Jurnal Teknologi

Full paper

A Low-Voltage and Label-Free Impedance-based Miniaturized CMOS Biosensor for DNA Detection

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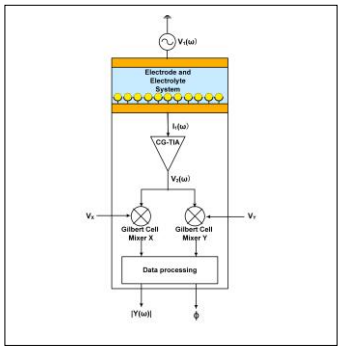
Article history

Received :1 October 2013
Received in revised form :
4 January 2014
Accepted :30 January 2014

Graphical abstract



Abstract

This study designs a low-voltage, label-free and fully integrated impedance-based biosensor using standard complementary metal oxide semiconductor (CMOS) technology to compute both capacitance and resistance of the electrode-electrolyte interface. The proposed biosensor circuit is composed of a common-gate transimpedance amplifier (CG-TIA) with two quadrature phase Gilbert cell double-balanced mixers and finally integrated with microelectrode using 0.18 µm Silterra CMOS technology process. The output value of the readout circuit was used to estimate the magnitude and phase of the measured admittance. The developed CG-TIA can achieve a gain of 88.6 dB up to a frequency of 50 MHz. The overall dynamic range was approximately 116 dB.

Keywords: CMOS; biosensor; impedance;lLabel-free DNA; low-voltage

Abstrak

Penyelidikan ini mereka satu impedans biosensor yang bervoltan rendah, penunjuk bebas dan boleh disepadukan secara lengkap menggunakan teknologi CMOS untuk mengira kemuatan dan rintangan bagi antara muka elektrod-elektrolit. Litar biosensor yang dicadangkan terdiri daripada CG-TIA dengan dua fasa kuadratur Gilbert sel *mixers* dua seimbang dan akhirnya disepadukan dengan mikroelektrod menggunakan 0.18 µm proses teknologi Silterra CMOS. Nilai keluaran bagi litar bacaan akan digunakan untuk menganggarkan magnitud dan fasa kemasukan tersebut. CG-TIA yang dicadangkan telah mencapai gandaan sebanyak 88.6 dB sehingga frekuensi 50 MHz. Julat dinamik keseluruhan adalah lebih kurang 116 dB.

Kata kunci: CMOS; biosensor; impedans; penunjuk bebas DNA; voltan rendah

1.0 INTRODUCTION

Deoxyribonucleic Acid (DNA) biosensor is a powerful tool that utilizes 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 of signals are indigestible and require various detection schemes to extract the relevant information.

Most conventional DNA biosensors are based on fluorescence-based detection, which provides an excellent selectivity and sensitivity. This method requires attachment of visible markers to analytes and also needs high intensity sources, optical filters and lenses, which made the system bulky, costly, time-consuming and not suited for point-of-care (POC) diagnostics. On the contrary, electrochemical biosensors allow increased sensitivities, label-free, require short analysis time, affordable and can be readily integrated using standard CMOS process technology.[2]

Several types of electrochemical biosensors such as charge transfer sensor, field-effect based sensor, capacitance-based sensor and impedance-based sensor have been reported for detecting DNA hybridization.[3,4,5] For example, Schienle *et al*.[3] proposed a fully electronic DNA sensor by using the amperometric detection, where the hybridization process was detected by means of the redox current between the two interdigitated sensing electrodes from the enzyme label of target DNA molecules. Meanwhile, Stagni *et al.*[4] proposed another label-free capacitance-based DNA sensor that used the change of capacitance between the electrolyte and electrode as the detection of hybridization process. Among these previous works, electrochemical impedance spectroscopy (EIS) is more favorable due to its label-free and real-time detection capabilities.

