HARDWARE IMPLEMENTATION FOR CARDIAC ELECTRICAL EXCITATION AND CONDUCTION USING AN FPGA

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A thesis submitted in partial
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For my beloved husband Zainul Idlan Bin Komar,
my adorable son Zainul Zafran and my beautiful daughter Zainur Zafrah,
all my family and to everyone who supports me, it just begins…

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ABSTRACT

Contraction of the heart is controlled by electrical excitations of cardiac cell membranes. The electrical excitations of the cells and their propagation in the heart tissue provide a basis of the physiological function of the heart through the cardiac excitation-conduction mechanism. One way to understand normal and abnormal dynamics of the heart is to simulate a comprehensive mathematical model of the cardiac excitation in order to study underlying mechanisms of the heart electrical system. However, simulating the dynamics of large numbers of a cellular model to form a tissue model requires an immense amount of computational time. In order to reduce the computational time required for the simulation, a hardware implementation of cardiac electrical excitation-conduction analysis system has been developed based on FitzHugh-Nagumo (FHN) model for a mammalian cardiac ventricular cell. In this research, one dimensional (1D) ring-shaped cable model with 80 compartments of the cell model designed using MATLAB Simulink blocks is able to be converted into synthesizable VHSIC (Very High Speed Integrated Circuit) of Hardware Description Language (VHDL) code by using an FPGA-based rapid-prototyping approach of MATLAB HDL Coder in order to simulate an action potential signal and its conduction through a hardware-implemented Field Programmable Gate Array (FPGA). Then, the VHDL design is functionally verified on an FPGA Xilinx Virtex-6 board using MATLAB HDL Verifier through FPGA-in-the-Loop (FIL) simulation approach. Simulations of cardiac cellular processes and reentrant arrhythmia are successfully conducted on Xilinx Chipscope Pro. High accuracy results have been obtained from the FPGA-on-board simulation compared to a software-based computer simulation with Percentage Error (PE) of 1.28% and 1.56% in performing the simulations of reentrant initiation and annihilation, respectively. The simulations are also capable to run in real time.

ABSTRAK

Kontraksi jantung dikawal oleh eksitasi elektrik pada membran sel jantung. Pengujaan elektrik pada sel dan perambakan sel-sel dalam tisu jantung memberikan asas fungsi fisiologi jantung melalui mekanisme eksitasi-kontraksi. Salah satu cara memahami dinamik normal dan tidak normal pada jantung adalah mensimulasikan satu model matematik yang komprehensif untuk mengkaji mekanisme sistem jantung. Walaubagaimanapun, simulasi dinamik model sel dengan jumlah yang banyak bagi membentuk tisu memerlukan tempoh masa pengiraan yang lama. Dalam usaha mengurangkan masa pengiraan simulasi, pelaksanaan perkakasan jantung elektrik bagi sistem analisis eksitasi-kontraksi telah dihasilkan berdasarkan model Fitzhugh-Nagumo (FHN) untuk sel ventrikel jantung pada mamalia. Dalam kajian ini, kabel bentuk cecincin satu dimensi (1D) dengan 80 sel direka menggunakan blok MATLAB Simulink seterusnya ditukar secara automatik kepada bahasa perihal peralatan litar bersepadu berkelajuan tinggi (VHDL) boleh sintesis menggunakan kaedah protataip-pantas MATLAB HDL Coder untuk mensimulasikan isyarat keupayaan tindakan dan konduksinya melalui pelaksanaan peranti tatasusunan get boleh aturcara (FPGA). Kemudian, fungsi reka bentuk VHDL itu disahkan pada satu papan tunggal FPGA Xilinx Virtex-6 menggunakan Pengesah HDL melalui simulasi gelung dalam FPGA (FIL). Simulasi proses sel jantung dan aritmia berjaya dikendalikan pada penganalisis logik terbenam Xilinx Chipscope Pro. Keputusan dengan ketepatan yang tinggi telah diperolehi daripada simulasi atas papan FPGA berbanding dengan simulasi komputer berasaskan perisian dengan peratus ralat (PE) 1.28% dan 1.56%, masing-masing dalam melaksanakan simulasi penghasilan dan penghapusan masuk-semula. Simulasi ini juga mampu beroperasi dalam masa nyata.

CONTENTS

LIST OF PUBLICATIONS

1. **N.A. Adon**, F. Mahmud, M.H. Jabbar & N. Othman. (2015). Optimization in MATLAB for Cardiac Excitation Modeling Towards FPGA Standalone Simulation Tools. *Applied Mechanics and Materials Trans Tech Publications, Switzerland*, Vol. 773-774, pp. 761-765. ISSN: 1662-7482.

2. **N.A. Adon**, M.H. Jabbar & F. Mahmud. (2015). FPGA Implementation for Cardiac Excitation-Conduction Simulation based on FitzHugh-Nagumo Model. *5th International Conference on Biomedical Engineering in Vietnam (IFMBE Proceedings)*, Vol. 46, pp. 117-120. Springer International Publishing. ISBN: 978-3-319-11775-1.

3. **N.A. Adon**, F. Mahmud, M.H. Jabbar & N. Othman. (2014). FPGA-in-the-Loop Co-simulation of Reentrant Arrhythmia Mechanism in One Dimensional (1D) Ring-Shaped based on FitzHugh-Nagumo Model. *2014 IEEE International Conference on Control System, Computing and Engineering*, pp. 239-244. ISBN: 978-1-4799-5685-2.

4. **N.A. Adon** & F. Mahmud. (2013). Simulation of Reentrant Arrhythmia Mechanism in One Dimension Ring-Shaped Model using Simulink. *Prosiding Seminar Kebangsaan Aplikasi Sains Dan Matematik (SKASM)*, Jilid 3: pp. 9-20. Penerbit UTHM. ISBN: 978-9-670-46850-1.

5. **N.A. Adon** & F. Mahmud. (2013). Cardiac Excitation-Conduction Modeling using MATLAB/Simulink for Real Time FPGA Implementation. *Proceeding of Microelectronics & Nanotechnology (PMiNT)*, pp. 1-3. Penerbit UTHM. ISBN: 978-9-670-76400-9.

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7. N. Othman, F. Mahmud, A.K. Mahamad, M.H. Jabbar &. **N.A. Adon**. (2016). Voltage-Clamp Simulation of Cardiac Excitation: Field Programmable Gate Array (FPGA) Implementation. *ARPN Journal of Engineering and Applied Sceinces 2016.* Vol. 11, no. 24, pp. 14056-14064. ISSN: 1819-6608.

8. N. Othman, **N.A. Adon** & F. Mahmud. (2017). FPGA in-the-loop Simulations of Cardiac Excitation Model under Voltage Clamp Conditions. *International Conference on Engineering, Science and Nanotechnology (ICESNANO) 2016*, Vol. 1788, pp. 030105-(1-7). American Institute of Physics (AIP) Conference Proceeding. ISBN: 978-0-7354-1452-5.

