Live Demonstration: A CMOS-based Lab-on-Chip Array for Combined Magnetic Manipulation and Opto-Chemical Sensing

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***Abstract*—We demonstrate a CMOS-based lab-on-chip platform for combined magnetic manipulation and opto-chemical sensing. Each pixel of the 8×8 array integrates a Programmable Gate (PG) ISFET chemical sensor and an active pixel sensor, encompassed within an inductive coil. The system can be used for simultaneous optical imaging and pH sensing, and includes an auto-calibration mechanism for eliminating sensor non-idealities. Through a MATLAB-based graphical user interface, the user can program a spatiotemporal magnetic field pattern for micro-scale magnetic manipulation, in addition to visualising chemical and optical images in real time.**

I. Introduction

Current advancements in biomedical research are supported by new frontiers created from integrating CMOS technology with lab-on-chip platforms. For example, CMOS-based ISFET chemical sensors [1] can be used to acquire a spatiotemporal map of chemical changes for applications of cell monitoring [2]. Despite these advances in CMOS-based lab-on-chip technology, integration of multiple sensing and actuation modalities into a single system has not been achieved, thus driving efforts in functional integration.

We demonstrate the first lab-on-chip array which combines both optical and chemical sensing in addition to magnetic manipulation using inductive micro-coils within a single pixel [3]. The platform is controlled via a MATLAB-based graphical user interface (GUI) developed for sensor calibration, real time data acquisition and magnetic field pattern programming. Fabricated in commercially available 0.35μm CMOS process, the system is scaled to form an 8×8 array. This presents a versatile platform for applications requiring magnetic actuation of biological samples, such as cell manipulation, DNA hybridisation as well as opto-chemical imaging of ongoing chemical reactions.

II. Demonstration Description

The demonstration setup shown in Fig 1 consists of power supplies, a PC for visualisation of real time sensor data, an external current sink for biasing the inductive micro-coils and a ADC clock signal generator for polling the sensor array. Integrated on a single PCB, a PIC 18LF4680 microcontroller executes action routines based on commands sent from the MATLAB GUI. A Veho-004 USB microscope is also employed to capture real time images of ongoing biochemical assays on the chip surface.

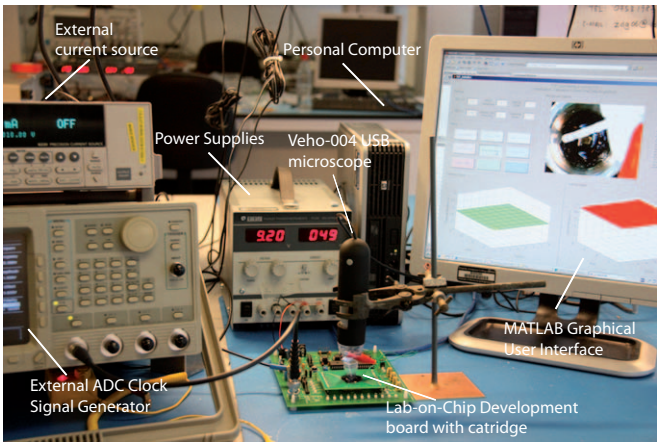

Fig. 1. Experimental setup comprising of the lab-on-chip development board, data acquisition system and external biasing devices.

III. Visitor Experience

During the demonstration, the visitor will be able to visualise changes to pH and illumination intensity detected by the lab-on-chip, as well as perform micro-scale magnetic bead manipulation in real time. The visitor will also be impressed by the high computing efficiency and convergence accuracy of the auto-calibration technique developed to eliminate sensor non-idealities, high pH sensitivity and optical detectability, as well as the versatility of micro-bead manipulation.

