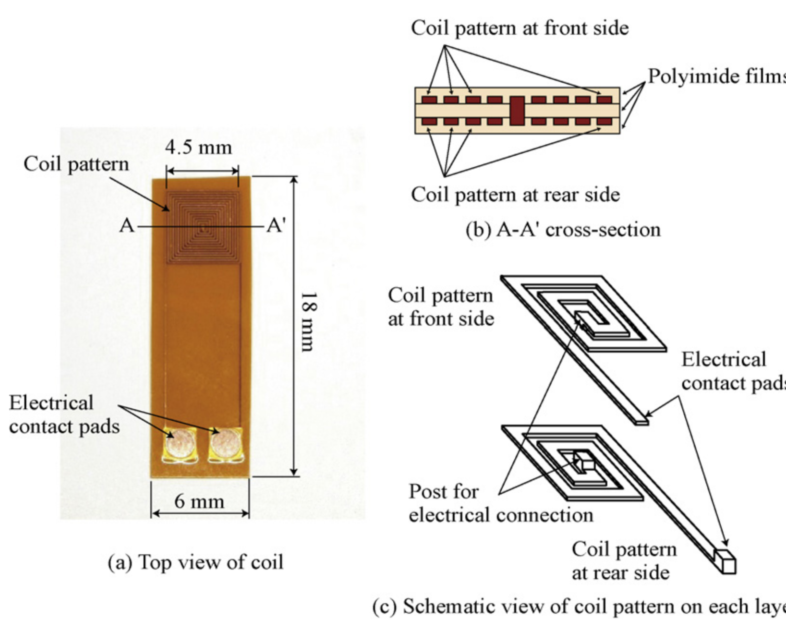

Fig. 2. Photograph and schematic view of flat coil.