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LIST OF ABBREVIATIONS

1D	One Dimensional
2D	Two Dimensional
3D	Three Dimensional
AIDS	Acquired Immune Deficiency Syndrome
ASIC	Application Specific Integrated Circuit
BER	Bit Error Rate
CAB	Configurable Analog Blocks
CLB	Configurable Logic Blocks
CoreGen	Core Generator
DDR	Double Data Rate
DEPE	Differential Equation Processing Element
DSP	Digital Signal Processing
FHN	FitzHugh-Nagumo
FIL	FPGA-In-the-Loop
FL	Fraction-Length
FMC	FPGA Mezzanine Cards
FPAA	Field Programmable Analog Array
FPGA	Field Programmable Gate Array
GPU	Graphics Processing Unit
HDL	Hardware Description Language
HIV	Human Immunodeficiency Virus
ICON	Integrated Controller
ILA	Integrated Logic Analyzer
IOB	Input Output Blocks
ISE	Integrated Software Environment
ISim	ISE Simulator

JTAG	Joint Test Action Group
LUT	Lookup Table
MAC	Multiply Accumulate Operations
MMCM	Mixed Mode Clock Managers
MSE	Mean Squared Error
NCD	Native Circuit Description
NGD	Native Generic Database
ODE	Ordinary Differential Equation
PAR	Place And Route
PC	Personal Computer
PCI	Payment Card Industry
PCR	Polymerase Chain Reaction
PDSP	Programmable Digital Signal Processors
PE	Percentage Error
PRC	Phase Resetting Curve
RAM	Random Access Memory
RTL	Register Transfer Language
SNR	Signal to Noise Ratio
SOC	System On Chip
SVPWM	Space Vector Pulse Width Modulation
VHDL	VHSIC Hardware Description Language
VHM	Virtual Heart Model
VHSIC	Very High Speed Integrated Circuit
VLSI	Very Large Scale Integration
VSI	Voltage Source Inverter
WHO	World Health Organization
WL	Word-Length
XSG	Xilinx System Generator

CHAPTER 1

INTRODUCTION

1.1 Background of the research

Since a decade ago, cardiovascular disease has remained the top major killer cause of death in the world issued by the World Health Organization (WHO). Referring to Figure 1.1, the ten leading causes of death in the world are ischemic heart disease, stroke, chronic obstructive pulmonary disease, lower respiratory infection, lung cancer, Human Immunodeficiency Virus (HIV) or Acquired Immune Deficiency Syndrome (AIDS), diarrhoeal disease, diabetes mellitus, road injury and hypertensive heart disease. According to the WHO, cardiovascular diseases killed 17.5 million people in 2012 that was 3 in every 10 deaths [1]. It was reported that 7.4 million people died of ischemic heart disease, 6.7 million from stroke and 1.1 million from hypertensive heart disease.

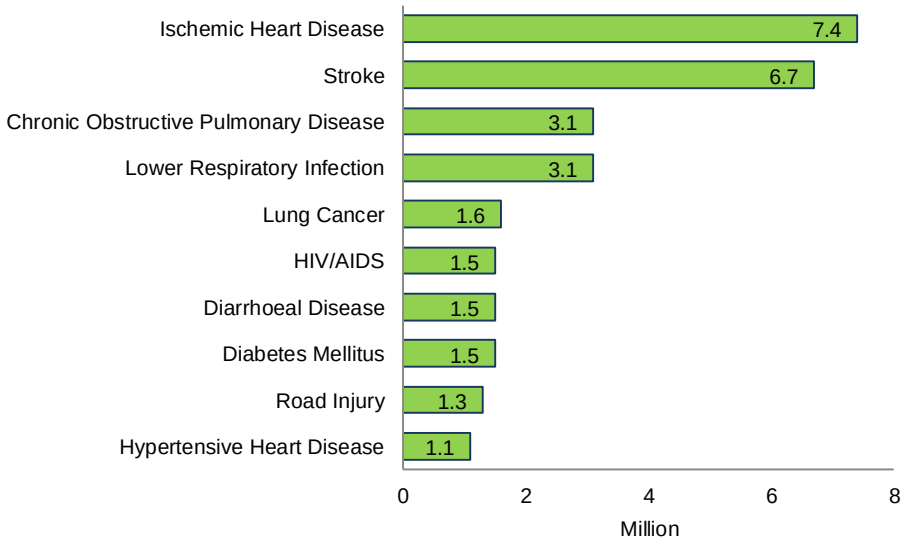

Figure 1.1: The ten leading causes of death in the world [1].

Ischemic heart disease caused by decreased blood flow and reduced oxygen supply to the heart muscle [2]. The disease can interrupt the electrophysiology function of the ion channels responsible for the cellular electrical activity of the heart. Changes in the intracellular and extracellular occur during ischemic and can alter the electrophysiology of several species of ionic channels are in fact related to disturbances in the cellular activity of cardiac myocytes [3]. Thus, until now, many studies have been done to elucidate the causes and interpret the underlying mechanisms in cardiac electrophysiological which are through experimental [4], [5] clinical measurement [6], [7] and computational model simulation [8], [9], [10] studies.

Although, experimental study is generally preferable, but it has several restrictions such as requires high variables quantity for monitoring, expensive and high-resolution data in investigating larger preparations [11], [12]. Meanwhile, clinical tools have become widely used in cardiac electrophysiological studies, often indispensable in evaluating patients with specific cardiac electrical activity [13]. Clinical data are used to validate computational modeling which allow integration of previous findings, quantitative assessments of the models and the projection across relevant spatial and temporal scales [14]. However, clinical tools have several drawbacks which are risk assessment tools, potential harms to patients and the effectiveness or difficulty in comparing results across studies [15], [16]. In contrast, a model simulation technique is not associated with such problems and also has the capability to increase study parameters through mathematical representations and decreasing the time responsible for investigating cardiac dynamics [17], [18].

There are numerous mathematical model had been represented in excitable media for the simulation studies such as Hodgkin–Huxley [19], FitzHugh-Nagumo (FHN) model [20], [21], continued with the Noble model [22], [23], Beeler and Reuter model [24], [25], Luo-Rudy model [26], [27] and details models in order to show different regions of the heart. However, advancement of the computational technique has initiated cardiac cell models to become more complicated as variable parameters in the mathematical descriptions are increased in order to present the cellular process in more details [28], [29]. Thus, a large number of the cell models in forming a tissue model cause drawback in the amount of computational processing which would increase a time required to run the model simulations [30].

