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Heterogeneously integrated impedance measuring system with disposable thin-film electrodes

Hanbin Ma, Jiahao Li, Xiang Cheng, Arokia Nathan*

Electrical Division, Engineering Department, University of Cambridge, 9 JJ Thomson Avenue, Cambridge CB3 0FA, UK

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ABSTRACT

We propose a novel integrated impedance measurement system with disposable thin-film electrodes. Most modern CMOS-based biosensors use on-chip electrodes to interface between the electronics and biosamples, which forces disposal of the CMOS chip after a few measurements, since most biological reactions are non-reversible. The sensor performance is also limited by the design of on-chip electrodes due to the physical dimensions and the CMOS design rules restrictions. In this work, we extract the electrodes from the silicon chip for relocation onto a low-cost, disposable substrate. This enables reusability of the high-performance CMOS chip, at the same time providing a low-cost route for manufacture of the active thin-film electrodes using large-area processing. The use of disposable thin-film chip also enables customised designed electrodes for different applications, such as extra high sensitivity concentration sensors. In this work, DNA concentration measurements are performed, and it shows a doubling of sensitivity over the previously reported system.

1. Introduction

Recent development of biosensing systems is being pushed towards high sensitivity, portability and low cost. For example, emerging technologies are enabling fluorescence-based detection to achieve high sensitivity and selectivity [1,2], and advanced luminescence assay can be specifically designed to fit different applications [3]. However, such performance requirements may not be necessary for most point-of-care (PoC) [4] and fast diagnostic applications where low cost and ease of operation are key design considerations. Indeed biosensors with compact and miniaturised design and moderate detection performance are potentially favourable candidates.

Electrochemical sensors, which detect and measure electrical signals instead of the fluorescence output in optical sensors, provides a label-free and rapid solution for biological detection [4,5]. They are now widely applied in detection of biomolecules from the macro to micro scale, such as cells [6], proteins [7] and DNA [8,9]. By taking advantage of CMOS technology, the performance of modern electrochemical sensors is significantly enhanced. High-performance systems can be integrated into a monolithic silicon chip, which is fast, low-cost and accurate. A variety of electrochemical methods based on CMOS chips have been developed. These include capacitance-based sensors [10], ion-sensitive field-effect transistor-based sensors [11,12] and impedance-based sensors [13,14]. Impedance measurement, which shows great promise for studying both the electrode-electrolyte interface and bulk solution, has been gaining popularity for biological sensing in recent years [15]. However, the development of CMOS-based solution for this application is limited by the on-chip electrodes. Most CMOS biosensors employ the top metal to create an electrode array reminiscent of the design principles used in CMOS image sensor arrays.

Unfortunately, top metal in a traditional CMOS process (e.g. copper) is not bio-compatible, thus requiring post-CMOS fabrication process for deposition of additional bio-compatible metal layers on top of the silicon chip. Manickam et al. [14] reported the use of an electroless nickel immersion Au (ENIG) process, which deposits an adhesive nickel layer followed by a gold layer. Apart from the post-CMOS fabrication process, the on-chip electrode surfaces can be difficult to clean, and the residue of previous sample can affect the accuracy of subsequent measurement. This forces the disposal of the CMOS chip after a few measurements, which is not practical due to cost and environmental considerations. In addition, large-size electrodes are desirable in some applications such as cell level analysis [16,17]. Due to the integration of the on-chip electrodes, the cost of the CMOS chip can be significantly increased by increasing the silicon die area.

In this paper, we developed a heterogeneous impedance measurement system with a reusable CMOS chip for signal processing, and an active thin-film electrode disposable system

* Corresponding author. Tel.: +44 01223 748302; fax: +44 01223 748322.
E-mail address: an299@cam.ac.uk (A. Nathan).

