FULLY INTEGRATED IMPEDIMETRIC DEOXYRIBONUCLEIC ACID BIOSENSOR DESIGN USING 0.18 μm COMPLEMENTARY METAL OXIDE SEMICONDUCTOR TECHNOLOGY

VINNY LAM SIU FAN

UNIVERSITI TEKNOLOGI MALAYSIA

FULLY INTEGRATED IMPEDIMETRIC DEOXYRIBONUCLEIC ACID BIOSENSOR DESIGN USING 0.18 μm COMPLEMENTARY METAL OXIDE SEMICONDUCTOR TECHNOLOGY

VINNY LAM SIU FAN

A thesis submitted in fulfilment of the
requirements for the award of the degree of
Master of Engineering (Electrical)

Faculty of Electrical Engineering
Universiti Teknologi Malaysia

DECEMBER 2014

To my beloved mother and father

ACKNOWLEDGEMENT

First of all, my special thanks to Dr. Yusmeeraz binti Yusof as my supervisor for her advice, direction and continued support throughout my research. She has shown me what a real researcher means, being a model of honesty and availability. She helped me with the analog IC design part and guided me in every journal publication. This research would not have been possible without her help.

I also want to express my gratitude to my friend Wong How Hwan, who has elaborated papers and articles based on my research. Thanks for his patience, explanations and talking about useful discussion. Discussion with him had greatly benefited my work.

I would like to express my deepest gratitude to my parents for the support and enthusiasm they provided for me to reach my goals.

Finally, I wish to acknowledge the MyBrain15 program, 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) for their financial support.

ABSTRACT

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. Label-free and fully integrated biosensor has favored the developing of a low cost Point-of-Care (POC) device. Recently several studies on electrical detection of biomolecules that is based on the changes in electrical double layer capacitance of the bio-functionalized electrode surface have been proposed. Such systems harness the unique impedance values i.e. permittivity of the biomolecules. However, this method does not present enough stable and accurate electrical signal since the double layer formed at the electrode-electrolyte interface is an imperfect insulator. In capacitive sensing, the occurrence of ion conduction through the permeable DNA layers can cause leakage by discharging the charge on the double layer capacitance. Therefore, a more efficient detection method is desirable. This work demonstrates an impedimetric DNA detection circuit using standard Complementary Metal-Oxide Semiconductor (CMOS) technology. In this approach, the electrical changes are defined by computing both capacitance and resistance of the electrode-electrolyte interface. A fully integrated biosensor circuit design consists of an on-chip microelectrode, a current-to-voltage converter (IVC) and two quadrature phase double-balanced Gilbert cell mixers using 0.18 μm Silterra CMOS process is carried out. The Direct Current (DC) output voltage of the detection circuit is used to estimate the magnitude and phase of the measured admittance. The IVC shows a transimpedance gain of 166 dB and an input referred noise current of 332 $fA/\sqrt{Hz}$ in 10 kHz bandwidth. The total power dissipation from 1.8 V DC supply is 97.2 μW and the size of the layout area is approximately 4485 μm^2. The developed biosensor has great potential for future array integration due to its low power and flexibility in miniaturization.

ABSTRAK

Biosensor asid deoksiribonukleik (DNA) adalah satu alat berkuasa yang menggunakan prosedur penghibridan DNA untuk mengesan penyakit bawaan bakteria dan virus melalui penggunaan jujukan DNA yang sangat terpelihara. Biosensor bersepadu sepenuhnya serta bebas label telah menggalakkan pembangunan peranti *point-of-care* (POC) berkos rendah. Baru-baru ini, beberapa kajian terhadap pengesanan elektrik biomolekul berdasarkan perubahan dalam kapasitan elektrik dua lapisan pada permukaan elektrod bio-fungsian telah dicadangkan. Sistem ini memanfaatkan nilai impedan unik iaitu ketelusan biomolekul. Walau bagaimanapun, kaedah ini tidak menunjukkan signal elektrik yang stabil dan tepat kerana lapisan dua elektrik yang terbentuk di permukaan elektrod-elektrolit bukanlah penebat yang sempurna. Dalam penderiaan kapasitan, konduksi ion berlaku melalui lapisan DNA dan menyebabkan kebocoran secara pembebasan cas terhadap kapasitan dua lapisan. Oleh yang demikian, kaedah pengesanan yang lebih efisien sangat dikehendaki. Kajian ini mendemonstrasikan litar pengesanan impedan DNA menggunakan teknologi standard oksida logam pelengkap semikonduktor (CMOS). Dalam kaedah ini, perubahan elektrik ditentukan dengan mengira kedua-dua kapasitan dan rintangan di permukaan elektrod-elektrolit. Rekabentuk litar biosensor bersepadu adalah terdiri daripada mikroelektrod, penukar arus voltan (IVC), pencampur sel Gilbert dengan dua fasa kuadratur seimbang berganda menggunakan proses 0.18 μm Silterra CMOS. Nilai keluaran arus terus (DC) litar pengesanan digunakan untuk membuat anggaran magnitud dan fasa lepasan yang diukur. IVC menunjukkan 166 dB gandaan transimpedans dan input arus hingar yang dirujuk adalah 332 $\mathrm{fA}/\sqrt{\mathrm{Hz}}$ dalam 10 kHz jalur lebar. Jumlah pelesapan kuasa daripada bekalan DC 1.8 V adalah 97.2 μW dan keluasan litar pelan adalah kira-kira 4485 $\mu\mathrm{m}^2$. Litar biosensor yang telah dibangunkan mempunyai potensi yang tinggi untuk integrasi pada masa depan kerana penggunaan kuasa yang rendah dan fleksibiliti dalam pengecilan.

TABLE OF CONTENTS

CHAPTER	TITLE	PAGE
	DECLARATION	ii
	DEDICATION	iii
	ACKNOWLEDGEMENT	iv
	ABSTRACT	v
	ABSTRAK	vi
	TABLE OF CONTENTS	vii
	LIST OF TABLES	xii
	LIST OF FIGURES	xiv
	LIST OF ABBREVIATIONS	xix
	LIST OF SYMBOLS	xxii
	LIST OF APPENDICES	xxvii
1	**INTRODUCTION**	1
	1.1 Introduction	1
	1.1.1 Components of the Biosensor	1
	1.1.2 Characteristics of the Biosensor	2
	1.2 Deoxyribonucleic Acid	3
	1.2.1 DNA Hybridization	5
	1.2.2 DNA Biosensor	6
	1.3 Problem Statement	6
	1.4 Research Objectives	8

