A CMOS Lab-On-A-Chip For Neuron Monitoring And Stimulation

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ABSTRACT

A lab-on-a-chip is presented in this paper including the results from a fabricated micro-fluidic chip that includes a novel sensor, titled as Differential Electric Field Effect Transistor (DeFET). DeFET is a novel CMOS electric field sensor and it was fabricated based on a standard 0.18-µm Taiwan Semiconductor Manufacturing Company (TSMC) CMOS technology. The proposed lab-on-a-chip can sense and characterize the neuron's action potential with high accuracy and in real time. Experimental results of the proposed lab-on-a-chip are presented and discussed.

Keywords: lab-on-a-chip, DeFET sensor, neurons, CMOS technology, electric field, biological cells, integrated sensors.

1 INTRODUCTION

Neurons are biological cells specialized in transmission and processing of information [1]. The elementary neural signals are action potentials, which are transient changes of the voltage drop across the cell membrane with a typical shape. The related peak-to-peak amplitudes of this transmembrane voltage approximately amount to 70 mV. The human brain contains a large number of neurons (in the 10's of billions) and about 1000 times as many synaptic connections. Today's standard tools used to characterize this parameter are patch pipettes [2] or microelectrodes [3, 4]. These tools have led to great achievements in the field of neural cell monitoring. However, these techniques suffer from drawbacks, such as they require an elaborate mechanical setup, which allows monitoring very few cells in parallel only. Thus, they are generally not suitable to fulfill high-throughput requirements. Also, long-term recording is restricted, due to the invasive type of contact, reducing the life time of the cell. Recently, extracellular, and therefore, noninvasive, recording techniques open a way to circumvent these drawbacks [5, 6]. The noninvasive recording is based on the fact that the action potentials to be considered correspond to sodium and potassium ion currents through ion channels in the cell membrane [1]. Consequently, the idea behind these approaches is to monitor these ion currents instead of the transmembrane voltage.

For extracellular recordings, cells are cultured directly on top of a transducing element, which is generally either a metallic electrode or an open-gate transistor [5, 6]. When an action potential occurs in a cell, the local flow of ions in and out of the cell causes the membrane to become nonuniformly polarized [23]. The ionic current flows across the cleft resistance and establishes an electric field which induces electrical charge in the underlying transducer, which is the recorded signal. The approaches presented in the literature use single transistor detectors which have very low sensitivity and low signal to noise ratio [5, 6].

On the other habd, Lab-on-a-chip is a device that integrates one or several laboratory functions on a single chip of only millimeters in size [7- 18]. Lab-on-a-chip deals with extremely small fluid volumes (Pico liters). Lab-on-a-chip brings many advantages and promises to the science and industry, such as spatial resolution, portability and disposability [4].

In this paper, a developed lab-on-a-chip based on Differential Electric-Field-Sensitive-Field Effect Transistor (DeFET) sensor is used [11, 14]. This lab-on-a-chip overcomes the signal attenuation and high noise challenges accompined with neuronal activity detection. The rest of the paper is orgainized as follows:

Part 2 provides brief summary about the DeFET sensor and its baic of operation. Par 3 shows the construction of the proposed lab-on-a-chipp which is used to detect the neuronal activities. The experimental results are provided at part 4. Part 5 concludes the paper.

2 DEFET'S THEORY

The DeFET consists of two complementary eFETs, one of them is a P eFET type and the second is an N eFET type [15, 16]. The eFET structure is shown in Figure 1. The equivalent circuit of the DeFET is shown in Figure 2. From Figure 2, the two gates of P eFET and N eFET are connected with each other, and there is a cross coupling between the two drains of the P eFET and the N eFET. The output current IOut is equal to the difference between the two drain currents Ip-In (i.e. $I_{Out} = I_p - I_n$, see Figure2). On the other hand, I_p and I_n are functions of the two applied gate voltages Vin1 and V_{in2}, respectively. The DeFET is designed to achieve an output voltage V_{Out}, directly related to the difference between the two applied gate voltages (V_{in1}-V_{in2}), and V_{in1}-V_{in2} is equal to the applied electric field above the two gates (E) multiplied by the distance between them (V_{in1}-V_{in2}/d = E), where d is the distance between the two split gates, which is constant. So, V_{Out} is related directly to the intensity of the applied nonuniform electric field. Thus by measuring V_{Out} we can detect the intensity of the nonuniform electric field to be as follows [1]:

$$V_{out} = g_m \, d \, R_L \, E + V_{Uni} \qquad (1)$$

Equation (1) shows a liner relationship between the DeFET's output voltage and the intensity of the applied electric field.

