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# Integration Module of Microcoil Magnetic Manipulation with High Sensitivity CMOS Photosensor Detection in Bio-Analyses

Chih-Yang Chen, Chien-Yu Huang, Chrong-Jung Lin and Ya-Chin King

Institute of Electronics Engineering, National Tsing-Hua University
101, Section 2, Kuang-Fu Road, Hsinchu, Taiwan 30013, R.O.C Taiwan
Phone/Fax: +886-3-5715131-34034 / +886-3-5721804 E-mail: cychen@well.ee.nthu.edu.tw

## 1. Introduction

In molecular biology, bio-cells manipulation through binding magnetic beads and optical monitoring reactions with illuminant dyes are two commonly used means in bio-assays to detect and analyze small amount of antigens or bio-molecules [1]. Following the improvement of semiconductor technology, millions of transistors and functions can be contained in a small chip operating in GHz frequency. To simultaneously detect bio-chemical reactions through a sensor array chip can significantly reduce the testing time and risks of delaying treatment. A module integrating magnetic sampling and optical detecting array for bio-analyzing application by microcoils and pulse frequency modulation (PFM) based photosensors are shown in Fig. 1. The PFM based sensor pixel is designed to accurately detect the bio-reaction when the emitting light is as low as ~0.04lux even though the circuit elements subject to some process variations.

## 2. Sample Manipulation Unit

Automatic handling of fluid and attendant samples has played an enabling role in many bio-assay fields like drug discovery, genetic synthesis, and cell sorting [2]. The development in semiconductor manufacturing led miniaturization of circuits for small scales with many manipulating ways, such as electromagnetic force, dielectrophorestic force (DEP), thermomechanical effect, and shape memory alloy [3].

Magnetic force is commonly used with iron-oxidation based beads in separating the solution and target samples in bio-assay [3]. In this work, the samples are made by 0.35μm CMOS logic process, where the microcoils are formed by top metal for high current tolerance. This microcoil architecture is directly patterned on the top of photosensing region of detector and addition post-processing steps, as shown in Fig. 2 and Fig. 3, and the sizes of detector and microcoil in cell are $(60\mu m)^2$ and $(100\mu m)^2$, respectively. A $SiO_2$ with 2000Å thickness is deposited by RF-sputtering in post process as a buffer to reduce stresses between chip surface and the 10μm-thick Parylene layer, a hydrophobic coating to decrease the effects of surface roughness and frictions. Finally, the module is packaged as shown in the inset of Fig. 4 with a trough of 3~5μl in volume for testing.

The electro-magnetic (EM) fields and forces generated by microcoil with 10mA static current are simulated by using EM field simulator. Fig. 5 illustrates the peak of ~9gauss in EM field generated by microcoil with 10mA current supply, and ~0.1pN force in lateral would be applied to pull samples in the center of near microcoils shown in Fig. 6. The polyimide based magnetic beads used in this experiment is ~23μm in diameter. The magnitude of force is high enough to move these micro-beads from one near cell to another adjacent cells in an array with an average speed of ~0.6μm/s illustrated in Fig. 7 when the microcoils are activated in turn.

## 3. Optical detection Unit

PFM sensor with analog pulse output is regarded as the solution of silica retina because of its high dynamic range [4]. A photodiode with a designed Schmitt trigger feedback module is a simple and reliable PFM sensor. The PFM allows real-time response to detect short-period bio-reactions using, more adequate than integration mode photosensors.

The circuit schematic of PFM sensor used in this work is illustrated in Fig. 8. The 2 triggering voltages are designed to be 1.48 and 1.61V as shown in Fig. 10, which results a output frequency in dark close to 1Hz (see measurement results in Fig. 11). The output frequency can be effectively tuned to enhance response time by increasing the bias voltage, as demonstrated in Fig. 12. The optical responses of this PFM sensor with-in/without microcoil are compared in Fig. 13. Forming a metal microcoil on top of the sensor reduces the light penetration, and slightly decreases the output frequency consequently.