2.0 PROBLEM STATEMENT

Several studies on the electrical detection of biomolecules based on the changes in the electrical 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 method based on this principle is capacitive detection method.[6,7] The notation 'd' from Figure 1 represents the distance between the polarized metal electrode and the attracted ions for the capacitance. After double-stranded DNA (ds-DNA) are formed due to hybridization event, the capacitance of the double layer, C_{DL}, decreases and the charge transfer resistance, R_{CT}, increases. However, the capacitive sensing does not present enough stable capacitance properties as the measured capacitance after the hybridization event may increase. As shown in Figure 1, the flexible single-stranded DNA (ss-DNA) transforms into a rigid rod upon binding and causes the ds-DNA to become straight up to the surface. Under this condition, some ions are able to access near to the electrode surface due to the opening space between the ds-DNA.[8,9,10] To overcome this problem, some efforts have focused on the modification of the probe layer on the surface of electrode.[11,12]

Therefore, the impedance-based biosensor that measures both capacitance and resistance of the electrode-electrolyte interface after hybridization event is able to provide a more stable and accurate result compared to the capacitive detection method.

This paper proposes a low-voltage, label-free and fully integrated impedance-based biosensor using standard CMOS technology to compute both capacitance and resistance of the electrode-electrolyte interface.

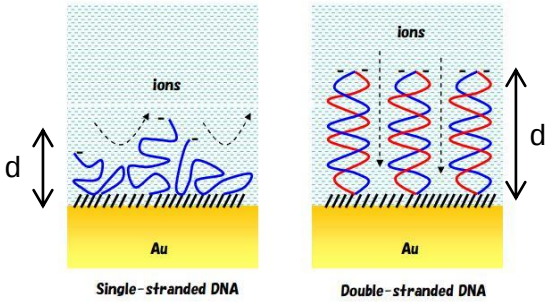


Figure 1 The DNA physical changes upon DNA hybridization[8]

3.0 IMPEDANCE DETECTION SCHEME

Figure 2 shows the conceptual block diagram of EIS detection method. A small excitation voltage, $V_1(\omega)$ was applied across the electrode-electrolyte system and the magnitude and the phase of the current flowing through the system was measured. The resulting current $I_1(\omega)$ was amplified and converted to $V_2(\omega)$ using a low-noise CG-TIA. The output voltage from CG-TIA, $V_2(\omega)$ was then multiplied by an orthogonal sinusoidal signal (X or Y) at the frequency ω. Signal Y is a quadrature phase of Signal X. Two DC outputs, V_X and V_Y, will be produced, which can be used to estimate the magnitude, $|Y(\omega)|$ and phase ϕ, of the admittance using Eq.(1) and Eq.(2):

$$A_D = \frac{|V_2(\omega)|}{|I_1(\omega)|}$$

$$|Y(\omega)| = \frac{\sqrt{V_X^2 + V_Y^2}}{A_D|\,V_1(\omega)|} \quad (1)$$

$$\phi = tan^{-1}\left(\frac{V_Y}{V_X}\right) \quad (2)$$

4.0 CIRCUIT IMPLEMENTATION

As illustrated in Figure 3, the main components of the proposed impedance-based readout circuit are a CG-TIA and two quadrature phase Gilbert cell double-balanced mixers[8] using 0.18µm Silterra CMOS technology. The proposed low input impedance CG-TIA consists of a common gate topology amplifier (MN_1, MN_2 and MP_1) with a gain boosting amplifier (MN_3, MN_4 and MP_2). The conversion gain can be boosted by enhancing the transconductance of MN_2 without sacrificing the signal bandwidth. The role of gain boosting amplifier is not only to enhance the gain of TIA, but also reduces the input impedance.

