CMOS Meets Bio

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Abstract— **There are burgeoning efforts to use CMOS ICs for biotechnology. This paper reviews one such effort, development of a CMOS/Microfluidic hybrid system for magnetic manipulation of biological cells originally reported by the authors in [1], [2]. Programmable magnetic field patterns produced by a CMOS microcoil array IC efficiently manipulate individual cells (tagged by magnetic beads) inside a microfluidic system fabricated on top of the IC.**

Keywords— **CMOS IC, microfluidics, lab-on-a-chip**

I. Introduction — CMOS + Bio

CMOS integrated circuits (ICs) impact us today in all aspects of life. Modern microprocessor, a prime example of the CMOS IC, contains tens of millions of transistors per square inch and computes Gbyte data at GHz frequencies, and with these complexity and speed, the microprocessor handles enormous amount of audio, video, graphics, and animation data of today's software, games, and web sites. In addition to these powerful functionalities and small size, CMOS ICs are manufactured inexpensively. With these advantages, CMOS ICs have revolutionized the way we process and communicate information.

While CMOS ICs have been predominantly used in information technology, there have recently emerged activities to exploit the power of CMOS ICs for biotechnology. Bio-analytical and -actuation instruments are being miniaturized on CMOS ICs for faster, repeatable, standardized bio experiments at low cost with a small volume of sample. CMOS ICs are for instance used to examine neural activities [3], [4], to monitor ion channels and electrochemical dynamics [4], [5], to probe DNAs [6], or as an actuator to electrically manipulate bio cells [7].

Working in the field, we recently developed a *CMOS/Microfluidic hybrid system* for magnetic manipulation of bio cells, which was originally reported in [1], [2]. This paper visits this work to closely share the results with the *ASSCC* audience, reviewing the basic concepts of the hybrid system along with design and experiment.

II. CMOS/Microfluidic Hybrid System - Basic Concepts -

The hybrid system consists of a CMOS IC and a microfluidic system fabricated on top [Fig. 1]. A microcoil array in the IC [Fig. 2(a) is an example] produces a microscopic magnetic field pattern to control the motion of many individual cells (tagged by magnetic beads: See Fig. 3) suspended inside the microfluidic system where biocompatibility is maintained. In a given field pattern, magnetic beads are attracted towards local field magnitude peak positions. Therefore, by reconfiguring the field pattern, the individual bead-bound cells can be transported to desired locations [1], [2]. The field reconfiguration is executed by changing the current distribution in the microcoil array using integrated control circuits, *e.g.*, each microcoil can be connected to its own current source [Fig. 2(b)] for current control. The IC allows for rapid and programmable field reconfigurations, making manipulation operations efficient and versatile. While different manipulations in the conventional microfluidic system require different specific microfluidic structures, the hybrid system can perform many different types of manipulations in a fixed microfluidic structure by reconfiguring the field pattern, and hence, the hybrid system is a *programmable microfluidic system.*

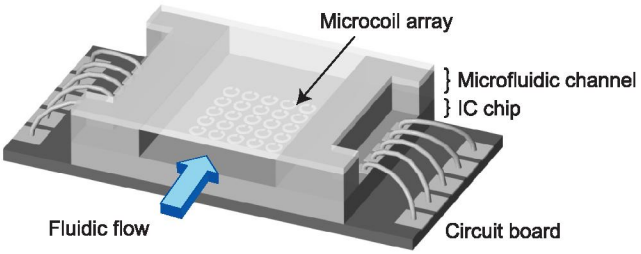

Fig. 1. CMOS/Microfluidic hybrid system - schematic.

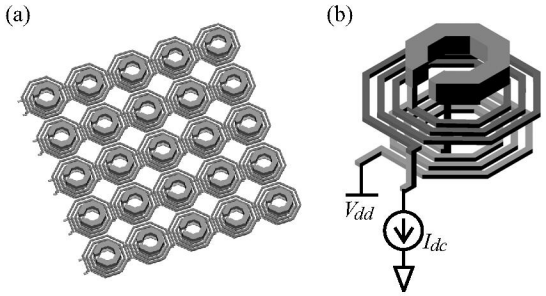

Fig. 2. (a) Microcoil array. (b) Microcoil with a current source.

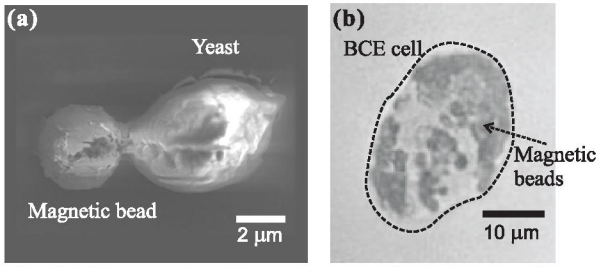

Fig. 3. (a) Magnetic-bead-bound yeast cell. A bead surface can be coated with a protein to target a specific cell [8]. (b) A cell can even engulf magnetic beads: a BCE cell example.