According to Prof. Yoshihiko Nakamura (2012), two second motion according of the neuromusculoskeletal model of human takes one hour to compute reduction of computation cost. These situations can be concluded that a real-time model simulation technique has been difficult to achieve especially in the electrophysiological that involves high level dimensional models and simulation conditions [31], [32]. However, a real-time model simulation system is very important in order to diagnose cardiac abnormalities due to heart failure since it simulate more realistically cardiac work and it would be a very useful and convenient system to be applied in medical education and training in cardiac surgical planning such as permanent pacemaker insertion, catheter-based intervention and invasive cardiovascular surgeries [33], [34], [35].

In order to overcome this computational challenge, high performance and low power consumption hardware-based implementation can provide valuable tools for real-time simulation analysis in electrophysiological studies applications such as in the medical and educational field [36], [37]. Currently, researchers have moved forward to use hardware-implemented of analysis tool for cardiac electrophysiology considering their several advantages of extremely fast and parallel mode execution, low power usage, reconfigurable, development ease and low cost [38], [39], [40]. Hence, various types of hardware had been used to simulate the electrical potentials exist across the membrane of cells using hardware such as analog-digital circuit [41], microcontroller [42], Graphic Processing Unit (GPU) [30], [43] and Field Programmable Analog Array (FPAA) [44], [45]. However, these previous studies have shown limitations due to their power consumption and inefficient regarding rapid calculations in performing the real-time operation [46].

Therefore, reconfigurable hardware in the form of Field Programmable Gate Array (FPGA) has appeared as a viable system solution with complex chips in the construction of high performance systems at an economical price [47], [48]. FPGA technology is now considered very useful by an increasing number of designers in various fields of application as it offers reconfigurable hardware, programmable circuit architecture, execute in parallel mode with million gate counts and a low power consumption [47], [49]. Moreover, it is also capable of solving higher orders of Ordinary Differential Equations (ODEs) describing the electrical behavior of the cell membrane [38].

In recent literature, a large number of studies using FPGA for biomedical application are reported [50], [51], [52]. As regards, these have given motivation to implement the FPGA to perform real-time simulations, primarily responsible for the cardiac abnormal activity. This research will emphasise the simulation of reentrant excitation-conduction of cardiac cells realised by coupling 80 active circuits in one dimensional (1D) ring-shaped based on FHN [53] model. In this research, the 1D ring-shaped cable model is constructed using MATLAB Simulink based FPGA rapid-prototyping method towards a real-time simulation in producing an analysis tool to study the underlying mechanism of the heart through understandings of non-linear dynamics in cardiac excitation.

The FPGA configuration is generally specified using a Hardware Description Language (HDL), therefore for rapid design and faster development, the HDL code is generated using MATLAB HDL Coder that is capable to convert the designed MATLAB Simulink model to Very High Speed Integrated Circuit (VHSIC) Hardware Description Language (VHDL) code. Furthermore, the FPGA-based model simulation system which is designed through MATLAB HDL Coder is verified using an FPGA-in-the-Loop (FIL) approach. Towards the hardware implementation in real-time model simulation analysis tool, the design system is then implemented on Xilinx Virtex-6 XC6VLX240T FPGA development board and simulated through embedded logic analyser Xilinx Chipscope Pro. The dynamics of the FHN model simulation using FPGA board are compared to those obtained from the conventional software-based computer simulation technique to evaluate the accuracy and performance of the simulation-based analysis system in order to demonstrate that the FPGA model can be utilised for simulating large scale cellular network in real-time as an alternative to the software-based computer simulation technique in the future.

1.2 Problem statement

As mentioned earlier in the introduction, due to a number of challenges in experimental and clinical investigations of the cardiac electrical behavior [54], mathematical models of cardiac tissue have been developed and analysed by simulating conduction of action potentials in a variety of conditions [18]. However, it is inevitable for those models to become large scale in the number of dynamical variables, requiring immense amounts of computational time for their dynamic simulations. This could cause difficulties in performing in-depth analysis on cardiac electrical functions since many hours of time is required to run dynamic simulations of electrical conduction in tissue or organ level on a conventional computer station. Although a high performance supercomputer is commonly used in conducting fast speed computations for the analysis, it usually requires high installation cost and high energy. Therefore, FPGA based hardware implementation of electrical excitation and conduction of a cardiac cell model simulation system is developed to overcome the challenges. The simulation of 1D ring-shaped cable model is conducted through this research work based on FHN model, a typical mathematical model of a cardiac cell.

1.3 Aim and research objectives

The aim of this research is to develop an analysis system in order to perform a real-time simulation of a cellular excitation reaction in tissue level based on a mathematical model by using FPGA hardware implementation. The proposed implementation can be deployed in a biomedical field for understanding and analysing the mechanism of abnormalities cardiac cycle and will function in the real FPGA-on-board application. To enable this, the thesis is presented in three objectives as follows:

Objective I: To construct a FHN model algorithm based on MATLAB HDL Coder for an FPGA implementation.

Objective II: To develop FPGA-based model simulation system for cardiac excitation and conduction towards real-time analysis tool implementation.

Objective III: To evaluate the technique with conventional simulation method in terms of its accuracy and performance based on simulation studies of the reentrant mechanism in a cardiac excitation-conduction.

1.4 Scope of the research

This research covers a study related to a mathematical model of the action potential conduction in a ventricular cardiac cell, which focuses on the FHN model for developing a new simulation-based analysis technique in cardiac excitation and conduction studies using FPGA. The FPGA-based hardware implemented real-time model simulation system will be developed by solving ODEs of the model based on a rapid-prototyping design flow through MATLAB HDL Coder. This technique accelerates the FPGA design process through automatic generation the VHDL code at a certain level in developing the system and faster optimisation. The rapid-prototyping method does not directly involve on a hardware architecture design of the FPGA by the developer which has more to do with an FPGA traditional design technique.

The reason for choosing the MATLAB HDL Coder as rapid-prototyping tool are because the MATLAB HDL Coder offers and keeps updating many advanced and latest functions for the FPGA design systems, and rapidly assembles system

models usually using only existing blocks of MATLAB Simulink compare to other tools such as Xilinx System Generator (XSG), Digital Signal Processing (DSP) Builder and Labview. Besides, the MATLAB HDL Coder also provides FIL approach to verify the designed system based on various types of FPGA development boards from different manufacturers. Lastly, the generated code by MATLAB HDL Coder is modified, synthesised and implemented by using Xilinx ISE software on the FPGA. The results are displayed on the Xilinx Chipscope Pro as it is able to log data for further analysis.

The FHN model will be used to understand of reentrant mechanisms by performing 1D ring-shaped cable model in cardiac tissue. A 1D ring-topology-network of 80 compartments of the cell model is constructed through interconnection of gap junction resistances for exhibiting the reentrant action potential conduction. The number of the cell models presented is relied on the FPGA specification used and 80 cells is an appropriate number to perform the simulation of the cardiac excitation-conduction in FHN model-based 1D ring-topology-network. However based on the design and type of model, the number could be different. For example, the design of a two dimensional (2D) model might require more number of cells. The simulation results from the FPGA-based model will be compared to those obtained numerically MATLAB software-based computer simulations of the cardiac excitation-conduction activity using the FHN model to verify the accuracy according to an acceptable error simulation of not more than $\pm 1.5\%$ [55] and the timing performance of the simulation system.