3 THE PROPOSED LAB-ON-A-CHIP

The Block diagram of the lab-on-a-chip system is shown in Figure 3. The CMOS Microsystem Board consists of: (a) Oscillator: can produce a square waveform with different frequencies (from 1M to 10 MHz) [19]. (b) Filter: filters the oscillator's output to provide a Sine wave which is required for the actuation part. (c) Phase shifter: it's an Op-Amp inverting configuration with a closed loop gain of -1 or less, it can change the input phase by 180°with a controllable gain. (d) Selection part: this part is composed of 8 switches, its inputs are the sine waves coming from the filter and the phase shifter, and it can distribute these signals as required to the inputs of the quadrupole electrodes. (5) Decoder: a 4-bit counter fed by a clock with a certain frequency, by which the multiplexer is controlled to scan the DeFET sensors continuously. (6) Level Shifter: used to adjust the output level of the counter from 5V to 1.8V to make it suitable for the multiplexer which is designed to work with 1.8 V. (7) LabView: is a development environment and platform for a visual programming language from National Instruments. Figure 4 shows a schematic block diagram of the proposed PCB that includes the lab-on-a-chip and the other conditioning, amplifying and control parts. The lab-on-a-chip is based on standard CMOS 0.18µm technology. It contains two main parts; they are the stimulation and the sensing parts. A Quadrupole electrode can be used to stimulate the neurons. For the action potential sensing, the DeFET sensor is used. Figure 4 shows a picture of the PCB. The proposed chip contained an array of DeFET sensors, as shown in Figure 4.

4 EXPERIEMENTAL RESULTS

4.1 Testing the DeFET sensor

The proposed DeFET is implemented in the standard CMOS 0.18-µm technology. Figure 4 shows a microscopic picture of the DeFET sensors and the electrodes used to apply the required electric-field pattern. To test experimentally the DC response of the DeFET, a DC voltage with different values,signs and different configuration have been applied to the four electrodes surrounding the DeFET sensors, hence, varying the magnitude and sign of the applied electric field (E) [. At the output, the output voltage associated with each value of the measured electric field above the gates are measured and compared with the simulation results, i.e., Specter's circuit Simulator. The result is shown in Figure 5, from which a good agreement between the experimental and the simulation results can be observed. Also, we can observe that the sensitivity of the DeFET, which is the slope of the line shown in Figure 5, is about 51.7mV/ (V/µm).

4.2 Testing the Lab-on-a-chip with Neuron

Snail neuron was stimulated chemically and the action potential was measured using the DeFET sensors. Figure 6 shows the experimental setup for testing the lab-on-a-chip. Figure 7 shows the lab-on-a-chip and a snail neuron situated above it. Figure 8 shows the oscilloscopic measured response of the DeFET sensor as a measure of the action potential of the stimulated neuron. The DeFET sensor shows a high sensitivity, which is suitable to detect the action potential. Also, the noise rejection is improved because of the higher common-mode rejection ratio of the DeFET sensor [16].

5 CONCLUSION

An integrated lab-on-a-chip based on DeFET sensors has been proposed. It's based on CMOS 0.18µm TSMC technology. The proposed lab-on-a-chip can invasively and sense the neuronal activities. Experimental results are provided to profe the principle operation of the lab-on-a-chip.

ACKNOWLEDGEMENT

This research was partially funded by Zewail City of Science and Technology, AUC, the STDF, Intel, Mentor Graphics, and MCIT.