For bio-samples monitoring with external light source, the light blockage would be enhanced by different cell sample sizes decorated with micro-beads. Fig. 14 illustrates the frequency differences in PFM sensor's output as the blocking region grows with sample size changed under the external light intensity of 70lux, 140lux and 260lux. Significant change in output frequencies is obtained with a slight blocking region growth less than 50% (from 23 to 32μm) to differentiate samples under these conditions. For detecting self-emitting light as a result of chemi-luminal reaction shown in Fig. 15, an illuminant source generating $5.77\times10^{-5}$ $W/m^2$ close to ultraviolet (as ~0.04lux in 555nm wavelength) is sufficient for the PFM to detect accurately. Under the low light region, the detection can be further extended to minimal sensing level and short the response time of the module in output by raising $V_{dd}$.

## 3. Conclusions

In this work, we present a module with sampling, manipulating, monitoring and detecting functions by combining microcoils with independent current sources and PFM detectors. The microcoil generals ~9gauss EM field and ~100fN pull force in micro-bead manipulation. PFM sensors detect the presence and size of samples in light blockage and identify bio-reactions in self-luminance process. A minimal detectable illuminant of $5.77\times10^{-5}$ W/m$^2$ is successfully demonstrated.

**Acknowledgements**

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**References**

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[2] P. Tabeling: *Introduction to Microfluidics* (Oxford University Press, NewYork, 2005) 241.
[3] H. Lee et al.: *CMOS Biothecnology* (Springer, 2007) 103.
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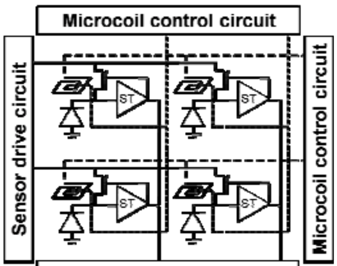


Fig. 1 The schematic of aintegrated photosensor and bead control array.

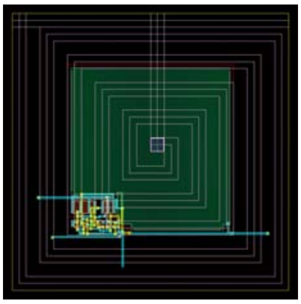

Fig. 2 The layout of single cell with a microcoil and a photodetector by CMOS process.

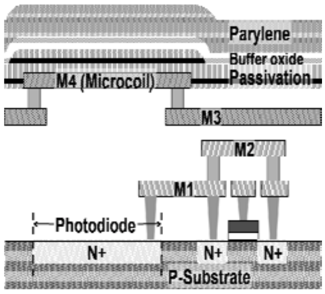


Fig. 3 The cross-section of single cell.

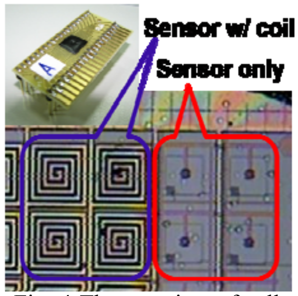


Fig. 4 The top view of cells and sensors, and microtrough package as inset.

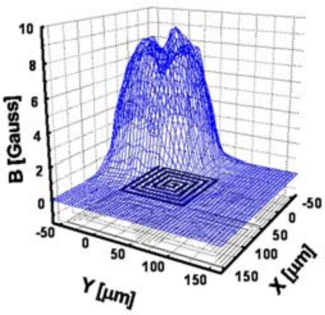


Fig. 5 Distribution of magnetic field when single coil (black) is activated.

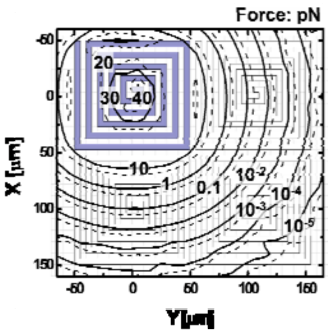


Fig. 6 Contour of pulling force when the top-left coil (dark) is turn on.