While magnetic manipulation of bead-bound cells *per se* is not a new technology [8], conventionally a large group of bead-bound cells are statistically pulled all at once using magnetic fields of low spatial resolution. In contrast, our approach uses microscopic magnetic field patterns gen-

erated by the microcoil array, permitting manipulation of many *individual* cells, moving each along a different path.

A CMOS *electric* cell manipulation system has been already reported [7]. Our system may be viewed as its magnetic counterpart with an enhanced microfluidic system. In comparison, the magnetic method requires more sample preparation steps (bead attachment), but is more biocompatible as magnetic fields are transparent to cells. Depending on specific needs, a proper technology choice could be made for optimum manipulation operation.

III. Hybrid Prototype Example

The micrograph in Fig. 4(a) is a CMOS microcoil array IC [2], which we will use as a vehicle to explain design and experiments. Figure 4(b) shows a microcoil array close-up along with the structure of a single microcoil. To construct the hybrid system, a microfluidic channel is post-fabricated on the IC [Fig. 5]. Before describing manipulation experiments performed with this prototype in Sec. V, let us first describe the design of the IC in the following section.

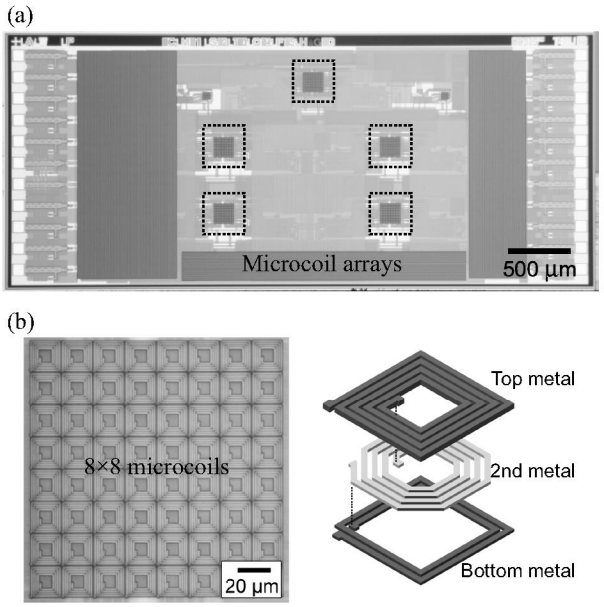

Fig. 4. (a) CMOS IC (0.18 μm) with microcoil arrays. (b) A microcoil array and a microcoil, whose outer diameter is 20 μm. The center-to-center distance between two adjacent coils is 21 μm.

IV. Design of the CMOS Microcoil Array IC

A. Microcoil Array Operation

The simplest protocol to operate an $N \times N$ microcoil array is to implement N^2 separate current sources, one for each microcoil, and to continuously flow a current through a microcoil while it is used for manipulation of a bead-bound cell. This protocol, however, suffers a severe power dissipation as N is increased to handle a large number of cells, which would lead to cell damage as well as chip failure. To overcome this, the CMOS IC incorporates an array operation protocol where all the microcoils share the same current source through switches [Fig. 6(a)] and the switches are operated according to the periodic switch signals of Fig. 6(b). In a given period $T_p = N^2 \cdot T_{on}$, each microcoil is activated only once for a duration of T_{on}. At any given moment, there is only one activated microcoil. As far as the off-time of each microcoil, $T_{off} = (N^2 - 1) \cdot T_{on}$, is shorter than the characteristic time for a bead-bound cell to escape a coil due to the Brownian motion, the microcoil array can maintain the trap of N^2 cells, one cell for each microcoil, sequentially sharing the common current source at different times, hence allowing low power operation. This scheme exploits the fact that CMOS electronics is orders of magnitude faster than motions of cells in fluid.