1.5 Scope of Work 9

1.6 Highlights on Research Methodology 9

1.7 Significance of the Study 11

1.8 Thesis Outline 11

2 LITERATURE REVIEW 12

2.1 DNA Detection Methods 12

2.1.1 Non-Electrochemical Based Methods 12

2.1.1.1 Fluorescence 13

2.1.1.2 Chemiluminescence 13

2.1.1.3 Surface Plasmon Resonance 14

2.1.1.4 Comparison of Different Non-Electrochemical Based DNA Detection 15

2.1.2 Electrochemical Based DNA Detection Methods 15

2.1.2.1 Amperometry 16

2.1.2.2 Potentiometry 16

2.1.2.3 Electrochemical Impedance Spectroscopy 17

2.1.2.4 Comparison of Different Electrochemical Based DNA Detection 18

2.1.3 Summary 19

2.2 Electrochemical Impedance Spectroscopy 19

2.2.1 Fundamental of Impedance 20

2.2.2 Phasor Diagram 20

2.2.3 Electrode-Electrolyte Interfaces 22

2.2.3.1 Equivalent Circuit Model of the Interfaces 23

2.2.3.2 Non-Faradaic Interfaces 24

2.2.3.3 Faradaic Interfaces 25

2.2.3.4 Summary 27

2.2.4 Impedance Measurements 27

2.2.4.1 AC Bridges 27

2.2.4.2 Phase-Sensitive Detection 28
2.2.4.2.1 Single Lock-In Amplifier 28
2.2.4.2.2 Dual Lock-In Amplifier 29
2.2.4.3 Frequency Response Analyzer 33
2.2.4.4 Summary 34
2.3 Analog CMOS Circuit Design 35
2.3.1 Transimpedance Amplifier 35
2.3.1.1 Common Gate TIA 37
2.3.1.2 Common Source TIA with Feedback 38
2.3.1.3 TIA with Gain-Boosting Amplifier 39
2.3.1.4 Differential TIA 41
2.3.2 Mixer 42
2.3.2.1 Unbalanced Mixer 43
2.3.2.2 Single-Balanced Mixer 44
2.3.2.3 Gilbert Cell Mixer 45
2.3.3 Bias Circuit 46
2.3.4 Summary 47

3 DESIGN OF IMPEDIMETRIC BIOSENSOR 48
3.1 Introduction 48
3.2 Process Technology 48
3.3 Flowchart of the IC Circuit Design 49
3.4 Impedance Detection Scheme 51
3.5 Analog Circuit Implementation 52
3.5.1 Current-to-Voltage Converter 52
3.5.1.1 Common Gate Transimpedance Amplifier with Gain-Boosting Amplifier 54
3.5.1.2 Voltage Amplifier 56
3.5.2 Double-Balanced Gilbert Cell Mixer 61

3.6 Analog Layout Design 62

3.6.1 Analog Design Issues 62

3.6.1.1 Layout of Large-Size Transistors and Compact Layout 62

3.6.1.2 Mismatch Consideration 64

3.6.1.3 Symmetry Approach 66

3.6.2 Floor-Planning of Single Pixel Sensor Circuit 68

3.6.3 CMOS IC Layout 69

4 RESULTS AND DISCUSSIONS 73

4.1 Introduction 73

4.2 Pre-Layout Simulation 73

4.2.1 Common Gate Transimpedance Amplifier with Gain-Boosting Amplifier 74

4.2.2 Voltage Amplifier 78

4.2.3 Current-to-Voltage Converter 80

4.2.4 Corners Analysis 83

4.3 Post-Layout Simulation 85

4.3.1 Frequency Response 85

4.3.2 Transient Analysis for IVC 86

4.3.3 Transient Analysis for Complete Single Pixel Sensor Circuit 87

4.3.4 Input Referred Noise 89

4.3.5 Randles Equivalent Circuit Model 90

4.4 Summary of the Performance of the Designed IC 94

4.5 Performance Comparison between the Proposed Circuit and Others 96

5 CONCLUSION 98

5.1 Conclusion 98

5.2 Future Work 99

REFERENCES 100

Appendices A-B 106 - 110

LIST OF TABLES

TABLE NO.	TITLE	PAGE
1.1	Problems in the Manickam et al. work	8
2.1	Comparison of different non-electrochemical based methods of detection	15
2.2	Comparison of different electrochemical based methods of detection	18
2.3	Advantages and disadvantages of PSD	28
2.4	Outputs from the low-pass filter	32
2.5	Advantages and disadvantages of FRA	34
3.1	Specifications of the proposed detection circuit	53
3.2	Aspect ratio of the transistors used in the CG-TIA with GBA	55
3.3	Ideal and practical op-amp comparison	57
3.4	Specifications of the differential amplifier used in IVC	57
3.5	Model parameters used in the differential amplifier design procedure	58
3.6	Aspect ratio of the transistors used in the simulated VA	60
3.7	Aspect ratio of the transistors used in the simulated double-balance Gilbert cell mixer	62

4.1	Summary of the performances of both CG-TIA and CG-TIA with GBA	77
4.2	AC Characteristics of the designed differential amplifier	80
4.3	Performance comparison between CG-TIA, CG-TIA+GBA and I-V converter	82
4.4	Process corner analysis of the IVC circuit	85
4.5	AC characteristic of the designed IVC	86
4.6	Components that used in the Randles equivalent circuit model for simulation in Figure 4.19	91
4.7	Components that used in the Randles equivalent circuit model for the simulation in Figure 4.20	92
4.8	Components that used in the Randles equivalent circuit model for the simulation in Figure 4.22	94
4.9	Summary of the performance of the proposed IVC	95
4.10	Comparison between the proposed circuit and other existing biosensors	97

LIST OF FIGURES

FIGURE NO.	TITLE	PAGE
1.1	Typical architecture of a biosensor	2
1.2	Diagram of DNA double helix	4
1.3	Diagram of denaturing and hybridization of DNA	5
1.4	DNA physical changes upon DNA hybridization	7
1.5	Research methodology of this research	10
2.1	Fluorescence-based DNA microarray detection procedure	13
2.2	Method of surface plasma resonance	14
2.3	(a) Structure of the MOSFET and (b) ISFET devices	17
2.4	Vector representation of the impedance	20
2.5	Phase diagram for a resistor, the potential and current are represented as vectors, respectively V (blue) and I (red)	21
2.6	Phase diagram for a capacitor, the potential and the current are presented as vectors, respectively E (blue) and I (red)	22
2.7	Circuit model of an electrode-electrolyte system	23

2.8	Charge profile example of non-faradaic interface. (a) Molecular level structure of the electrode (b) Charge distribution of the electrode	24
2.9	Simplified principle sketch of a single lock-in amplifier	29
2.10	Simplified principle sketch of a dual lock-in amplifier	29
2.11	Outputs of the dual lock-in amplifier , V_X	30
2.12	Output of the dual lock-in amplifier, V_Y when the input and reference signals are out of phase	31
2.13	Low-pass filter outputs by phase difference between the input and reference signals	32
2.14	Conversion of current-to-voltage by a resistor. (a) Schematic (b) Equivalent circuit for noise calculation. (c) Effect of resistor value	35
2.15	Schematic view of the common gate TIA	38
2.16	Common source TIA with shunt feedback	39
2.17	CG-TIA with GBA	40
2.18	Pseudo-differential CG stage.	41
2.19	Single-ended to differential conversion	42
2.20	Mixer symbol	42
2.21	Unbalanced mixer topology	44
2.22	Single-balanced mixer	45
2.23	Double-balanced cell mixer	46
2.24	Voltage dividers implemented in CMOS	46
3.1	Flow chart for the IC circuit design	50

3.2	Conceptual block diagram of an impedance detection scheme	51
3.3	Block diagram of the proposed impedimetric DNA detection circuit	52
3.4	Schematic diagram of the CG-TIA with GBA	55
3.5	Schematic diagram of the voltage amplifier	56
3.6	The double-balance Gilbert cell mixer	61
3.7	Parasitic capacitance in a large NMOS	63
3.8	The effects of transistor parasitic OS	63
3.9	Rearrangement of the CMOS transistor geometry	64
3.10	Different device orientations	65
3.11	Schematic of the symmetry circuit for voltage amplifier	67
3.12	Schematic of the symmetry circuit for double-balanced Gilbert cell mixer	67
3.13	Floor plan of the layout of the DNA biosensor	68
3.14	Final layout of the designed DNA biosensor	70
3.15	Layout of CG-TIA with GBA	71
3.16	Layout of Voltage Amplifier	71
3.17	Layout of Mixer X and Mixer Y	72
4.1	Comparison of simulated AC frequency responses of both CG-TIA (red line) and CG-TIA + GBA (blue line)	74
4.2	Input impedance of both CG-TIA (red line) and CG-TIA+GBA (blue line)	75

