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Design of fully integrated impedimetric CMOS biosensor for DNA detection

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Abstract

This paper described a label-free and fully integrated impedimetric biosensor using standard Complementary Metal Oxide Semiconductor (CMOS) technology to measure both capacitance and resistance of the electrode-electrolyte interface. Conventional impedance biosensors usually use bulky and expensive instruments to monitor the impedance change. This paper demonstrates a low power, high gain and low cost impedance readout circuit design for detecting the biomolecular interactions of deoxyribonucleic acid (DNA) strands at the electrode surface. The proposed biosensor circuit is composed of a transimpedance amplifier (TIA) with two quadrature phase mixers and finally integrated with 5µm x 5µm microelectrode based on 0.18µm Silterra CMOS technology process with 1.8V supply. The output value of the readout circuit is used to estimate the amplitude and phase of the measured admittance. The developed TIA can achieve a gain of 88.6dB up to a frequency of 50MHz. It also has very good linearity up to 2.7mA and the overall dynamic range is approximately 90dB.

Keywords: CMOS; Biosensor; Impedance; Label-free DNA.

1. Introduction

DNA biosensor is a powerful tool that utilized the DNA hybridization procedures to detect the presence of bacterial and virus diseases through the use of highly conserved DNA sequences [1]. These biological responses can be converted into an electrical, chemical or acoustic signal. However, these rawest form signals are indigestible. Therefore, various detection schemes can be used to extract the relevant information. There are different types of biosensor have been reported. Among the detection methods, optical and electrochemical method is widely implemented. In the most optical based DNA biosensor, the fluorescence-based detection provides an excellent selectivity and sensitivity. However, this system requires the use of high-intensity sources, optical filters and lenses that make this system bulky, expensive and labeling is required. On the contrary, DNA sensors based on electrochemical-based detection is labeling free and can be readily integrated using CMOS technology [2].

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Several studies on electrical detection of biomolecules which are based on the changes in electric double layer properties of the functionalized electrode surface have been proposed. Such systems harness the unique impedance values from biomolecules such as DNA, proteins and other cells. One of the detection methods that based on this principle is capacitive detection methods [3,4]. However, the capacitive sensing does not present enough stable capacitance properties because the electrode-electrolyte interface is not a perfect insulator and thus some ion's conduction is occurring by through the DNA layer and can cause a leakage by discharging the charge on the capacitance [5,6,7]. Therefore, the impedance based biosensor which measure both capacitance and resistance of the electrode-electrolyte interface is desirable as it can to provide a more stable and accurate result if compared to the capacitive detection method. The scope of this paper only focuses on the single pixel analog part readout circuits. The proposed biosensor circuit is composed of a TIA and two quadrature phase mixers. The output value of the readout circuit is used to estimate the amplitude and phase of the measured admittance. The Synopsys HSPICE is used as the simulation tool. The design is characterized at the typical process corner based on 0.18μm Silterra CMOS technology process.

2. Impedance Spectroscopy Detection Method

Electrochemical impedance spectroscopy (EIS) is a widely used to characterize the interaction between molecules and the sensor surface.