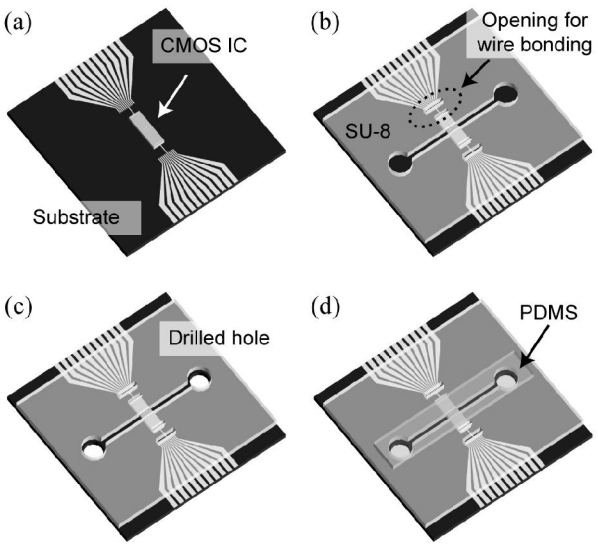

Fig. 5. (a) An IC is glued on a substrate containing leads. (b) An SU-8 layer is coated and litho-patterned to form a microfluidic channel and to open pad areas for bonding. (c) Drilled holes form fluidic ports. (d) A PDMS layer is placed to seal the channel.

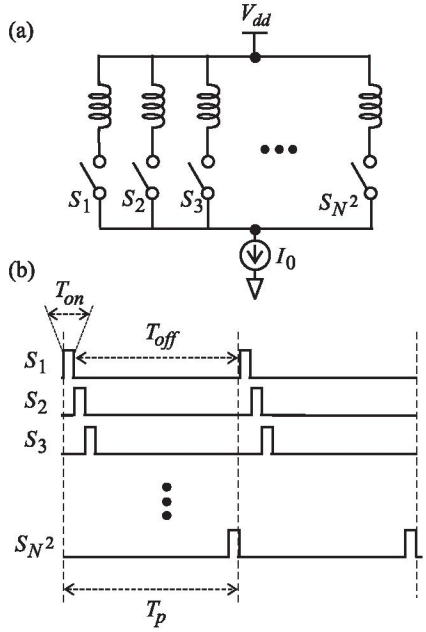

Fig. 6. (a) Current sharing among N^2 microcoils. (b) Switch control signals for low-power operation.

B. Spatial Resolution Enhancement

The CMOS IC controls directions and magnitudes of currents in more than one microcoil to create field magnitude peaks at positions other than coil centers, enhancing spatial

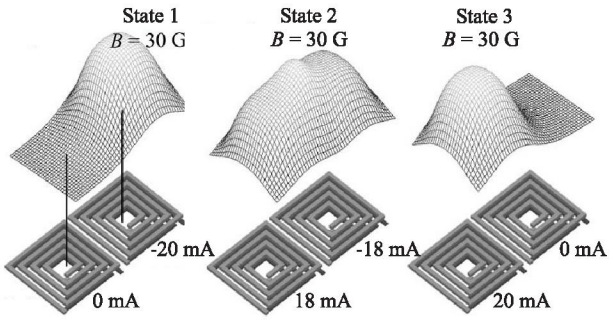

Fig. 7. Enhancement of the spatial manipulation resolution.

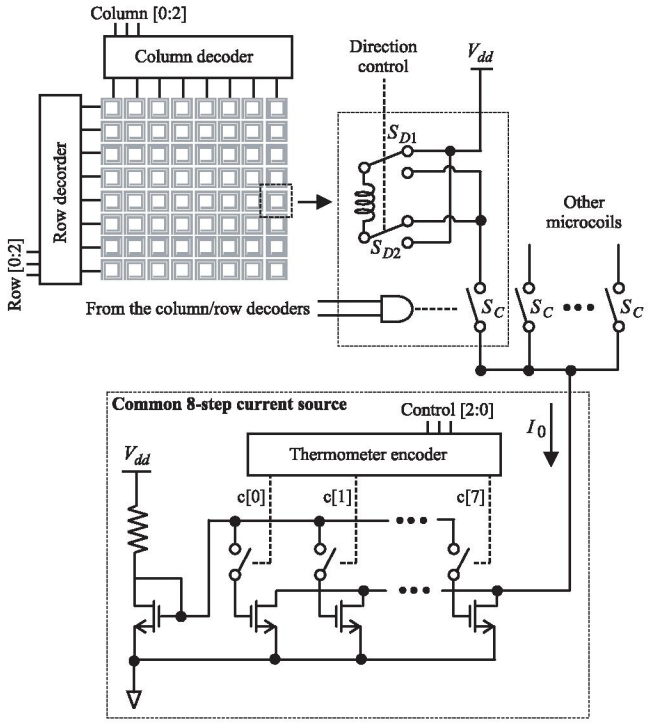

Fig. 8. The overall architecture of the CMOS IC.

manipulation resolution. For example, Fig. 7 illustrates a case where a field peak is created at the midpoint between two coil centers (State 2) along with the two straightforward cases where a field peak is generated at either coil center (States 1 and 3). State 2 is obtained by drawing *dc* currents of the same magnitude but in opposite directions in the two coils. To perform this simultaneously with the sequential current sharing protocol, the common current source can be switched back and forth between the two coils with the current direction changed in each switching.