4.3	Transient response of both CG-TIA (red line) and CG-TIA+GBA (blue line) with applied input current of 20 fA	76
4.4	Transient response of both CG-TIA (red line) and CG-TIA+GBA (blue line) with applied input current of 1 pA	76
4.5	Transient response of both CG-TIA (red line) and CG-TIA+GBA (blue line) with applied input current of 30 nA	77
4.6	Large-signal voltage transfer function for CMOS differential amplifier	78
4.7	Frequency response of the designed voltage amplifier. Gain (red line) and phase (blue line) of VA	79
4.8	Diagram of an IVC that consists of two CG-TIA+GBA and a VA	80
4.9	Frequency response of CG-TIA, CG-TIA+GBA and IVC	81
4.10	The noise response of the IVC	82
4.11	Corner analysis of the AC response of the IVC	84
4.12	Corner analysis of the noise response of the IVC	84
4.13	Post-layout frequency response of the IVC	86
4.14	Post-layout transient simulation of the IVC with 3.0 nA of input current at 10 kHz	87
4.15	Output voltage from IVC, V_{IVC} (Blue Line) and output voltage from double-balanced Gilbert cell mixer, V_X (Purple Line) and V_Y (Red Line)	88
4.16	Input referred noise current	89

4.17	Post-layout noise response of the readout circuit	90
4.18	Randles equivalent circuit model	91
4.19	Sensitivity of the designed IVC due to change of C_{DL}. (a) Input current (red line) (from the Randles equivalent circuit model). (b) Output voltage (green line)	91
4.20	Sensitivity of the designed TIA circuit due to change of R_{CT}. (a) Input current (from the Randle's equivalent circuit model). (b) Output voltage	92
4.21	Output voltage of designed TIA circuit with the changes of the C_{DL}	93
4.22	Comparison of transient response of the Mixer X and Y (before and after DNA hybridization event)	94

LIST OF ABBREVIATION

A	-	Adenine
AC	-	Alternating current
ADC	-	Analog-to-digital converter
C	-	Cytosine
cDNA	-	Complementary ssDNA or target DNA
CEDEC	-	Collaborative Microelectronic Design Excellence Centre
CG-TIA	-	Common gate transimpedance amplifier
CMFET	-	Charge-modulated field-effect transistor
CMOS	-	Complementary metal oxide semiconductor
CMRR	-	Common-mode rejection ratio
DC	-	Direct current
DNA	-	Deoxyribonucleic acid
DRC	-	Design rule check
dsDNA	-	Double-Stranded deoxyribonucleic acid
EDA	-	Electronic design automation
EIS	-	Electrochemical impedance spectroscopy
etc.	-	And so on
FF	-	Fast NMOS fast PMOS

FGMOS	-	Floating gate field-effect MOSFET
FRA	-	Frequency response analyser
FS	-	Fast NMOS slow PMOS
G	-	Guanine
GBA	-	Gain boosting amplifier
GBW	-	Unity gain bandwidth
G_{OX}	-	Glucose oxidase
IC	-	Integrated circuit or microchip
ICMR	-	Common mode voltage range
ILO	-	Interlevel oxide
ISFET	-	Ion-selective field-effect transistor
I-V	-	Current-to-voltage
IVC	-	Current to voltage converter
LVS	-	Layout versus schematic check
MOSFET	-	Metal oxide field-effect transistor
PEX	-	Parasitic extraction
PO	-	Protective overcoat
POC	-	Point-of-care
PSD	-	Phase-sensitive detection
PSRR	-	Power supply rejection ratio
RC	-	Resistor-capacitor
SF	-	Slow NMOS fast PMOS

SS	-	Slow NMOS slow PMOS
ssDNA	-	Single-stranded deoxyribonucleic acid
T	-	Thymine
TIA	-	Transimpedance amplifier
TT	-	Typical NMOS typical PMOS
USM	-	Universiti Sains Malaysia
UTM	-	Universiti Teknologi Malaysia
VA	-	Voltage amplifier

LIST OF SYMBOLS

a	-	Standard deviation constant
A	-	Area of the electrode
A_{TIA}	-	Transimpedance gain
C	-	Capacitance
C1A	-	Orthogonal signal of Mixer X
C1B	-	Inverted orthogonal signal of C1A
C2A	-	Orthogonal signal of Mixer Y and quadrature phase of orthogonal signal C1A
C2B	-	Inverted orthogonal signal of C2A Mixer Y and quadrature phase of orthogonal signal C1B
$C_0(0,t)$	-	Concentration of the oxidised species at time t
C_{DL}	-	Capacitance of the double layer
C_{GC}	-	Gouy-Chapman capacitance
C_H	-	Capacitance of the stern layer
C_{OX}	-	Oxide capacitance
C_L	-	Load capacitance
C_{PD}	-	Parasitic capacitance
$C_R(0,t)$	-	Concentration of the reduced species at time t

e	-	Charge of an electron = 1.6 x 10^{-19}C
E^0	-	Standard equilibrium potential
f_{-3dB}	-	-3dB cut-off frequency
g_m	-	Transconductance
I	-	Current
I_D	-	Drain current
I_{DA}	-	Drain current of VA
I_{DS}	-	Drain to source current
I_{if}	-	Current through transistor (MN_{13} TO MN_{16}) in double-balanced Gilbert cell mixer
I_{IN}	-	Input signal of IVC
$\overline{I_n^2}$	-	Noise current
$\overline{\lvert i_{n,in} \rvert^2}$	-	Input referred noise current
k^0	-	Standard rate constant
k_1	-	Rate constant of the forward reaction
k_2	-	Rate constant of the reverse reaction
k_B	-	Boltzmann constant = 1.38 x 10^{-23} J/K
L	-	Length of transistor
MN	-	NMOS transistor
MP	-	PMOS transistor
N_A	-	Avogadro's number = 6.022 x 10^{-23}
N_b	-	Doping concentration

ne^-	-	Number of electron
Ox	-	Oxidation state of an element
P_{diss}	-	Power dissipation
Q	-	Amount of charge
Re	-	Reduction state of an element
R_B	-	Bit rate
R_{CT}	-	Charge-transfer resistance
R_F	-	Feedback resistance
R_{in}	-	Input Resistance
R_L	-	Load resistance
R_{out}	-	Output resistance
R_S	-	Bulk resistance of the solution
S_{Vt}	-	Standard deviation of the threshold voltage mismatch
T	-	Temperature
t_{ox}	-	Transistor gate oxide thickness
V	-	Voltage, V
V_{CG_TIA}	-	Output voltage of CG-TIA with GBA
$V_{CG\_TIA\_R}$	-	Output voltage of Replica CG-TIA with GBA
V_{DD}	-	Power supply voltage
V_{DS}	-	Drain-to-source voltage
V_{GS}	-	Source-to-gate voltage
V_{if}	-	Intermediate frequency signal

V_{input}	-	Input voltage of dual lock-in amplifier
V_{IVC}	-	Output signal of IVC
V_{IVC_R}	-	Output voltage of replica IVC
V_{lo}	-	Local oscillator frequency signal
$\overline{V_{n,OUT}^2}$	-	Noise voltage
V_{out}	-	Output voltage
V_{ref}	-	Reference voltage of dual lock-in amplifier
V_{rf}	-	Output frequency signal
$\|V_S\|$	-	Magnitude of input signal dual lock-in amplifier
V_{SG}	-	Source-gate voltage
V_{TN}	-	Threshold voltage for NMOS transistor
V_{TP}	-	Threshold voltage for PMOS transistor
V_X	-	Output of the mixer X in dual lock-in amplifier
V_Y	-	Output of the mixer Y in dual lock-in amplifier
W	-	Width of transistor
$\|Y\|$	-	Magnitude of admittance
$\|Z\|$	-	Magnitude of impedance
z	-	Avalence or charge number
Z'	-	Real part of the impedance
Z''	-	Imaginary part of the impedance
α	-	Transfer coefficient
β	-	Transconductance coefficient.