1.5 Overall contributions

This project of developing a cardiac reentrant excitation-conduction simulation system has two significant contributions. Firstly, a new approach of FPGA system design based rapid-prototyping that can provide a high performance system and high accuracy result has demonstrated a significant contribution. Through this rapid-prototyping approach, various types of parameters are involved to analyse and optimise the system performances such as area, maximum frequency and power consumption in a much more convenient way. Secondly, the realisation of a real-time simulation of FHN model based cardiac action potential through FPGA

implementation itself has contributed in introducing a new technique of conducting a hardware-based model simulation for real-time performance in cardiac electrophysiological studies.

1.6 Thesis organisation

The thesis organisations are as follows:

Chapter 2 (Literature Review): The second chapter of the thesis will review on the technique of cardiac electrophysiological analysis, which takes a closer look at the most recent studies related to mathematical models focusing on the FHN mathematical model. Besides, topics related to real-time hardware implementation approaches of cardiac model for cardiac excitation simulation and analysis, and a potential application related to the analysis system also being will be discussed in this chapter.

Chapter 3 (Methodology): The third chapter will present the method and design strategies for developing the proposed FPGA hardware implemented model simulation-based analysis system. The workflows of the FPGA development methods used in this research which include rapid-prototyping method for VHDL coding using MATLAB HDL Coder and FPGA programming method for on-board implementation will be concisely explained.

Chapter 4 (Results and Analysis): The fourth chapter will present the results obtained throughout the development of FPGA implemented cardiac simulation-based analysis system using the rapid-prototyping method by MATLAB HDL Coder. The FPGA-on-board simulation and software-based computer simulation results of cardiac excitation-conduction relating to the reentrant mechanism will be presented and a comparative study of the FPGA implementation results for the FHN model for both simulations will also be discussed.

Chapter 5 (Conclusions): The last chapter will summarise the conclusion drawn from the results acquired in this thesis based on the achievements and limitations discovered from this research. Several recommendations for potential future works for further improvement in the development system will also be discussed.

CHAPTER 2

LITERATURE REVIEW

2.1 Overview

In this research, several related topics from previous researches have been studied in order to further understand the situation and the relevance in developing a model simulation-based analysis system implemented on FPGA hardware for real-time simulations of cardiac electrophysiological mechanism. The summarised topic of review in this chapter is illustrated in Figure 2.1. They are identified based on five main topics which are electrical system of the heart, approaches in cardiac electrophysiological analysis, cardiac mathematical models, real-time hardware implementation and its potential application. The oval shape shows the approaches used in this research and selected based on the previous studies according to the advantages and disadvantages that have been identified and discussed in section 2.5 of this chapter.

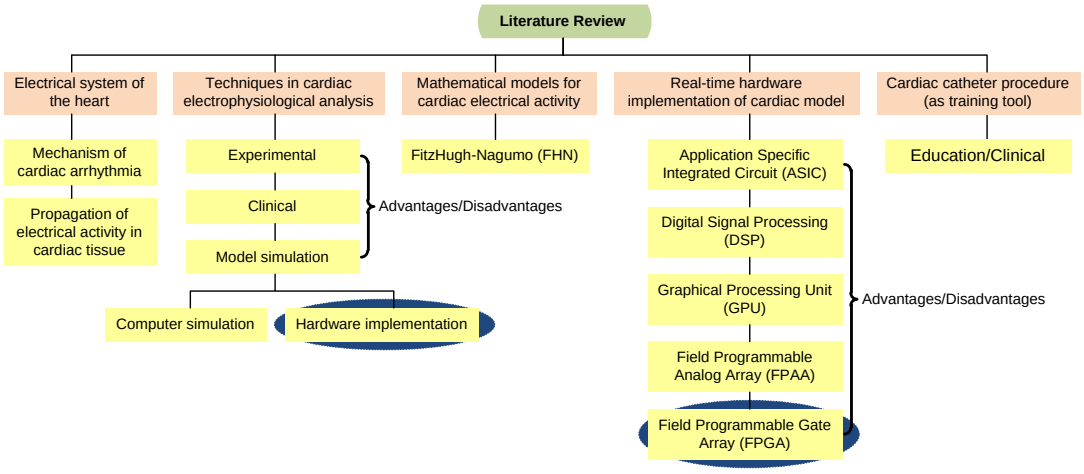

Figure 2.1: Overall of related literature review.

2.2 Electrical system of the heart

The heart is responsible for pumping blood through the blood vessels by an electrical conduction system that coordinates the contraction of the various chambers of the heart. The conduction system is based on a regularly generated electrical impulse by a sinoatrial (SA) node located in the right atrium chamber of the heart and it travels down through the conduction pathway which causes the cardiac cells to excite and the heart to contract in order to allow the heart pumps out blood to the entire body.

The electrical impulse travels from the SA node to the atrioventricular (AV) node. There, impulses are slowed down for a very short period and continue down the conduction pathway via the Bundle of His into the ventricles as shown in Figure 2.2. The Bundle of His divides into right and left pathways to provide electrical stimulation to the right and left ventricles. Normally at rest, as the electrical impulse moves through the heart, the heart contracts about 60 to 100 times a minute, depending on a person's age. Each contraction of the ventricles represents one heartbeat. The atria contract a fraction of a second before the ventricles so their blood empties into the ventricles before the ventricles contract, in other words, the right and left atria are stimulated first and contract for a short period of time before the right and left ventricles.

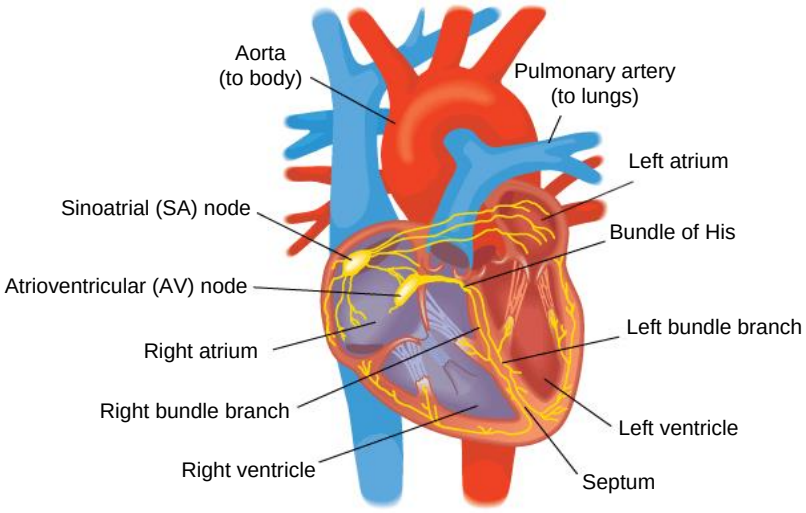

Figure 2.2: The heart system component [56].