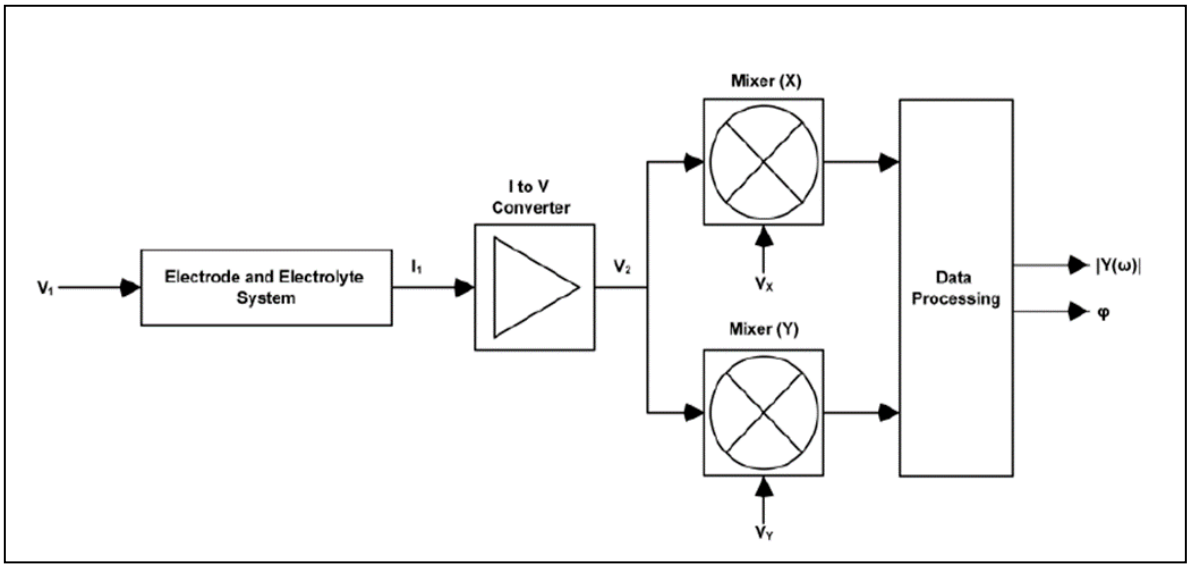

Fig. 1: Impedance detection architecture for impedance measurement.

The conceptual block diagram is shown in Fig. 1. A small signal excitation voltage, V_1 (ω) is applied across the electrode-electrolyte system and the amplitude and the phase of the current that are flowing through the system is measured. The current I_1 (ω) is amplified and converted to V_2 (ω) using a low-noise TIA. The V_2 (ω) is then multiplied by an orthogonal sinusoidal signal (V_X or V_Y) at the frequency ω. Signal Y is a quadrature phase of Signal X. Each pixel produced two DC output i.e. V_X and V_Y which can be used to estimate the amplitude, |Y (ω)| and phase φ, of the admittance using Eq.1 and Eq. 2.

$$|Y(\omega)| \cong K \,.\sqrt{{V_X}^2 + {V_Y}^2} \tag{1}$$

$where\ K = \frac{1}{A|V_1(\omega)|}$ and A= $Transimpedance\ gain$

$$\varphi = \tan^{-1}(\frac{V_X}{V_Y} \tag{2}$$

3. Circuit Implementation and Result

As illustrated in Fig. 2, the single pixel readout circuit consists of TIA and two quadrature phase mixer using 0.18µm Silterra CMOS technology is proposed. The low input impedance TIA is based on a common gate topology with a gain boosting differential amplifier. The conversion gain can be boosted by enhancing the transconductance of M2,g_{M2} without scarifying the signal bandwidth.

The output voltage from TIA is connected to the input of two Gilbert Cell mixer with source degeneration [8]. To avoid the mismatch of the input mixer, V_{ref}, a replica of the TIA is designed and integrated within the single pixel circuit.