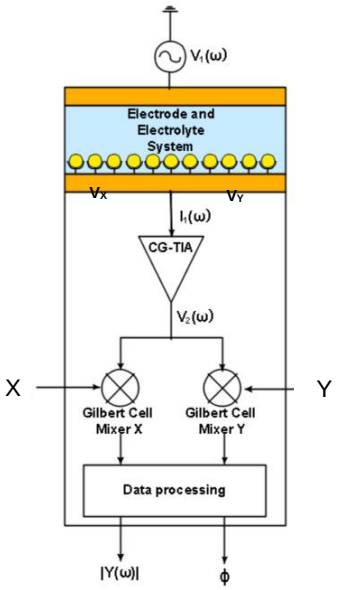


Figure 2 Impedance detection architecture

To multiply $I_1(\omega)$ by the X and Y quadrature signals, the output voltage from CG-TIA, $V_2(\omega)$ was directly connected to the input of two Gilbert cell mixers (MN_5 – MN_{19}) as shown in Figure 3.[13] To avoid the mismatch of the input mixers, a replica of the TIA (MN_{20}-MN_{23}, MP_3-MP_4) was designed and integrated within the readout circuit. Under the operation of the mixer (X), the $V_2(\omega)$ voltage and the output voltage of the replica circuit were applied to transistor MN_6 and MN_7 respectively, which performed a voltage to current conversion. MN_8 – MN_{12} formed a multiplication function, multiplied the current from MN_6 and MN_7 with the X and $\bar{X}$ signal applied across MN_8 – MN_{12}, which provided the switching function. MN_6 and MN_7 provided ± current and MN_8 and MN_{12} switched between them to provide the inverted X signal to the left hand load. MN_9 and MN_{10} switched between them for the right hand load. The two load resistors formed a current to voltage transformation, giving differential output voltage, Vx. The same operations above were applied to the mixer (Y). The load resistors were realized by using active PMOS load in this design so that the less layout area was used by the load resistor.

The current through the CG-TIA with gain-boosting amplifier bias current (I_2) in this design is 7 µA. The bias current used in this design was lower compared to the impedance-based biosensor proposed by M. Arun[14,15]. This will allow the CG-TIA to achieve a lower minimum detectable input current, which is 4.28 pA. The overall current consumption of the readout circuit was 58 µA with a 1.8 V supply.