Contraction of the heart is controlled by electrical excitations of cardiac cell membranes. The electrical excitations of the cells and their propagation in the heart tissue provide a basis of the physiological function of the heart through the cardiac excitation-contraction mechanism [57]. The initiating event in cardiac excitation-contraction coupling is finely controlled by the influx and efflux of transmembrane currents through various types of ion channels permeable to specific kinds of ions. This event is also known as called action potential.

Most generally, cardiac action potential waveform is defined by five phases as shown in Figure 2.3. The cardiac action potential is often generated in responses where stimulus current from adjacent myocytes (muscle cells) to a threshold value such that fast inward Na^+ current cause rapid depolarisation and transient outward current due to movement of Cl^- and K^+ (phase 0). Then, initial rapid repolarization occurs when closure of the fast inward Na^+ current and outward of K^+ (phase 1), sustained by the balance between the slow inward movement of Ca^{2+} and outward movement of K^+ current for producing plateaus action potential (phase 2). A final repolarization then takes place, when K^+ current remain active to build up outside the cell and K^+ current will inactivate when the membrane voltage reaches a certain level (phase 3). Finally, the membrane voltage in resting phase (phase 4), when the cardiac cell has at rest remained in until stimulated [3].

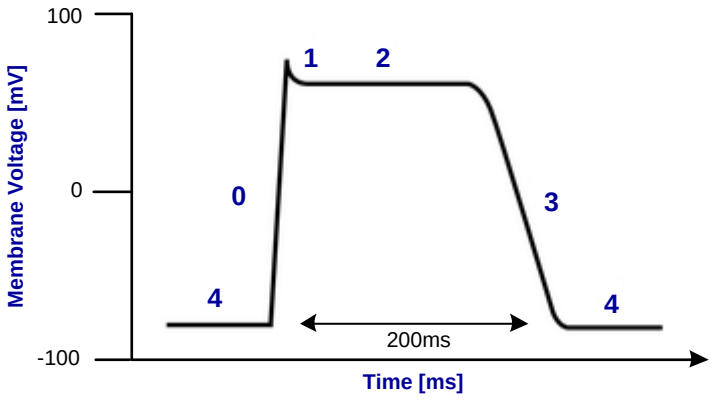

Figure 2.3: Cardiac action potential phases [30].

2.2.1 Propagation of electrical activity in cardiac tissue

The important feature of cardiac cellular interaction is the propagation of action potential waves through interconnected cells in a complex network [58]. Among other factors, the flow of various ions throughout the cardiac tissue is responsible for the propagation of electrical waves through heart tissue. The cells that constitute cardiac muscle, known as myocytes are coupled to each other by intercalated discs, referred to as gap junctions as illustrates in Figure 2.4, allowing the inward current in a single-cell to depolarise another cell and causing repolarization to be synchronised between cells [59] to accommodate the electrophysiological function of the heart through the cardiac excitation-contraction mechanism [57].

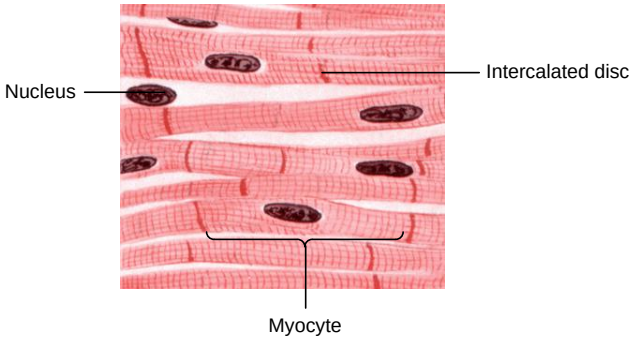

Figure 2.4: The cardiac muscle [11].

By coupling membrane models together, it is possible to take these interactions into account and to create tissue models in which propagating activation can be simulated [29]. Thus, it may be possible to identify the underlying mechanisms that are primarily responsible for the abnormal activity in excitable systems such as cardiac arrhythmias [60], [61]. As for the heart dynamics, some cardiac arrhythmias are perpetuated by reentrant mechanisms. To model the action potential propagation, the cardiac tissue is often represented by a 1D cable model, as a design modeling for a single fiber [62]. By assuming that the effect of the extracellular potential is negligible and it is therefore can be considered as the ground [11] as shown in Figure 2.5.

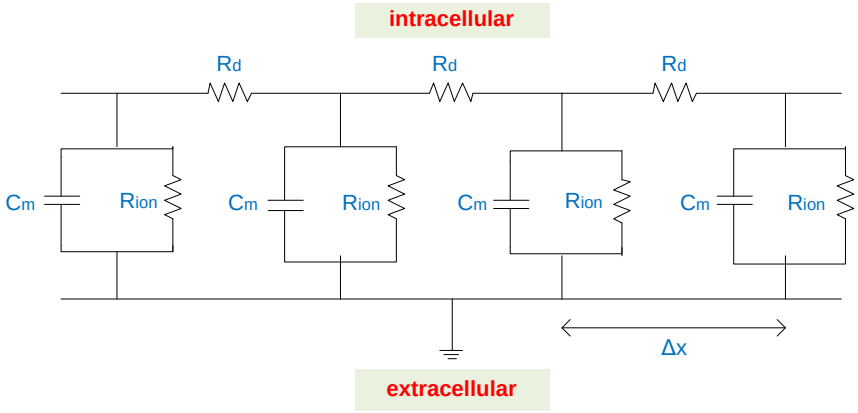

Figure 2.5: An equivalent circuit for a single fiber of cardiac tissue model [11].

The parameters are as follows; R_d is the intracellular resistance which also known as the gap junction resistance, R_{ion} is the membrane resistance referring to specific ionic channels and C_m is the membrane capacitance. This continuous structure described as the limit of an infinite number of resistor and capacitor elements found by subdividing the continuum into segments of length Δx, and every Δx also can be referred as a spatial of one cardiac cell model. As $\Delta x \rightarrow 0$, the discrete representation approaches a continuous presentation [11], [63].