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***Abstract*—This paper presents a CMOS-based lab-on-chip platform for combined magnetic manipulation and opto-chemical sensing. Within each pixel, a Programmable Gate (PG) ISFET chemical sensor is combined with an active pixel sensor, and is encompassed within an inductive coil. The integrated pixel is tesselated to form an 8×8 array. Fabricated in a commercially available 0.35μm CMOS technology, the system can be used for simultaneous optical imaging and pH sensing, and includes auto-calibration mechanisms for eliminating sensor non-idealities. A spatiotemporal magnetic field pattern generator has also been embedded for micro-scale magnetic manipulation. Controlled via a MATLAB based graphical user interface, the system achieves real time data acquisition at 6fps, a pH sensitivity of 57mV/pH and demonstrates magnetic manipulation of micro-beads.**

I. Introduction

The analysis of biological systems and miniaturisation of analytical methods are few of the driving forces behind research in the field of lab-on-chip. Lab-on-chip is a multi-disciplinary approach to designing integrated micro-scale devices for monitoring and performing biochemical assays. Technology miniaturisation allows for controlled transport and manipulation of biological molecules and cells [1], while spatiotemporal chemical and optical detection can be achieved by integrating CMOS-based micro-sensors into lab-on-chip devices [2].

Despite technological advances in CMOS-based lab-on-chip devices, efforts at integrating multiple sensing and acuation modalities into a single programmable system have been limited. Previous designs of CMOS lab-on-chip devices focus mainly on systems which offer a single sensing or actuation modality [3], [4], contributing only to a small portion of a complete biochemical ssay.

We report the first lab-on-chip array which combines both optical and chemical sensing in addition to magnetic manipulation using inductive micro-coils within a single pixel. The platform is controlled via a MATLAB-based graphical user interface (GUI) developed for sensor calibration, real time data acquisition and programming a spatiotemporal magnetic field pattern. Fabricated in commercially available 0.35μm CMOS process, the system is scaled to form an 8×8 array. This presents a versatile platform for applications requiring magnetic manipulation of biological samples, such as cell movement, DNA hybridisation as well as opto-chemical imaging of ongoing chemical reactions.

II. System Overview

The top level system architecture and integrated pixel schematic is shown in Fig. 1. The array combines three sub-systems for sensory acquisition, and generating magnetic stimulus. The system uses a common programming/calibration interface based on the SPI protocol to load data serially. This data includes 8×8×10-bit words for the chemical imager calibration, 64×10-bit words to define the magnetic field pattern and one additional word to control the amplifier gains. The outputs are sampled using a 10-bit successive approximation ADC by interleaving the chemical and optical image data.

A. Magnetic Pattern Generator

This is based on a 64×10-bit rolling buffer that cycles a 10-bit instruction onto the magnetic controller. The 10-bit instruction is defined as follows: bits 9-7 = x-coordinate, bits 6-4 = y-coordinate, bit 3 = polarity and bits 2-0 = magnitude. The current is first generated using a 3-bit DAC (based on a binary-weighted current mirror) and the polarity can then be reversed using an H-bridge configuration. The coordinate bits are then used to control two demultiplexers (for X and Y) that current steer the stimulus towards the active pixel.

1) Micro-coil: The manipulation of micro-beads is achieved by employing a magnetic trapping force [5]:

$$\vec{F} = \frac{V\chi}{\mu_0} \cdot \vec{\nabla}|B|^2 \tag{1}$$

where, V and χ are the volume and magnetic susceptibility of the micro-bead, μ_0 is the magnetic permeability in vacuum and B is the magnetic field generated by the micro-coil.

B. Sensor array

A timing generator defines the phases and array control signals to poll through the sensor array. The chemical sensors are sampled during the second half clock period and the optical sensors are sampled during the first half clock period. Simulated results are reported in [6].

1) Chemical sensor: This is based on the PG-ISFET [7] chemical sensor that is biased using a unity-gain buffer at pixel level. The outputs are switched into a shared column bus, selected at the column header and buffered through a programmable gain amplifier for data acquisition. The control gate input is fed from a DAC that is driven by a lookup table.

