Micro/Nanoparticle Detection: An Impedimetric Microsensor Based on CMOS Technology

Zhao Lu, S*tudent Member, IEEE,* Ryan Denomme*, Student Member, IEEE,* Sylvain Martel*, *Senior Member, IEEE*

***Abstract*— This paper proposes a microsensor designed for the detection of a single particle. The complete system, comprised of a sensing microelectrode array, a microelectronic circuit and a microfluidic device, is implemented on a conventional complementary metal oxide semiconductor (CMOS) chip. To establish a Lab-on-Chip system intended for detecting particles by impedance measurement, the microelectrode array is constructed with multiple metal and via layers by a standard 0.18µm CMOS process. The impedance variations caused by the presence of a particle are detected by a sensing circuit connected with microelectrodes on the same substrate. The system structure and post-processing of the CMOS chip are presented. The finite element method (FEM) simulation and preliminary experiments completed thus far have proved that identifying a single cell or particle is feasible with the system described here. Also presented are some potential micro and nanoscale applications of this chip that go beyond single particle detection that could be investigated in the future.**

***Index Terms*— Microsensor, CMOS, Impedimetry, micro/nanoparticle.**

I. INTRODUCTION

Detection of single particles rather than a large concentration of particles is of great importance in food-borne disease control, biological analysis, and pharmaceutical research. Flow cytometry [1], the most widely adopted technology for this type of task, is based on fluorescent reaction when the targeted particles pass through the detecting area. Confined by its complication of the required light source and detector, parallel detection is very difficult to achieve. Further more, the targeted particles or cells have to be prepared, generally by coating them with a fluorescent label, before the detection. This not only limits the application of this technology, but also increases the overall detection time. Another particle detection and analysis technology is based on electrochemical sensors [2, 3], also referred to as amperometric or impedimetric sensors. These sensors detect changes in the electrical characteristics of the medium containing the bacterial culture or targeted particles. Although these types of sensors offer advantages such as high sensitivity, low cost and ease of integration onto a MEMS/NEMS device, long detection times (usually a 12 hour to 7 day process) are expected. The long detection time is due to the fact that most bacteria and particles are not motile, and the diffusion rate of the bacteria and particles is very slow; especially under low Reynolds number laminar conditions.

In our previous paper, a new class of biosensors based on magnetotactic bacteria (MTB) [4-6] aimed at detecting pathogenic bacteria with shorter detection periods and specificity was presented. Here, a new type of microsensor utilizing the MTB is presented. Instead of implementing the planar microelectrodes on the top of the CMOS chip [7], face to face microelectrode pairs are constructed by the metal and via layers of the CMOS structure. Only a two-step post processing procedure is required to release the microelectrodes after obtaining the raw die from the foundry company. With the proposed structure, this sensing platform offers several advantages. First, the high compatibility of the CMOS technology allows the integration of numerous microelectrode pairs, allowing simultaneous detection to be achieved. This will greatly decrease the detection time required for a given sample and will increase detection sensitivity. Second, with the assistance of MTB, active detection can be realized by bringing the targeted cell or microparticles to the microelectrodes, thus avoiding the long waiting time for the diffusion of cells or particles to the detection area. Third, the highly reconfigurable microelectronic circuit can realize the function of simultaneously detecting different cells or particles on the same platform. Moreover, combining the conventional CMOS technology with the simple post processing procedure ensures the low cost and high yield of this sensor. In this paper, the design and simulation of an impedance sensing platform based on CMOS processes are discussed. Then, the design and fabrication of planar microelectrodes used to verify the concept of detecting single cells or microparticles by impedance measurement are introduced. Preliminary experimental results indicate that a microbead, 10µm in diameter, can be detected by measuring the variations of impedance between a pair of fabricated planar electrodes.

