Keynote Paper

Micro-nano robotic manipulation and biomedical applications

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ABSTRACT

Micro-nano robotic manipulation is one of the promising methods for the treatment of biological cell instead of human handling due to its non-skill dependent, high throughput, and high repeatability. Integration of the microfluidic chip and robotics based on MEMS technology is key challenge for biomedical innovations. In addition to the advantage of environmental control by microfluidic chip, robot enables physical operation to the cell with high throughput. A high power, high precision and high speed microrobot actuated by permanent magnets are introduced and designed for cell handling, cutting, and stimulation in a microfluidic chip.

Keywords: MEMS, μ-TAS, Micro-Nano Robotics, On-chip Robotics, Microfluidic Chip

1. INTRODUCTION

Microfluidic chip is the device which contains various functions to imitate laboratory environment in a small size of the chip. It allows achieving high throughput screening, separation, detection and reaction for various liquid solutions in a small confined space taking advantages of the ability to use very small quantities of samples, low cost, short times for analysis. The application of the microfluidic chip is extending rapidly to single cell analysis, evaluation, cultivation and so on. However, the fluid is not always suitable tool for precise control of objects like cells, and evaluation of mechanical interactions because it is easy to change the shape by external force.

On the other hand, a micromechanical manipulator is widely used for medical and life science applications because of its capability of high accuracy, high power output, and flexibility of the manipulation. However, the manipulation is conducted in an open environment to the air due to the huge size of the manipulator and it leads to the cell contamination issues. In addition, the manipulation requires a high skill to the operator because the manipulator has to be controlled in 6 degrees of freedom.

In order to obtain advantages of both of microfluidic device and micromechanical manipulator, we have proposed microrobot in a microfluidic chip since 1999 [1]. On-chip robot has great potential to achieve powerful and accurate cell manipulations for broad range of biological applications with high throughput taking advantage of flow control of microfluidic chip. In additions, the cost of on-chip robot is generally low owing to the small size of the manipulator and microfluidic chip and thus it is disposable after the operation is conducted to prevent cell contaminations. Furthermore, closed environment of microfluidic chip also help to prevent cell contamination as well as provide stable environment for the robot actuations.

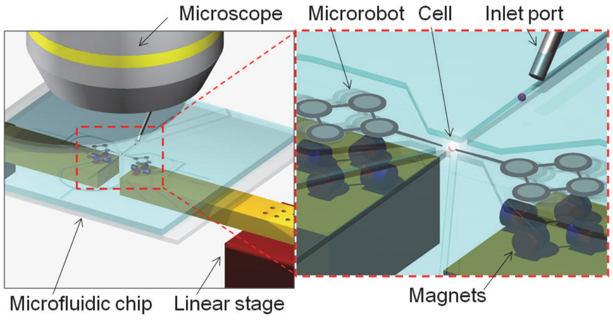

Figure 1. Conceptual view of on-chip robot.

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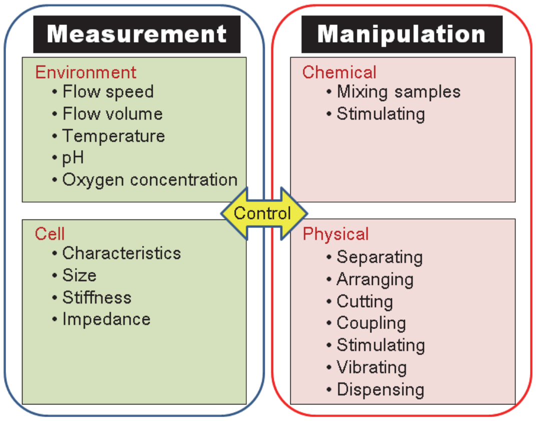
Table 1. Classification of tasks in a microfluidic chip.