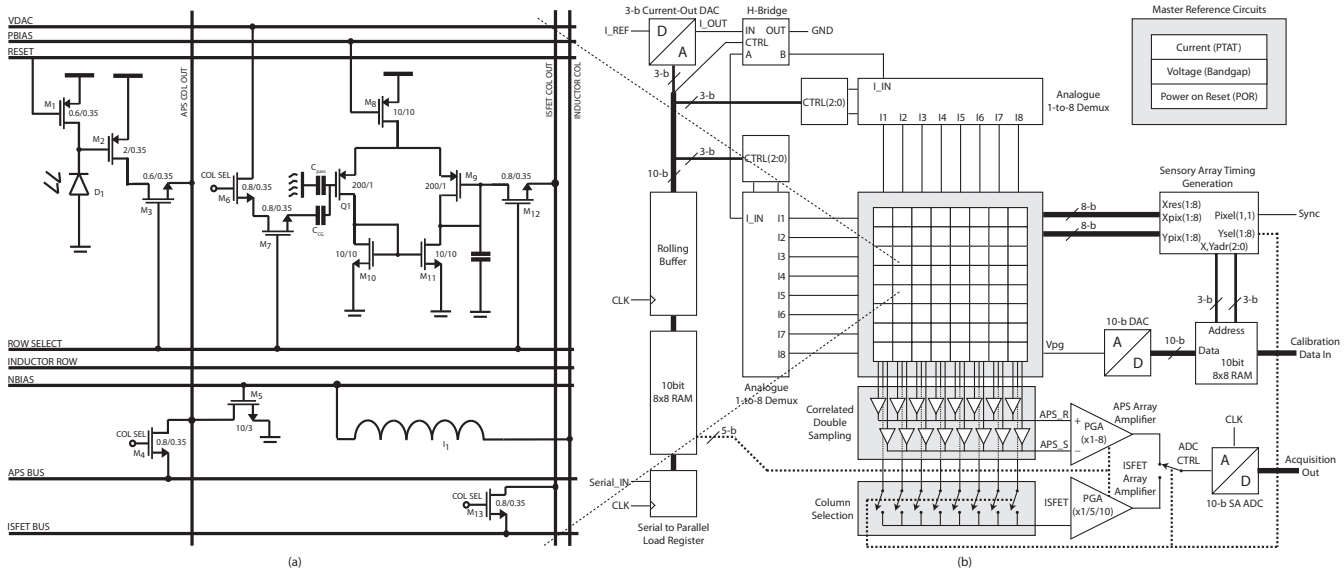

Fig. 1. Sytem overview: (a) a schematic of the integrated pixel (left) and (b) a top level architecture of the system (right)

When the PG-ISFET is biased, ions in solution bind to the passivation surface, causing an accumulation of charge which creates a pH dependence according to:

$$V_G' = V_{ref} - V_{tc} - \gamma + \frac{2.3\alpha kT}{q} pH \tag{2}$$

whereby V_{tc} is the non-ideal effects of trapped charge and pixel mismatch, V_{ref} is the bias voltage of the reference electrode, U_t is the thermal voltage of the device, γ is a grouping of non-chemically related potentials and α is a number ranging from 0-1, describing the reduction in sensitivity from the Nernstian response, typically 59mV/pH [8].

2) Optical sensor: This implements a standard active pixel sensor utilising a standard 3-transistor pixel. The photodiode is based on a n-well/p-substrate parasitic pn-junction of dimension 16μm$\times$36μm. The shared column bus lines are fed into column-level correlated double sampling buffers and differential signal switched into a difference amplifier.

III. Fabricated Platform

The platform shown in Fig. 2 was fabricated in a commercially available 0.35μm CMOS technology. Using a four-metal layer process, a multi-layer spiral micro-coil with 5 turns was implemented. A split padring was implemented to achieve an isolated power supply for the analogue and digital sections. This allows for planar manipulation of the sensing surface, which is crucial for encapsulating the system [9].

IV. Test Platform

A. Instrumentation

The test platform shown in Fig. 3 was developed for programming and acquiring data from the lab-on-chip. Action routines are executed by a microcontroller, based on commands sent via a standard UART interface from MATLAB.

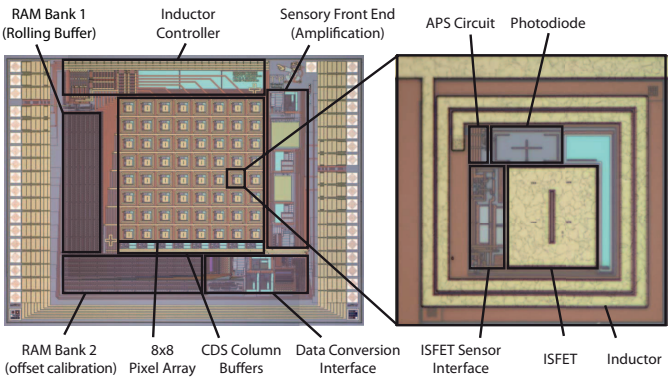

Fig. 2. Microphotograph and overlaid floorplan of: (a) complete system (left) and (b) multimodal pixel (right).