λ_D	-	Debye length
ε	-	Permittivity
ε_0	-	Vacuum permittivity = 8.854 x 10^{-12} F/m
ε_r	-	Relative permittivity of the material
μ_n	-	Electron mobility
μ_p	-	Hole mobility
η	-	overpotential
η_{sol}	-	Bulk concentration
φ	-	Phase shift
ω	-	Angular frequency
ω_{if}	-	Intermediate frequency
ω_{lo}	-	Local oscillator frequency
ω_{rf}	-	Output frequency

LIST OF APPENDICES

APPENDIX	TITLE	PAGE
A	Publication List and Other Contributions	106
B	CMOS18 Core 1.8V SPECTRE Models	107

CHAPTER 1

INTRODUCTION

1.1 Introduction

Biosensor is an analytical tool used to convert the detected biological signal from the interaction of biological component with the analytes into an electric signal. However, these detected biological signals are indigestible and require various detection schemes to extract the relevant information.

1.1.1 Components of the Biosensor

First, the components of the biosensor are introduced in this section. Based on the principle of specific biological recognition measurements, biosensors can be divided into three parts as shown in Figure 1.1:

i. Sensitive biological elements which able to interact specifically with an analytes. These biological elements can provide us useful information. For instance, physical properties such as temperature and pressure or biological and chemical entities such as ion, bacteria, etc.

ii. The transducer from biosensor can be defined as a device to transfer or translate a detected biological signal into another signal form, which is readable and quantified output [1]. These signals can be in the form of electrical, mechanical, optical, magnetic or thermal.

iii. Signal processor is responsible in processing the transformed signal from the transducer in a user-friendly way for information storage, display, analyzing and transmission.

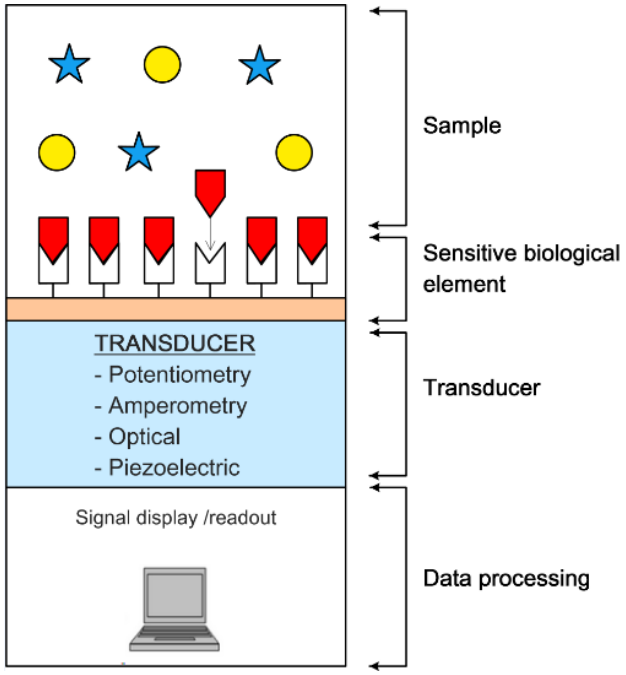

Figure 1.1 Typical architecture of a biosensor.

1.1.2 Characteristics of the Biosensor

To build a high-performance biosensor has been always a motivation for scientific and industrial research. Some of the performance characteristics are described as follows [2]:

i. **Sensitivity**: The change in output of sensor to per unit change in analytes concentration. For instance, in a linear sensor system, the sensitivity is the slope of the calibration curve.

ii. **Selectivity**: The ability of the sensor only reacts to the specific target analytes and no reaction to the other interfering chemical. For an ideal sensor system, the selectivity is infinity, which mean it just react to a particular target analytes.

iii. **Range**: The concentration range over which the sensitivity of the sensor is good and is also called as dynamic range or linearity.

iv. **Response time**: The time required for the sensor to indicate 63% of its final response due to a step change in analytes concentration. Many factors can affect the system response time such as the sensor's response time and the transducer's response time.

v. **Detection limit**: The lowest concentration of the analytes to which there is a measurable response.

vi. **Lifetime**: The time period over which the sensor can be used without significant deterioration in performance characteristics. This parameter is particularly important for biomedical sensor systems since the failure of the sensor system might put the patient in a dangerous situation.

vii. **Stability**: Characterizes the change in its baseline or sensitivity over a fixed period of time. High stability allows the long-term monitoring into a specific substance.

Other than the performance characteristics listed above, there are some other characteristics that still need to be put into consideration when designing a sensor system which are size, cost and power consumption. The main goal of these three characteristics is to make them as small as possible so that the miniaturization of the sensor system can be developed. The need of the miniaturization of the system sensor is driven by the demands for portable or implantable sensor systems especially in the medical sector.

1.2 Deoxyribonucleic Acid

Deoxyribonucleic acid (DNA) is an essential macromolecule which carrying the genetic code of living organisms. The chromosomes in the DNA molecules contain huge amount of information that used to synthesize proteins and define their functions.

The genetic disorder can affect an individual from birth that makes an individual disease-prone because of his or her gene. Some examples of gene-based diseases are cancer, diabetes, cardiovascular diseases and Alzheimer disease [3]. Therefore, genetic testing has become an important part of the health care checking among the people. Due to this demand, such effort is spent to develop reliable, low cost and accurate devices for genetic testing. On the other hand, the DNA technology can be used in identification of individuals by their respective DNA profiles. This technology is especially useful in criminal investigation.

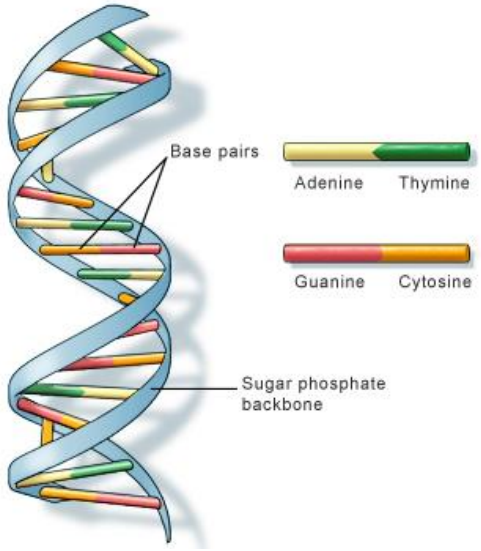

Figure 1.2 Diagram of DNA double helix. [4]

DNA is a molecule strand that consists of four different types of nucleotides, which are named as adenine (A), thymine (T), cytosine (C) and guanine (G). A diagram of DNA double helix [4] is shown in Figure 1.2. The genetic code or gene is defined by the sequence of these nucleotides in a single strand. Nucleotides are composed of three building blocks, which are sugar deoxyribose, a phosphate group and a nitrogen base. The nitrogen bases determine the type of a nucleotide, while the sugar-phosphate group forms the backbone of the strand. The adenine only combines with thymine while cytosine combines with guanine. This complementary property has been used in many DNA detection mechanisms.

