MICROFABRICATED MAGNETIC POTENTIAL WELL ARRAYS AND MECHATRONIC SYSTEM FOR JOYSTICK-BASED MASSIVELY PARALLEL MANIPULATION OF MAGNETIC PARTICLES

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ABSTRACT

Cellular processes are controlled by many factors, including the location of signals within the intracellular space. While many micromanipulation technologies used to explore spatial effects on cellular processes have shed light on many biological questions, they face major drawbacks including low throughput due to their serial nature, and limited biocompatibility. To address this need we constructed a massively parallel particle manipulator, based on microscopic amplification of magnetic field gradients, that can maneuver many thousands of micro- or nano-scale superparamagnetic particles with nanometer-scale precision. We are currently developing this tool for studying cell surface reactions in a massively parallel manner.

KEYWORDS: Micromanipulation, Massively Parallel, Magnetic MEMS

INTRODUCTION

Gaining quantitative understanding of fundamental cellular processes continues to be an essential step in progressing biomedical and pharmacological research. Importantly, cellular processes are often a function of intracellular or extracellular location such that adding quantitative control of stimuli in space to cell-based experiments is critical. For example, migrating cells demonstrate relatively high localization of kinase enzymes at their leading edge [1].

While current micromanipulation technologies commonly used to explore cellular processes, such as optical trapping, magnetic tweezers, AFM and micropipetting [2], have furthered our knowledge, they have several limitations. Primarily, current micromanipulators operate on one location at a time, not in a parallel fashion. Additionally, these manipulation architectures can be invasive to the cells under study and difficult to use for long time-scale experiments. Furthermore, many systems require costly components to faithfully de-amplify motion.

To address the need to explore intracellular and extracellular phenomenon in a massively parallel and minimally invasive manner, we have developed a micromanipulation system that maneuvers superparamagnetic particles with high precision for massively parallel interrogation of biological systems.

THEORY

The principal of operation for this micromanipulation system relies on microscopically amplifying magnetic field gradients provided by a magnetic belt consisting of several rare earth magnets with alternating magnetization direction (Figure 1a). Amplification of the field gradients is achieved via a magnetic potential array (Figure 1a) which is composed of an array of permalloy micropillar elements coated in a planarizing layer of polystyrene. When the magnetic belt is brought within close proximity to the microarray (Figure 1a), the permalloy elements magnetize in alignment with the bulk field. In response to the micromagnetic field within the elements, the superparamagnetic particles will coalesce at the micromagnetic field maxima, where the gradient is zero. As the magnet belt is cycled the particles can be manipulated to different positions or continuously moved along the substrate with the shifting field maxima, allowing a user to pilot the nanoparticles to a desired location (Figure 1b).

Figure 1: Mechanism of particle motion due to ratcheting magnetic fields. When the Magnetic Belt is brought into close proximity to the Magnetic Potential Array (a), the permalloy elements in the array magnetize to align with the bulk field, leading to localization of the superparamagnetic (Fe\textsubscript{3}O\textsubscript{4}) particles which coalesce at the micromagnetic field maxima.
maxima (b). As the Magnetic Belt is translated or cycled continuously, the particles are manipulated to local positions or continuously moved along the substrate microarray with the shifting field maxima.

EXPERIMENTAL
We fabricated an integrated system to achieve user-controlled particle motion from three main components; (i) a joystick controlled robotic system which drives the orientation and translation of the magnetic belt lined with 0.6 T rare earth magnets, (ii) a microarray of polystyrene coated and planarized permalloy micro-elements on a transparent slide, and (iii) dextran coated superparamagnetic iron oxide micro or nanoparticles (Figure 2).

When loaded onto a fluorescence microscope, the system can enable a user to direct the motion of thousands of superparamagnetic particles via the joystick interface. As shown in Figure 3e, particles can be manipulated in bulk across the active substrate in orthogonal directions. This bulk motion is linearly coupled to the magnetic belt speed (Figure 3f) demonstrating a motion de-amplification by a factor of approximately 2000. In addition to bulk manipulation, particles can be manipulated angularly and radially across the magnetic elements at a resolutions of ± 2º and 1.47 ± 0.06 µm respectively.

RESULTS AND DISCUSSION
As a preliminary application of this technology, we developed a massively parallel platform for studying cell surface reactions. Shown in Figure 4a is the cell surface reaction chip consisting of two large particle reservoirs which connect 1677 cell adhesion zones (Figure 4b) which are lined with magnetic elements. Using a lithographic stencil and pluronic blocking technique, fibrinogen/fibronectin patches were created at the cell adhesion zones to constrain cell adhesion. HeLa cells were then cultured and allowed to adhere (Figure 4c cell in blue) and 1µm particles (red) were added to the chip. Using the manipulation system the particles were concentrated at the lower right hand edge of the cell adhesion zone and then piloted to make contact with the cells at a controlled position (Figure 4c).
Figure 4: Massively Parallel Platform for Cell Surface Reaction Studies. The chip (a) has two large particle loading reservoirs (large grey bars) and 1677 cell adhesion zones (b) with connection lanes. A fibronectin protein pattern, not shown, is centered on each cell adhesion zone to ensure cell alignment. As a proof of concept experiment, HeLa cells (c, cells shown in blue) were cultured and adhered onto the device. 1µm superparamagnetic particles (red) were loaded onto the devices, concentrated to the lower right hand corner of the cell adherence zones and piloted to make contact with the cell.

In future work we plan to conduct highly parallelized cell surface reaction studies with the platform. A stimuli of choice can be tethered to the microparticles, stored in the particle reservoirs, loaded into the cell adhesion zones and then piloted to a user defined point on the cell membrane.

CONCLUSION
The micromagnetic ratcheting system offers the biomedical research community a powerful new tool to explore cellular processes on the subcellular length scale. The system boasts several advantages over other micromanipulation architectures including high biocompatibility, temporal stability in incubated conditions and highly parallelized motion control. The system can move particles at relatively high speeds but also achieve highly resolved nanometer scale manipulations, both of which can be easily automated. Furthermore, we are beginning to transition the technology to biomedical applications, the first step in developing a massively parallel platform for studying cell surface reactions. Our goal is to present the research community with a high-throughput tool that can help answer fundamental biological questions quickly with statistically relevant results.

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