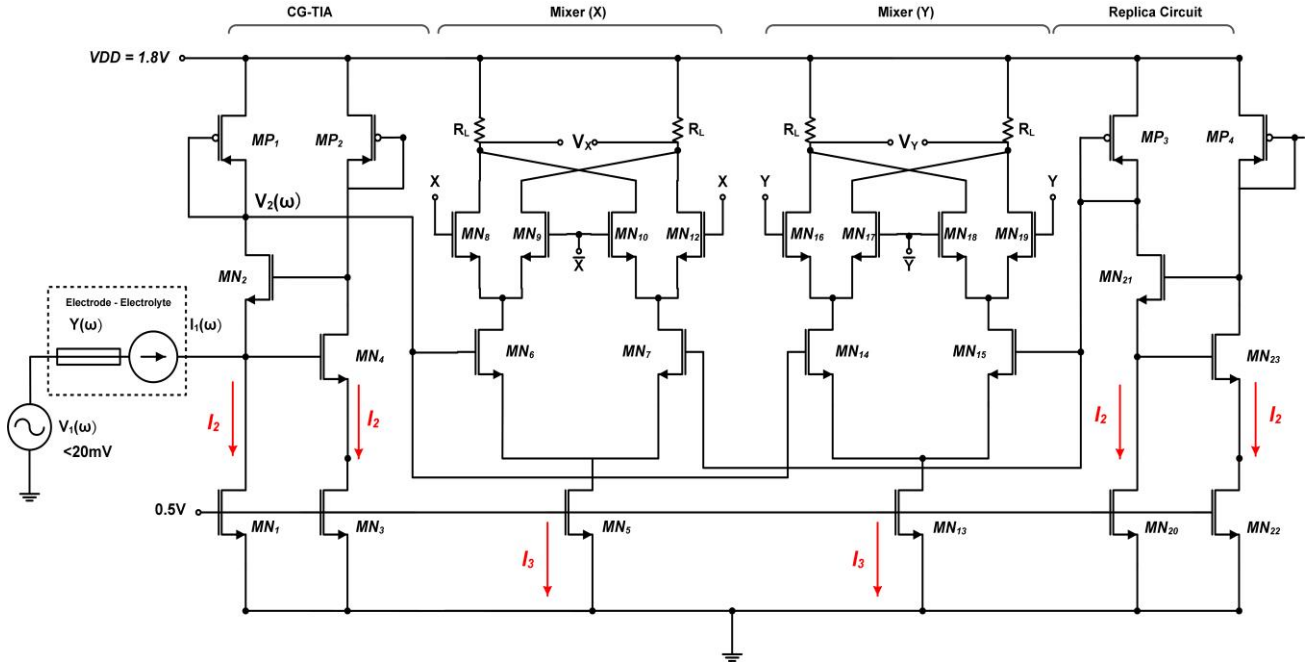


Figure 3 The schematic of the proposed impedance-based readout circuit (excluding bias circuits)

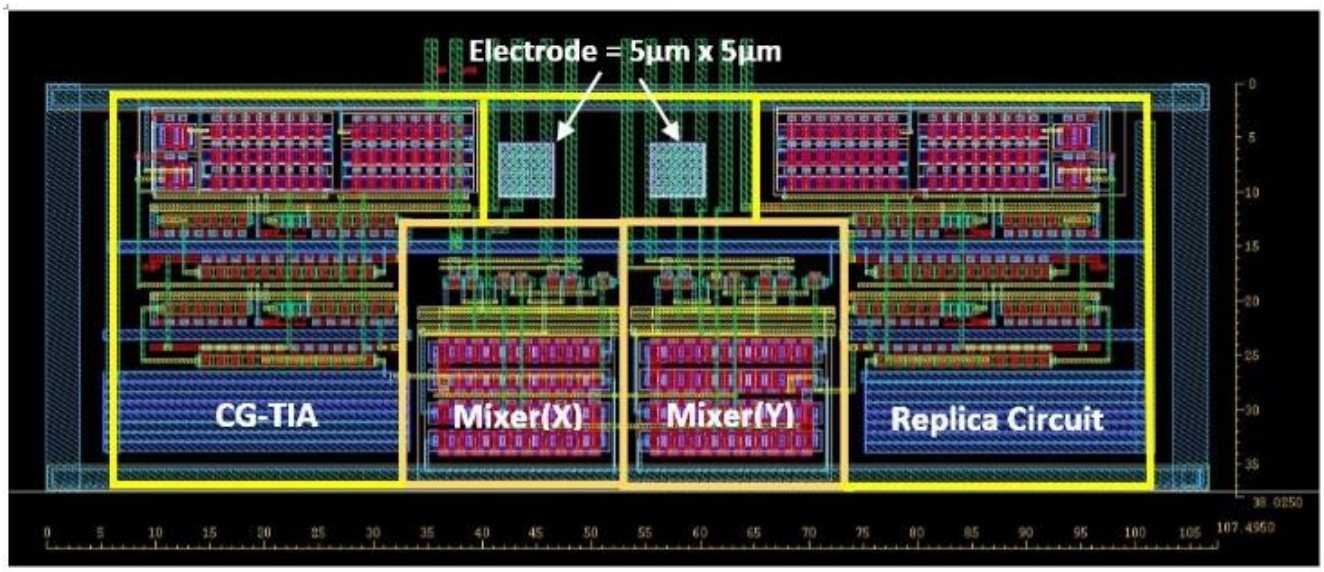


Figure 4 The layout of the proposed impedance-based readout circuit with a pair of electrode (excluding the bonding pads)

5.0 SIMULATION RESULTS AND DISCUSSION

The proposed layout is shown in Figure 4 using 0.18 µm 1P6M Silterra CMOS process. The layout measured 107.495 µm by 38.025 µm for a total area of 0.00041 mm^2. Post-layout simulation results of AC analysis for the layout of CG-TIA are shown in Figure 5. The proposed CG-TIA exhibited a 26.9 kΩ transimpedance gain. The cut-off frequency of CG-TIA was about 57 MHz. Moreover, the CG-TIA showed a phase-response within 10^0 from 100 MHz to 7.94 MHz, thus the in-phase control of the system was achieved. The input impedance of the CG-TIA was always less than 70 Ω, much less than the electrode-electrolyte impedance of about 10 kΩ.