Propagation of action potentials in an excitable tissue is often modeled by using significantly simplified quantitative method that can be represented by the 1D cable model. It is necessary to specify the currents resulting from the intercellular coupling, which can usually be approximated by a monodomain reaction-diffusion and can be described as Equation 2.1 [53].

$$\frac{\partial V_m}{\partial t} = D\left(\nabla^2 V_m\right) - \frac{I_m}{C_m} \tag{2.1}$$

Where,

V_m : Cardiac cell membrane voltage

D : Conductivity tensor (10^{-3}cm^2/ms)

C_m : Diffusion coefficient (1μF/cm^2)

I_m : Time and space dependent injected current

2.2.2 Mechanism of cardiac arrhythmia

In a normal dynamics of the cardiac cycle, the electrical excitation wave dies when it reaches a complete activation of myocardium because of a refractoriness effect of the cardiac tissue according to a previous electrical excitation event. Nevertheless, under abnormal conditions generally due to an abnormal excitation generation or propagation, the propagating wave does not die out completely but re-excite the myocardium that has recovered from the refractoriness which disrupt the mechanical functioning of the heart from supplying sufficient blood to the body [64]. The abnormalities of cardiac excitation basically will cause an irregular heartbeat or known as cardiac arrhythmia. There are two categories of arrhythmias encompass bradyarrhythmias and tachyarrhythmias [65] as depicted in Figure 2.6. Bradyarrhythmias defined as the slow heart beat than normal condition, whereas tachyarrhythmias cause the heart to beat more rapidly than normal.

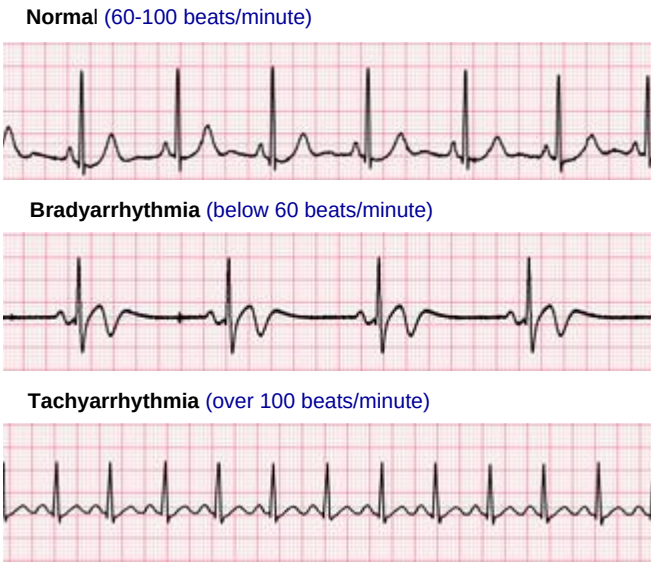

Figure 2.6: Normal and abnormal heart rate [66].

Tachyarrhythmias come from much more varied mechanisms and cause more major problems than bradyarrhythmias. This vastly perpetuated by reentrant mechanism and mostly is caused from the ischemic heart disease as discussed in previous section 1.1. In other words, tachyarrhythmias usually spontaneous onset and thereby may lead to a rapid loss of consciousness and death, while bradyarrhythmias usually exhibit a more gradual onset that provides sufficient time for diagnosis and

therapy, thereby leading to lower levels of death [66]. Therefore, this research will focus on the simulation and analysis aspects of tachyarrhythmias related to the reentrant mechanism.

Reentrant is a mechanism that occurs when cardiac tissue is excited repeatedly by the action potential wave that keeps reentering the same anatomical region [67]. Such reentry could lead to ventricular tachycardia that causes extremely rapid excitation of the heart and even more dangerous cause ventricular fibrillation (VF) [68]. This potentially causes a fatal risk of the heart's ability to efficiently pump blood throughout the body which could lead to a sudden death [61]. The reactivation occurs indefinitely until the excitability of the tissue in the reentrant circuit is somehow affected. In many situations, the cessation of reentrant activity occurs through the interaction of the reentrant activation wave with an activation wave originating from some other part of the heart [11].

2.2.2.1 Anatomical circus movement reentry

By far, the most common type of reentry is circus movement reentry [69], [70]. The name refers to the circulation of an action potential wavefront around an anatomical obstacle, which leads to repetitive activation of the tissue at a frequency that is dependent on the velocity at which the wavefront conducts around the obstacle, and the length of the path around the obstacle [67].

The simplest model of circus movement reentry is the closed ring, where the activation wavefront rotates around an anatomical obstacle. Reentry around a closed ring can typically be identified by the following characteristics: (i) the activation wavefront moves around an anatomically distinct pathway, returning to its origin and then following the same path again; (ii) the activation wavefront moves in one direction only around the ring as a result of the unidirectional conduction block when the reentry is initiated; and (iii) interruption of the reentrant circuit at any point along its path terminates the reentry [71], [72].

For a given closed circuit to form a reentrant ring, the rotation time around the ring must also be longer than the recovery period of all segments of the circuit, which is another way of saying that the front and back of the action potential wave must be separated by an excitable gap [73]. An example of the spatio-temporal

dynamics underlying the interaction of an ectopic action potential with a normal propagating action potential wavefront in the genesis of anatomical circus movement reentry in a closed ring are shown in Figure 2.7.

Initially, the ring is stimulated at the point marked by the solid circle in (b), causing action potentials to propagate around both sides of the ring (waves 1 and 2, initiated at t = 0 ms and t = 400 ms in (a)). These action potentials collide at the point of the ring diametrically opposite the stimulation site, resulting in the annihilation of the action potential waves (as shown in the first two beats of (a), at spatial location x = 12.5 cm). Following the second beat, an ectopic beat occurs at a position slightly offset from the original stimulation point (shown schematically as the solid circle in (c)). The resulting excitation wave (wave 3, initiated at t = 680 ms at spatial location x = 1 cm in (a)) attempts to propagate in both directions around the ring, but one direction is refractory because of insufficient recovery from the previous excitation wave. As a result, the wave propagates in one direction (counter-clockwise in (c)) and blocks in the other direction (indicated by the ‘‘T’’ in (c)). After wave 2 has annihilated, only wave 3 remains, thereby initiating circus movement reentry (waves 4, 5, and beyond in (d)).