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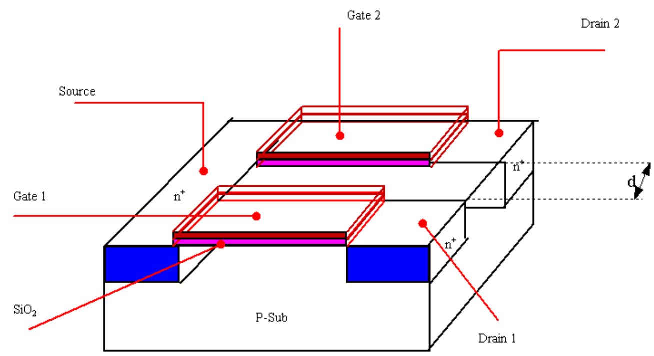

Figure 1 Physical structure of an eFET [14]

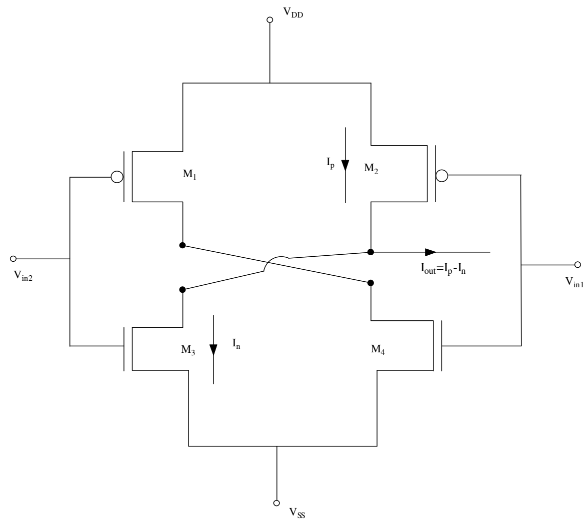

Figure 2 An equivalent circuit of a DeFET [14]

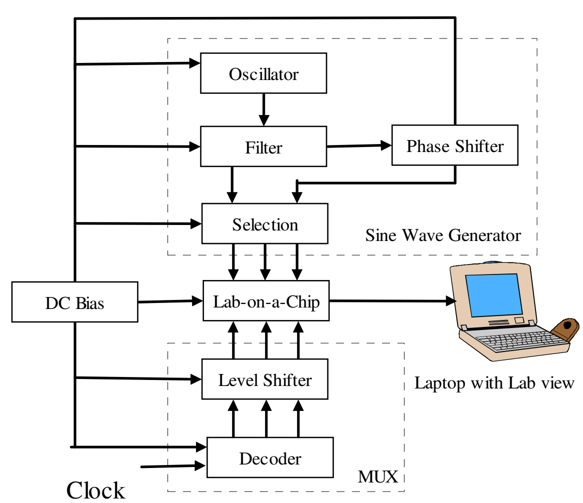

Figure 3 Lab-on-a-Chip board block diagram [19]

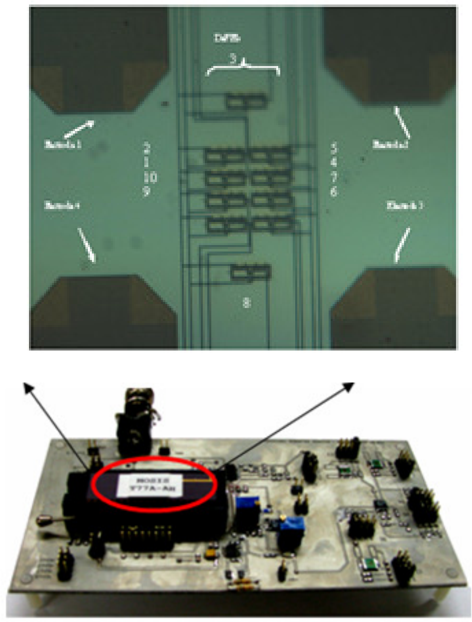

Figure 4 Top: The microscopic picture of the CMOS Die (die size is 0.7mm x 0.6mm)
Bottom: proposed lab-on-a-chip PCB [19]