C. CMOS IC Architecture

Figure 8 shows the overall architecture of the CMOS IC executing both the sequential current sharing and the resolution enhancement scheme. Each microcoil has FET switches around. Switches S_{D1} and S_{D2} are used to change current direction. Switch S_C connects and disconnects a microcoil to and from the *common* 8-step current source.

The sequential current sharing is executed by sequentially connecting a select group of microcoils needed for a specific manipulation to the common current source. This is done by sending a proper sequence of clock signals to the

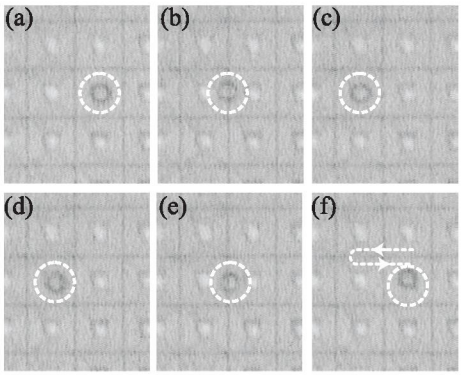

Fig. 9. Manipulation of a single magnetic bead over 2 coils.

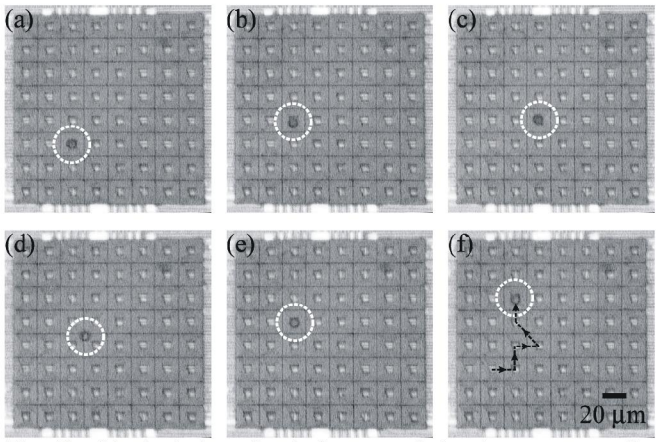

Fig. 10. Manipulation of a single magnetic bead over many coils.

S_C switches using the column and row decoders.

The resolution enhancement scheme requires controls in both current magnitude and direction. The magnitude is set by the 8-step current source, where each branch sinks 2.5 mA and is individually controlled by the thermometer encoder. To choose between two possible current directions in each microcoil, S_{D1} and S_{D2} switches are gated by a current direction control signal. Because only one coil is activated at a given time due to the sequential current sharing, a single direction control signal line is shared by all the coils. When the current source is switched from one microcoil to another, the direction control signal flips its polarity if the current direction is to be changed.

V. Experiments

Figure 9 shows manipulation of a single magnetic bead (diameter 8.5 μm; $\mu = 0.2\mu_0$). By moving a field magni-

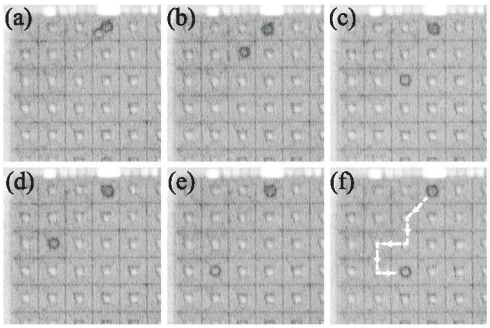

Fig. 11. Manipulation of 2 magnetic beads.

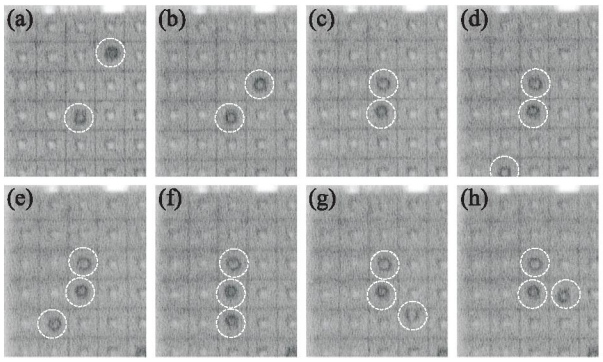

Fig. 12. Manipulation of 3 magnetic beads.