Measurement

Environment
- Flow speed
- Flow volume
- Temperature
- pH
- Oxygen concentration

Cell
- Characteristics
- Size
- Stiffness
- Impedance

Control

Manipulation

Chemical
- Mixing samples
- Stimulating

Physical
- Separating
- Arranging
- Cutting
- Coupling
- Stimulating
- Vibrating
- Dispensing

Figure 1 shows concept of on-chip robot. The microrobots are placed in a microfluidic chip and actuated by non-contact power source. Then, the microrobots manipulate the inserted cells under the microscope just like a micromechanical manipulator does, but the size of the manipulator is significantly smaller and the environment is more stable than in the case of micromechanical manipulator owing to the closed space of the microfluidic chip. In addition, the advantage of the microfluidic chip allows manipulating cells continuously by flowing cells in a designed channel. Table 1 shows the category of microfluidic chip function. Microrobot can take full advantages for the underlined jobs.

2. NONCONTACT ACTUATOR

In order to achieve microrobot actuation in a closed environment of microfluidic chip, noncontact actuation is required. Many research related to noncontact actuators such as optical tweezers, dielectrophoresis, and magnetic force, are investigated and each of them has advantages and disadvantages. On the other hand, it is very important to take into account of cell elasticity when mechanical cell manipulation by on-chip robot is considered. For example, the Young's module of inner ear cell is about 2.1 kPa, oocyte (zona pellucida) is 22 kPa, yeast cell is 3 MPa, and tomato cell is 2.0 GPa and the range of Young's module reaches mega order. From this fact, the required force can be estimated to nano-newtons to milli-newtons. Therefore, a force in the order of mN will be desired for microrobot actuation by noncontact actuation. Optical tweezers are one of the promising tools for single cell manipulations but its output force is about pico-newtons and it is not always suitable for force required jobs.

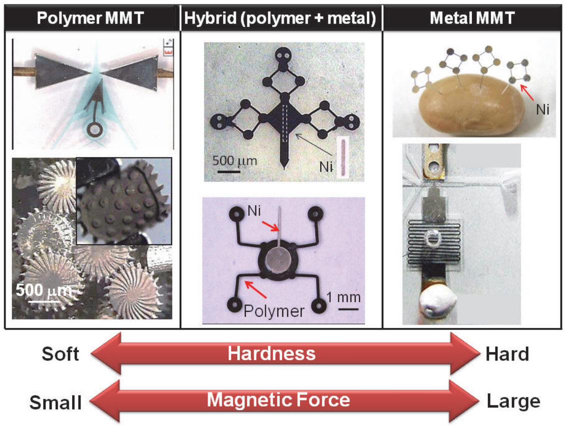


Figure 2. Classification of MMT by materials.

We have developed magnetically driven microtool (MMT) in order to apply the microrobot for the wide range of cell manipulations. A permanent magnet has a more than 10-100 times stronger magnetic field to drive an MMT than an electromagnetic coil of the same size and it is easy to output mN order forces.

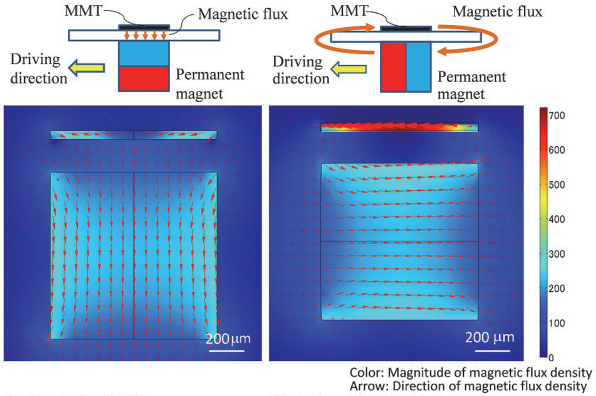
The novelty of the MMT is that powerful actuation of permanent magnet drive can be achieved and the material of the MMT has choice depending on the applications. Figure 2 shows the classification of the MMT based on the composed material. Polymer MMT is fabricated by mixture of the polydimethylsiloxane (PDMS) and magnetite particles. This type of MMT can manipulate biological cells without damage since PDMS is soft and biocompatible material. On the other hand, metal based MMT, which is fabricated by electroplating after photolithography, is hard material and it can receive strong magnetic force since it is ferromagnet. Therefore, it can apply force required job such as cutting cells. In addition, it can be used as movable electrode because Ni is conducting body as well and the electric currency can be applied [2]. Hybrid of metal and polymer structure is in the middle of these materials. This type of MMT can be used for several applications such as particle sorter [3], loader, and droplet generation to relatively large cell / particle, whose size is ϕ 100 μm or more.