An auxiliary catridge was fabricated to providing a platform for fluidic assays to be conducted on. The chip was encapsulated using glob-top resin and the cartridge was interfaced to the development board. A 2ml fluidic well was fabricated and adhered to the catridge using epoxy resin. An external Ag/AgCl reference electrode was also grounded on the PCB.

B. User Interface

A MATLAB-based GUI was developed for sensor calibration, real time visualisation of optical and chemical images, and for programming a magnetic field pattern.

1) Magnetic Field Pattern Programming: A GUI was developed for programming the magnetic field pattern, whereby the user specifies the polarity and magnitude of the biasing current through each pixel of interest. The current drawn through each micro-coil during RAM playback can be simulated in a 3D plot to visualise regions of peak magnetic field strength. The data is then encoded into a 64$\times$10-bit instruction set and clocked into the lab-on-chip via the microcontroller.

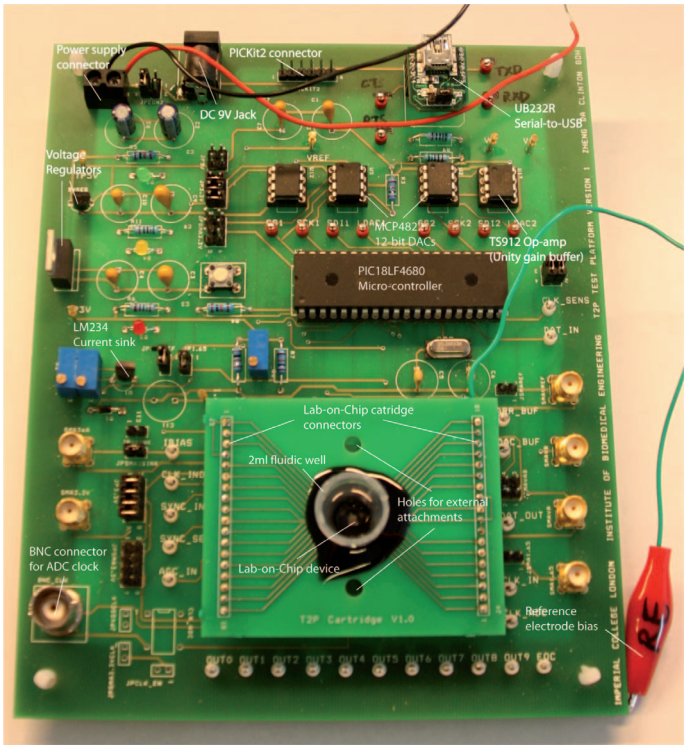

Fig. 3. Development board consisting of a microcontroller and peripheral components, interfaced to the lab-on-chip cartridge for fluidic assays.

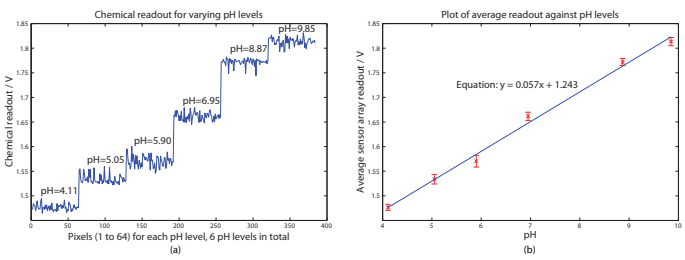

Fig. 5. Chemical readouts for varying pH levels. (a) Recordings from all pixels for each pH level (left) and (b) an averaged array readout for varying pH levels (right). Data is shown as the mean ± standard deviation