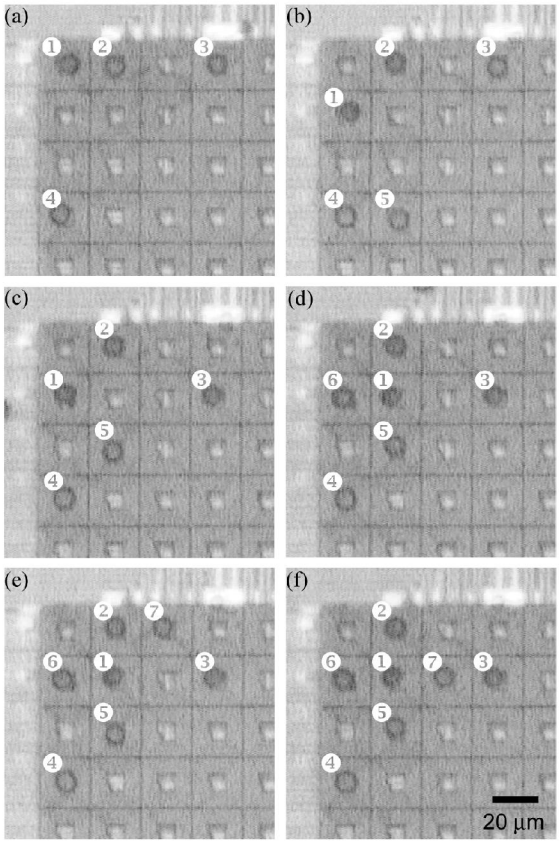

Fig. 13. Manipulation of up to 7 magnetic beads.

tude peak of B=30 G ($F \sim 40$ pN) produced with a current of 20 mA, the bead is moved back and forth between two coil centers. Also the bead is also positioned and held in the microcoil edge [Figs. 9(b) & (e)], which shows the manipulation resolution enhancement. Figure 10 shows manipulation of a single bead over many microcoils: the bead is transported over a distance of 100 μm with the average speed of 11 μm/s following a prescribed path shown in Fig. 10(f).

The low-power sequential current sharing scheme is utilized to simultaneously manipulate 2 magnetic beads [Fig. 11], 3 magnetic beads [Fig. 12], and up to 7 magnetic beads [Fig. 13]. Every microcoil used in these manipulations is sequentially activated with T_{on} = 10 ms, while sharing the same *dc* current of 20 mA. In Fig. 13, initially four magnetic beads are trapped in the array [Fig. 13(a)]. While rearranging the four beads, another magnetic bead is trapped and moved [Figs. 13(b) and (c)]. This process

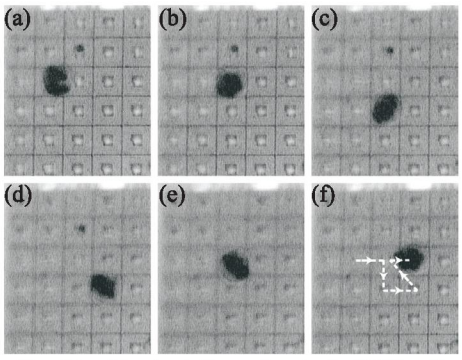

Fig. 14. Manipulation of a single BCE cell.

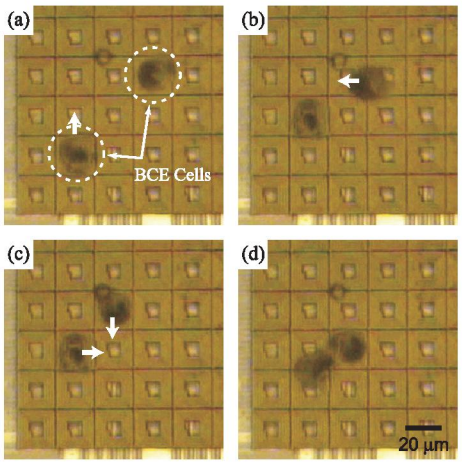

Fig. 15. Manipulation of two BCE cells for a simple cellular assembly.

is repeated to eventually arrange six magnetic beads in a cross shape [Figs. 13(d) to (f)].

Figure 14 shows a manipulation of a single BCE cell that has engulfed many magnetic beads. In Fig. 15, two cells that have engulfed many magnetic beads are transported simultaneously towards each other, and are eventually joined by holding them together. This experiment suggests interesting possibilities for assembling an artificial 2D biological tissue at the microscale by bringing cells one by one with precise spatial control. The engineered tissue can be used to study communications between different types of cells or to test drug efficacy [2].

References

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