On the other hand, permanent magnet drive had weakness in positioning accuracy and thus the controllability was quite low. The MMT was not required for precise movement in these actuations. Inomata et al. actuated hybrid type of MMT by permanent magnet set on the XY linear stages and achieved enucleation process by MMTs [4]. In order to compensate the low controllability of the MMT, they anchored polymer part to control the posture of the MMT by assembling the hole prepared on the MMT leg to the PDMS pillar in the microfluidic chip, but still it took time to operate enucleation process by the developed MMT.

3. ON-CHIP ROBOT ACTUATION

3.1. Low friction drive unit

A disadvantage associated with an MMT driven by a permanent is that of low positioning accuracy and response speed against the drive stage. The low performance of an MMT is attributed to the fact that the applied friction force is relatively large compared to the magnetic force in driving direction component.



(a) Conventional Drive (b) Horizontal Polar Drive

Figure 3. FEM analysis for magnetic flux density distribution (a) conventional method, (b) HPD.

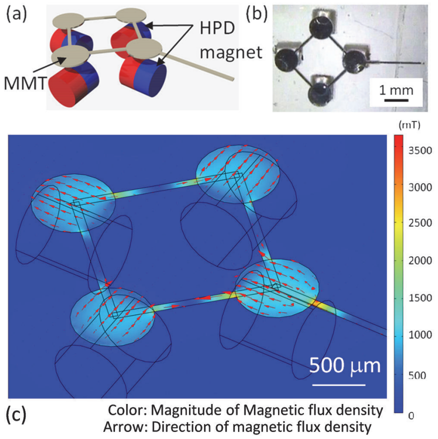


Figure 4. Multi-DOF MMT (a) concept, (b) actual picture, (c) FEM analysis for magnetic flux density.

In order to counter the large friction force, we developed horizontally arranged permanent magnet drive [5].When the MMT is set such that the permanent magnet pole is parallel to the driving direction of a magnet that has the same size as the MMT, the magnetic force in the downward direction is considerably reduced. Here we describe the driving method of the MMT in such setup as the horizontal polar drive (HPD). Figure 3 shows the magnetic flux density distributions by a finite element method (FEM). Comparing to the conventional drive unit (Figure 3 (a)), there is considerably less magnetic flux in the vertical direction around the center of the MMT shown in Figure 3 (b). As a result, the friction on the MMT reduced and we achieved 10 times higher positioning accuracy and 5 times faster response speed of the MMT.

However, HPD is only available with 1 DOF. In the case of cell manipulations, more than 2 DOFs are required for precise control. Therefore, we extended the HPD to multi-DOF precise control actuation by combining four magnets under the HPD conditions. Figure 4 (a) shows the concept of the multi-DOF MMT driven by HPD, and Figure 4 (b) shows the actual design. Two pairs of magnets under the HPD conditions are set with the polar axis normal to each other. The cell manipulation is conducted on the head of the extended part. Figure 4 (c) shows the FEM result of the magnetic flux density for the MMT. It can be seen that the magnets independently actuate the circular disc part of the MMT as it is shown in Figure 3 (b). By combining two pairs of HPD, we have achieved the same level of positioning accuracy and the response speed of the 3-DOF (x-y-θ) MMT as those of the 1-DOF MMT.

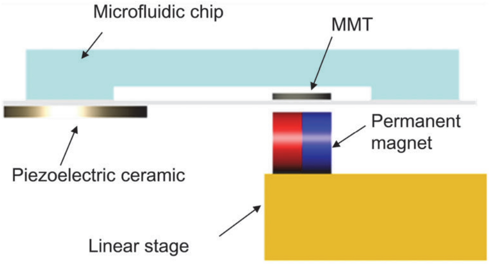


Figure 5. Driving concept of MMT with ultrasonic vibrations.