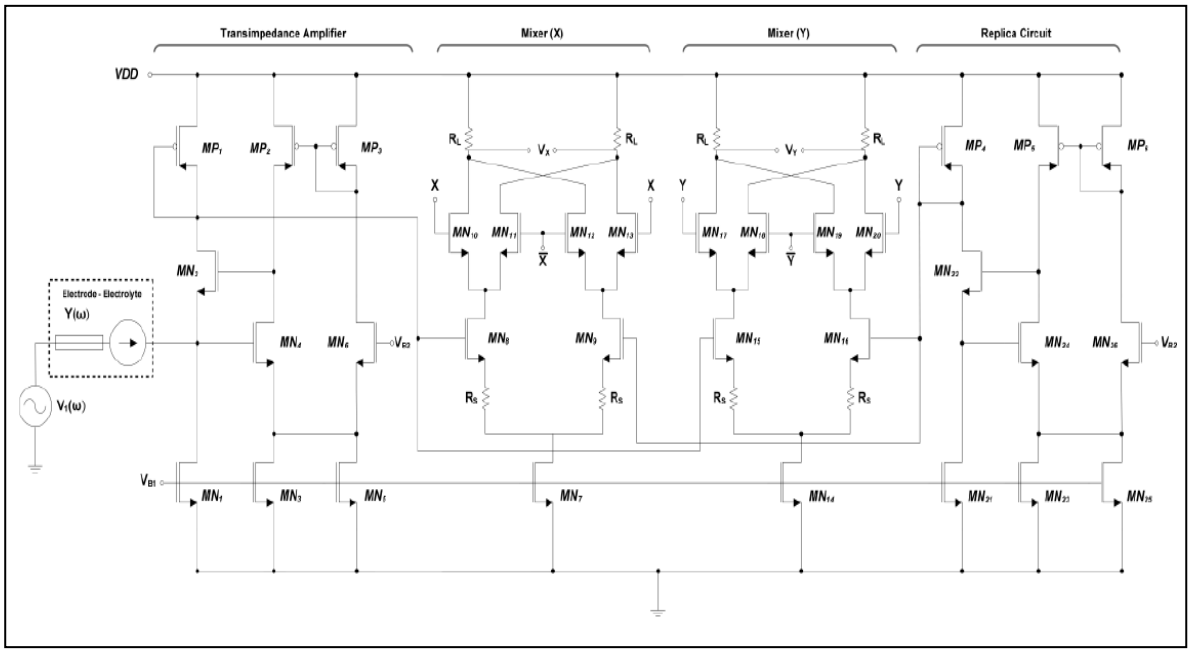

Fig. 2: Circuit diagram of a single pixel readout circuit (excluding bias circuits).

The linear performance of the single pixel output voltage is shown in Fig. 3. Using the 10kΩ resistor at the input TIA and amplitude of $V_1(\omega)$ is varied from 0 to 70mV, the output amplitude is then calculated using Eq. 1. For input current less than 2.7µA, the output response is linear with a constant slope. As the current increases, the circuit enters a non-linear region.

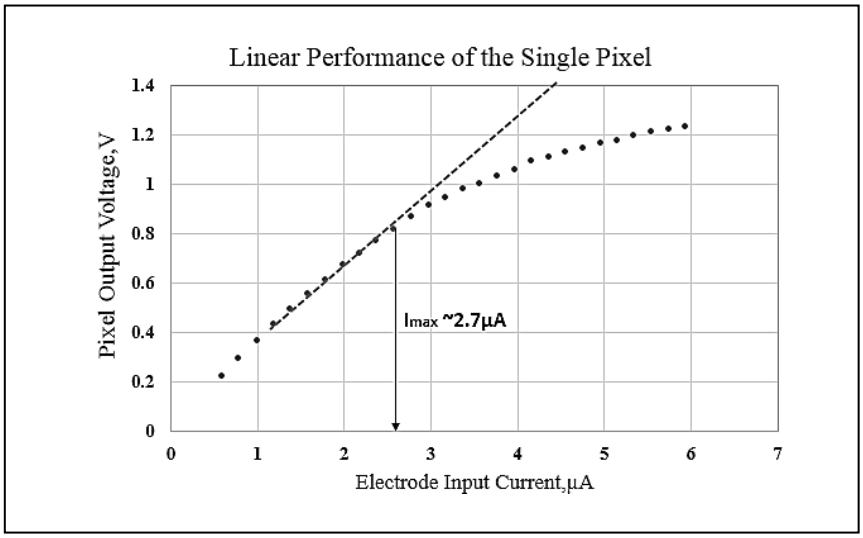

Fig. 3: Linear performance of the single pixel.

An equivalent circuit model was used for emulating an electrode-electrolyte system is shown in Fig. 4. Before hybridization, the C_{DL} is set to 1000pF, and R_{CT} is set to 10GΩ. After hybridization, the C_{DL} is set to 500pF, and R_{CT} is set to 15GΩ. R_B remains constant, which is set to 10kΩ.

The response of this emulated sensor is shown in Fig. 5. The formation of double-stranded DNA due to hybridization will increase the thickness of the double layer, thus decreasing the capacitance. When the double-stranded DNA is formed can block the flow of the current through the interface, leading to an increase in the interface resistance, R_{CT}. Therefore, the amplitude and phase of the admittance are decreased. The overall chip performances are listed in Table 1.