1.2.1 DNA Hybridization

In the 1960s, the DNA hybridization technique was developed by Roy Britten as a way of analysing the composition of the genome [5]. At high temperatures (~84 ^{o}C), a double-stranded DNA (dsDNA) will separate into two single-stranded DNAs (ssDNA). This phenomenon is called as denaturing the DNA. These two single strands will anneal when the temperature is lowered because of the base pairing interactions of the complementary strands. This is called as DNA hybridization. Diagram of denaturing and hybridization of DNA is shown in Figure 1.3. If the ssDNA (probe DNA) from one source is immobilized by attachment to a solid surface such as nitrocellulose, complementary ssDNA (target DNA) from another source will hybridize with the probe and be retained by the immobilized ssDNA. This is the basis for various DNA detection techniques.

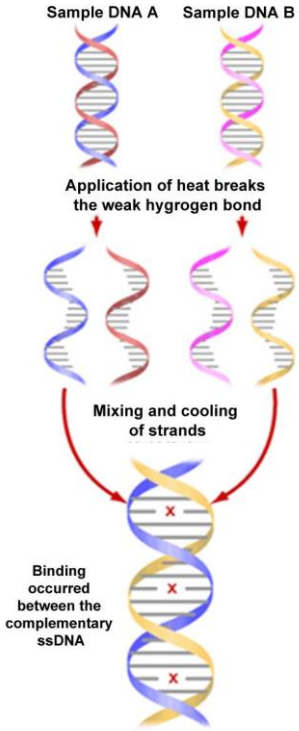

Figure 1.3 Diagram of denaturing and hybridization of DNA. [5]

1.2.2 DNA Biosensor

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. The sensitive element is composed of ssDNA molecules that allow the hybridization of the complementary DNA (cDNA). Different methods can be used to transduce these hybridization signals, including optical transducers [2], electrochemical transduction [6] and the piezoelectric transduction [7].

Hybridization biosensors rely on the immobilization of the ssDNA probes onto the transducer surface. The hybridization with duplex arrangement can be detected by means of hybridization signal or by other changes obtained as a result of the hybridization event. There are two important characteristics when developing DNA biosensors, the sensitivity and the selectivity [7]. Selectivity gives a measure of the ability of the system to detect the analytes in the presence of other interfering molecules, while sensitivity is referred to the lowest detectable analytes concentration.

Electrochemical impedance spectroscopy (EIS) is a useful method to characterize the interaction between molecules and the sensor surface [8]. A small excitation sinusoidal voltage is applied to analyze the properties of the electrode-electrolyte interface. The impedance value can be obtained from the relationship between the applied voltage and the resulting current across the electrode, and it can be expressed as the sum of the real and the imaginary parts. The measured value is the result of the sum of all contributions of all resistances and capacitances of the electrode-electrolyte interface.

1.3 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 methods that based on this principle is the capacitive detection method [9][10]. The notation‘d’ in Figure 1.4 represents the distance between the polarized metal electrode and the attracted ions for the capacitance. After dsDNA is formed due to the 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 electrical properties as the measured capacitance after the hybridization event may increases. As shown in Figure 1.4, the flexible ssDNA transforms into a rigid rod upon hybridization and causes the dsDNA (complementary binding) 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 dsDNA [11][12][13]. To overcome this problem, some efforts have focused on the modification of the probe layer on the surface of the electrode [14][15].

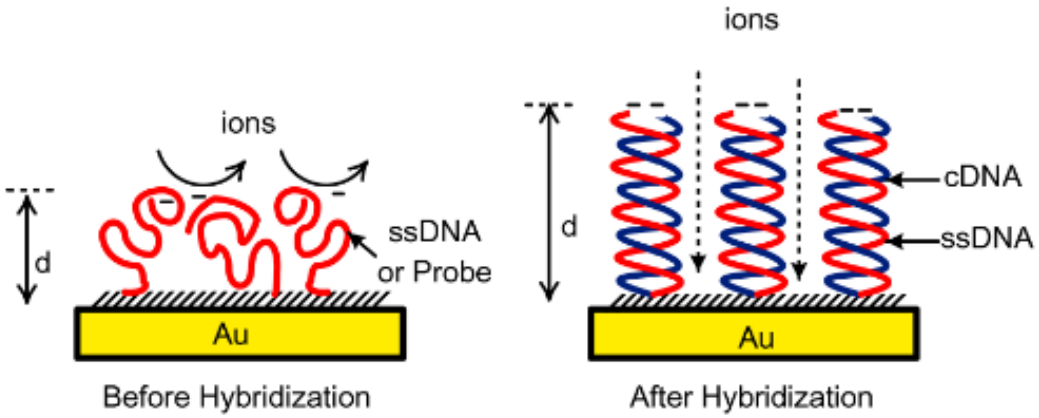

Figure 1.4 DNA physical changes upon DNA hybridization [11].

Therefore, the impedance-based biosensor that measures both capacitance and resistance of the electrode-electrolyte interface after the hybridization event can provide a more stable and accurate result compared to the capacitive detection method. This work proposes a low voltage, label-free and fully integrated impedance-based detection circuit using standard CMOS technology to compute both capacitance and resistance of the electrode-electrolyte interface. Manickam et al. proposed an impedance-based DNA biosensor that utilized the phase-sensitive detection (PSD) technique in year 2010 [13]. The existing problems in the Manickam et al. work are summarized in Table 1.1. Therefore, the main characteristics of detection circuit to be

improved are transimpedance gain, input referred noise and power dissipation. Circuit optimization will be done to reduce the number of transistors used in order to cut the area consumption.

Table 1.1: Problems in the Manickam et al. work.

Parameter	**Units**	**(Manickam et al., 2010) [13]**	**Problems to be solved**
Impedance Measurement Technique	-	Phase-Sensitive Detection (PSD)	Lower attainable gain if compared to other methods.
Gain	dB	86	Not sensitive enough for small electrode.
Minimum detectable input current	A	330 p	
Technology	µm	0.35	-
Power Supply	V	3.3	
Power Consumption	W	511.5 µ	Too large for low voltage applications.
Layout Area	μm^2	10000	Can be optimized by reducing the circuit complexity.

1.4 Research Objectives

The objectives of the study are stated as below:

i. To design a CMOS detection circuit and physical layout based on the current to voltage converter (IVC) for impedimetric sensing of DNA biomolecules.

ii. To analyze the electrical performance of the designed detection circuit.