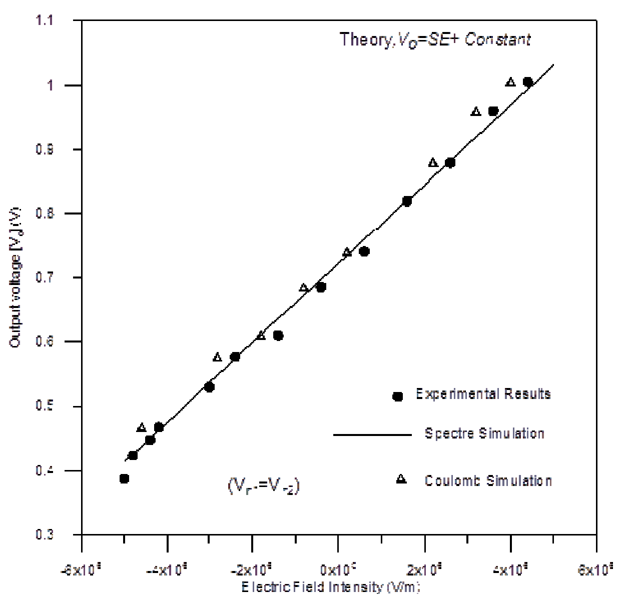

Figure 5 The measured results of the DeFET sensor [16]

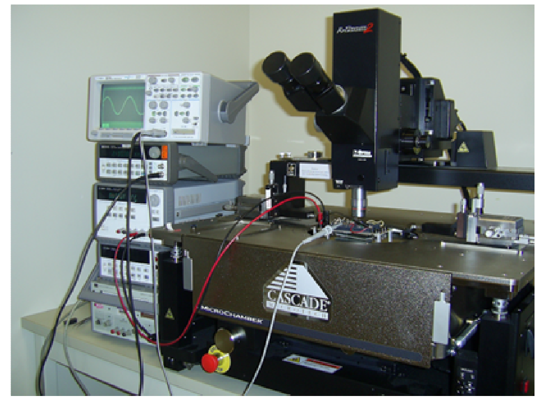

Figure 6 Equipment used to experimentally test the lab-on-a-chip

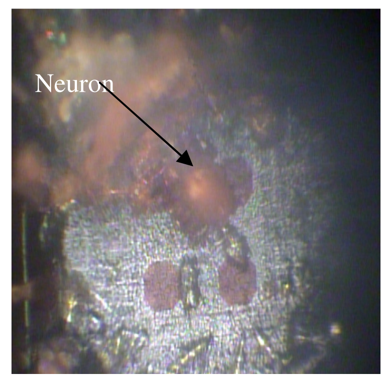

Figure 7 Neuron situated above the chip

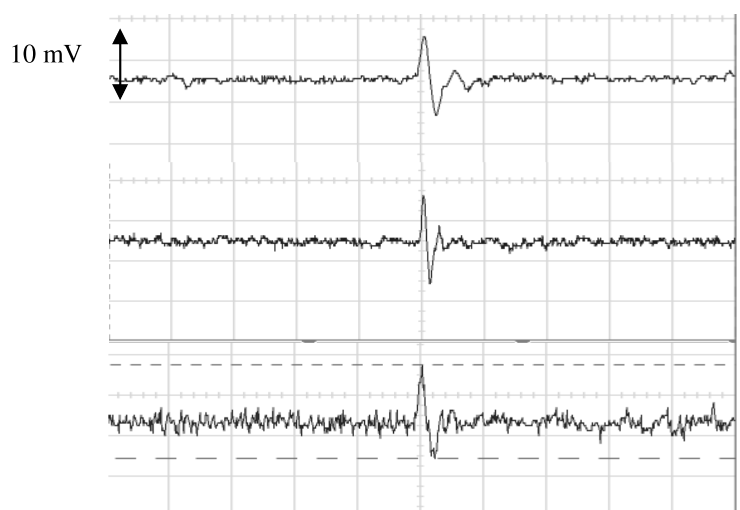

Figure 8 Different sensor readings of the stimulated neuron's action potential (demonstrating a response amplitude greater than 10mV without any amplification circuitry)

NSTI-Nanotech 2014, www.nsti.org, ISBN 978-1-4822-5827-1 Vol. 2, 2014