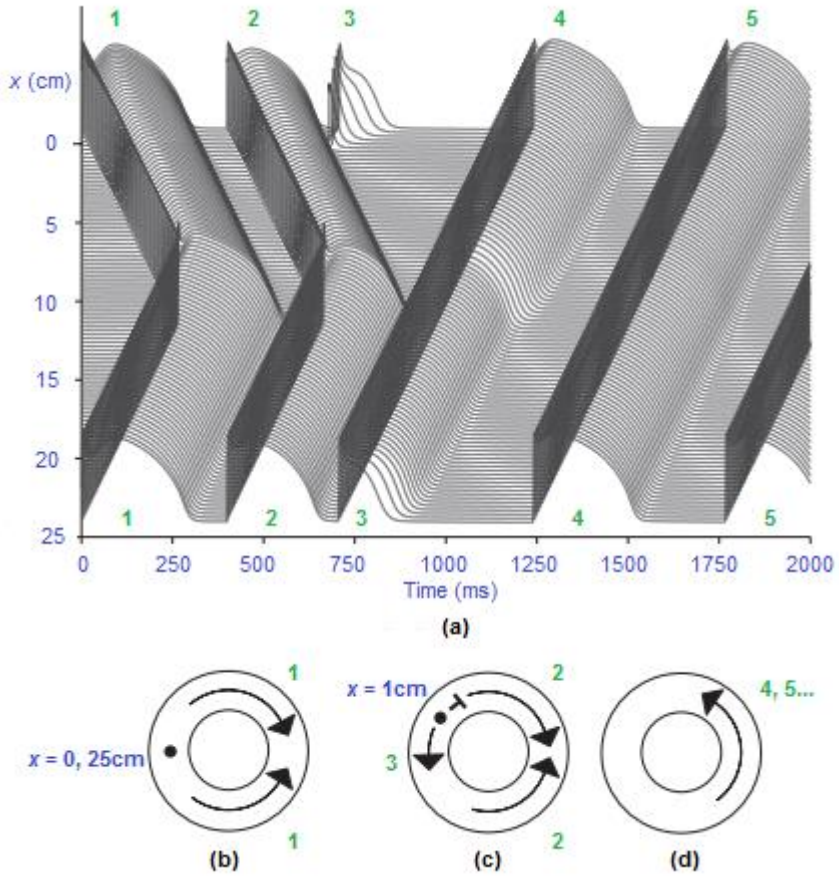

Figure 2.7: Unidirectional block and circus movement reentry. (a) A space-time diagram showing trans-membrane voltage as a function of time and position around the ring (b) - (d) Schematic diagrams of the scenario depicted in panel (a), The numbers in the panel (b) - (d) correspond to the wave number in the panel (a) [74]

2.3 Approaches in cardiac electrophysiological analysis

Previously mentioned in section 1.1 research backgrounds, there are three types of analysis tools to explore and interpret the underlying mechanisms in cardiac electrophysiological which are experimental, clinical and computational model simulation. This subtopic will discuss further details of these three methods.

2.3.1 Experimental approach

Experimental approach is used to reveal the underlying mechanisms in the electrical state of the heart based on a lot of experimental researches performed on the heart of mammalian animal such as rat, guinea pig, rabbit and dog as illustrated in Figure 2.8. However, due to the limited procedures and study parameters of this invasive analysis approach, discovering underlying mechanisms of the heart primarily the cardiac arrhythmias is quite challenging [75], [76], [77].

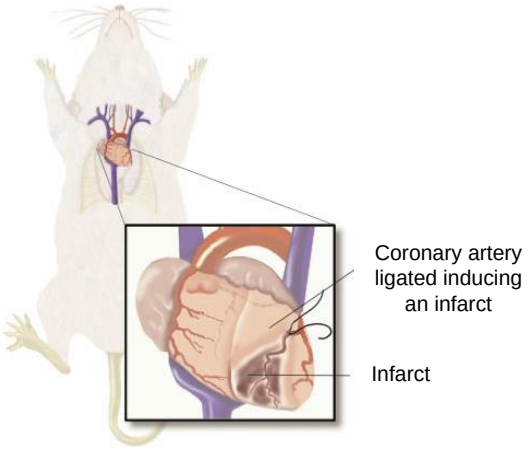

Figure 2.8: Rat model of myocardial infarction [78].

Another major limitation of any experimental study of ventricular arrhythmias is that patterns of excitation can be recorded with reasonable resolution only from the surface of the heart, whereas the underlying excitation patterns are three dimensional (3D). Moreover, the spatial resolution of 3D current measurement technique used in the experimental study is insufficient to identify the reentrant sources of arrhythmias and to study their dynamics [79]. Thus, computational model

simulation, especially detailed quantitative modeling of the human heart, can play an important role in overcoming these types of limitations [80].

2.3.2 Clinical approach

At its most basic, a clinical measurement electrophysiology study requires equipment to allow recording of cardiac activity and delivery of electrical stimulation to the human heart. Besides, clinical cardiac electrophysiology approach, involving intracardiac recording and electrical stimulation, have been a major importance in elucidating the mechanisms of cardiac arrhythmias. Therefore, such simple procedures are now rarely performed and modern clinical electrophysiology equipment is designed to undertake more complex studies, with recordings from multiple intracardiac electrode catheters, and programmed electrical stimulation for the induction and investigation of tachyarrhythmias. The induction of ventricular fibrillation (VF) by electrical currents which associated with abnormal wave propagation caused by reentrant sources of excitation, was demonstrated as early as 1899 by Prevost and Battelli [81], but the electrical induction and termination of arrhythmias essentially started in the early 1950s. Reentry as a mechanism for tachyarrhythmias is proposed initially by Mines [82] and the presence of potential substrate for reentry was identified by Moe [83].

Although the clinical studies are generally favourable, investigating the cardiac electrical behavior clinically poses a number of challenges such as various risk assessment procedures to the patient, limited sources of data and uncertainty or less informative with respect to the long-term performance of the device [84], [85]. In this case, the procedures of clinical testing may significantly influence to elucidate the underlying the mechanism in cardiac electrophysiological determination while independent of the clinical findings. Therefore, the use of model simulation is to avoid the limitations of clinical study and improve the knowledge of arrhythmia mechanism. These aspects provide a better understanding of abnormal cardiac electrical activity at various levels such as in the ion channels, cells, tissues and organ.

2.3.3 Model simulation approach

The availability of precise information on the formation and transmission of cardiac impulses, under both normal and pathological conditions, has helped elucidate the underlying mechanisms of cardiac arrhythmia. Several relevant topics have been considered in a number of experimental and clinical studies in the field of cardiac electrophysiology. These include analyses of the structure and function of the ionic channels that determine the action potential of cardiac cells, as well as the factors that regulate transmembrane ionic currents, such as voltage, time elapsed since activation, frequency, and ion concentrations [86]. However, the understanding of underlying mechanism of the cardiac electrophysiology is still incomplete in many aspects, and there are limitations to some of the procedures used to treat various cardiac arrhythmias for instance fibrillation processes.

The creation of models for an example, theoretical simulations of the electrophysiological phenomena based on mathematical model, forms a part of the efforts aimed at enhancing understanding of these phenomena and predicting behavior in various normal and abnormal mechanisms. The development of such models has been driven by several factors, including; i) Precise experimental and clinical data collection. This has been essential to constructing models based on real data and verifying how well such models work. ii) Advances in information processing and compilation capabilities through the use of faster, increasingly more complex computers. iii) The use of the models and simulations themselves to improve our understanding of the underlying cardiac arrhythmia mechanism and to predict responses under conditions that is sometimes hard to reproduce in experimental preparations. A look at the historical evolution of the mathematical models will be discussed afterwards in section 2.4.

The technique in the model simulation can be divided into two types which are a software-based simulation and a hardware-based simulation. The detail reviews regarding both methods are discussed in the section 2.3.3.1 and 2.3.3.2.