1.5 Scope of Work

The scope of this research is stated as below:

i. DNA is chosen as the target of biomolecules.

ii. Phase-sensitive detection (PSD) is used as the impedance measurement method in this study.

iii. Main characteristics to be improved are transimpedance gain, input referred noise and power dissipation of the IVC. Circuit optimization will be done to reduce the number of transistors used in the gain-boosting amplifier in order to cut the area consumption.

iv. Silterra 0.18 μm CMOS process (CL180G) will be used in the design of fully integrated biosensor circuit.

v. The Cadence EDA is used as the simulation tool throughout the research.

vi. This work is limited to circuit design consideration and no experimental work will be carried on.

1.6 Highlights on Research Methodology

The methodology of this research is shown in Figure 1.5. The research begins with determination of the design specifications of DNA biosensor. Then, literature review based on various impedimetric detection circuits is done. Next, the impedimetric detection circuit is designed and simulated under the Cadence EDA environment. The simulated performances of the transistor level circuit are analyzed in terms of its gain, noise and frequency range. After the obtained performances are met with the initial specifications, the IC layout of the designed circuit is created with Cadence EDA Tools. After that, the performance of completed IC layout design is analyzed with the existence of parasitic parameters. The performance of the IC layout design is again compared with the specifications. The study will proceed to

improvements and discussion if the specifications are achieved. Analysis and validation will be done on the simulated results before all the simulated results are taken as final results.

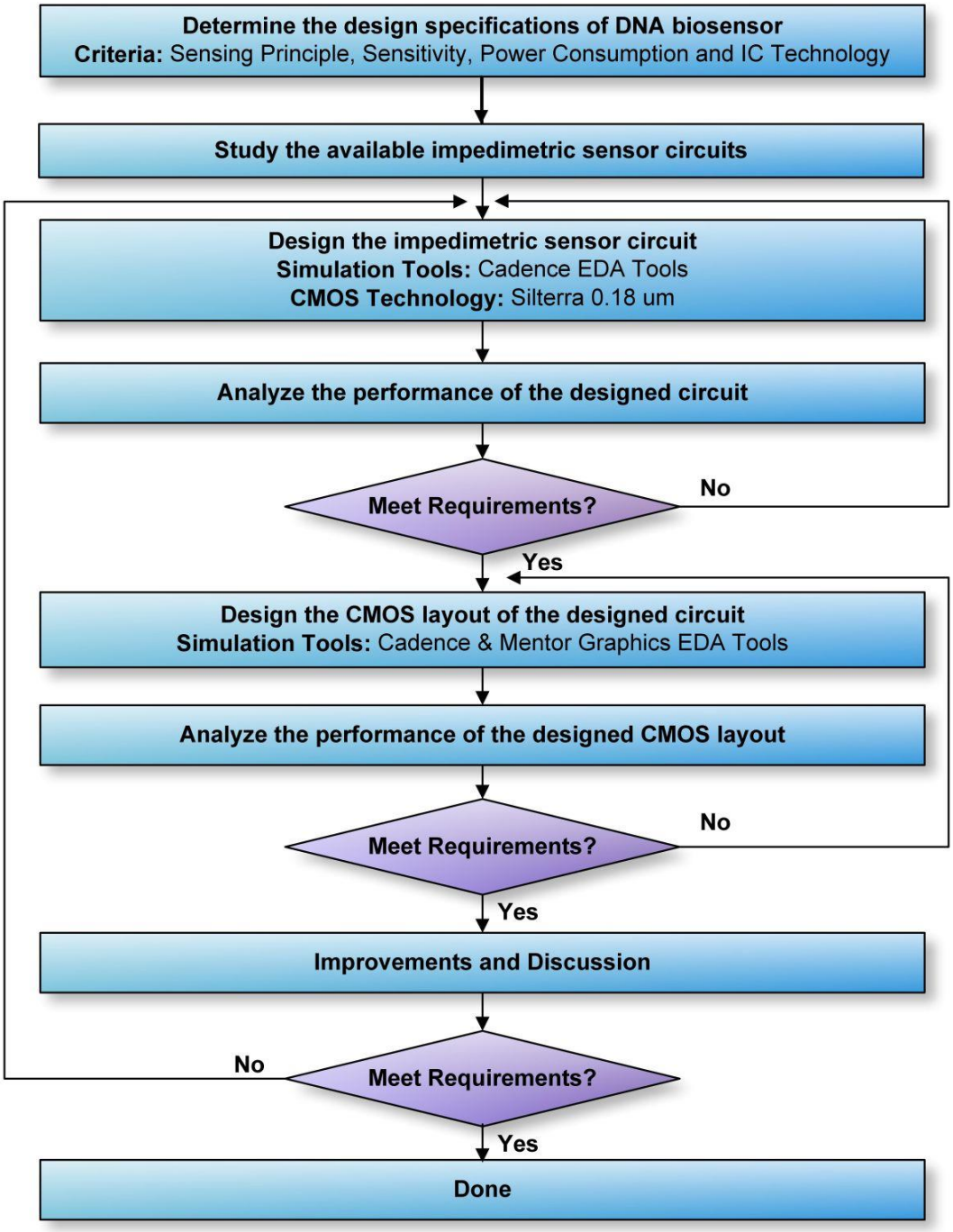

Figure 1.5 Research methodology of this research.

1.7 Significance of the Study

The principal goal of this work is to design a high sensitivity and low voltage (< 2 V) impedance-based detection circuit for DNA hybridization detection. The impedance-based detection circuit that measures the changes of both capacitance and resistance of the electrode-electrolyte interface due to hybridization event is expected to provide a more stable and accurate result compared to the capacitive detection method. With a highly sensitive detection circuit, DNA testing can be performed with small volume of DNA sample. Besides that, it is able to detect short-stranded DNA which is less than 10-mer.

In this study, the optimized detection circuit has simpler topology and lower power consumption compared to [13] by reducing the number of transistors. The achieved low power and small area consumption shows high possibility towards future array intergration for massively parallel analysis of DNA detection, which is highly desirable in POC applications.

1.8 Thesis Outline

In this thesis, the background of the basic architecture of the biosensor and DNA molecules is provided in the Chapter 1. Chapter 2 discusses the various kinds of existing DNA detection methods. The principles and the advantages of these DNA detection methods are discussed in detail. Furthermore, this chapter also gives an overview of the operational principles and the building blocks of the impedance-based detection circuit. Chapter 3 describes the design procedures of the impedance-based detection circuit in a 0.18 μm CMOS process. The schematic and IC layout of the detection circuit are presented in this chapter. Chapter 4 presents and discusses the simulated performance results of the designed impedance-based detection circuit, and Chapter 5 concludes and summarizes the contribution of this work.

REFERENCES

1. Lambrechts, M. and Sansen, W. *Biosensors: Microelectrochemical Devices*. Bristol:Institute of Physics Publishing, 1992.

2. Fan, X. D., White, I. M., Shopova, S. I., Zhu, H. Y., Suter, J. D. and Sun, Y. Sensitive Optical Biosensors for Unlabeled Targets: A Review. *Analytica Chimica Acta*. 2008. 620(1-2):8–26.

3. Sweet, K. M. and Michaelis, R. C. *The Busy Physician's Guide to Genetics, Genomics and Personalized Medicine*. New York:Springer, 2011.

4. Diagram of DNA Double Helix. *US National Library of Medicine*. [Accessed 12 February 2014]. Available from: http://ghr.nlm.nih.gov/handbook/basics/dna

5. Gold, B. Automated DNA Hybridization and Detection. In: Patrinos, G. and Ansorge, W. eds. *Molecular Diagnostics*. 2nd. USA:Academic Press. 501-511;2009.

