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Biomedical Integrated Circuit Design
for
An Electro-Therapy Device

A Thesis Presented in Partial Fulfilment
of The Requirements for The Degree of

Doctor of Philosophy

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(Bioelectronics)
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In the name of God

Most Gracious, Most Merciful

Dedication

To my parents, whose boundless love and belief in me, from the core of my being, empowered me to be the woman that I am.

To my lovely children and to my talented kids, Zain, Taim and Yoseph, whom are the light in my life.

"Our Actions Today are The Future of The Human Being."

Abstract

A biomedical integrated circuit design (IC) is utilized for the development of a novel non-invasive electro-therapy device, for low frequency multi-channel biomedical stimulation to transform immune activity and induce anti-viral state. Biomedical integrated circuit design is an important branch of modern electronic engineering that uses the application of electronic engineering principles for biomedical disciplines, to develop bioelectronics devices that are implanted within the body and for non-invasive devices to improve patient's lives. These devices use the application of an electric field to stimulate reactions to restore normal cell functions and activate the cells to treat a variety of disorders or disease conditions. Bioelectronics devices can be designed for use as alternative treatments to overcome the deficiencies of several conventional medical treatments. It could potentially assist as drug-free relief when therapeutic drugs become ineffective, costly, with serious side effects and cannot be replaced, loss of future treatment options, and hence, life threatening, as for drug resistant Human immunodeficiency virus (HIV-1) patients.

Since the underlying mechanisms of the biological system and disease state is dominated by electrostatic interactions, specifically, the interaction between HIV-1 and the host cell that is predominantly by electrostatic interactions (protein charge-charge interaction) has an important role in its life cycle replication. At given pulses, the charge distribution and polarization of the electro-active protein molecules takes place, inducing conformation change which can enhance immune activity and inhibit the interaction of HIV-1 and host cells, disturbing its life cycle, leading to the mechanisms of the inactivation signal-induced virus death. These electrically induced protein transformations is used in this research as blood-cell treatment and as anti-HIV-1 electrotherapy.

Advances in bioelectronics technology, which involve new CMOS IC design, and in bio-electrochemistry science, which include cellular function, electro-active biomolecules and their responses, have contributed to this project to develop the concept of a novel electro-therapy device, for biomedical treatment applications. This involves understanding of the underlying mechanisms of the biological system and disease condition from an electronic engineer's point of view as well as the interface

between the electronic signal and the biological cells, and how electronic devices and circuitry directly communicate with the electro-active body tissue and blood cells.

This research project addresses the design and development of a novel energy-efficient miniature biomedical device using a new CMOS technology. It can generate, deliver and control an appropriate periodical low frequency electrical pulses, through the low-resistance skin surface to a patient's blood. The notable feature of such a smart device is its cellular specificity: the parameters of the generated electrical pulse which are designed and selected in order to stimulate only one particular type of tissue (blood) leaving the others unaffected. The device comprises a mixed-signal low power dual-band waveform generator (WFG) chip along with a novel two band tuning system. It was fabricated using Global Foundries (GF) 8RF-DM 130-nm CMOS process with a supply voltage of ±1V for the analog circuit and +1V for logic circuits. The WFG core (band I) can be tuned in the range 6.44 kHz - 1003 kHz through bias current adjustment, while a lower frequency (band II) in the range 0.1 Hz to 502 kHz can be provided digitally. Two WFG approaches, that comprise relaxation oscillators with different relaxation timing networks, have been developed for comparison.

Since the aim of this work is to transfer electrical signal in a specifically controlled fashion through the tissue, a novel low power active electrode-pair signal delivery system, compatible with human skin with high signal integrity, is developed. The circuit was fabricated in a 130-nm CMOS process using a low supply-voltage of +1.2V to deliver bi-phase square waveform signals from 16 selectable low-frequency channels. The individual active electrode can also be used to deliver mono-phase square/triangular waveform output signals. Accuracy, safety, low power, light-weight, miniature and low-cost characteristics are the main concerns. Being a miniature bioelectronics component with low power consumption, the proposed device is suitable both as a non-invasive and as an implantable biomedical device, in which WFG and electrodes circuitry can communicate with the electro-active biomolecule, strongly stimulating certain events in a complex biological system.