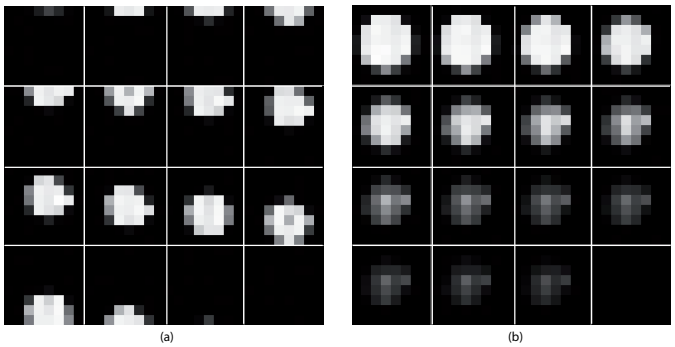

Fig. 6. Optical images of a light stimulus on the chip surface: (a) Left to right translation (left) and (b) varying illumination intensity (right).

2) Sensor Calibration: A gradient based algorithm was implemented to calibrate the PG-ISFET array. The algorithm optimises the control gate vector through a negative feedback system which adjusts the bias of each pixel based on the difference between the operating point and actual readout.

3) Real Time Data Acquisition: This was achieved by polling the sensor array with the microcontroller. Each end-of-conversion pulse triggers the sampling of a 10-bit output which is ordered and stored in memory. Stored bits are streamed to MATLAB after data from each frame is acquired and displayed in the GUI shown in Fig. 4. The cycle is repeated to achieve real time optical sensing and pH detection. A USB microscope was also used to monitor the lab-on-chip.

Software routines were also developed to allow the user to bias the micro-coil of a pixel during real time data acquisition. This is done by temporarily pausing the data acquisition process, clocking the relevant instruction bits into the lab-on-chip and then resuming data acquisition. Through the GUI, real time micro-scale manipulation of micro-beads and simulaneous opto-chemical sensing is achieved.

V. Measured Results

A. Sensor Calibration and pH Sensitivity

The calibration algorithm biases the PG-ISFET array at mid-supply voltage of 1.65V with a pH 7 buffer solution, where it demonstrated a fast rate of convergence (≈500ms per iteration) and a convergence accuracy of 45mV (2% pixel-to-pixel variation) on a gain of 10.

Solutions of varying pH were used to evaluate the pH sensitivity of the lab-on-chip. The device was first calibrated and the chemical readout was recorded with solutions of known pH. In all experiments, an Ag/AgCl reference electrode was used to maintain the fluid potential at 0V. Fig 5 shows the system response to varying pH levels. The system demonstrated a chemical sensitivity of 57mV/pH on a gain of 10, which is very close to the Nernstian sensitivity of 59mV/pH [8].

B. Optical Detection

A spot of light was focused onto the chip surface with varying intensity and at different locations across the chip. Fig. 6 shows the real time system response to a translation in optical stimulus as well as varying stimulus intensity.

C. Magnetic Bead Manipulation

Magnetic micro-bead movement is achieved by biasing individual microcoils with a current of -20mA as shown in Fig 7. The period of the current pulse is 3s with a duty cycle of 50%, and the total time required to move beads to the biased pixel was approximately 180 seconds.

VI. Conclusion

This paper has presented the design, fabrication and characterisation of a novel lab-on-chip array combining real time opto-chemical sensing and magnetic field generation for micro-scale magnetic manipulation. It is the first lab-on-chip device which integrates multiple sensing and actuation modalities on a single platform.