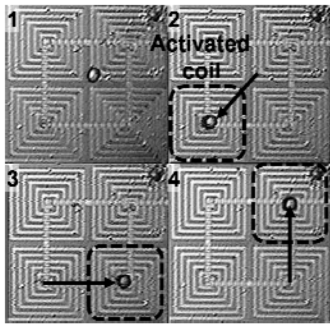


Fig. 7 A individual bead manipulated by magnetic force when the microcoils are activated in turn.

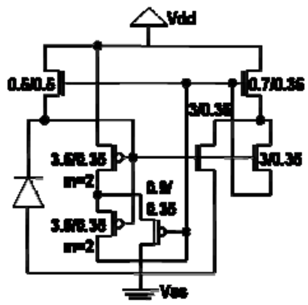


Fig. 8 Schematic diagram of the PFM sensor with Schmitt trigger.

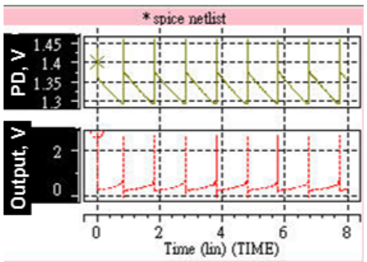


Fig. 9 Simulated photodiode voltage sensor output in dark condition.

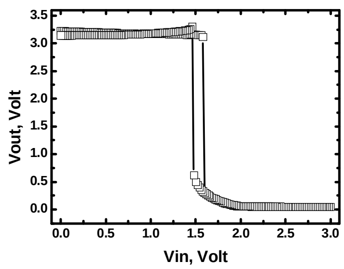


Fig. 10 The measured transfer characteristics of implemented Schmitt trigger.

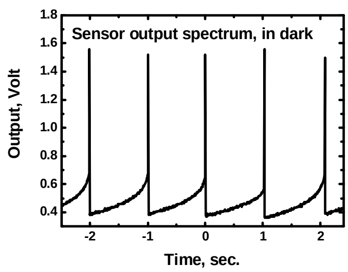


Fig. 11 The output waveform of the PFM sensor in dark condition.

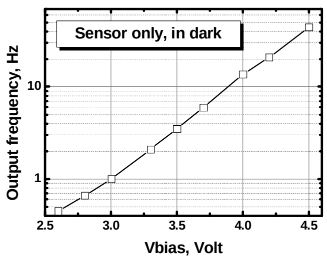


Fig. 12 PFM sensor's output frequency as a function of bias voltage, $V_{dd}$.

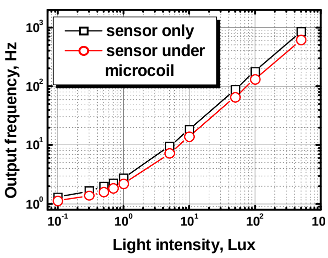


Fig. 13 Output frequency of the PFM sensors with and without microcoil.

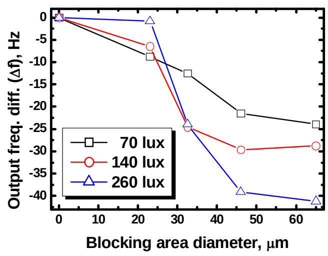


Fig. 14 Output frequency difference as the light blockage area growth.

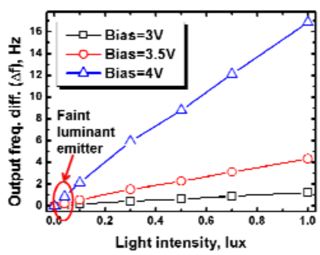


Fig. 15 Under low emitting light, output freq. diff. as the light range can be improved by modifying bias condition.