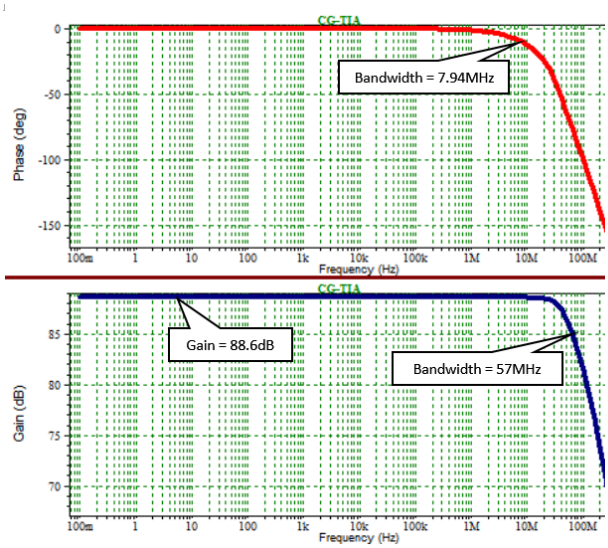


Figure 5 Transimpedance gain and phase response for the CG-TIA

The linear performance of the readout circuit output voltage is shown in Figure 6. Using the 10 kΩ resistor at the input TIA and the current through the resistor was varied from 0 to 7 µA, the output amplitude was then calculated using Eq.(1). For input current less than 2.7 µA, the output response was linear with a constant slope. As the current increased, the circuit entered a non-linear region. Normally, the applied excitation voltage is quite small (less than 20 mV) for the impedance-based biosensor.[16] This is because the current to voltage relationship is usually linear only for small disturbance, and only in this situation impedance is strictly defined. Furthermore, this can avoid disturbing the biomolecular probe layer as the probe covalent bond energies are on the order of 1 – 3 eV but the probe-target binding energies can be much less, and applied voltages will apply a force on charged molecules.

In order to simulate the response of the readout circuit upon the DNA hybridization event, a Randles equivalent circuit model was used for emulating an electrode-electrolyte system as shown in Figure 7. Two capacitance values for the double layer, C_{DL} were used, which are 10 pF (before hybridization event) and 5 pF (after hybridization event). The charge transfer resistance, R_{CT} and solution resistance, R_B were set to 10 GΩ and 10 kΩ, respectively. The response of this emulated sensor is shown in Figure 8. The magnitude, |Z| and phase, ϕ of the impedance increased when the C_{DL} decreased, which means the readout circuit was able to detect the change of impedance of the DNA.

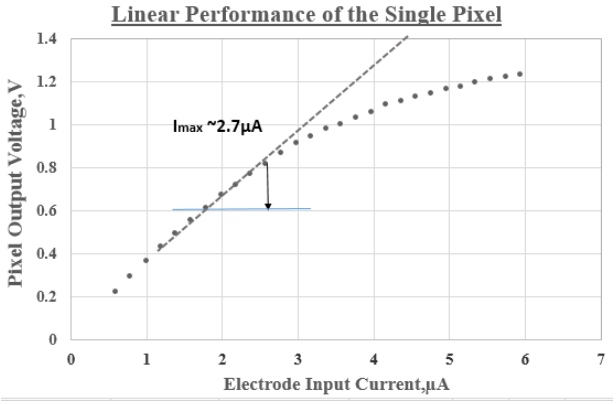


Figure 6 Linear performance of the readout circuit

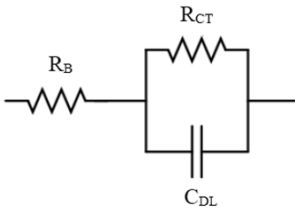


Figure 7 The Randles equivalent circuit model for an electrode-electrolyte system[16]