A theoretical analysis, experiment design and performance are carried out in in-vitro environments to examine the effect of the designed signal on human blood cellular proteins. Proteins that display a heterogeneous structure have various conductivities and permittivity (determining the interaction with the electrical field) and possess dielectric properties with a large conformation change, undergoing structural rearrangements in

response to cellular signals. The frequency-dependent dielectric present in proteins involves the redistribution and alignment of the proteins charged molecule and its polar molecule in response to an applied external electrical field can also induce conformation change. Interference polarization within proteins could interrupt the interaction between both sides of predominantly host cell proteins and of the HIV-1 infective envelope and its protein particles. This could disturb the signalling proteins for cell activation, and, hence, the virus cannot conjugate with the target cells and control the host cell protein activity. Since the virus is unable to reproduce out of a host cell, hence the virus cannot mutate and develop resistance easily, and use alternative binding and entry mechanisms as in the pharmacological approaches. After carefully studying the interaction of the HIV-1 virus and the host cell, with respect to signal transfer, CD4 receptor, co-receptors CCR5 and nuclear transport factor nucleoporins FGNup153 proteins of the lymphatic system, which are essential targets for HIV-1 infection and its life cycle replication represent an attractive target to investigate in this research project. The activities of the underlying mechanism of the target cell are then examined utilizing immunofluorescence microscopy technique with specific fluorescent labelled antibodies, and accurate results are obtained with relatively low cost. The results demonstrated that the low frequency electrical pulse could inhibit virus attachment and fusion. It is also could provide a permeability barrier, that prevents the import and export of large macromolecule virus particles through the nuclear pore complex. These effects could induce an antiviral state for a period of time, and stope HIV-1 virus replication, with no potential risks and harm to the host cells, compared to the common drugs. This is promising for the conception of HIV-1 treatment in vivo. Although further investigations are required in order to fully use the application of electrical stimulation in vivo for treatment, the result is provides the necessary impetus for the applications of low frequency electrical stimulation on human immune response. This might offer important antiviral therapy against the most devastating pathogens in human history.

This doctoral research is not only of academic interest but also highly relevant to medical applications. It is considered potentially beneficial in the development of knowledge in advanced technology for electro-medical treatment devices, their design, structure and applications to extend life, and for future growth in the biotechnology industry, therefore beneficial for the patients, physicians and for humanity.

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List of Abbreviations

AA	Amino Acid
Ab	Antibody
D	Aspartic Acid
BJT	Bipolar Technology
BSA	Bovine Serum Albumin
CCII	Current Conveyor
CFOA	Current Feedback Operational Amplifier
Clk	Clock
Clk_bar	Clock_bar
CM	Current-Mode
CSE	Clocked Storage Element
D-FF	D-Flip Flop
DRC	Design Rule Checking
ELF	Extra Low Frequency
FBS	Fetal Bovine Serum
FD	Frequency Divider
FF	Flip Flop
FG	Phenylalanine-Glycine
h	Hour
HCl	Hydrochloric acid
HIV-1	Human immunodeficiency virus
IC	Integrated Circuit
Kap	Karyopherin
LVS	Layout Versus Schematic
mAbs	Monoclonal Antibodies
min	Minute
MLF	Moderate Low Frequency
MUX	Multiplexer
NES	Nuclear Export Signal
NLS	Nuclear Localization Signal
nm	Nano-metric

NPC	Nuclear pore complex
Op-Amp	Operational Amplifier
OTA	Operational Trans-conductance Amplifiers
PFA	Paraformaldehyde
PG	Pass Gate
PIC	Pre-Integration Complex
PS	Path Selector
PVT	Process And Temperature Variation
Q	Glutamine
SC	Stratum Corneum
SDL	Schematic-Driven Layout
ST	Schmitt Trigger
STG	Stage
TG	Transmission-Gate
TGFF	Transmission-Gate Flip Flop
VTC	Voltage Transfer Characteristic
WFG	Waveform Generator
WFG_{INTG}	Waveform Generator Based on Integrator Timing Network
Y	Tyrosine

List of Symbols

A	Area	Meter Square
C	Capacitor	Farad
C_{ox}	Gate oxide capacitance	Farad
gm	Trans-conductance	Microampere/microvolt
W	Channel width of the MOSFET	Micro-meter
L	Channel length of the MOSFET	Micro-meter
ro	Output resistance of MOSFET	Ohms
μn	Electron mobility	Meter square/Volts seconds
IB	Bias Current of MOSFET	Microamperes
ID	DC Drain current of MOSFET	Microamperes
V_C	Capacitor Voltage Output	Volts
VDD	Positive Supply Voltage	Volts
V_{INT}	Integrator Voltage Output	Volts
Vo	Output Voltage	Volts
VSS	Negative Supply Voltage	Volts
V_{GS}	Gate-source voltage of MOSFET	Volts
V_{LTH-}	Lower Threshold Voltage	Volts
V_{ST}	Schmitt Trigger Voltage Output	Volts
V_{TH}	Threshold voltage	Volts
V_{UTH+}	Upper Threshold Voltage	Volts
V_{in}	Input Voltage	Volts
V_{sat-}	Low Negative Saturation Level	Volts
V_{sat+}	High Positive Saturation Level	Volts
R	Resistor	Ohms
P	Power	Watts
f	Frequency	Hertz
$\boldsymbol{\tau}$	Time constant	Seconds
T	Time Period	Seconds
ω	Angular frequency	Radians per second

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