2.3.3.1 Software-based simulation

Computer simulations referred to the cardiac simulations that are performed on computer software such as Visual Studio software by using the C++ Programming Language, MATLAB Simulink by using graphical programming blocks, and etc. Recent advancements in computational science and the development of high performance computers have increased the usage of the computer simulation approaches in order to study the underlying mechanism of the cardiac. The computer simulation is the most favourable approach as it enabled the creation of multi-scale simulation by using the cardiac models. However, the computer simulations require huge computational resources, thus computational efficiency becomes a prime concern [87].

The computer simulations based on various types of mathematical models used to study cardiac arrhythmias show that the available information of the models has grown in complexity and advances in computational techniques have been made in the capacity to process it rapidly and efficiently. Parallel to the development parameters and variables of the mathematical models to study the formation of the action potential of cardiac cells, fast computational speed has been essential in order to analyse the data which contributed to the usage of supercomputer for analysis [88]. However, supercomputer is expensive and sizable which require a large room to store them [89]. Therefore, a new solution needs to be introduced to elucidate the mechanism of the heart such as hardware implementation.

2.3.3.2 Hardware-based simulation

Hardware implementation represents here is the cardiac mathematical model that is adapted into the hardware to perform real-time simulations such as by using FPGA, FPAA, GPU, DSP, Application Specific Integrated Circuit (ASIC) and etc. Recently, the hardware is widely chosen by researchers as the computational tool to study the underlying mechanism of the cardiac since it provides faster execution time compare to computer simulation according to its real-time and parallel mode execution. Furthermore, certain types of the hardware platform require very low power consumption in their operation.

2.3.4 Comparison between experimental, clinical and model simulations approaches

Table 2.1 shows the differences among the experimental, clinical and model simulation approaches that are used to study the underlying mechanism of the heart. It can be noticed that the experiments and clinical approaches have several limitations; limited studied parameters [90], surface recording only, and unable to perform in large scale due to the high cost of in-vivo or in-vitro cell setting [12]. On the other hands, the clinical could cause various risk assessment procedures to the patient [85], has limited sources of data and has uncertainty or less informative with respect to the long-term performance of the device [91]. Meanwhile, the model simulation approach which includes software- and hardware-based simulations is able to be performed in any numbers of parameter studies and its procedure is much simpler to conduct thus lesser cost is needed to run the analysis compare to the experimental and clinical approaches [92]. Besides, through this approach, the simulations can be performed in large scale, from 1D up to 3D. Furthermore, by performing the cardiac cell model simulation in the hardware, a real-time simulation is achieved compared to computer simulation which needs vast amounts of computational time to conduct the simulation [69].

Table 2.1: Comparison of experimental, computer simulation and hardware implementation.

Main Features	Approaches of analysis		
	Experimental/Clinical	Computer simulation	Hardware implementation
Limited parameters	Yes	No	No
Surface recording observations	Yes	No	No
1D - 3D, Large scale	No	Yes	Yes
Cost	High	Low	Low
Real-time simulation	-	Computation time consuming	Real-time
Cellular/Tissue process	Qualitative	Quantitative	Qualitative & Quantitative

2.4 Mathematical models for cardiac electrical activity

Cardiac electrophysiology concerns on the studies of the electrical activity of the heart under both normal and abnormal conditions. A cardiac excitation occurs when ions flowing through ion channels in and out of the plasma membrane that generates currents and causes changes in membrane potential from resting to an action potential. In a definition, an action potential is the electrical signal of cell that passes through the cardiac during the cell is excites. Commonly, the action potential is triggered by a voltage spike from the action potential of its neighboring tissue or from an artificial pacing signal [93].

Action potential models have been very useful in investigating different features of cardiac physiology, from action potential generation in a single-cell to action potential conduction in a multidimensional structure of cardiac tissues [94]. In which, the action potential models of cardiac cells are defined by mathematical descriptions of electrical events at the cellular level that give rise to cardiac action potentials. The models that describe action potentials and the ion transport across the cell membrane are also referred to as ionic models [66].

Most the ionic models of cardiac cells are based on the Hodgkin-Huxley formulation, which first that intend to formulate mathematically the cellular processes to lead the generation of the action potential in the squid nerve axon [95]. The model has been built in 1952 which are proposed an ion model that is specialized by three types of ion channel currents that are involved in the generation of the action potential to represent the sodium, potassium and chloride (leakage or background) through the membrane of squid axon [19]. The currents are characterised as the product of conductance and the differences of the driving forces for ions, namely chemical gradient and electrical gradient. The conductance of sodium and potassium are time-dependent and voltage-dependent, and modeled by using gating variables, which are formulated by first-order ODEs. The Hodgkin-Huxley model described the way in which ionic currents vary with membrane potential and time. Its structure forms a basis for almost all models of excitable membrane behavior [96].

FitzHugh and Nagumo, are two of the first researchers reduce ODEs in the Hodgkin-Huxley model from four state variables of gates in the potassium, sodium

and leakage conductance which describe the ionic channel currents to two state variables of excitation membrane voltage and refractory period [97]. FHN model used a single mathematical process to represent multiple channel properties and it preserved the essential behavior of the membrane while offering a lower computational cost compared to other models, it has been frequently used as the excitability component of cardiac action potential propagation [98]. Consequently, the FHN model is applied in this study in developing a new simulation-based analysis technique in cardiac excitation and conduction studies.

In 1962, Noble published one of the first mathematical models of a cardiac cell applicable for long lasting action and pacemaker potentials of the Purkinje fibers of the heart [23]. The Noble model adopted all the gating variables from Hodgkin-Huxley, and is also the four-variable differential system [22]. Then, continued by Beeler-Reuter model issued in 1977, is a pioneering effort to describe the cardiac ventricular action potential [25]. The experimental data used in the Beeler-Reuter model is subjected to limitation in available voltage clamp techniques and their application to multicellular preparations of cardiac muscle [99].

The Luo-Rudy I model, a system of eight variable ODEs for describing six types of ion channel currents (I_{K1}, I_{Kp}, I_b, I_{Na}, I_K, I_{si}) to present the flow of sodium, potassium, calcium and chloride currents is based on the data derived from the new measurement techniques. The Luo-Rudy I model is published in 1991 [26] and Luo-Rudy II model further developed in 1994 which described the electrophysiology of guinea pig ventricular cells [27]. The Luo-Rudy II model a system of fourteen variable ODEs. This model is also based on guinea pig ventricular cells from a single-cell experimental data [100]. It provides a framework for future development of models of the excitation-contraction coupling process in cardiac cells.

Since then, the mathematical models turn out numerous onward, but complicated from year to year as variable parameters in the mathematical descriptions are increased in order to represent the cellular processes in more detail. Progress in mathematical modeling has facilitated simulations as a tool for investigating cardiac dynamics. However, simulating the dynamics of large numbers of cellular models forming a tissue model requires an immense amount of computational time, while, hardware implementation could provide a high performance simulation system for the electrophysiological analysis.

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