6. Cagnin, S., Caraballo, M., Guiducci, C., Martini, P., Ross, M., Santaana, M., Danley, D., West, T. and Lanfranchi, G. Overview of Electrochemical DNA Biosensors:New Approaches to Detect the Expression of Life. *Sensors*. 2009. 9(4):3122-3148.

7. Cansiz, S. *Development of a Sandwich-Type DNA Array Platform for the Detection of Label-Free Oligonucleotide Targets*. Master Philosophy, Middle East Technical University, Turkey. 2010.

8. Trujillo, R. M., Cattani-Scholz, A., Bora, A., Vandalo, V., Madrid, R. and Tornow, M. Impedance Spectroscopy Measurements of a Label Free Functionalized Silicon Sensor. *XVIII Congreso Argentino de Bioingenieria SABI*. September 29 - 30, 2011. Mar Del Plata, Argentina:SABI 2011. 151-160.

9. Lee, K. H., Lee, J. O., Sohn, M. J., Choi, S. H., Wang, S. W., Yoon, J. B. and Cho, G. H. An Electronic DNA Sensor Chip Using Integrated Capacitive Read-out Circuit. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. August 31- September 4, 2010. Buenos Aires, Argentina:IEEE. 2010. 6547-6550.

10. Lee, K. H., Cho, S. C., Lee, J. O., Yoon, J. B. and Cho, G. H. CMOS Capacitive Biosensor with Enhanced Sensitivity for Label-free DNA Detection. *IEEE International Solid-State Circuits Conference*. February 19-23, 2012. San Francisco, CA:IEEE. 2012. 120-122.

11. Yusof, Y. *Nonfaradaic Impedimetric Sensing of Biomolecules on Gold Electrodes for Applications in Label-free Biosensors*. PhD Philosophy, Nagoya University, Nagoya, Japan. 2010.

12. Lee, K. H., Lee, J. O., Sohn, M. J., Lee, B., Choi, S. H., Kim, S. K., Yoon, J. B. and Cho, G. H. One-chip Electronic Detection of DNA Hybridization Using Precision Impedance-based CMOS Array Sensor. *Biosensors & Bioelectronics*. 2010. 26(4):1373–1379.

13. Manickam, A., Chevalier, A., McDermott, M., Ellington, A. D. and Hassibi, A. A CMOS Electrochemical Impedance Spectroscopy Biosensor Array for Label-free Biomolecular Detection. *IEEE International Solid-state Circuit Conference*. February 7 - 11, 2010. San Francisco, CA:IEEE. 2010. 130-131.

14. Carrara, S., Benini, L., Bhalla, V., Stagni, C., Ferretti, A., Cavallini, A., Ricco, B. and Samor ì B. New Insights for Using Self-assembly Materials to Improve the Detection Stability in Label-free DNA-chip and Immuno-Sensors. *Biosensors & Bioelectronics*. 2009. 24(12):3425–3429.

15. Carrara, S., Cavallini, A., Leblebici, Y., Micheli, G., Bhalla, V., Valle, F., Samori, B., Benini, L., Ricco, B., Inger, V. L. and Munter, T.. Capacitance DNA Bio-Chips Improved by New Probe Immobilization Strategies. *Microelectronics Journal*. 2009. 41(11):711–717.

16. Wolfbeis, O. S. *Fluorescence Methods and Applications: Spectroscopy, Imaging, and Probes*. New York:New York Academy of Science, 2008.

17. Wiedemann, E. Ueber Fluorescenz Und Phosphorescenz. *Annalen der Physik*. 1888. 34:446-443.

18. Homola, J., Yee, S. S. and Gauglit, G. Surface Plasmon Resonance Sensors: Review. *Sensors and Actuators B: Chemical*. 1999. 54(1-2):3–15.

19. Schena, M., Shalon, D., Davis, R. W. and Brown, P. O. Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray. *Science*. 1995. 270(5235):467–470.

20. Jang, B., Cao, P., Chevalier, A., Ellington, A. and Hassibi, A. A CMOS Fluorescence-Based Biosensor Microarray. *ISSCC Digest of Technical Papers*. February 8-12, 2009. San Francisco, CA:IEEE. 2009. 436–437.

21. Zhao, X. J., Tapec-Dytioco, R. and Tan, W. H. Ultrasensitive DNA Detection Using Highly Fluorescent Bioconjugated Nanoparticles. *Journal of the American Chemical Society*. 2003. 125(38):11474–11475.

22. Chen, L., Zhang, L., Qiu, T. and Cao, W. Chemiluminescent Detection of DNA Hybridization Based on Signal DNA Probe Modified with Gold and Cobalt Nanoparticles. *International Journal of Electrochemical Science*. 2011. 6(11):5325–5336.

23. Lin, J. M., Shan, X., Hanaoka, S. and Yamada, M. Luminol Chemiluminescence in Unbuffered Solutions with a Cobalt(II)-ethanolamine Complex Immobilized on Resin as Catalyst and its Application to Analysis. *Analytical Chemistry.* 2001. 73(21):5043–5031.

24. Hegyi, G., Kardos, J., Kovacs, M., Malnasi-Csizmadia, A., Nyitray, L., Pal, G., Radnai, L., Remenyi, A., and Venekei, I. *Introduction to Practical Biochemistry*. Hungary:ELTE, Eotvos Lorand University, 2013.

25. Levine, P. M., Gong, P., Levicky, R. and Shepard, K. Active CMOS Sensor Array for Electrochemical Biomolecular Detection. *IEEE Journal Solid-State Circuits*. 2008. 43(8):1859–1871.

26. Nakazato, K., Ohura, M. and Uno, S. CMOS Cascode Source-Drain Follower for Monolithically Integrated Biosensor Array. *IEICE Transactions Electronics*. 2008. E91-C(9):1505–1515.

27. Bard, A. J. and Faulkner, L. R. *Electrochemical Methods: Fundamentals and Applications*. New York:Wiley and Sons, 2001.

28. Schienle, M., Paulus, C., Frey, A., Hofmann, F., Holzapfl, B., Schindler-Bauer, P. and Thewes, R. A Fully Electronic DNA Sensor with 128 Positions and In-Pixel A/D Conversion. *IEEE Journal Solid-State Circuits*. 2004. 39(12):2438-2445.

29. Wang, J. Electrochemical Glucose Biosensors. *Chemical reviews*. 2008. 108(2):814–825.

30. Bergveld, P. Development of an Ion-Sensitive Solid-State Device for Neurophysiological Measurements. *IEEE Transactions on Bio-medical Engineering*. 1970. BME-17(1):70–71.

31. Uslu, F., Ingebrandt, S., Mayer, D., Bocker-Meffert, S., Odenthal, M. and Offenhausser, A. Labelfree Fully Electronic Nucleic Acid Detection System Based on a Field-Effect Transistor Device. *Biosensors & Bioelectronics*. 2004. 19(12):1723–1731.

32. Barbaro, M., Caboni, A., Loi, D., Lai, S., Homsy, A., Van der Wal, P. D. and De Rooij, N. F. Label-free, Direct DNA Detection by Means of a Standard CMOS Electronic Chip. *Sensors and Actuators B: Chemical*. 2012. 171-172(Aug-Sept):148–154.

33. Dill, K. and Ghindilis, A. Electrochemical Detection on Microarrays. In: Dill, K., Liu, R. H. and Grodzinski, P. eds. *Microarrays Preparation, Microfluidics, Detection Methods, and Biological Application*. USA:Springer. 25–35; 20099.