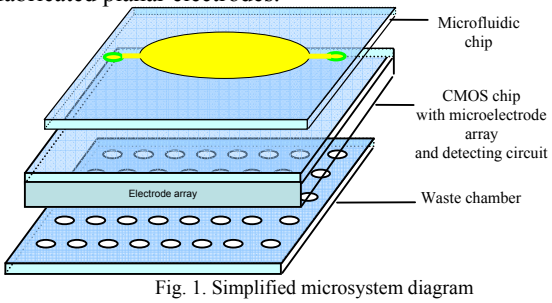

Fig. 1. Simplified microsystem diagram

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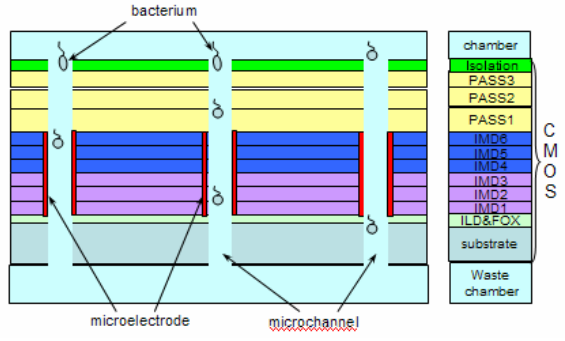
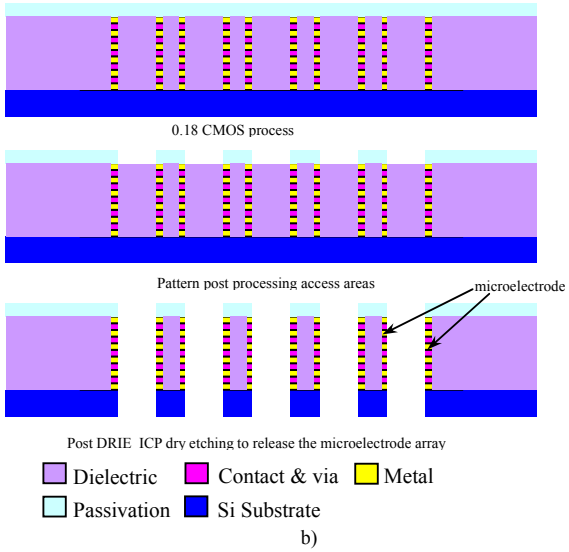
II. METHODOLOGY, MATERIALS AND FABRICATION

The main structure of the microsystem will be comprised of two microchips. Illustrated in Fig. 1, the microfluidic microchip, which is made of polydimethylsiloxane (PDMS) [8], provides outlets, microchambers and microchannels for the injection of aqueous medium containing the targeted cells or particles. Meanwhile, the dielectric property of PDMS also helps to insulate the surrounding bonding pads and wires from the liquid samples. The microelectrode pairs and connected sensing circuits will be implemented onto a CMOS chip fabricated using 0.18μm CMOS technology. On the CMOS chip, metal layers and via in between are used to construct the electrode array in the sensing area, as depicted in Fig. 2 (a). Six layers of metal and five layers of via are stacked together to construct pairs of microelectrodes with a thickness of 8μm. Each microelectrode pair is isolated by a layer of dielectric material, which is silicon oxide in this case. For each pair of microelectrodes, the dielectric material will be etched off and a microchannel will be formed to allow cells or microparticles to pass between the microelectrodes.

Post processing using DRIE-ICP dry etching technology [9] will be utilized to remove the dielectric material from between the microelectrodes. The top passivation layer is patterned with windows using a mask for the DRIE-ICP etching procedure. Extra photo mask and complicated alignment procedures can be avoided. This dry etching procedure involves two steps. Firstly, the silicon-oxide will be removed from in between the microelectrodes. Secondly, the silicon substrate will be etched through to create channels to allow the liquid sample to flow through the microchannel between the pairs of microelectrodes. Fig. 2(b) illustrates the micrograph of the CMOS microchip before and after the post micromachining processing. Connected circuits for measuring the impedance and for signal amplification are implemented around the sensing area. To minimize the potential background electric noise, reference microelectrodes are also implemented on the same substrate. By carefully matching the layout and the connection of the reference and detection electrodes, better resolution can be achieved. By continuously measuring the impedance signal between the electrodes, this sensor can detect whether a cell or particle is passing through the microchannel. The number of the targeted cells or particles can be recorded, and their characteristics, such as diameter, composition, or variability can also be analyzed.



a)



b)

Fig. 2. a) the schematic of sensors and related CMOS layers, b) CMOS chip before and after post micromachining processing.