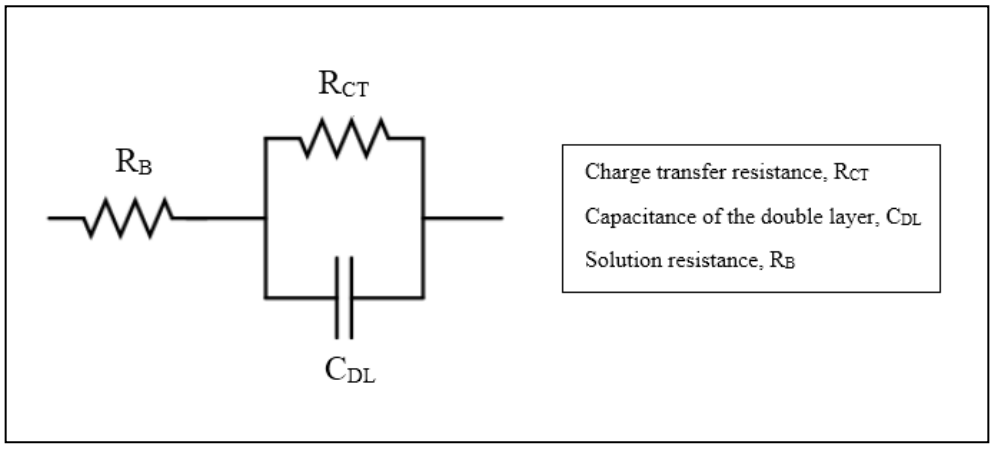

Fig. 4: Equivalent circuit model of an electrode-electrolyte system.

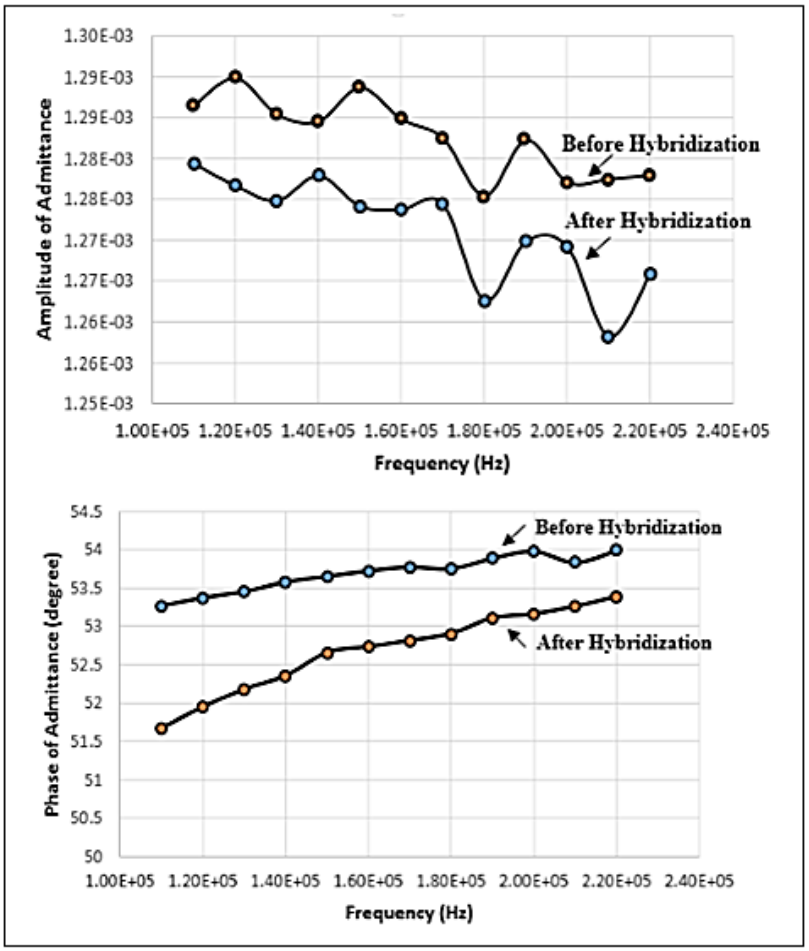

Fig. 5: The amplitude and phase of the admittance response.

Table 1: Single Pixel Performance

Specification	
Technology	0.18µm CMOS , 1.8V supply
Detector input impedance	65Ω (100kHz)
Detector transimpedance gain	88.6dB up to 50MHz
Input referred noise of TIA	4.28pA (10Hz)
Bandwidth of TIA (-3dB)	57MHz
Dynamic Range	90dB
Maximum input current	2.7µA

4. Conclusion

A single pixel readout circuit is designed using 0.18µm CMOS technology. As the result, the developed TIA can achieve a gain of 88.6dB up to 50MHz. The overall dynamic range is approximately 90dB. Impedance based measurement is more stable compared to the capacitive based biosensor, and the impedance based biosensor has been great potential to be developed as integrated stand-alone DNA-lab-on-a-chip, much smaller and less expensive than the commercial microarrays currently used.

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