34. Allen, P. E. and Holberg, D. R. *CMOS Analog Circuit Design*. 3rd. New York:Oxford University Press, 2011.

35. Prodromidis, M. Impedimetric Biosensors and Immunosensors. *Proceedings of 2nd International Seminar on Analytical Sciences*. 2007. 8(1):69–71.

36. Daniels, J. and Pourmand, N. Label-Free Impedance Biosensors: Opportunities and Challenges. *Electroanalysis*. 2007. 19(12):1239–1257.

37. Manickam, A. *Integrated Impedance Spectroscopy Biosensors*. PhD Philosophy, University of Texas, Austin, United States. 2012.

38. Matsuoka, Y. and Yamamoto, T. Integration of Ultra-Sensitive On-Chip Electric Circuit for Non-Faradaic Electric Current Based Flow Sensing. *The 16th International Conference on Miniaturized Systems for Chemistry and Life Sciences*. October 28, 2012. Okinawa, Japan:T2R2. 2012. 1789–1791.

39. Gomez, M. M., Motilla, R. and Diez, E. Adsorption of Proline on a Mercury Electrode in Neutral Solution. *Electrochimica Acta*. 1989. 34(6):831–839.

40. Pillai, K. C., Waghome, W. E., and Wilson, O. An Electrochemical Study of the Mercury/Lithium Perchlorate Interface in Dimethylsulphoxide + Propylene Carbonate Mixtures at 298 K. *Journal of Electroanalytical Chemistry and Interfacial Electrochemistry*. 1988. 252(1):151–168.

41. Macdonald, J. R. *Impedance Spectroscopy: Emphasizing Solid Materials and Systems*. New York:Wiley, 1987.

42. Lasia, A. Electrochemical Impedance Spectroscopy and its Applications. In: Conway, B. E., Bockris, J. O., and White, R. E. eds. *Modern Aspects of Electrochemistry*. Vol. 32. USA:Springer. 143–248; 2002.

43. De Marcellis, A., Ferri, G., Patrizi, M., Stornelli, V., D Amico, A., Di Natale, C., Martinelli, E., Alimelli, A. and Paolesse, R. An Integrated Analog Lock-In Amplifier for Low-Voltage Low-Frequency Sensor Interface. *2nd International Workshop on Advances in Sensors and Interface*. June 26 - 27, 2007. Bari:IEEE. 2007. 1–5.

44. Meade, M. L. *Lock-in Amplifier: Principles and Applications*. England:Short Run Press Ltd, 1983.

45. Razavi, B. *Design of Integrated Circuits for Optical Communications*. 2nd. United States:John Wiley and Sons, 2012.

46. Nikne, A. M. and Hashemi, H. *mm-Wave Silicon Technology: 60 GHz and Beyond*. USA:Springer, 2008.

47. Lann, A. M. *RF CMOS Power Mixer Design for Short Range Wireless Applications with Focus On Polar Modulation*. Master Philosophy, Linkoping University, Linkoping, Sweden. 2006.

48. Zhang, F., Skafidas, E. and Shieh, W. A 60-GHz Double-Balanced Gilbert Cell Down-Conversion Mixer on 130-nm CMOS. *IEEE Radio Frequency Integrated Circuits (RFIC) Symposium*. June 3-5, 2007. Honolulu, HI:IEEE. 2007. 141–144.

49. Bosco, L. *VLSI for Wireless Communication*. New York:Prentice Hall, 2002.

50. CEDEC MPW. [Accessed 23 April 2014]. Available from: http://www.cedec.usm.my/MPW/technology.html

51. Daniels, J. S. and Pourmand, N. Label-Free Impedance Biosensors: Opportunities and Challenges. *Electroanalysis*. 2008. 19(12):1239–1257.

52. Suni, I. I. Impedance Methods for Electrochemical Sensors Using Nanomaterials. *Trends in Analytical Chemistry*. 2008. 27(7):604–611.

53. Bravo-Anaya, L. M., Macias, E. R., Ramos, F. C., Alvarez-Ramirez, J. G., Casillas, N., Soltero, J. F. A. and Larios-Duran, E. R. DNA Transitions by an Adsorption Impedance Study. *Journal of the Electrochemical Society*. 2013. 160(4):G69–G74.

54. Razavi, B. *Design of Analog CMOS Integrated Circuits*. New York:McGraw-Hill, 2001.

55. Samadiboroujeni, M. *High Performance CMOS Integrated Circuits for Optical Receivers*. Phd Philosophy, Texas A&M University, Texas, United States. 2006.

56. Filho, E. J. D. C., Ribeiro, L. E. B. and Fruett, F. Full Design of an Electrochemical Impedance Spectroscopy Sensor. *Workshop on Circuits and Systems*. September 3 - 6, 2013. Curitiba, Brazil:IEEE. 2013. 3–6.

57. Ping, Lo. *A Fully Differential CMOS Operational Amplifier Implemented with MOS Gain Boosting Technique*. Master Philosophy, Texas Tech University, Texas, United States. 1996.

58. Roberge, J. K. and Lundberg, K. H. *Operational Amplifiers: Theory and Practice*. Massachusetts:John Wiley & Sons, 2007.

59. Texas Instrument. *μA741x General-Purpose Operational Amplifiers Datasheet*. 2014.

60. Baker, R. J. *CMOS Circuit Design, Layout and Simulation*. 3rd. New Jersey: John Wiley & Sons, 2010.

61. Clein, D. *CMOS IC Layout: Concepts, Methodologies, and Tools*. United States:Butterworth-Heinemann, 2000.

62. Schneider, M. C. and Galup-Montoro, C. *CMOS Analog Design Using All-Region MOSFET Modeling*. United States:Cambridge University Press, 2010.

63. Liu, Z. H., Bian, C., Wang, Z. H. and Zhang, C. Full Custom Design of a Two-Stage Fully Differential CMOS Amplifier with High Unity-Gain Bandwidth and Large Dynamic Range As Output. *IEEE International Midwest Symposium on Circuits and Systems*. August 7 - 10, 2005. Covington, KY:IEEE. 2005. 984 - 987.

64. Bakhshiani, M., Suster, M. A. and Mohseni, P. A Broadband Biosensor Interface IC for Miniaturized Dielectric Spectroscopy From MHz to GHz. *Custom Integrated Circuits Conference (CICC)*. September 22 - 25, 2013. San Jose, CA:IEEE. 2013. 1–4.

65. Massoud, A. *Investigation of a Biosensor for DNA Detection*. Master Philosophy, Massey University, Auckland, New Zealand. 2011.

66. Rivera-Gandia, J., Maldonado, M., Torre-Melendez, Y., Ortiz-Quiles, E. O., Vargas-Barbosa, N. M. and Cabrera, C. R. Electrochemical Capacitance DNA Sensing at Hairpin-Modified Au Electrodes. *Journal of Sensors*. 2011. 2011(2011):1-6.

67. Silterra CMOS Logic CL180G. [Accessed 15 March 2014]. Available from: http://www.silterra.com/c1180g.html..

68. Balasubramanian, V., Ruedi, P. F., Temiz, Y., Ferretti, A., Guiducci, C. and Christian, C. A 0.18 μm Biosensor Front-End Based on 1/f Noise, Distortion Cancelation and Chopper Stabilization Techniques. *IEEE Transactions on Biomedical Circuit and System*. 2013. 7(5):660–673.