III. SIMULATION

Finite Element Method (FEM) simulation is chosen to model the proposed microsensor. The purpose of developing a simulation of the microsensor is to verify the feasibility of detecting a single bacterium or particle and to investigate the sensitivity threshold of numerous different microsensor designs without having to spend time and money to fabricate each different design and experimentally investigate their sensitivity. The simulation uses polymer microbeads to investigate the affect of microchannel and electrode geometry, object size, and object position on sensitivity. These results will be used to optimize the sensor and to compare to experimental results.

The orientation of the microelectrodes will affect the detection sensitivity. The electrodes are modeled in two different orientations: planar and face to face. The planar electrodes are placed side by side on the bottom of the microchannel, with a center to center separation of 35 μm. For the face to face electrodes, one is placed on top of the channel and the other on the bottom of the channel (separation of 20 μm). Polymer microbeads with diameters from 2 μm to 15 μm are placed in the center of the sensing region for both electrode orientations to investigate the difference in sensitivity between the two orientations over a range of microbead sizes. Shown in Fig. 3(a) and Fig. 3(b) are images from the FEM simulation showing the face to face and planar electrode models.

The ability of the microsensor to detect very small objects, such as a single pathogenic bacterium, and its ability to differentiate between objects of similar size is very important. Beads with diameters from 2 μm to 6 μm were placed into the channel and the relative impedance change was calculated to determine sensors ability to detect small objects and objects of similar size. Results are shown in Fig. 4.

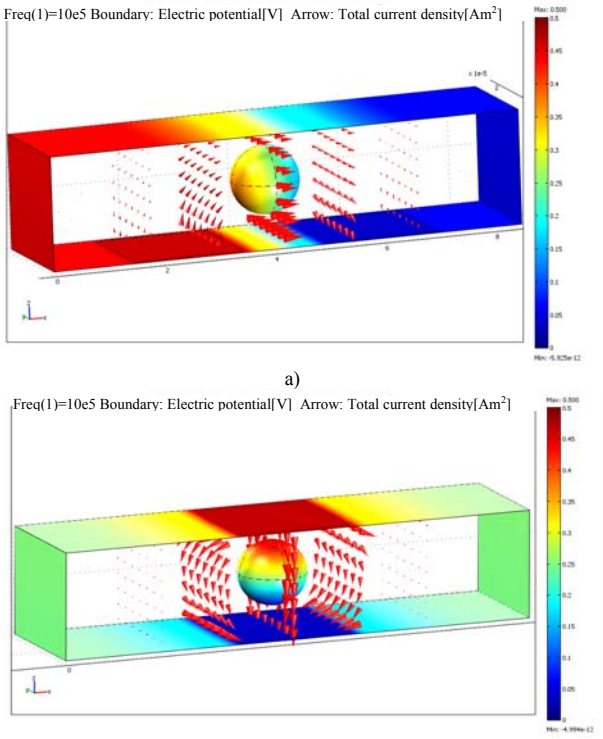


Fig. 3. FEM simulation image of the microchannel with a) planar electrodes and (b) face to face electrodes, and a 12 µm polymer bead situated in the center of the sensing region. Applied potential is 0.5 V at a frequency of 1 MHz.

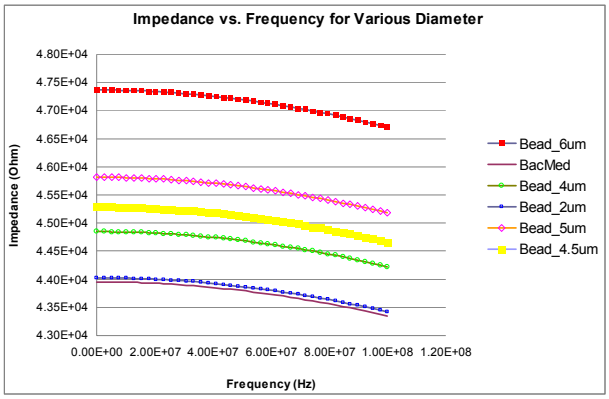


Fig. 4. Simulation results of the impedance of microbeads of different radii over a range of frequencies. The reference solution is the bacteria medium (BacMed).

The results of the optimization simulations have shown that adequate sensitivity can be achieved by using face to face electrodes with a separation of 20 µm in a channel with maximum dimensions of 20 µm x 20 µm (W x H). The simulations also showed that the highest level of sensitivity will be obtained if the impedance measurements are recorded when the micro-object is in the center of the sensing region and close to the source electrodes. Simulated impedance results for microbeads of varying radii obtained from this model are shown in Fig. 4.