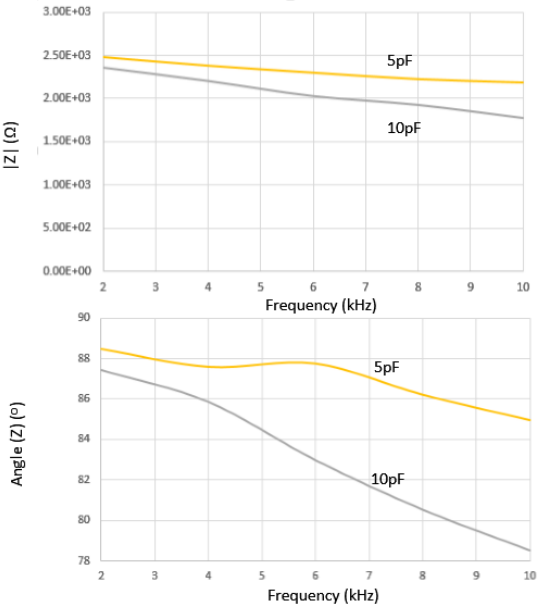


Figure 8 The magnitude and phase of the impedance response

Table 1 shows the simulation results of important performance parameters of the readout circuit. When compared to other op-amp topologies, the proposed CG-TIA design was able to achieve a better gain and frequency range. The overall performance of this work showed significant improvements when compared with the other CMOS biosensor works in terms of input referred noise, dynamic range and linearity, as shown in Table 2.

Table 1 Impedance-based readout circuit performance

Specification	
Technology	0.18 µm CMOS , 1.8 V supply
Electrode size	5 µm x 5 µm
Area	0.004 mm^2
Detector input impedance	65 Ω (100 kHz)
Detector transimpedance gain	88.6 dB up to 50 MHz
Input referred noise of TIA	4.28 pA (10 Hz)
Bandwidth of TIA (-3 dB)	57 MHz
Dynamic Range	116 dB
Maximum input current	2.7 µA

Table 2 Performance comparison

References	THIS WORK	17	18	15	8	19
Technology	0.18 µm	0.18 µm	0.35 µm	0.35 µm	1.20 µm	0.25 µm
Supply Voltage	1.8 V	0.9 V	1.5 V	3.3 V	±2.5 V	±2.5 V
Detector Gain	88.6 dB	48.09 dB	28.22 dB	86 dB	<80 dB	94 dB
Bandwidth at -3 dB	57 MHz	1 MHz	MHz-GHz	50 MHz	<50 MHz	<10 kHz
Input Referred Noise	4.28 pA/√Hz (@10 Hz)	7.55 µA/√Hz	>0.2 µA/√Hz	330 pA/√Hz (@10 Hz)	-	4 µA/√Hz (@ 10Hz)
Maximum Input Current	2.7 µA	> 7.55 µA	5 mA	40 µA	-	>4 µA
Dynamic Range	116 dB	-	74.8 dB - 88.5 dB	97 dB	70 dB	-

■6.0 CONCLUSION

In this paper, a label-free impedance-based CMOS biosensor for DNA detection was proposed as it has great potential to be developed as an integrated stand-alone DNA-lab-on-a-chip, much smaller and less expensive than the commercial microarrays currently used. A single pixel readout circuit was designed using 0.18µm CMOS technology. The proposed TIA can achieve a gain of 88.6 dB up to 50 MHz The overall dynamic range was approximately 116 dB.

Acknowledgement

This work was supported by the Malaysia Ministry of Higher Education under Exploratory Research Grant Scheme (Vote No. 4L123) and the Universiti Teknologi Malaysia under Research University Grant (Vote No. 08J90).

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