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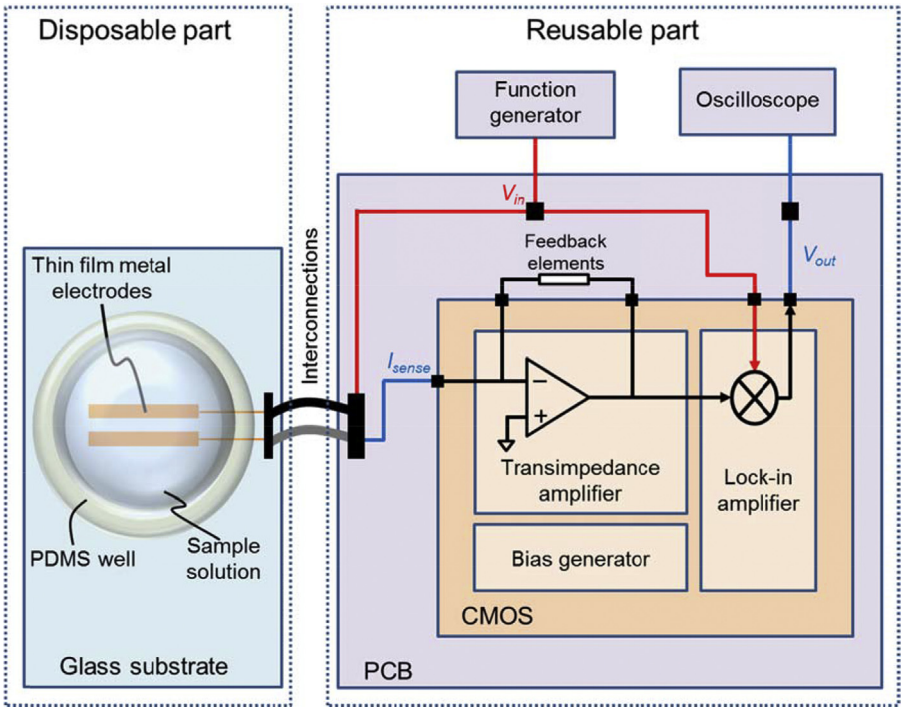

Fig. 1. Schematic of heterogeneously integrated impedance measurement system. The disposable part is thin-film metal electrodes on the glass substrate and reusable part includes a function generator for stimulus, a CMOS chip for signal amplification and processing and an oscilloscope.

as an electronics-biological interface. The disposable chip enables large-area fabrication technologies, which provide great freedom for the selection of electrode materials and electrode configurations. In addition, the design of the electrodes is separated from the CMOS chip, which can be customised for different applications. With the use of disposable electrodes, it can be used as a powerful platform for multifunctional impedance-based measurements. In this paper, the system performance was examined using suspended DNA samples in different concentrations.

2. Materials and methods

2.1. The impedance sensing system

Fig. 1 shows a schematic of the integrated impedance measurement system. The system consists of two parts, including a disposable glass chip and a reusable part. Eight Cr/Au (20 nm/80 nm) double layer metal electrodes were fabricated by a thermal evaporator with a shadow mask on a glass substrate. Both the width of each electrode and the separation between the electrodes are 500 μm. After the metal deposition, the electrodes were then attached to connection pins by silver paste. A 5 mm diameter metal cap was used to cover the centre part of the electrodes. The rest of the glass chip was covered by liquid PDMS to passivate and hold the connection pins. After the PDMS solidified, the cap was removed to leave a 5 mm diameter well on top of the electrodes. This well was used to contain the sample solution during the measurement. The fabrication of the electrode chip is low-cost and highly reproducible. The glass chip is the interface between sensor and the sample, which can be disposed after each measurement.

The impedance measurement chip was designed in a Cadence analogue IC design suite, and the prototype was fabricated using AMS 0.18 μm CMOS process. The design was an extended work to our previous impedance-based CMOS chip, but here sensing electrodes are extracted from the silicon chip on to a disposable glass substrate.

A complete measurement system is shown in Fig. 1. The CMOS chip is mounted on a PCB and connected to a disposable sensor via Dupont wires. The excitation signals applied to the electrodes on a disposable sensor and lock-in amplifier in CMOS chip are provided by dual-channel function generator. The voltage signal from the CMOS IC is further filtered and readout from oscilloscope. A detailed CMOS design plan can be found in Appendix A.

Although commercial ICs for electrochemical impedance measurement are available in the market, they are only suited to sensors with general purpose specifications. Custom-designed ICs provide the needed freedom to circuit designers for more specific requirements given by a certain sensor type.

2.2. System validation

A simple impedance circuit with three discrete elements was built to validate the performance of the impedance chip. As shown in Fig. 2(a) subplot, a 10 kΩ resistor (R_2) in parallel with a 1 nF capacitor (C_1) is connected to a 1 kΩ resistor (R_1). The tolerances of metal film resistors and ceramic capacitor are 10% and 20% respectively. The elements were mounted by the standard soldering technique. Ideal values were used for post-layout simulation by the Cadence Virtuoso software. Measurements with the three-element circuit and CMOS chip were carried out from 100 Hz to 10 MHz.

2.3. Preparation of DNA samples with different concentrations

Herring sperm DNA was ordered from Sigma–Aldrich (D7290). The single-stranded DNA fragments ranged in size from 587 to 831 base pairs. This DNA was provided as a ready-to-use concentrated solution (9–12 mg/ml DNA). According to the supplier's instructions, we boiled the solution for 10 min and then cooled it on ice for another 10 min to reduce the likelihood of re-annealing the fragments. We first diluted 20 μl of the concentrated DNA sample with 180 μl of DI water to prepare the stock solution. The concentration