IV. Experimental Results and Discussion

For the actual experiment, dedicated planar microelectrodes (size of 20µm × 20µm) are fabricated on microscope slides with standard lift-off technique and then bonded with the microfluidic device made of PDMS. The pictures of the microelectrodes taken from an optical microscope are shown in Fig. 5. An impedance analyzer (Agilent 4294A) is used to record impedance variations as particles move into the electrode sensing regions. The impedance results from preliminary experiments using the impedance analyzer are shown in Fig. 6 for a melamine bead of 10 µm in diameter.

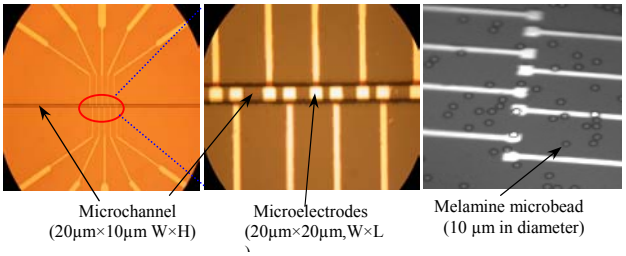


Fig. 5. Optical microscopy images of the fabricated planar microelectrodes and microbeads for proof of concept experiments.

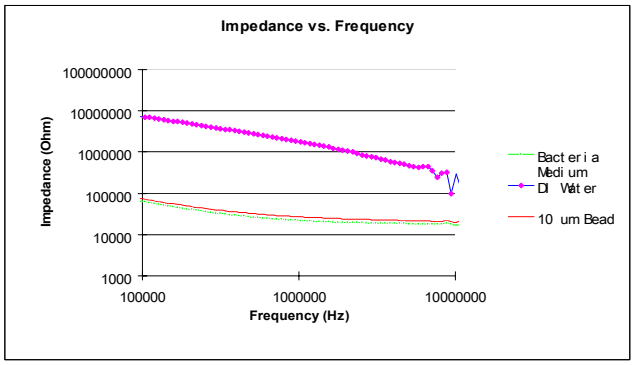


Fig. 6. Experimental results showing the impedance signals of de-ionized water, bacteria medium, and a 10 µm melamine bead in the bacteria solution over the signal range 0.1 MHz to 10 MHz..

Simulation and preliminary experimental results have demonstrated that planar microelectrodes can differentiate the size variation of microparticles and cells within minutes by measuring the impedance signal variation. The advantage of using CMOS technology is that a high density of electrodes with face to face geometry can be easily achieved with a relatively simple post-processing procedure. The CMOS chip will therefore allow for higher sensitivity, faster detection times, and total device integration. The whole system, including related circuits, can be integrated onto a single chip.

This CMOS based microsensor could not only be used for the fast detection of bacteria or particles, but in numerous other applications involving interactions and properties at the nanoscale. For example, sensing the binding efficiency of

nanoparticles, such as antibodies or bacterial phages, on the surface of microbeads or bacteria could be achieved with this chip. This would be achieved by mixing antibodies/phages with microbeads or bacteria in the microfluidic chamber, then allowing the solution to flow through the detection channels, where the impedance signal would be continuously recorded. A different signal would be observed for a microbead or bacteria that had successfully been tagged by the antibody or phage, allowing the binding efficiency to be determined. It could also be used for investigation into the electrical properties of very thin cell membranes that contain numerous protein and ion channels. The electrical properties of these membranes change depending on the conditions inside the cell; a healthy cell, a dead cell, and a cancerous cell will all exhibit differences in their membrane properties. This chip could be used for single cell investigate into the differences in the electrical properties of such cell membranes by measuring the electrical signal across the pairs of microelectrodes as the cells pass through. Furthermore, this system could be used to characterize the electrical properties (conductivity, resistance, etc.) of particles that are coated with a layer of metal or insulator of a few nanometers thick. This would be achieved simply by coating the particles with the desired coating material and thickness and running a small sample through the microchannels while monitoring the electronic signal. This would allow for accurate and timely characterization of the coating without having to use a large amount of the sample.

V. Acknowledgement

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