3.2. Friction reduction by ultrasonic vibration

HPD surely improved the positioning accuracy of the MMT; however, it remains in the order of dozens of micrometers leading to difficulties in treating smaller cells. Even though the cell sizes such as oocytes are relatively large, precise accuracy is often required for cell manipulation.

In order to reduce the friction on the MMT more, we employed ultrasonic vibration to the grass substrate [6]. It is known that the effective friction decreases significantly when ultrasonic vibration is applied to the sliding surface of the moving object. Kumar et al. analyzed this phenomena and derived the friction reduction ratio is the function of the velocity ratio of the moving object and the sliding surface as follows [7].

$$F_a \big/ F_0 = 2 \big/ \pi \sin^{-1} \frac{V_s}{a\omega} \approx \frac{2 \cdot V_s}{\pi \cdot a\omega} \qquad (1)$$

where F_0 is the frictional force in the absence of vibration, F_a is resultant average frictional force with vibration, V_s is the velocity of the sliding object, a and ω are the amplitude and the angular frequency of the vibration respectively.

Figure 5 shows the driving concept of the MMT by HPD with ultrasonic vibration. Radially displaceable piezoelectric ceramic is attached to the glass substrate under the microfluidic chip and oscillates the sliding surface of the MMT. The MMT is actuated by HPD and the permanent magnet is set on the linear stages. We achieved to obtain 1.1 μm positioning accuracy when the drive speed was 0.16 mm/sec and the amplitude of the vibration was 0.25 μm. In addition, the output force of the MMT was also increased twice as much as the case without vibration owing to the friction reduction. The maximum output force was 6.5 mN, which was enough to manipulate biological cell such as handling, stimulating, and cutting.

3.3. High speed actuation by three dimensional surface

It seems MMT already has enough performance for cell manipulation; however, there are several weaknesses on the MMT actuation mentioned above. As shown in the equation (1), the friction reduction ratio by vibration is depends on the MMT velocity. Therefore, the positioning accuracy was deteriorated considerably in high speed region while micrometer order accuracy was achieved in low speed region. In addition, there are two major concerns in Ni based microrobot, which are biocompatibility and precise fabrication.

In order to counter these problems, we employed Si and Ni composite structure for the MMT [8]. Taking advantage of flexibility of Si fabrication, three dimensionally patterned surface is produced on the robot in order to reduce fluid friction. Riblet surface, which is regularly arrayed V groove, was fabricated on the microrobot surface. Figure 6 shows the calculated fluid pressure distribution by Reynolds equations, when MMT actuates with drive speed of 5 mm/sec. As shown in the Figure, upward force is generated on the front surface of the riblet and downward force is generated on back surface of the riblet. When integrating the all fluid pressure over the surface area, the total pressure force is always upward. This upward force makes the lubricant film thickness increase and as a result, fluid force decreases.

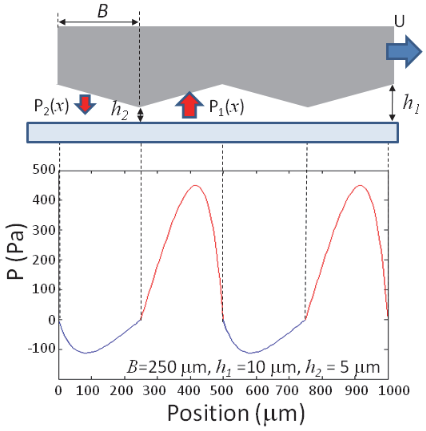


Figure 6. Pressure distribution on the riblet surface (B = 250 µm, h1 = 10 µm, h2 = 5 µm, U = 5 mm/sec).