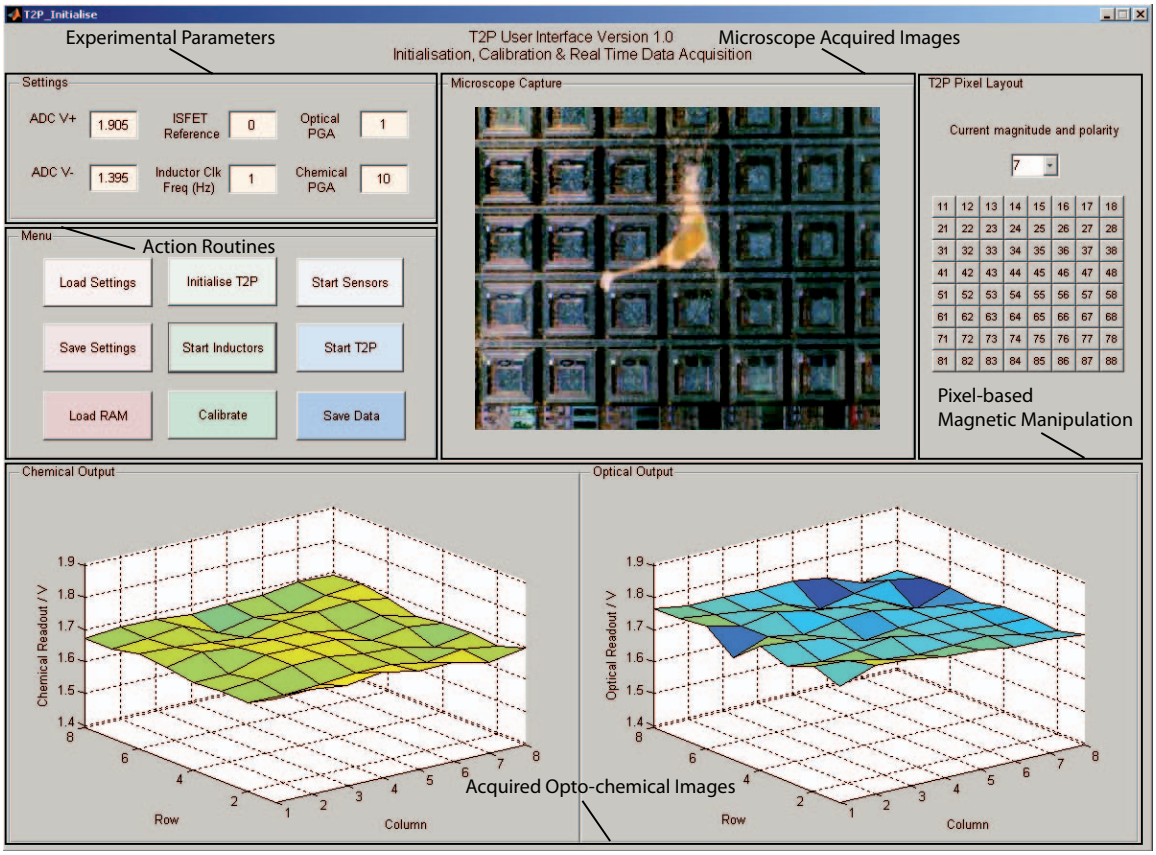

Fig. 4. Graphical user interface for experimental set up and data acquisition.

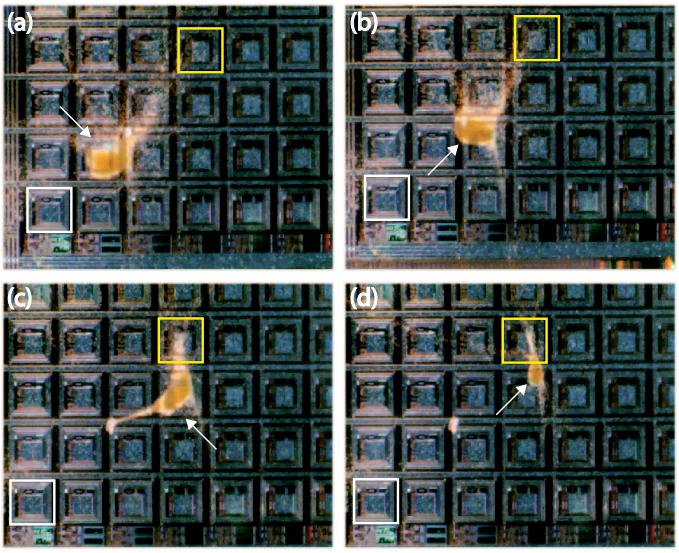

Fig. 7. Magnetic micro-beads (indicated by the arrow) move towards the biased pixel (boxed in yellow). Pixel (8,8) is boxed in white to provide a reference point.

The system demonstrated high pH sensitivity and optical detectability in real time, as well as fast and accurate sensor calibration which eliminates sensor non-idealities such as device mismatch. The motion of micro-beads was also controlled by a user configurable magnetic field pattern. Fabricated in unmodified CMOS, the chip can be combined with microfluidic platforms for applications such as cell manipulation, DNA hybridisation detection as well as for reaction monitoring.

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