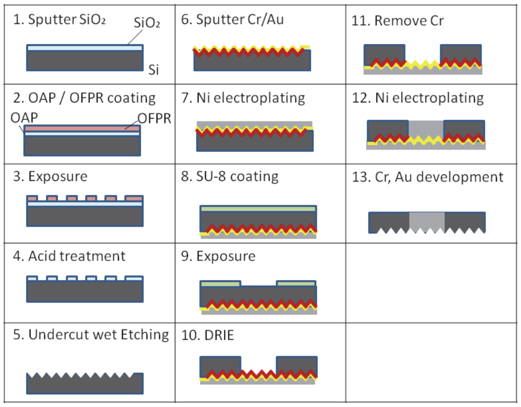
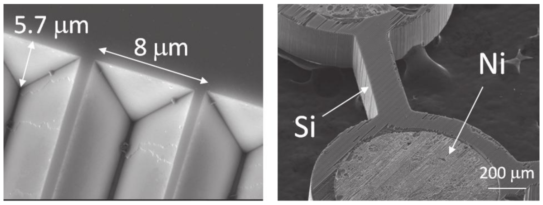


Figure 7. Fabrication process for Si-Ni composite MMT with riblet surface .



(a) SEM image of after wet etching (b) SEM image of Si-Ni hybrid MMT

Figure 8. SEM image of fabricated MMT (a) after wet etching, (b) composite structure of Si and Ni.

Figure 7 shows the fabrication process of the Si–Ni composite MMT with riblet surface. Figure 8 (a) shows SEM image after wet etching. The angle of the V groove was 55 degree due to (100) crystal orientation, and the depth of the V groove was 5.7 µm Figure 8 (b) shows fabricated Si-Ni composite structure of microrobot. The fabrication was conducted precisely as designed owing to the Si facility of the fabrication. In addition, there is no risk of bio-compatibility since the Si is well known as bio-compatible material.

The experiment validate the performance that the MMT with riblet surface can follow the stage up to 90 Hz (282.6 mm/sec) when the drive direction was forward direction, while the conventional Ni based MMT does not follow properly after 10 Hz (31.4 mm/sec). Also, Si-Ni hybrid MMT without riblet delayed at 3 Hz (9.4 mm/sec) and does not follow properly. This result shows that the riblet surface successfully improved the MMT capability of the drive speed by 10 times.

4. BIOMEDICAL APPLICATIONS

Now that the MMT can achieve precise positioning up to 1.1 μm, high speed actuation up to 90 Hz, and high power output force in the order of several millinewtons, a wide range of applications for cell manipulations can be achieved in a microfluidic chip. There are a lot of applications on MMT. For example, (1) MMTs arrays oocytes in a microfluidic chip. The MMTs are operated like chopsticks to pick and place the oocyte one by one. (2) MMT can manipulate cells in a microfluidic chip without contact. A local streamline is generated when high-frequency oscillation of the microtool is induced in a microfluidic chip [9]. The streamline can be controlled by tuning the oscillation parameters of the tool, such as the amplitude and phase of the oscillation. Cells then flow in the microchannel in accordance with the streamline, and their position, posture, and trajectories are controlled. Bovine oocyte manipulations, which were attraction, repulsion, and rotation, were conducted to demonstrate the capability of the proposed method without any contact by the oscillation tool. (3) MMT can cut stained oocyte to remove the nucleus [10]. The swine oocyte is easily cut by the MMT in a few second [11]. (4) MMT can capture swimming Paramecium [12]. By applying online high speed vision sensor (1000 frame/sec), we could detect high speed microorganism under the large magnification vision easily. Then, high speed microrobots could move faster than the microorganisms, and capture the Paramecium physically. We can investigate physical property of the swimming microorganisms, while it was quite difficult by conventional mechanical micromanipulator due to their agility.

5. CONCLUSIONS

The combination of robotics and microfluidics has great potential for biomedical innovations. Both of physical and environmental control enables high throughput physical cell manipulations continuously. Here we introduced magnetically driven microtool for high power, high precision and high speed on-chip robotic manipulation. Using the MMT, the wide range of cell manipulations can be achieved. The final goal is fully automated cell manipulation, and then the production line in manufacturing can be developed in a small chip.

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